



Comparative Effectiveness Review  
Number 224

# Treatment of Depression in Children and Adolescents: A Systematic Review



## **Treatment of Depression in Children and Adolescents: A Systematic Review**

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
5600 Fishers Lane  
Rockville, MD 20857  
[www.ahrq.gov](http://www.ahrq.gov)

**Contract No. 290-2015-00011-I**

**Prepared by:**

RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center  
Research Triangle Park, NC

**Investigators:**

Meera Viswanathan, Ph.D.  
Sara M. Kennedy, M.P.H.  
Joni McKeeman, Ph.D.  
Robert Christian, M.D.  
Manny Coker-Schwimmer, M.P.H.  
Jennifer Cook Middleton, Ph.D.  
Carla Bann, Ph.D.  
Linda Lux, M.P.A.  
Charli Randolph, B.A.  
Valerie Forman-Hoffman, Ph.D., M.P.H.

**AHRQ Publication No. 20-EHC005-EF  
April 2020**

## **Key Messages**

### **Purpose of Review**

The purpose of the review is to examine the benefits and harms of pharmacological and nonpharmacological treatments for child and adolescent depressive disorders.

### **Key Messages**

- Cognitive behavioral therapy (CBT), fluoxetine, escitalopram, and combined fluoxetine plus CBT may reduce depressive symptoms in the short term; clinical significance is unclear.
- CBT may improve symptoms and functional status. CBT plus medications may help prevent relapse.
- Selective serotonin reuptake inhibitors (SSRIs) as a class may improve response and functional status.
- However, SSRIs may be associated with a higher risk of serious adverse events and with a higher risk of withdrawal. Paroxetine may be associated with a higher risk of suicidal ideation or behaviors. Evidence to judge the risk of suicidal ideation or behavior for SSRIs other than paroxetine is insufficient for major depressive disorder. However, this report excluded data on inpatients and those without depressive disorders whom the Food and Drug Administration included in finding an increased risk of suicidality for all antidepressants across all indications.

This report is based on research conducted by the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00011-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

**None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.**

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report is made available to the public under the terms of a licensing agreement between the author and the Agency for Healthcare Research and Quality. This report may be used and reprinted without permission except those copyrighted materials that are clearly noted in the report. Further reproduction of those copyrighted materials is prohibited without the express permission of copyright holders.

AHRQ or U.S. Department of Health and Human Services endorsement of any derivative products that may be developed from this report, such as clinical practice guidelines, other quality enhancement tools, or reimbursement or coverage policies, may not be stated or implied.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program website at [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov). Search on the title of the report.

People using assistive technology may not be able to fully access information in this report. For assistance contact [EPC@ahrq.hhs.gov](mailto:EPC@ahrq.hhs.gov).

**Suggested citation:** Viswanathan M, Kennedy SM, McKeeman J, Christian R, Coker-Schwimmer M, Cook Middleton J, Bann C, Lux L, Randolph C, Forman-Hoffman V. Treatment of Depression in Children and Adolescents: A Systematic Review. Comparative Effectiveness Review No. 224. (Prepared by the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center under Contract No. 290-2015-00011-I.) AHRQ Publication No. 20-EHC005-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. DOI: <https://doi.org/10.23970/AHRQEPCCER224>. Posted final reports are located on the Effective Health Care Program [search page](#).



## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see [www.effectivehealthcare.ahrq.gov/reference/purpose.cfm](http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm).

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

Gopal Khanna, M.B.A.  
Director  
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.  
Director  
Center for Evidence and Practice  
Improvement  
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.  
Director  
Evidence-based Practice Center Program  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Kim Wittenberg, M.A.  
Task Order Officer  
Evidence-based Practice Center Program  
Center for Evidence and Practice  
Improvement  
Agency for Healthcare Research and Quality

## Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project and deeply appreciate their considerable support, commitment, and contributions: Aysegul Gozu, M.D., M.P.H., and Kim Wittenberg, M.A., our AHRQ Task Order Officers (TOOs); RTI International–University of North Carolina at Chapel Hill EPC staff: Rania Ali, M.P.H.; Sharon Barrell, M.A.; Josh Green, B.A.; Loraine Monroe; Christiane Voisin, M.S.L.S.; Rachel Weber, Ph.D.; Carol Woodell, B.S.P.H. We also thank representatives from the American Academy of Child and Adolescent Psychiatry (Heather Walter, Ronald Szabat, and Karen Ferguson). Finally, we thank Tiffany R. Farchione, M.D., Deputy Director (Acting), Division of Psychiatry Products, Center for Drug Evaluation and Research, Office of New Drugs, U.S. Food and Drug Administration.

## Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who provided input to this report follows:

Joan Asarnow, Ph.D.\*  
University of California Los Angeles  
Los Angeles, CA

Nathaniel Counts, B.A., J.D.\*  
Mental Health America  
Alexandria, VA

Boris Birmaher, M.D.  
University of Pittsburgh  
Pittsburgh, PA

Justine Larson, M.D., M.P.H., M.H.S.\*  
Substance Abuse and Mental Health  
Services Administration  
Rockville, MD

Rebecca Bitsko, Ph.D.  
Centers for Disease Control and Prevention  
Atlanta, GA

V. Robin Weersing, Ph.D.  
San Diego State University  
San Diego, CA

\*Provided input on draft report.

## Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:

Joan Asarnow, Ph.D.\*  
University of California Los Angeles  
Los Angeles, CA

Boris Birmaher, M.D.  
University of Pittsburgh  
Pittsburgh, PA

Rebecca Bitsko, Ph.D.  
Centers for Disease Control and Prevention  
Atlanta, GA

Nathaniel Counts, B.A., J.D.\*  
Mental Health America  
Alexandria, VA

Justine Larson, M.D., M.P.H., M.H.S.\*  
Substance Abuse and Mental Health  
Services Administration  
Rockville, MD

Joel Sherrill, Ph.D.\*  
National Institute of Mental Health  
Bethesda, MD

Ruth Stein, M.D.\*  
Albert Einstein College of Medicine  
New York City, NY

V. Robin Weersing, Ph.D.  
San Diego State University  
San Diego, CA

\*Provided input on draft report.

## Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

John Campo, M.D.  
West Virginia University  
Morgantown, WV

Daniel Castellanos, M.D.  
Florida International University  
Miami, FL

Mary Fristad, Ph.D.  
The Ohio State University  
Columbus, OH

Brian Hepburn, M.D.  
National Association of State Mental Health  
Program Directors  
Alexandria, VA

# Treatment of Depression in Children and Adolescents: A Systematic Review

## Structured Abstract

**Background.** Depressive disorders can affect long-term mental and physical health functioning among children and adolescents, including increased risk of suicide. Despite access to several nonpharmacological, pharmacological, and combined treatment options for childhood depression, clinicians contend with sparse evidence and are concerned about harms associated with treatment.

**Methods.** We conducted a systematic review to evaluate the efficacy, comparative effectiveness, and moderators of benefits and harms of available nonpharmacological and pharmacological treatments for children and adolescents with a confirmed diagnosis of a depressive disorder (DD)—major depressive disorder (MDD), persistent depressive disorder (previously termed dysthymia) or DD not otherwise specified. We searched five databases and other sources for evidence available from inception to May 29, 2019, dually screened the results, and analyzed eligible studies.

**Results.** We included in our analyses data from 60 studies (94 articles) that met our review eligibility criteria. For adolescents (study participants' ages range from 12 to 18 years) with MDD, cognitive behavioral therapy (CBT), fluoxetine, escitalopram, and combined fluoxetine and CBT may improve depressive symptoms (1 randomized controlled trial [RCT] each, n ranges from 212 to 311); whether the magnitude of improvement is clinically significant is unclear. Among adolescents or children with MDD, CBT plus medications (8–17 years) may be associated with lower rates of relapse (1 RCT [n = 121]). In the same population (6–17 years), selective serotonin reuptake inhibitors (SSRIs) may be associated with improved response (7 RCTs [n = 1,525]; risk difference [RD], 72/1,000 [95% confidence interval (CI), 2 to 24],  $I^2 = 9\%$ ) and functional status (5 RCTs [n = 941]; standardized mean difference, 0.16 [95% CI, 0.03 to 0.29];  $I^2 = 0\%$ ). For adolescents or children with any DD (7–18 years), CBT or family therapy may be associated with improvements in symptoms, response, or functional status (1 RCT each, n ranges from 64 to 99). Among children with any DD (7–12 years), family-based interpersonal therapy may be associated with improved symptoms (1 RCT, n = 38). Psychotherapy trials did not report harms. SSRIs may be associated with a higher risk of serious adverse events among adolescents or children with MDD (7–18 years; 9 RCTs [n = 2,206]; RD, 20/1,000 [95% CI, 1 to 440];  $I^2 = 4\%$ ) and with a higher risk of withdrawal due to adverse events among adolescents with MDD (12–18 years; 4 RCTs [n = 1,296], RD, 26/1,000 [95% CI, 6 to 45];  $I^2 = 0\%$ ). Paroxetine (1 RCT [n = 180]) may be associated with a higher risk of suicidal ideation or behaviors among adolescents with MDD (12–18 years). Evidence was insufficient to judge the risk of suicidal ideation or behavior for other SSRIs for adolescents and children with MDD or other DD (7–18 years) (10 RCTs [n = 2,368]; relative risk, 1.14 [95% CI, 0.89 to 1.45];  $I^2 = 8\%$ ). However, this report excluded data on inpatients and those without depressive disorders, whom the Food and Drug Administration included in finding an increased risk of suicidality for all antidepressants across all indications.

**Conclusions.** Efficacious treatments exist for adolescents with MDD. SSRIs may be associated with increased withdrawal and serious adverse events. No evidence on harms of psychotherapy were identified.

# Contents

<b>Evidence Summary .....</b>	<b>ES-1</b>
<b>Chapter 1. Introduction .....</b>	<b>1</b>
Background .....	1
Scope and Key Questions .....	4
Scope of the Review .....	4
Key Questions and Analytic Framework .....	5
<b>Chapter 2. Methods .....</b>	<b>9</b>
Literature Search Strategy .....	9
Inclusion and Exclusion Criteria.....	9
Study Selection .....	10
Data Abstraction .....	10
Assessment of Methodological Risk of Bias of Individual Studies.....	10
Data Synthesis.....	10
Grading the Strength of Evidence .....	11
Assessing Applicability .....	12
<b>Chapter 3. Results.....</b>	<b>14</b>
Literature Searches and Study Characteristics.....	14
KQ 1a: Benefits and Harms of Nonpharmacological Interventions .....	17
CBT Versus Pill Placebo: Benefits .....	17
CBT Versus Pill Placebo: Harms.....	18
CBT Versus Wait-List Control: Benefits.....	19
CBT Versus Wait-List Control: Harms .....	21
CBT (Delivered to Adolescent and Parent) Versus Wait-List Control: Benefits .....	21
CBT (Delivered to Adolescent and Parent) Versus Wait-List Control: Harms .....	21
CBT + TAU Versus TAU/UC: Benefits .....	22
CBT + TAU Versus TAU/UC: Harms.....	25
CBT (Modified) Versus UC: Benefits .....	26
CBT (Modified) Versus UC: Harms .....	27
CBT Versus Active Control: Benefits .....	27
CBT Versus Active Control: Harms .....	29
Relapse Prevention CBT + Continued Antidepressant Medication Management Versus Continued Medication Management: Benefits .....	30
Relapse Prevention CBT + Continued Antidepressant Medication Management Versus Continued Medication Management: Harms .....	32
IPT Versus Wait-List Control: Benefits .....	33
IPT Versus Wait-List Control: Harms .....	34
IPT Versus Active Control: Benefits .....	34
IPT Versus Active Control: Harms .....	35
Family-Based IPT Versus Active Control: Benefits.....	36
Family-Based IPT Versus Active Control: Harms .....	36
Attachment-Based Family Therapy Versus Wait-List Control: Benefits .....	37
Attachment-Based Family Therapy Versus Wait-List Control: Harms.....	38
Attachment-Based Family Therapy Versus TAU: Benefits .....	39
Attachment-Based Family Therapy Versus TAU: Harms .....	40
Family Therapy Versus Pill Placebo: Benefits .....	40

Family Therapy Versus Pill Placebo: Harms .....	41
Family Therapy Versus Active Control: Benefits.....	41
Family Therapy Versus Active Control: Harms .....	43
PCIT Versus Active Control: Benefits .....	44
PCIT Versus Active Control: Harms .....	44
Short-Term Psychoanalytic Therapy Versus Active Control: Benefits .....	45
Short-Term Psychoanalytic Therapy Versus Active Control: Harms.....	46
Exercise Versus Active Control: Benefits .....	47
Exercise Versus Active Control: Harms .....	49
Spirituality-Informed Online Sessions Versus Wait-List: Benefits.....	49
Spirituality-Informed Online Sessions Versus Wait-List: Harms .....	49
Omega-3 Versus Pill Placebo: Benefits .....	50
Omega-3 Versus Pill Placebo: Harms.....	51
KQ 1b: Benefits and Harms of Nonpharmacological Interventions by Subpopulation.....	51
CBT Versus Pill Placebo: Subpopulations .....	51
CBT Versus Wait-List Control: Subpopulations .....	52
CBT (Delivered to Adolescent and Parent) Versus Wait-List Control: Subpopulations.....	52
CBT + TAU Versus TAU/UC: Subpopulations .....	52
CBT (Modified) Versus UC: Subpopulations.....	52
CBT Versus Active Control: Subpopulations.....	52
Relapse Prevention CBT + Continued Antidepressant Medication Management Versus Continued Medication Management: Subpopulations .....	53
IPT Versus Wait-List Control: Subpopulations.....	53
IPT Versus Active Control: Subpopulations.....	53
Family-Based IPT Versus Active Control: Subpopulations .....	53
Attachment-Based Family Therapy Versus Wait-List Control: Subpopulations .....	54
Attachment-Based Family Therapy Versus TAU: Subpopulations.....	54
Family Therapy Versus Pill Placebo: Subpopulations.....	54
Family Therapy Versus Active Control: Subpopulations .....	54
PCIT Versus Active Control: Subpopulations.....	55
Psychoanalytic Therapy Versus Active Control: Subpopulations .....	55
Exercise Versus Active Control: Subpopulations.....	55
Spirituality Versus Wait-List: Subpopulations .....	55
Omega-3 Versus Pill Placebo: Subpopulations .....	55
KQ 2a: Benefits and Harms of Pharmacological Interventions.....	56
SSRIs Versus Placebo: Benefits .....	56
SSRIs Versus Placebo: Harms .....	65
Fluoxetine for Relapse Prevention Versus Placebo: Benefits.....	74
Fluoxetine for Relapse Prevention Versus Placebo: Harms .....	76
SNRIs Versus Placebo: Benefits.....	76
SNRIs Versus Placebo: Harms .....	78
TCAs Versus Placebo: Benefits.....	81
TCAs Versus Placebo: Harms.....	84
MAOIs Versus Placebo: Benefits .....	85
MAOIs Versus Placebo: Harms.....	86
Venlafaxine + Active Control Versus Placebo + Active Control: Benefits.....	87



Venlafaxine + Active Control Versus Placebo + Active Control: Harms .....	87
KQ 2b: Benefits and harms of pharmacological interventions subpopulation .....	88
SSRIs Versus Placebo: Subpopulations.....	88
Fluoxetine for Relapse Prevention Versus Placebo: Subpopulations .....	90
SNRIs Versus Placebo: Subpopulations .....	90
TCAs Versus Placebo: Subpopulations .....	90
MAOIs Versus Placebo: Subpopulations.....	91
Venlafaxine + Active Control Versus Placebo + Active Control: Subpopulations .....	91
KQ 3a: Benefits and Harms of Combination Interventions.....	91
Fluoxetine + CBT Versus Placebo: Benefits .....	91
Fluoxetine + CBT Versus Placebo: Harms .....	92
Omega-3 + Family Therapy Versus Placebo: Benefits.....	93
Omega-3 + Family Therapy Versus Placebo: Harms .....	94
KQ 3b: Benefits and Harms of Combination Interventions by Subpopulation .....	94
Fluoxetine + CBT Versus Placebo: Subpopulations.....	94
Omega-3 + Family Therapy Versus Pill Placebo: Subpopulations .....	95
KQ 4a: Benefits and Harms of Collaborative Care Interventions .....	95
KQ 4b: Benefits and Harms of Collaborative Care Interventions by Subpopulation.....	95
KQ 5a: Comparative Benefits and Harms of Treatments .....	95
CBT Versus Other Psychotherapy: Benefits.....	95
CBT Versus Other Psychotherapy: Harms .....	99
Psychotherapy Within-Type Comparisons of Delivery Methods or Approaches:	
Benefits .....	100
Psychotherapy Within-Type Comparisons of Delivery Methods or Approaches:	
Harms .....	103
Psychotherapy Versus Pharmacotherapy: Benefits.....	103
Psychotherapy Versus Pharmacotherapy: Harms .....	105
Psychotherapy Plus Pharmacotherapy Versus Psychotherapy: Benefits .....	107
Psychotherapy Plus Pharmacotherapy Versus Psychotherapy: Harms .....	110
Psychotherapy Plus Pharmacotherapy Versus Pharmacotherapy: Benefits.....	112
Psychotherapy Plus Pharmacotherapy Versus Pharmacotherapy: Harms .....	116
Omega-3 Versus Other Therapies: Benefits .....	117
Omega-3 Versus Other Therapies: Harms .....	118
SSRIs Versus SNRIs: Benefits .....	119
SSRIs Versus SNRIs: Harms .....	120
SSRIs Versus TCAs: Benefits .....	121
SSRIs Versus TCAs: Harms .....	122
Pharmacotherapy Dose Comparisons: Benefits.....	124
Pharmacotherapy Dose Comparisons: Harms .....	125
Treatment-Resistant Depression Interventions: Benefits.....	128
Treatment-Resistant Depression Interventions: Harms .....	130
KQ 5b: Comparative Benefits and Harms of Treatments by Subpopulation.....	132
CBT Versus Other Psychotherapy: Subpopulations .....	132
Psychotherapy Within-Type Comparisons of Delivery Methods or Approaches:	
Subpopulations.....	133
Psychotherapy Versus Pharmacotherapy: Subpopulations .....	133

Psychotherapy Plus Pharmacotherapy Versus Psychotherapy: Subpopulations.....	134
Psychotherapy Plus Pharmacotherapy Versus Pharmacotherapy: Subpopulations .....	134
Omega-3 Versus Other Therapies: Subpopulations.....	135
SSRIs Versus SNRIs: Subpopulations.....	135
SSRIs Versus TCAs: Subpopulations.....	135
Pharmacotherapy Dose Comparisons: Subpopulations .....	135
Treatment-Resistant Depression Interventions: Subpopulations .....	136
<b>Chapter 4. Discussion .....</b>	<b>137</b>
Findings in Relation to What Is Already Known.....	141
Limitations .....	143
Applicability .....	144
Future Research Needs .....	144
Conclusion .....	150
<b>References .....</b>	<b>151</b>

## Tables

Table A. Key characteristics of included studies.....	ES-7
Table B. Strength of evidence for outcomes of nonpharmacological interventions versus active or wait-list control .....	ES-10
Table C. Strength of evidence for outcomes of pharmacotherapy versus placebo .....	ES-12
Table D. Strength of evidence for outcomes of fluoxetine + CBT versus placebo .....	ES-17
Table E. Strength of evidence for outcomes of comparative effectiveness studies.....	ES-19
Table 1. Current clinical practice guidelines for the treatment of child and adolescent DDs .....	2
Table 2. Nonpharmacological interventions used to treat child and adolescent depression.....	4
Table 3. Pharmacological agents used to treat child and adolescent depression .....	5
Table 4. Inclusion/exclusion criteria.....	7
Table 5. Definitions of the grades of overall SOE.....	12
Table 6. Key characteristics of included studies.....	16
Table 7. Strength of evidence for benefits of CBT versus pill placebo .....	18
Table 8. Strength of evidence for harms of CBT versus pill placebo .....	19
Table 9. Strength of evidence for benefits of CBT versus wait-list control .....	20
Table 10. Strength of evidence for benefits of CBT (delivered to adolescents and parents) versus wait-list control.....	21
Table 11. Strength of evidence for benefits of CBT + TAU versus TAU/UC .....	23
Table 12. Strength of evidence for harms of CBT + TAU versus TAU/UC .....	26
Table 13. Strength of evidence for benefits of CBT (modified) versus UC .....	27
Table 14. Strength of evidence for benefits of CBT versus active control.....	28
Table 15. Strength of evidence for harms of CBT versus active control.....	30
Table 16. Strength of evidence for benefits of relapse prevention CBT + continued antidepressant medication management versus continued medication management ...	31
Table 17. Strength of evidence for harms of relapse prevention CBT + continued antidepressant medication management versus continued medication management ...	32
Table 18. Strength of evidence for benefits of IPT versus wait-list control .....	34
Table 19. Strength of evidence for benefits of IPT versus active control (clinical monitoring) .....	35
Table 20. Strength of evidence for harms of IPT versus active control (clinical monitoring) .....	36

Table 21. Strength of evidence for benefits of family-based IPT versus active control (child-centered therapy).....	37
Table 22. Strength of evidence for benefits of attachment-based family therapy versus wait-list control .....	38
Table 23. Strength of evidence for harms of attachment-based family therapy versus wait-list control .....	39
Table 24. Strength of evidence for benefits of attachment-based family therapy versus TAU....	39
Table 25. Strength of evidence for benefits of family therapy versus pill placebo .....	40
Table 26. Strength of evidence for benefits of family therapy versus active control .....	41
Table 27. Strength of evidence for harms of family therapy versus active control .....	43
Table 28. Strength of evidence for benefits of PCIT versus active control .....	44
Table 29. Strength of evidence for benefits of short-term psychoanalytic therapy versus active control.....	45
Table 30. Strength of evidence for harms of short-term psychoanalytic therapy versus active control .....	47
Table 31. Strength of evidence for benefits of exercise versus active control .....	48
Table 32. Strength of evidence for benefits of spirituality versus wait-list control.....	49
Table 33. Strength of evidence for benefits of omega-3 versus pill placebo.....	50
Table 34. Strength of evidence for benefits of SSRIs versus placebo .....	58
Table 35. Strength of evidence for harms of SSRIs versus placebo .....	68
Table 36. Strength of evidence for benefits of relapse prevention of fluoxetine versus placebo .....	75
Table 37. Strength of evidence for harms of relapse prevention of fluoxetine versus placebo .....	76
Table 38. Strength of evidence for benefits of SNRIs versus placebo .....	77
Table 39. Strength of evidence for harms of SNRIs versus placebo .....	79
Table 40. Strength of evidence for benefits of TCAs versus placebo .....	82
Table 41. Strength of evidence for harms of TCAs versus placebo .....	84
Table 42. Strength of evidence for benefits of MAOIs versus placebo.....	86
Table 43. Strength of evidence for harms of MAOIs versus placebo.....	86
Table 44. Strength of evidence for benefits of venlafaxine plus active control versus placebo plus active control .....	87
Table 45. Strength of evidence for harms of venlafaxine plus active control versus placebo plus active control .....	88
Table 46. Strength of evidence for benefits of fluoxetine + CBT versus placebo.....	92
Table 47. Strength of evidence for harms of fluoxetine + CBT versus placebo.....	93
Table 48. Strength of evidence for benefits of family therapy versus pill placebo .....	94
Table 49. Strength of evidence for benefits of CBT versus other psychotherapies.....	96
Table 50. Strength of evidence for harms of CBT versus other psychotherapies.....	100
Table 51. Strength of evidence for comparative benefits of psychotherapy interventions comparing varying delivery methods or approaches .....	101
Table 52. Strength of evidence for benefits of psychotherapy versus pharmacotherapy .....	104
Table 53. Strength of evidence for harms of psychotherapy versus pharmacotherapy .....	106
Table 54. Strength of evidence for benefits of psychotherapy plus pharmacotherapy versus psychotherapy .....	108

Table 55. Strength of evidence for harms of psychotherapy plus pharmacotherapy versus psychotherapy .....	111
Table 56. Strength of evidence for benefits of psychotherapy plus pharmacotherapy versus pharmacotherapy.....	113
Table 57. Strength of evidence for harms of psychotherapy plus pharmacotherapy versus pharmacotherapy.....	116
Table 58. Strength of evidence for benefits of omega 3, family therapy, and combined therapy .....	118
Table 59. Strength of evidence for benefits of SSRIs versus SNRIs.....	119
Table 60. Strength of evidence for harms of SSRIs versus SNRIs.....	120
Table 61. Strength of evidence for benefits of SSRIs versus TCAs.....	121
Table 62. Strength of evidence for harms of SSRIs versus TCAs.....	123
Table 63. Strength of evidence for benefits of pharmacotherapy dose comparisons .....	124
Table 64. Strength of evidence for harms of pharmacotherapy dose comparisons .....	126
Table 65. Strength of evidence for benefits of treatment-resistant depression intervention comparisons .....	128
Table 66. Strength of evidence for harms of treatment-resistant depression intervention comparisons .....	131
Table 67. Numbers needed to treat to benefit and numbers needed to treat to harm for interventions for childhood depression.....	137
Table 68. Evidence map for interventions for childhood depression .....	<b>Error! Bookmark not defined.</b>

## Figures

Figure A. Analytic framework for depression in children and adolescents.....	ES-3
Figure B. Article flow diagram.....	ES-6
Figure 1. Analytic framework for depression in children and adolescents.....	6
Figure 2. Article flow diagram.....	15

## Appendixes

Appendix A. Search Strategy
Appendix B. Inclusion/Exclusion Criteria
Appendix C. Excluded Studies
Appendix D. Study Characteristics
Appendix E. Evidence Tables
Appendix F. Harms Tables
Appendix G. Subpopulation Tables
Appendix H. Risk of Bias of Randomized, Controlled Trials
Appendix I. Risk of Bias of Nonrandomized, Controlled Trials
Appendix J. Meta-Analysis
Appendix K. Appendix References

# Evidence Summary

## Introduction

### Background

Depressive disorders (DD) can affect long-term mental and physical health conditions, lead to poor functional status among children and adolescents, and increase risk of suicide.<sup>1</sup> The potential for lasting negative effects of child-onset depression underscores the importance of its early identification, diagnosis, and subsequent treatment.<sup>2</sup>

Several nonpharmacological, pharmacological, and combined treatment options for childhood DDs are available to clinicians. Uncertainty persists regarding their overall efficacy and variations in efficacy by age and disorder. Developmental changes that occur over the course of childhood and adolescence likely have widespread impacts on outcomes, and children and adolescents may experience differential benefits and harms depending on treatment type.<sup>3</sup> In addition, differences in outcomes may vary by severity and type of DD (e.g., major depressive disorder [MDD], persistent depressive disorder [PDD, previously termed dysthymia] or DD not otherwise specified [DD NOS]). Although the evidence on PDD is relatively sparse, PDD can be a gateway to MDD and signal high risk of recurrent mood disorders.

Most existing clinical practice guidelines offer separate recommendations by age and DD type or level of severity (mild, moderate, severe). Guidelines generally recommend either active support and monitoring or psychotherapy for patients with mild DDs, and selective serotonin reuptake inhibitor (SSRI) medications or a combination of psychotherapy and SSRIs for patients with moderate or severe disorders and for patients with mild disorders who do not improve. However, substantial concern surrounds the use of pharmacological interventions to treat childhood depression. Although the Food and Drug Administration (FDA) has approved two types of SSRIs to treat MDD (fluoxetine for children ages 8 years or older and escitalopram for adolescents ages 12 to 17 years), FDA issued several warnings in the early 2000s. These warnings stemmed from reports of possible increased risk of suicidal ideation and suicide attempts associated with one SSRI, paroxetine, as well as the possibility of increased risk of suicidality in some children and adolescents treated with antidepressants.<sup>4</sup> Other areas of uncertainty include treatment of children, disorders other than MDD, and partial or no response to initial therapy.

In sum, clinicians contend with numerous challenges in treating childhood depression appropriately. Clinical uncertainty persists regarding how the harms may vary according to dose of medication or how the efficacy of treatments may vary by frequency or intensity of the nonpharmacological intervention. Moreover, few nonpharmacological studies have systematically collected and reported harms data (e.g., re-experiencing trauma, suicidality),<sup>5</sup> which leads to uncertainty about weighing the risks and benefits of different types of treatment. Finally, the evidence base on comparative effectiveness of depression interventions in childhood is sparse.<sup>6</sup> These uncertainties obscure best practices in selecting a treatment most likely to benefit each individual patient.

## Scope and Key Questions

### Scope of the Review

This systematic review (SR) addresses the efficacy, comparative effectiveness, and harms of commonly used types of nonpharmacological and pharmacological treatments for childhood depression.

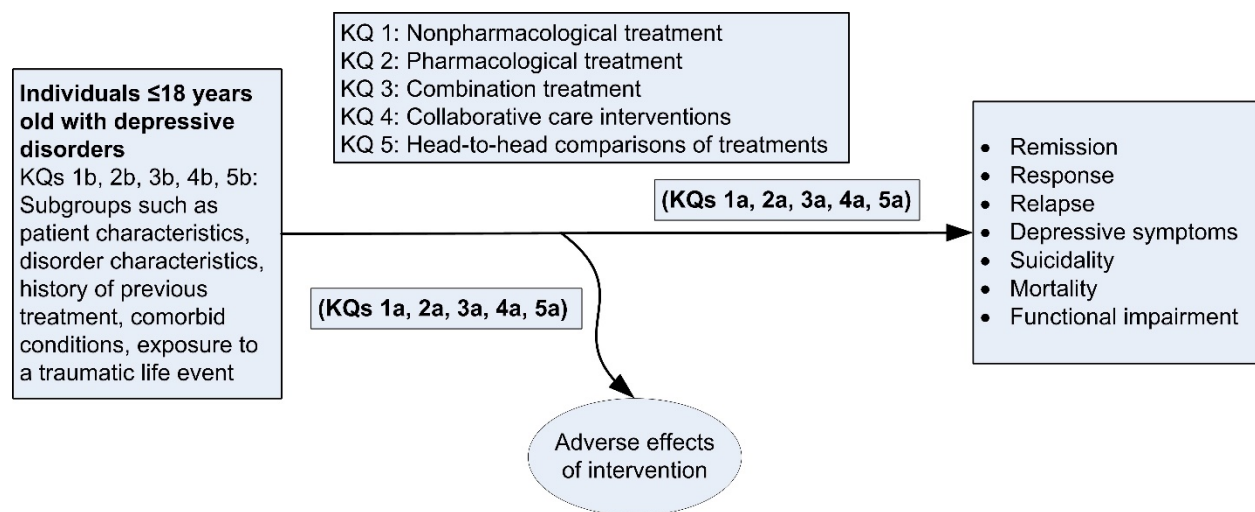
### Key Questions and Analytic Framework

Multiple Key Informants and members of a Technical Expert Panel helped finalize the following Key Questions (KQs). We developed an analytic framework to guide SR (Figure A). The full report lists the related PICOTS (population, interventions, comparators, outcomes, timing, and setting).

- KQ 1a.** In adolescents and children, what are the benefits and harms of nonpharmacological interventions for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?
- KQ 1b.** How do the benefits and harms vary by subpopulation (e.g., patient characteristics, parent/caregiver characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?
- KQ 2a.** In adolescents and children, what are the benefits and harms of pharmacological interventions for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?
- KQ 2b.** How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?
- KQ 3a.** In adolescents and children, what are the benefits and harms of combination interventions for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?
- KQ 3b.** How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?
- KQ 4a.** In adolescents and children, what are the benefits and harms of collaborative care interventions for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?

- KQ 4b.** How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?
- KQ 5a.** In adolescents and children, what are the comparative benefits and harms of treatments (pharmacological, nonpharmacological, combined, collaborative care interventions) for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?
- KQ 5b.** How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?

**Figure A. Analytic framework for depression in children and adolescents**



KQ = Key Question.

## Methods

We followed established methodologies of SRs as outlined in the Agency for Healthcare Quality and Research (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>7</sup> The study protocol is registered in the international prospective register of systematic reviews (PROSPERO #: CRD42018112150) and published on AHRQ's website at <https://effectivehealthcare.ahrq.gov/topic/childhood-depression/protocol>.

## Literature Search Strategy

We conducted focused searches of MEDLINE®, the Cochrane Library, the Cochrane Central Trials Registry, the Cumulative Index to Nursing and Allied Health Literature®, and PsycINFO® from inception to May 29, 2019. We also searched relevant SRs and gray literature.

Eligible studies had to meet all the following criteria: (1) children and adolescents 18 years or younger with a confirmed diagnosis of MDD, PDD [or dysthymia, as previously defined], or DD NOS; (2) study participants received any nonpharmacological interventions; pharmacotherapy, alone or combined; interventions delivered in collaborative care systems that consisted of at least 6 weeks of treatment; and (3) study participants reported outcomes of interest (standardized depression or functional impairment benefit measures or harms outcomes). We included randomized controlled trials (RCTs) for benefits and RCTs or observational studies for harms. We further restricted the studies to those conducted in countries with a very high Human Development Index (HDI; at least one country in multiple-country studies had to be on the very high HDI list) and those published in English. The full report lists detailed inclusion and exclusion criteria, organized by PICOTS.

## Study Selection

We imported all citations identified through searches and other sources into EndNote v.7. Independent reviewers screened the titles and abstracts of all citations using the inclusion and exclusion criteria using Covidence (systematic review software).<sup>8</sup> Studies included by either reviewer were retrieved for full-text screening. Independent reviewers then screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus or consultation with a third reviewer.

## Data Abstraction

We developed and pilot tested a standardized data extraction form to extract relevant study data. Trained reviewers abstracted the relevant data; a second member of the team reviewed abstractions. For the studies that addressed the subgroup KQs (KQs 1b, 2b, 3b, 4b, 5b), we only included studies that directly compared the efficacy or effectiveness between subgroups of interest.

## Assessment of Methodological Risk of Bias of Individual Studies

The criteria set forth by AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* guided our assessment of methodological risk of bias. To assess the risk of bias (i.e., internal validity), we used the ROBINS-1<sup>9</sup> tool for observational studies and the Cochrane RCT tool<sup>10</sup> for RCTs.

Two independent reviewers assigned risk-of-bias ratings for each study with disagreements resolved by discussion and consensus. Reviewers assigned a rating of low risk of bias (study met all criteria), some concerns (study met some criteria), high risk of bias (methodological shortcomings leading to high risk of bias in one or more categories), or unclear risk of bias (methods not reported clearly).

## Data Synthesis

If we found three or more studies with low levels of heterogeneity (similar populations, interventions, comparators, outcomes), we considered meta-analysis. For all analyses, we used random effects models to estimate pooled or comparative effects; unlike a fixed-effects model, this approach allowed for the likelihood that the true population effect may vary from study to study. To determine whether quantitative analyses were appropriate for bodies of evidence that contained three or more similar studies, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance.<sup>11</sup>



When possible, for each intervention/comparator grouping, we present benefits and harms findings clustered by age of sample. We elected to use age categories as defined by study authors (adolescents as defined by study authors [typically age 11 or 12 years or older], children as defined by study authors [typically age 10 or 11 years or younger], and mixed adolescent and child samples [typically age 7 or 8 to 17 or 18 years]) rather than our own a priori definitions (adolescents [sample age >12 and ≤18]: RCTs, children [sample age ≤12]) to capture all available evidence. In addition, we present findings clustered by the sample's required DD diagnoses for inclusion—MDD only or a wide range of depressive disorders (MDD, PDD/dysthymia, or DD NOS) (i.e., having at least one DD diagnosis such as MDD, PDD/dysthymic disorders, or other DDs like DD NOS). We generally use the same diagnostic term as the original study (e.g., PDD or dysthymia). We also note special characteristics of the sample required for study inclusions such as females only, those with treatment-resistant depression, those with a comorbid disorder like substance use disorder, or those with exposure to a traumatic life event. Studies that test different delivery systems of similar interventions (e.g., in person versus online or targeting adolescents only versus adolescents and parents) or different aspects of DDs (e.g., acute episodes versus relapse after successful treatment) are reported separately as well. We present end-of-treatment data for all studies; these vary widely from weeks to months. We also present longer-term outcomes when available. We synthesized the data qualitatively when quantitative analyses were not appropriate (e.g., due to heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting).

## **Grading the Strength of Evidence**

We graded the strength of evidence (SOE) based on the guidance established for the Evidence-based Practice Center Program.<sup>12</sup> Grades of high, medium, low, or insufficient reflect the strength of the body of evidence to answer KQs on the comparative effectiveness, efficacy, and harms of the interventions included in this review. Grades represent the degree of confidence that the evidence reflects the true effect and the likelihood that further research will change the estimate of effect. Insufficient grades are assigned when evidence is either unavailable or does not permit estimation of an effect.

Based on input from Key Informants, we chose to report depression symptom reduction, remission, relapse, recovery, functional impairment, mortality, suicidality, serious adverse events (AEs), and withdrawal due to AEs in the main text of the report. Two reviewers assessed each domain for each key outcome with differences resolved by consensus. For bodies of evidence for which we could conduct sensitivity analyses, we based the final SOE grade on the evidence base without high risk-of-bias studies for benefits. For harms, if the results continued to be consistent, we retained the overall SOE from the entire evidence base, in order to capture the potential for a signal of harms. We appended a footnote to SOE tables to indicate when sensitivity analyses changed the SOE grade.

## **Assessing Applicability**

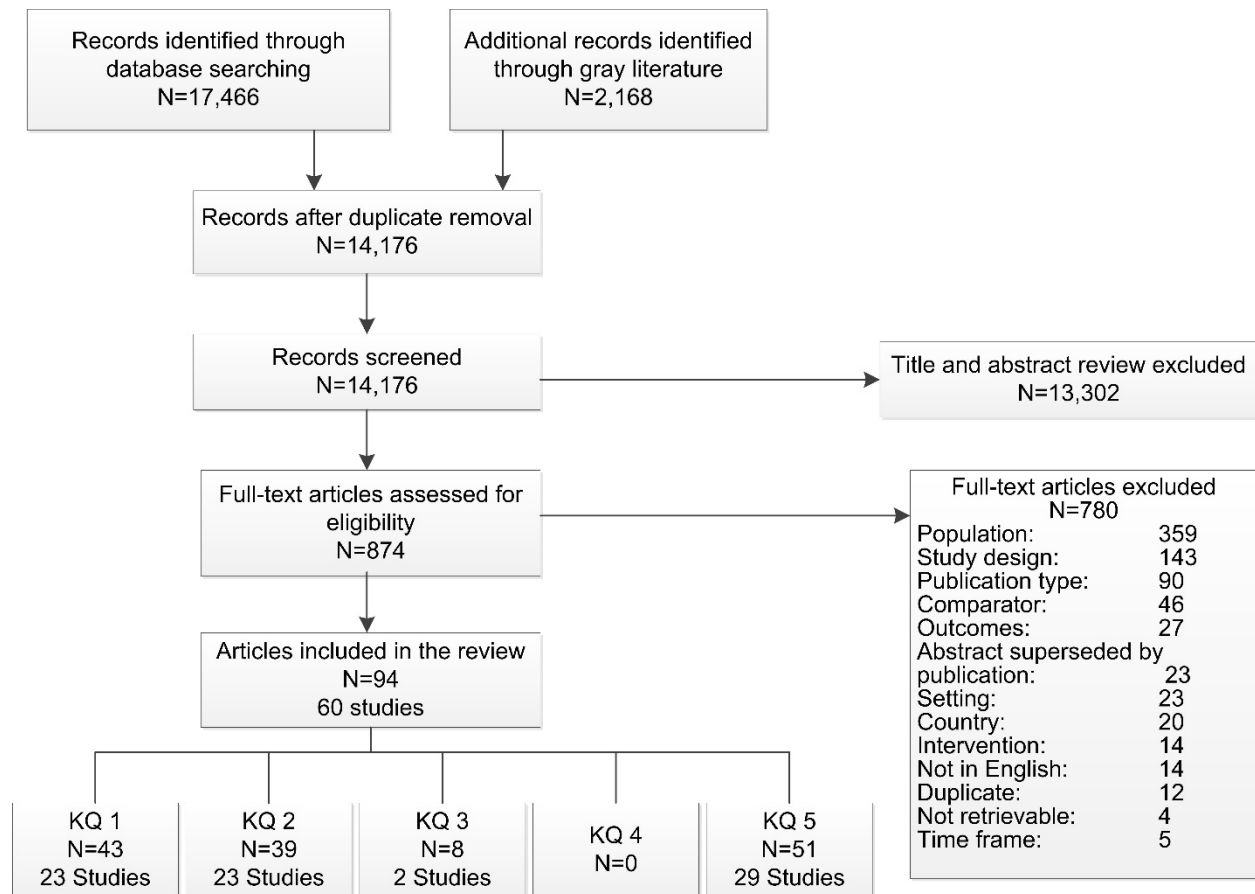
We assessed the applicability of individual studies as well as the applicability of a body of evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>13</sup> We indicated age and type of DD in the analysis and otherwise called out characteristics of the study populations that might limit applicability.

# Results

## Literature Searches and Evidence Base

The electronic search, gray literature, and reference mining identified 14,176 citations. After title and abstract screening, we retrieved 874 studies for full-text review. A total of 60 studies (94 articles) met eligibility criteria and were included in the analyses (Figure B).

**Figure B. Article flow diagram**



KQ = Key Question; N = number.

For KQ 1, we identified 23 RCTs of nonpharmacological treatments. Five RCTs compared cognitive behavioral therapy (CBT) with pill placebo, wait-list, usual care or treatment as usual (TAU). Three RCTs compared CBT with an active control. Two RCTs compared relapse prevention CBT plus continued antidepressant medication with continued medication management alone. Eleven trials addressed other psychotherapy approaches (i.e., interpersonal therapy [IPT], family-based IPT, attachment-based family therapy, family therapy, Parent-Child Interaction Therapy (PCIT), and psychoanalytic therapy) compared with wait-list, TAU, or active controls. Two trials address omega-3 versus pill placebo. Single RCTs compared exercise with an active control and spirituality with wait-list. One omega-3 fatty acid and family therapy RCT, one family therapy RCT and three CBT RCTs provided subpopulation evidence.

For KQ 2, we identified 23 RCTs comparing pharmacological approaches. Fourteen RCTs examined SSRIs compared with placebo. Two RCTs compared relapse prevention with fluoxetine compared with placebo. Five RCTs compared serotonin and norepinephrine reuptake inhibitors (SNRIs) with placebo. Four RCTs compared tricyclic antidepressants (TCAs) with placebo. One RCT examined monoamine oxidase inhibitors (MAOIs) with placebo and one RCT of venlafaxine plus active control versus placebo plus active control. Seven RCTs of SSRIs and TCAs compared with placebo provided evidence on subpopulations.

For KQ 3, we identified one RCT comparing fluoxetine plus CBT with placebo and one RCT comparing omega-3 plus family therapy with placebo. Both provided evidence on subpopulations. We found no studies for KQ 4. For KQ 5, we found 29 studies including 28 RCTs and one nonrandomized trial addressing comparative effectiveness. Three RCTs compared CBT with other psychotherapy. Seven RCTs compared the delivery methods of psychotherapy. Three RCTs compared psychotherapy and pharmacotherapy; six compared psychotherapy plus pharmacotherapy and psychotherapy; seven compared psychotherapy plus pharmacotherapy and pharmacotherapy. One RCT compared omega-3 with other therapies. Two RCTs each compared SSRIs with SNRIs, SSRIs with TCAs and interventions for treatment-resistant depression. Three RCTs were dose comparison studies. Seven studies addressed subpopulations for comparative effectiveness.

Table A presents the aggregated study characteristics of our included studies. A majority of the studies (56.7%) had some concerns for risk of bias for benefits, and 41.7 percent had high risk of bias. We rated one RCT as low risk of bias. For studies reporting on harms, 23 of 39 were assessed as some concern for risk of bias, 14 of 39 as high risk of bias, one study as low risk of bias, and one as uncertain. The full report contains additional details of the quality assessment for each study.

**Table A. Key characteristics of included studies**

Study Characteristics	Subcharacteristics	Number of Studies	Percent
Study quality for benefits	Low risk-of-bias studies	1	1.7
	Some concerns for risk-of-bias studies	34	56.7
	High risk-of-bias studies	25	41.7
Study quality for harms	Low risk-of-bias studies	1	1.7
	Some concerns for risk-of-bias studies	23	38.3
	High risk-of-bias studies	14	23.3
	Unclear risk of bias	1	1.7
	Not applicable (did not report on harms)	21	35.0
Population characteristics:	Child (mean age <13, ages range from 5 to 12)	5	8.3
Child or adolescent	Adolescent (mean age ≥13, ages range from 11 to 18)	30	50.0
	Both (mean age varies, age ranges from 7 to 18)	25	41.7
Population characteristics:	Mostly female	40	66.7
Gender	Mostly male	20	33.3
Population characteristics:	Mostly white	40	66.7
Race	Mostly nonwhite	4	6.7
	Not reported	16	26.7
Population characteristics:	MDD	46	76.7
Diagnosis	MDD, PDD, DD NOS, combinations	14	23.3
Intervention characteristics:	Nonpharmacological	27	45.0
Types of interventions	Pharmacological	24	40.0
	Both	9	15.0

Study Characteristics	Subcharacteristics	Number of Studies	Percent
Comparator	Active comparator	20	33.3
	Placebo comparator	27	45.0
	Usual care comparator	13	21.7
Geographic setting	United States of America	43	71.7
	United Kingdom	3	5.0
	Canada	1	1.7
	Australia	2	3.3
	Multiple countries	7	11.7
	Israel	1	1.7
	Norway	1	1.7
	Romania	1	1.7
	South Korea	1	1.7
KQ 1: Benefits and harms of nonpharmacological interventions	Cognitive behavioral therapy	10	NA <sup>a</sup>
	Other therapies (IPT, family-based IPT, attachment-based family therapy, family therapy, parent-child interaction therapy)	11	NA <sup>a</sup>
	Omega-3	2	NA <sup>a</sup>
	Exercise	1	NA <sup>a</sup>
	Spirituality	1	NA <sup>a</sup>
	SSRIs	14	NA <sup>a</sup>
KQ 2: Benefits and harms of pharmacological interventions	SNRIs	5	NA <sup>a</sup>
	TCAs	4	NA <sup>a</sup>
	Relapse prevention with fluoxetine versus placebo	2	NA <sup>a</sup>
	MAOIs	1	NA <sup>a</sup>
	Venlafaxine plus active control versus placebo plus active control	1	NA <sup>a</sup>
KQ 3: Benefits and harms of combined interventions	Cognitive behavioral therapy + fluoxetine	1	NA <sup>a</sup>
	Omega-3 + family therapy	1	NA <sup>a</sup>
KQ 4: Benefits and harms of collaborative care interventions	Collaborative care interventions	0	NA <sup>a</sup>
KQ 5: Benefits and harms from head-to-head comparisons of interventions	CBT versus other psychotherapy	3	NA <sup>a</sup>
	Comparison of psychotherapy delivery methods	7	NA <sup>a</sup>
	Psychotherapy versus pharmacotherapy	3	NA <sup>a</sup>
	Psychotherapy plus pharmacotherapy versus psychotherapy	6	NA <sup>a</sup>
	Psychotherapy plus pharmacotherapy versus pharmacotherapy	7	NA <sup>a</sup>
	Omega-3 versus other therapies	1	NA <sup>a</sup>
	SSRIs vs SNRIs	2	NA <sup>a</sup>
	SSRIs vs TCAs	2	NA <sup>a</sup>
	Dose comparison	3	NA <sup>a</sup>
	Interventions for treatment-resistant depression	2	NA <sup>a</sup>

<sup>a</sup> The number of studies sum to more than 100% because studies may address multiple KQs.

CBT = cognitive behavioral therapy; DD = depressive disorder; DD NOS = depressive disorder not otherwise classified; IPT = interpersonal therapy; KQ = Key Question; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; NA = not applicable; PCIT = parent child interaction therapy; PDD = persistent depressive disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; vs = versus.

A minority (33.3%) of studies offered an active comparator: most compared treatments with placebo, usual care, or wait-list controls. Usual care participants were free to initiate or continue nonstudy mental health or other healthcare services.<sup>14-16</sup> For pharmacotherapy studies, usual care participants may have received the index medication.<sup>16</sup> For psychotherapy studies, therapists offered treatment that they believed to be effective.<sup>17</sup> Usual care could include therapy, medications, or combined therapy and medications.<sup>18</sup>

We generally used study-defined categorizations of outcomes and footnoted exceptions (for example, one study reported a common measure of remission [a score of 28 or more on the Children's Depression Rating Scale—Revised, or CDRS<sub>≤</sub>28] as response);<sup>19</sup> we reclassified this outcome as remission but footnoted the decision. We did not find anchor-based data to identify minimal clinically important differences [MCIDs] for continuous scales measuring depressive symptoms and functional status. Distribution-based data for MCIDs suggest a 0.5 standard deviation (SD) of the baseline value as a clinically meaningful difference.<sup>20</sup> Studies did not report suicidal ideation or behavior consistently. We generally relied on the most comprehensive available measure; in some studies, this measure also included suicide attempts. Studies that defined serious adverse events generally used FDA's definition, that is, events resulting in death, life-threatening events, new or prolonged hospitalization, disability or permanent damage, congenital anomalies, or other serious events.<sup>21-23</sup> In some instances, authors did not specify serious adverse events. Studies evaluated a number of moderator variables (clinical, demographic, caregiver, and study characteristics). We highlight results for variables that showed a moderating effect. The full report appendices list all moderator analyses.

## **KQ 1a: Benefits and Harms of Nonpharmacological Interventions**

The full report contains details about all studies included in KQ 1a. Table B summarizes the SOE for outcomes graded as having at least low evidence of benefit or harms. In sum, variation in the types of nonpharmacological interventions, comparators (e.g., wait-list or active control), and populations (e.g., children, adolescents, or both and MDD only or with a wider range of depressive disorders (MDD, PDD, or DD NOS) precluded any meta-analyses of findings. No comparison exceeded low SOE for any outcome. The point estimates generally exceeded the distribution-based MCIDs (0.5 of SD of baseline or control group values); the confidence intervals (CIs) generally did not. As a result, the clinical significance of the reported change is unclear.

Evidence on three therapies (CBT plus TAU vs. TAU or usual care [UC], exercise vs. active control, and spirituality-informed online sessions vs. wait-list), from one small trial each (with sample sizes ranging from 25 to 212), included adolescents with MDD and suggested benefit for depressive symptoms, response, recovery, or functional status. Among adolescents and children with MDD, CBT for relapse prevention in combination with continued antidepressant medication may be associated with lower risk of relapse at post-treatment and followup assessments, when compared with antidepressants alone.<sup>21, 24</sup>

Evidence from studies of participants with a wide range of depressive disorders (MDD, PDD, or DD NOS) suggests improved depressive symptoms, response, or functional status with CBT or family therapy versus wait-list or active control among adolescents or children<sup>25-27</sup> and of family-based IPT versus active control among children.

We graded many interventions as insufficient because of imprecision, inconsistency, or bias. Interventions with insufficient evidence of benefits (or harms) included CBT versus pill placebo, modified CBT vs. usual care, CBT delivered to adolescents and parents versus wait-list control,

CBT versus active control, IPT versus wait-list or active control, attachment-based family therapy versus wait-list or treatment as usual, family therapy versus pill placebo, PCIT versus active control, short-term psychoanalytic therapy versus active control, and omega-3 versus placebo. Additionally, we found no eligible evidence on a range of other psychotherapies, including play therapy and psychodynamic therapy, and therefore cannot comment on their effectiveness.

**Table B. Strength of evidence for outcomes of nonpharmacological interventions versus active or wait-list control**

Comparison (Duration of Treatment)	Outcome	Conclusion <sup>a</sup>	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. wait-list control 8 weeks	Depressive symptoms, self-reported	Mean difference (BDI): -5.90; 95% CI, -10.89 to -0.92	1 RCT (n=64) <sup>25</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit	Adolescents with MDD or dysthymia
	Functional status, clinician reported	Mean difference (GAF): 6.5; 95% CI, 0.68 to 12.32	1 RCT (n=64) <sup>25</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit	Adolescents with MDD or dysthymia
CBT + TAU vs. TAU/UC 12-16 weeks	Depressive symptoms, clinician-reported	Mean difference (CDRS): -7.11; 95% CI, -10.3 to -3.90	1 RCT (n=212) <sup>28</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Weeks to recovery	Mean difference (weeks): -7.40; 95% CI, -13.4 to -1.42	1 RCT (n=212) <sup>28</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Recovery (at least 8 weeks of no or minimal depressive symptoms)	Risk difference: 192/1,000; 95% CI, 80 more to 304 more cases recovered	1 RCT (n=212) <sup>28</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Response	Risk difference: 212/1,000; 95% CI 78 more to 346 more cases	1 RCT (n=212) <sup>28</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Functional status, clinician reported	Mean difference (CGAS): 5.32; 95% CI, 2.73 to 7.91	1 RCT (n=212) <sup>28</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Relapse prevention CBT + continued antidepressant medication management vs. continued medication management 30 weeks	Risk difference (CDRS of 40 or more): -260/1,000; 95% CI, 433 fewer cases to 87fewer cases	1 RCT (n=115) <sup>21, 24</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents and children with MDD

Comparison	Outcome	Conclusion <sup>a</sup>	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Relapse prevention CBT + continued antidepressant medication management vs. continued medication management 30 weeks (continued)	Relapse (78 weeks)	Risk difference: -273/1,000; 95% CI, 444 fewer cases to 102 fewer cases	1 RCT (n=121) <sup>21, 24</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents and children with MDD
Family-based IPT vs. active control (child-centered therapy) 14 weeks	Depressive symptoms, clinician report	Mean difference (CDRS-R): -7.8; 95% CI, -12.73 to -2.87	1 RCT (n=38) <sup>29</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Children with MDD, dysthymia, DD NOS
	Depressive symptoms, self-report	Mean difference (MFQ-C): -6.50; 95% CI, -7.85 to -5.15	1 RCT (n=38) <sup>29</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Children with MDD, dysthymia, DD NOS
	Depressive symptoms, parent-report	Mean difference (MFQ-P): -5.60; 95% CI, -6.49 to -4.71	1 RCT (n=38) <sup>29</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Children with MDD, dysthymia, DD NOS
Family therapy vs. active control 22 weeks	Response	Risk difference (CDRS-R decrease of 50% or more): 179/1,000; 95% CI, 25 more cases to 333 more cases	1 RCT (n=99) <sup>27</sup>	Imprecision, (small sample size), unknown consistency	Low for benefit	Adolescents or children with MDD, dysthymia, or DD NOS
Exercise vs. active control 12 weeks	Response	Risk difference (CGI of 2 or less and at least a 50% reduction in CDRS): 333; 95% CI, 59 more cases to 607 more cases	1 RCT (n=26) <sup>30</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit	Adolescents with MDD
Spirituality vs. wait-list 8 weeks	Depressive symptoms, clinician report	Mean difference (CDRS-R), -13.99; 95% CI, -22.65 to -5.33	1 RCT (n=25) <sup>31</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD

<sup>a</sup> For BDI, the 0.5\* standard deviation for baseline control arms is 5.4.<sup>32</sup> For CGAS, the 0.5\* standard deviation for baseline control arms ranges from 2.5<sup>33</sup> to 3.8.<sup>34</sup> For CDRS-R, the 0.5\* standard deviation for baseline or followup control arms ranges from 4.0<sup>31</sup> to 5.7.<sup>29</sup> For GAF, the 0.5\* standard deviation for baseline control arms is 3.2.<sup>32</sup> For MFQ-C, the 0.5\* standard deviation for baseline control arms is 8.3.<sup>29</sup> For MFQ-P, the 0.5\* standard deviation for baseline control arms is 6.5.<sup>29</sup>

BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CDRS = Children's Depression Rating Scale; CDRS-R = Children's Depression Rating Scale—Revised; CGAS = Children's Global Assessment Scale; CGI = Clinical Global Impressions; CI = confidence interval; DD = depressive disorder; GAF = Global Assessment of Functioning; IPT = interpersonal therapy; MDD = major depressive disorder; MFQ-C = Mood and Feelings Questionnaire-Child; MFQ-P = Mood and Feelings Questionnaire-Parent; n = number; NOS = not otherwise specified; RCT = randomized controlled trial; RR = relative risk; TAU = treatment as usual; UC = usual care; vs. = versus.

## KQ 1b: Benefits and Harms of Nonpharmacological Interventions by Subpopulation

In studies published from a trial of CBT versus pill placebo,<sup>35,36</sup> statistically significant moderators included family income and comorbid attention deficit hyperactivity disorder (ADHD). CBT resulted in greater improvements in functional status among those with higher family income. CBT also resulted in greater improvements in depressive symptoms among those with comorbid ADHD. For the two trials of CBT versus active control,<sup>37,38</sup> statistically significant moderators included lifetime suicidality, race, prior MDD episodes, and coping skills. One study found that when families reported fewer psychosocial stressors, the omega-3 arm had a significant decline in depression severity and little impact in the pill placebo arm.<sup>39</sup>

## KQ 2a: Benefits and Harms of Pharmacological Interventions

The full report contains details about all studies included in KQ 2a. Table C summarizes the SOE across the trials or groups of pooled trials that had one or more outcomes graded as having at least low evidence of benefit or harms. In sum, studies that found evidence of benefit did not include participants with a wide range of depressive disorders; all included adolescents with MDD only and only a few samples also included children. We describe the results below first for individual drugs, and then the drug class.

Evidence from single fluoxetine<sup>23,34,40</sup> and escitalopram<sup>33</sup> trials provided evidence of benefits for symptoms among adolescents with MDD. Escitalopram also improves functional status and response and remission at 24 weeks.

SSRIs as a class showed benefit for response<sup>6,22,41-45</sup> and functional status<sup>6,41,45-47</sup> in studies of adolescents and children. Although the point estimates generally exceeded the distribution-based MCIDs (0.5 of SD of baseline or control group values) for escitalopram, the CIs did not. As a result, the clinical significance of the reported change is unclear.

The evidence for adolescent-only populations with MDD was heterogenous. Fluoxetine, as noted above, demonstrated benefit for clinician-rated depression symptoms. For SSRIs other than fluoxetine, the evidence was generally insufficient to judge benefit for depressive symptoms or response. The evidence for adolescent-only populations suggested no benefit for remission for SSRIs as a class.

**Table C. Strength of evidence for outcomes of pharmacotherapy versus placebo**

Comparison (Duration of Treatment)	Outcome	Conclusion <sup>a</sup>	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Fluoxetine 12 weeks	Depressive symptoms, clinician report	Mean difference (CDRS-R): -7.98; 95% CI: -10.12 to -5.84	1 RCT (n=221) <sup>23</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Response	Risk difference (CGI-I): 258/1,000 cases; 95% CI; 131 more cases to 385 more cases	1 RCT (n=221) <sup>23</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD



Comparison (Duration of treatment)	Outcome	Conclusion <sup>a</sup>	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Escitalopram 16-20 weeks	Depressive symptoms, clinician report (24- week followup)	Mean difference (CDRS-R): -4.40; 95% CI, -8.15 to -0.65	1 RCT (n=311) <sup>33</sup>	Imprecision (wide CIs), unknown consistency	Low for benefit	Adolescents with MDD
	Remission (24 weeks)	Risk difference (CDRS-R): 149/1,000; 95% CI, 40 more cases to 258 more cases	1 RCT (n=311) <sup>33</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Response (24 weeks)	Risk difference (CDRS-R): 130/1,000; 95% CI, 21 more cases to 239 more cases	1 RCT (n=311) <sup>48</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Functional status, clinician report	Mean difference (CGAS): 3.60; 95% CI, 0.13 to 7.07	1 RCT (n=301) <sup>33</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
SSRI: Paroxetine 8-12 weeks	Suicidal ideation or behaviors	Risk difference, 32; 95% CI, 8 fewer cases to 71 more cases, I <sup>2</sup> =0%  Risk difference without high risk- of-bias study, 9 more cases; 95% CI, 23 fewer cases to 42 more cases, N=206 <sup>45</sup>	3 RCTs (n=662) <sup>45, 49, 50</sup>	Imprecision (wide CIs), high risk of bias <sup>49, 50</sup>	Low for harms <sup>b, c</sup>	Adolescents or adolescents and children with MDD
	Withdrawal due to AEs	Risk difference: 60/1,000; 95% CI, 19 more cases to 101 more cases; I <sup>2</sup> =0%  Risk difference without high risk- of-bias study: 70/1,000; 95% CI, 8 more cases to 131 more cases, N=203 <sup>45</sup>	3 RCTs (n=658) <sup>45, 49, 50</sup>	Imprecision (wide CIs), high risk of bias <sup>49, 50</sup>	Low for harms	Adolescents or adolescents and children with MDD

Comparison	Outcome	Conclusion <sup>a</sup>	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRIs: fluoxetine, citalopram, escitalopram, paroxetine, or vilazodone 8-10 weeks	Response	Risk difference (HAM-D, MADRS, CGI-I), 72/1,000; 95% CI, 2 to 124, I <sup>2</sup> =9%  Risk difference without high risk-of-bias studies: 80/1,000; 95% CI, 16 more to 143 more cases, I <sup>2</sup> =0%, N=847	7 RCTs (n=1,525) <sup>6, 22, 41-45</sup>	Imprecision (wide CIs), high risk of bias <sup>41-43</sup>	Low for benefit	Adolescents and children with MDD
	Remission	Risk difference (HAM-D, CDRS-R), 45/1,000; 95% CI, 8 fewer cases to 107 more cases; I <sup>2</sup> =0%  Risk difference without high risk-of-bias studies: 37/1,000; 95% CI, 26 fewer to 100 more cases, I <sup>2</sup> =0%, N=870	4 RCTs (n=1,050) <sup>40, 48, 51, 52</sup>	Imprecision, (wide CIs), high risk of bias <sup>51</sup>	Low for no benefit	Adolescents with MDD
	Functional status, clinician report	SMD (GAF, CGAS), 0.16; 95% CI, 0.03 to 0.29, I <sup>2</sup> =0%  Without high risk-of-bias studies, SMD: 0.17; 95% CI, 0.02 to 0.33, I <sup>2</sup> =0%, N=626	5 RCTs (n=941) <sup>6, 41, 45, 47</sup>	Imprecision (wide CIs), high risk of bias <sup>41, 46</sup>	Low for benefit	Adolescents and children with MDD
	SAEs	Risk difference, 20/1,000; 95% CI, 1 more case to 440 more cases; I <sup>2</sup> , 4%  RR without high risk-of-bias studies (three fluoxetine studies and one paroxetine studies), 2.38; 95% CI, 1.13 to 5.01; I <sup>2</sup> =0%; N=1,358	9 RCTs (n=2,206) <sup>22, 23, 41-43, 45, 47, 52, 53</sup>	Imprecision (wide CIs, few events), high risk of bias <sup>41-43, 53</sup>	Low for harms <sup>b, d</sup>	Adolescents and children with MDD, adolescents with MDD

Comparison	Outcome	Conclusion <sup>a</sup>	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRIs: fluoxetine, citalopram, escitalopram, paroxetine, or vilazodone 8-10 weeks (continued)	Withdrawal due to AEs	Risk difference, 26/1,000; 95% CI, 6 more cases to 45 more cases; I <sup>2</sup> , 0%  CIs for RR without high risk-of-bias studies span the null	4 RCTs (n=1,296) <sup>48-50, 52</sup>	Serious imprecision, high risk of bias <sup>49, 50</sup>	Low for harms <sup>b</sup>	Adolescents with MDD
SSRI: Relapse prevention fluoxetine 32 weeks	Relapse	CIs for one of two studies span the null  Without high risk-of-bias, risk difference (CDRS-R): -272/1,000; 95% CI, 458 fewer cases to 86 fewer cases	2 RCTs (n=142) <sup>54, 55</sup>	Serious imprecision (wide CIs, small sample size), inconsistency, high risk of bias <sup>54</sup>	Low for benefit <sup>e</sup>	Adolescents and children with MDD
SNRI: Desvenlafaxine 8 weeks	Depressive symptoms, clinician report	SMD (CDRS-R) of -0.11 and 0.04, CIs of both studies cross the null	2 RCTs (n=590) <sup>22, 56</sup>	Inconsistency (direction of effect)	Low for no benefit	Adolescents and children with MDD
	Response	RR (CGI-I) of 1.06 and 1.10 Both 95% CIs cross the null	2 RCTs (n=511) <sup>22, 56</sup>	Imprecision (wide CIs)	Low for no benefit	Adolescents and children with MDD
ALL SNRIs (venlafaxine, desvenlafaxine and duloxetine) 8-10 weeks	Depressive symptoms, clinician report	Mean difference (CDRS-R), -1.48; 95% CI, -2.690 to -0.06; I <sup>2</sup> =8%,  Without high risk-of-bias study, two studies remain. CIs for RR without high risk-of-bias studies span the null	5 RCTs (n=1,260) <sup>22, 42, 56</sup>	Inconsistency (direction of effect), high risk of bias <sup>42, 57</sup>	Low for no benefit <sup>f</sup>	Adolescents and children with MDD
SNRI: Duloxetine 10 weeks	Withdrawal due to AEs	Risk difference (high-dose duloxetine): 78/1,000; 95% CI, 11 more cases to 145 more cases	1 RCT (n=346) <sup>42</sup>	Imprecision (wide CIs), high risk of bias, <sup>42</sup> unknown consistency	Insufficient for low dose, low for high dose	Adolescents and children with MDD

<sup>a</sup> For CGAS, the 0.5\* standard deviation for baseline control arms ranges from 2.5<sup>33</sup> to 3.8.<sup>34</sup> For CDRS-R, the 0.5\* standard deviation for baseline or followup control arms ranges from 4.0<sup>31</sup> to 5.7.<sup>29</sup>

<sup>b</sup> Without high risk-of-bias studies, the grade would have been rated as insufficient for imprecision. With high risk-of-bias studies, the evidence suggests increased risk of harms. We have retained the high risk-of-bias in these ratings to communicate the potential for a signal of harm.

<sup>c</sup> One high risk-of-bias study (n=180) reported a substantial risk (relative risk: 5.15, 95% CI, 1.17 to 22.56; risk difference: 95, 95% CI, 22 to 168).<sup>50</sup>

<sup>d</sup> One study<sup>23</sup> reported the total number of SAEs that met FDA's definition for an adverse event (N=23) but did not report results by study arm; this estimate of effect draws from harm-related adverse events, which were reported by study arm. Not all harm-related adverse events are SAEs.

<sup>e</sup> With the high risk-of-bias studies, the evidence would have been downgraded for inconsistency and imprecision and would have been downgraded to insufficient.

<sup>f</sup> Without the high risk-of-bias study (duloxetine), the results continued to span the null; the SOE did not change as a result of the sensitivity analysis.

AE = adverse event; CDRS = Children's Depression Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions Scale; CI = confidence interval; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; n/N = number; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SOE = strength of evidence; SMD = standardized mean difference; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

Although the pooled evidence for suicidal ideation or behaviors with paroxetine suggested uncertainty (3 RCTs [n = 662]; risk difference [RD], 32/1000 [95% CI, 8 fewer cases to 71 more cases];  $I^2=0\%$ ),<sup>45, 49, 50</sup> one study (n=180) reported a substantially increased risk (RD, 95/1000, 95% CI, 22 to 168)<sup>50</sup> leading to low SOE for harms. The evidence suggests that paroxetine is associated with increased risk of withdrawal due to AEs (3 RCTs [n=658]; RD, 60/1,000 [95% CI, 19 more cases to 101 more cases];  $I^2=0\%$ ).

Regarding harms for SSRIs as a class, we found an increased risk of suicidal ideation or behaviors for paroxetine. We found no statistically significant differences in suicidal ideation or behavior for the entire class, although the risks of suicidal ideation or behavior were higher with SSRIs. We conducted sensitivity analyses that included selected data from the FDA meta-analyses<sup>58</sup> that prompted a boxed warning for antidepressants. With the addition of selected data unavailable in the individual published studies, we continued to find increased but not statistically significant risk, with relatively wide CIs spanning both benefit and harm. We found an increased risk of serious adverse events with SSRIs in studies with adolescents or adolescents and children with MDD and an increased risk of withdrawals due to adverse events in adolescents with MDD.

One trial found evidence of benefit for relapse in a relapse prevention trial that included children and adolescents with MDD.<sup>55</sup>

The evidence for desvenlafaxine (2 studies)<sup>22, 56</sup> and SNRIs as a class (5 studies, including two venlafaxine studies in a single publication<sup>57, 22, 42, 56, 57</sup>) suggest no benefit among children and adolescents with MDD for depressive symptoms. In addition, evidence from one trial suggested risk of harms (withdrawal due to AEs) for high-dose duloxetine (60 mg) versus placebo among children and adolescents with MDD (low SOE for harms).<sup>42</sup>

Interventions with insufficient evidence included TCAs versus placebo, monoamine oxidase inhibitors versus placebo and venlafaxine versus placebo.

## **KQ 2b: Benefits and Harms of Pharmacological Interventions by Subpopulation**

For fluoxetine, statistically significant moderators of benefits included sex, family income, depression severity, depression chronicity, and comorbid conditions.<sup>35, 36, 41, 46, 59-61</sup> Some studies suggest greater benefits for a few outcomes among males; lower income families; and study participants with greater severity of depression, chronicity of depression, and comorbid conditions. These findings are very limited: not all studies examining the moderator found effects, and when studies reported findings for specific outcomes, they did not rule out the

possibility of chance findings. For paroxetine, most moderators did not influence the effect of the drug on benefits. Studies suggested varying results by age. In one study of children and adolescents, age did not moderate outcomes. In another, depression symptoms and response were better in older adolescents than younger adolescents.<sup>49</sup> The difference in the incidence of harms between paroxetine and placebo patients was more pronounced in older adolescents than in younger adolescents.<sup>49</sup> None of the other SSRI or other types of pharmacotherapy trials found statistically significant moderators of benefits, and no pharmacotherapy trials found statistically significant moderators of harms.

## KQ 3a: Benefits and Harms of Combination Interventions

The full report contains additional details about the single trial that met criteria for KQ 3a. Table D summarizes the SOE of the outcomes graded as having at least low evidence of strengths or harms. For adolescents with MDD, fluoxetine plus CBT had low evidence of benefit for depressive symptoms, response, remission, and functional status as compared with placebo.<sup>23, 34, 40</sup> Interventions with insufficient evidence include omega-3 plus family therapy versus pill placebo. We did not find evidence on any other combination interventions.

**Table D. Strength of evidence for outcomes of fluoxetine + CBT versus placebo**

Comparison	Outcome	Conclusion <sup>a</sup>	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Fluoxetine + CBT vs. placebo 12 weeks	Depressive symptoms, clinician report	Mean difference (CDRS-R): -7.98; 95% CI, -10.13 to -5.83	1 RCT (n=219) <sup>23</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Response	Risk difference (CGI-I of 1 or 2 indicating very much improved or improved): 362/1,000; 95% CI, 239 more cases to 485 more cases	1 RCT (n=219) <sup>23</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Remission	Risk difference (CDRS of 28 or lower at end of treatment): 200/1,000; 95% CI, 85 more cases to 315 more cases	1 RCT (n=219) <sup>40</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Functional status clinician report	Mean difference (CGAS): 7.3; 95% CI, 4.03 to 10.57	1 RCT (n=219) <sup>34</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD

<sup>a</sup> For CGAS, the 0.5\* standard deviation for baseline control arms ranges from 2.5<sup>33</sup> to 3.8.<sup>34</sup> For CDRS-R, the 0.5\* standard deviation for baseline or followup control arms ranges from 4.0<sup>31</sup> to 5.7.<sup>29</sup>

CBT = cognitive behavioral therapy; CDRS = Children's Depression Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions Scale; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; vs. = versus.

### **KQ 3b: Benefits and Harms of Combination Interventions by Subpopulation**

The publications that examined efficacy of combined fluoxetine and CBT did not determine any significant moderators of combined fluoxetine plus CBT versus placebo. One study reported greater efficacy for omega-3 plus family therapy compared with pill placebo among those with greater psychosocial stressors and a history of maternal depression.

### **KQ 4a: Benefits and Harms of Collaborative Care Interventions**

We found no studies of collaborative care interventions that met our inclusion and exclusion criteria.

### **KQ 4b: Benefits and Harms of Collaborative Care Interventions by Subpopulation**

We found no studies of collaborative care interventions that met our inclusion and exclusion criteria.

### **KQ 5a: Comparative Benefits and Harms of Treatments**

The full report contains details about all studies included in KQ 5a. Table E summarizes the SOE for the outcomes graded as having at least low evidence of benefit or harms. With a single exception, variation in the types of interventions, comparators, and populations precluded any meta-analyses of findings. Comparative effective studies did not exceed low SOE for any outcome. The evidence from one study suggests benefit for fluoxetine versus CBT on depressive symptoms, although CBT had fewer treatment-emergent AEs.<sup>23, 34-36, 40, 62, 63</sup>

Combination pharmacotherapy plus psychotherapy may be associated with improved depressive symptoms, remission, and functional status when compared with *psychotherapy* alone.<sup>23, 34-36, 40, 62-65</sup> Not all combination pharmacotherapy plus psychotherapy is superior to *pharmacotherapy* alone. Combination pharmacotherapy may not be associated with improved depressive symptoms when compared with *pharmacotherapy* alone.<sup>23, 34-36, 40, 62, 63, 66-68</sup> Interventions were varied: studies provided sertraline, fluoxetine, or unspecified SSRIs and group, individual, or brief CBT; the only study suggesting benefit compared CBT plus fluoxetine with fluoxetine alone. Evidence from a single study each suggests benefit of combined CBT plus fluoxetine versus fluoxetine on remission in adolescents with MDD and combined CBT plus bupropion versus bupropion on depressive symptoms in adolescents with MDD.<sup>68</sup>

Interventions with insufficient evidence included CBT versus other psychotherapy; head-to-head comparisons of psychotherapy; omega-3, family therapy, or their combination; SSRIs versus SNRIs; SSRIs versus TCAs; pharmacotherapy dose comparisons; and head-to-head comparisons of interventions for treatment-resistant depression (increasing or switching medications with or without CBT).

**Table E. Strength of evidence for outcomes of comparative effectiveness studies**

Comparison	Outcome	Conclusion <sup>a</sup>	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy vs. pharmacotherapy 12 weeks	Depression (clinician rated)	Mean difference (CDRS-R): 5.76; 95% CI, 3.46 to 8.06	1 RCT (n=220) <sup>23, 34-36, 40, 62, 63</sup>	Imprecision (small sample size), unknown consistency	Low (benefit for pharmacotherapy)	Adolescents with MDD
	Treatment-emergent psychiatric AEs	Risk difference: -100/1,000; 95% CI, 160 fewer cases to 40 fewer cases	1 RCT (n=220) <sup>23, 34-36, 40, 62, 63</sup>	Imprecision (small sample size), unknown consistency	Low (benefit for psychotherapy)	Adolescents with MDD
Psychotherapy plus pharmacotherapy vs. psychotherapy 8 to 12 weeks	Depression (clinician rated)	Mean difference (CBT + fluoxetine vs. CBT) (CDRS-R): -8.27; 95% CI, -10.59 to -5.95	1 RCT (n=218) <sup>23, 34-36, 40, 62, 63</sup>	Imprecision (small sample size), unknown consistency	Low for benefit for combination therapy	Adolescents with MDD
	Depression (clinician rated)	Mean difference (CBT + imipramine vs. CBT) (CDRS): -11.1; 95% CI, -17.68 to -4.52	1 RCT (n=63) <sup>64, 65</sup>	Imprecision (small sample size), unknown consistency	Low for benefit for combination therapy	School-refusing adolescents with comorbid anxiety and MDD
	Remission from MDD	Risk difference (CBT + fluoxetine vs. CBT): 210/1,000; 95% CI, 96 more cases to 324 more cases	1 RCT (n=378) <sup>23, 34-36, 40, 62, 63</sup>	Imprecision (small sample size), unknown consistency	Low for benefit for combination therapy	Adolescents with MDD
	Functional status	Mean difference (CBT + fluoxetine vs. CBT) (CGAS): 6.60; 95% CI, 3.23 to 9.97	1 RCT (n=185) <sup>23, 34-36, 40, 62, 63</sup>	Imprecision (small sample size), unknown consistency	Low for benefit for combined therapy	Adolescents with MDD
Psychotherapy plus pharmacotherapy vs. pharmacotherapy 8-28 weeks	Depressive symptoms (self-rated)	SMD (CBT + SSRI vs. SSRI, based on CDI, RADS, CES-D, and MFQ): -0.15; 95% CI, -0.34 to 0.03, N=450 (4 studies), I <sup>2</sup> =0%  SMD without high risk-of-bias studies, -0.14; 95% CI, -0.36 to 0.08, N=427, I <sup>2</sup> =22%	4 RCTs (n=450) <sup>23, 34-36, 40, 62, 63, 66-68</sup>	Imprecision (wide CIs), inconsistent, high risk of bias <sup>67</sup>	Low for no benefit of adding CBT to SSRIs	Adolescents with MDD

Comparison	Outcome	Conclusion <sup>a</sup>	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. pharmacotherapy 8-28 weeks (continued)	Depressive symptoms (self-rated)	Mean difference, CBT + bupropion vs. bupropion (based on BDI) -5.2; 95% CI, -9.31 to -1.09	1 RCT (n=65) <sup>68</sup>	Imprecision (small sample size), unknown consistency	Low for benefit of adding CBT to bupropion	Adolescents with MDD
	Remission from MDD	Risk difference (combination vs. medication): 140/1,000; 95% CI, 19 more cases to 261 more cases	1 RCT (n=216) <sup>40</sup>	Imprecision (wide CIs, small sample size)	Low for benefit of adding CBT to fluoxetine	Adolescents with MDD

<sup>a</sup> For CGAS, the 0.5\* standard deviation for baseline control arms ranges from 2.5<sup>33</sup> to 3.8.<sup>34</sup> For CDRS-R, the 0.5\* standard deviation for baseline or followup control arms ranges from 4.0<sup>31</sup> to 5.7.<sup>29</sup>

AE = adverse event; BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS = Children's Depression Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; CES-D = Center for Epidemiologic Studies Depression Scale; CGAS = Children's Global Assessment Scale; CI = confidence interval; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n/N = number; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitors; vs. = versus.

## KQ 5b: Comparative Benefits and Harms of Treatments by Subpopulation

Three companion publications to a single trial of adolescents with MDD<sup>23</sup> found that CBT was inferior to fluoxetine in groups with lower family income, marked/severe baseline depressive symptom severity, and comorbid ADHD.<sup>35, 36, 69</sup> CBT plus fluoxetine was superior to fluoxetine in groups with ADHD, higher treatment expectations, or mild to moderate baseline depression symptoms. In addition, for those with treatment-resistant depression, when compared with no CBT plus new medication, CBT plus new medication increased response rates among those with no abuse history, who had at least one comorbid condition, and those with low levels of hopelessness.<sup>70-72</sup>

## Discussion

Current recommendations support CBT, combined therapy, and fluoxetine for adolescents<sup>73</sup> with moderate to severe depression.<sup>74-76</sup> Uncertainty persists regarding treatment of children, disorders other than MDD, and partial or no response to initial therapy. We conducted an SR to examine the effectiveness and safety of treatments for child and adolescent DDs (i.e., MDD, dysthymia/PDD, and/or DD NOS). The SR examined efficacy and comparative effectiveness of nonpharmacological, pharmacological, and combination treatments. Our findings are generally consistent with current recommendations but offer some additional insights specific to disorders other than MDD and to children. In summary, our results, when parsed by population and disorder, suggest that for adolescents with MDD, CBT, fluoxetine, escitalopram, and combined fluoxetine plus CBT may reduce depressive symptoms in the short term. Notably, although the point estimates for improvement on continuous measures of symptom improvement and



functional status for escitalopram and nonpharmacological interventions generally exceeded the distribution-based MCIDs (0.5 of SD of the control group, generally from baseline when available, for the studies contributing to strength-of-evidence results), the CIs did not. As a result, the clinical significance of the reported change is unclear.

SSRIs as a class may improve response and functional status among adolescents and children with MDD. However, they may be associated with a higher risk of serious AEs among adolescents and children with MDD and with a higher risk of withdrawal due to AEs among adolescents with MDD. Paroxetine may be associated with a higher risk of suicidal ideation or behaviors in adolescents with MDD. For adolescents or children with MDD, PDD, or DD NOS, CBT and family therapy may improve symptoms, response, or functional status. For adolescents and children with MDD, CBT plus medications may help prevent relapse. Evidence on children with MDD alone or with a wider range of depressive disorders (MDD, PDD, or DD NOS) is sparse.

Across populations and disorders, the findings of this review indicated that several interventions may be associated with low SOE of benefits such as CBT, fluoxetine, escitalopram, and combined fluoxetine and CBT in the short term; we found insufficient evidence on harms for these individual interventions but note that our analysis was underpowered to detect rare harms. As noted above, paroxetine had a higher risk of suicidal ideation or behaviors in adolescents with MDD, but the evidence was insufficient for other SSRIs as a drug class across populations and disorders. FDA's boxed warning was issued in 2004 and was based on a meta-analysis finding of increased risk of suicidality when pooling across all antidepressants and all indications.<sup>58</sup> Our review included several publications after 2004 but was restricted to studies focusing on depression, outpatients, and publications that allowed extraction of study-level data. These limitations likely further reduced the power necessary to find differences in suicidality in our analysis.

Results for interventions were not always consistent across age and underlying DD. Notably, we did not find evidence that therapies such as CBT and IPT are universally superior to inactive or active controls. CBT, for example, offers benefits when compared with wait-list control (adolescents with MDD or dysthymia) or treatment as usual (adolescents with MDD), but the evidence is insufficient when compared with pill placebo or active control (adolescents with MDD). Given the heterogeneity of populations and comparators, we were unable to determine if the lack of consistency in demonstrating benefits of CBT or IPT arose from differences in effectiveness by age and disorder or from differences in study size, design, and conduct.

Broadly speaking, the evidence base is characterized by large areas of uncertainty or lack of information; these large gaps in the evidence occur more frequently in the nonpharmacological evidence base where the evidence on benefits comes from single studies, and few studies examined harms.

More specifically, several issues stand out as gaps and may serve as areas for future research. First, we found insufficient evidence on many interventions and outcomes. Greater certainty in the estimate of effect will require more and better evidence for nearly all evaluated interventions. In some instances, we found no eligible evidence of benefits or harms in our specified populations, as with collaborative care. Second, we found limited information on subpopulations (based on patient characteristics, parent/caregiver characteristics, disorder characteristics, history of previous treatment, comorbid condition, or exposure to a traumatic life event). Third, we found preliminary evidence for moderators of efficacy and effectiveness, such as baseline depression severity and comorbid conditions. These subgroup analyses, when available, were

generally hypothesis generating because studies were rarely designed to measure differences in moderating variables. Some studies evaluated several demographic, clinical, caregiver, and study characteristics and found evidence of moderation for a subset of variables only. These findings could be explained by chance; we could not arrive at conclusions as a result. The paucity of evidence limited our ability to support recommendations tailored by underlying patient characteristics. A robust trial focusing on sequencing treatments would help provide patient-centered evidence that accounts for underlying patient characteristics. Fourth, psychotherapy studies rarely reported on harms. Fifth, we had difficulty interpreting the clinical significance of some reported changes in continuous scales in the absence of evidence on minimally important differences for patients (that is, the smallest amount an outcome must change to be meaningful to patients) on those scales. In summary, further research is needed on the effects of interventions in children, in groups with DDs other than MDD, and over the long term. Further research is also needed on head-to-head comparisons of interventions. In addition, new research should establish minimally important differences to help understand the trade-offs between benefits and harms.

## **Conclusion**

Efficacious treatments exist for adolescents with MDD. The evidence is largely insufficient for other ages and DDs. SSRIs may be associated with increased withdrawal and serious AEs. No evidence on harms of psychotherapy was identified.

## References

1. Bang KS, Chae SM, Hyun MS, et al. The mediating effects of perceived parental teasing on relations of body mass index to depression and self-perception of physical appearance and global self-worth in children. *J Adv Nurs*. 2012 Dec;68(12):2646-53. doi: 10.1111/j.1365-2648.2012.05963.x. PMID: 22384945.
2. Avenevoli S, Swendsen J, He JP, et al. Major depression in the national comorbidity survey-adolescent supplement: Prevalence, correlates, and treatment. *J Am Acad Child Adolesc Psychiatry*. 2015 Jan;54(1):37-44 e2. doi: 10.1016/j.jaac.2014.10.010. PMID: 25524788.
3. Gordon MS, Tonge B, Melvin GA. Outcome of adolescent depression: 6 months after treatment. *Aust N Z J Psychiatry*. 2011 Mar;45(3):232-9. doi: 10.3109/00048674.2010.538838. PMID: 21128873.
4. U.S. Food and Drug Administration. Suicidality in children and adolescents being treated with antidepressant medications. Silver Spring, MD: U.S. Food and Drug Administration; 2004.  
<http://wayback.archive-it.org/7993/20170113164717/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161679.htm>. Accessed on February 25 2019.
5. Lilienfeld SO. Psychological treatments that cause harm. *Perspect Psychol Sci*. 2007 Mar;2(1):53-70. doi: 10.1111/j.1745-6916.2007.00029.x. PMID: WOS:000207450300005.
6. Wagner KD, Jonas J, Findling RL, et al. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J Am Acad Child Adolesc Psychiatry*. 2006 Mar;45(3):280-8. doi: 10.1097/01.chi.0000192250.38400.9e. PMID: 16540812.
7. Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2014.  
[www.effectivehealthcare.ahrq.gov/methodsguide.cfm](http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm).
8. Covidence. Covidence systematic review software. Melbourne, Australia: Veritas Health Innovation; n.d. [www.covidence.org](http://www.covidence.org). Accessed on March 19 2019.
9. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919. PMID: 27733354.
10. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration; 2011.  
[www.handbook.cochrane.org](http://www.handbook.cochrane.org). Accessed on January 10 2017.
11. West SL, Gartlehner G, Mansfield AJ, et al. Comparative effectiveness review methods: clinical heterogeneity methods research report. (Prepared by RTI International-University of North Carolina Evidence-based Practice Center under Contract No. 290-2007-10056-I). AHRQ Publication No: 10-EHC070-EF. Rockville, MD: Agency for Healthcare Research and Quality; September 2010.
12. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. *J Clin Epidemiol*. 2010 May;63(5):513-23. doi: 10.1016/j.jclinepi.2009.03.009. PMID: 19595577.
13. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011 Nov;64(11):1198-207. doi: 10.1016/j.jclinepi.2010.11.021. PMID: 21463926.

14. Clarke GN, Hornbrook M, Lynch F, et al. Group cognitive-behavioral treatment for depressed adolescent offspring of depressed parents in a health maintenance organization. *J Am Acad Child Adolesc Psychiatry*. 2002 Mar;41(3):305-13. doi: 10.1097/00004583-200203000-00010. PMID: 11886025.
15. Storch EA, Wilhelm S, Sprich S, et al. Efficacy of augmentation of cognitive behavior therapy with weight-adjusted d-cycloserine vs placebo in pediatric obsessive-compulsive disorder: a randomized clinical trial. *JAMA Psychiatry*. 2016 Aug 1;73(8):779-88. doi: 10.1001/jamapsychiatry.2016.1128. PMID: 27367832.
16. Clarke G, Debar L, Lynch F, et al. A randomized effectiveness trial of brief cognitive-behavioral therapy for depressed adolescents receiving antidepressant medication. *J Am Acad Child Adolesc Psychiatry*. 2005 Sep;44(9):888-98. PMID: 16113617.
17. Shirk SR, Deprince AP, Crisostomo PS, et al. Cognitive behavioral therapy for depressed adolescents exposed to interpersonal trauma: an initial effectiveness trial. *Psychotherapy (Chic)*. 2014 Mar;51(1):167-79. doi: 10.1037/a0034845. PMID: 24377410.
18. Israel P, Diamond GS. Feasibility of attachment based family therapy for depressed clinic-referred Norwegian adolescents. *Clin Child Psychol Psychiatry*. 2013;18(3):334-50. doi: 10.1177/1359104512455811. PMID: 108668356. Language: English. Entry Date: 20160426. Revision Date: 20160426. Publication Type: Article.
19. Strasser F, Sweeney C, Willey J, et al. Impact of a half-day multidisciplinary symptom control and palliative care outpatient clinic in a comprehensive cancer center on recommendations, symptom intensity, and patient satisfaction: a retrospective descriptive study. *J Pain Symptom Manage*. 2004 Jun;27(6):481-91. doi: 10.1016/j.jpainsymman.2003.10.011. PMID: 15165646.
20. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003 May;41(5):582-92. doi: 10.1097/01.MLR.0000062554.74615.4C. PMID: 12719681.
21. Kennard BD, Emslie GJ, Mayes TL, et al. Sequential treatment with fluoxetine and relapse--prevention CBT to improve outcomes in pediatric depression. *Am J Psychiatry*. 2014 Oct;171(10):1083-90. doi: 10.1176/appi.ajp.2014.13111460. PMID: 24935082.
22. Weihs KL, Murphy W, Abbas R, et al. Desvenlafaxine versus placebo in a fluoxetine-referenced study of children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2018 Feb;28(1):36-46. doi: 10.1089/cap.2017.0100. PMID: 29189044.
23. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004 Aug 18;292(7):807-20. doi: 10.1001/jama.292.7.807. PMID: 15315995.
24. Emslie GJ, Kennard BD, Mayes TL, et al. Continued effectiveness of relapse prevention cognitive-behavioral therapy following fluoxetine treatment in youth with major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. 2015 Dec;54(12):991-8. doi: 10.1016/j.jaac.2015.09.014. PMID: 26598474.
25. Clarke GN, Rohde P, Lewinsohn PM, et al. Cognitive-behavioral treatment of adolescent depression: efficacy of acute group treatment and booster sessions. *J Am Acad Child Adolesc Psychiatry*. 1999 Mar;38(3):272-9. doi: 10.1097/00004583-199903000-00014. PMID: 10087688.
26. Rossello J, Bernal G. The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. *J Consult Clin Psychol*. 1999 Oct;67(5):734-45. PMID: 10535240.

27. Thompson MC, Sugar CA, Langer DA, et al. A randomized clinical trial comparing family-focused treatment and individual supportive therapy for depression in childhood and early adolescence. *J Am Acad Child Adolesc Psychiatry*. 2017 Jun;56(6):515-23. doi: 10.1016/j.jaac.2017.03.018. PMID: 28545757.
28. Clarke G, DeBar LL, Pearson JA, et al. Cognitive behavioral therapy in primary care for youth declining antidepressants: a randomized trial. *Pediatrics*. 2016 May;137(5). doi: 10.1542/peds.2015-1851. PMID: 27244782.
29. Dietz LJ, Weinberg RJ, Brent DA, et al. Family-based interpersonal psychotherapy for depressed preadolescents: examining efficacy and potential treatment mechanisms. *J Am Acad Child Adolesc Psychiatry*. 2015 Mar;54(3):191-9. doi: 10.1016/j.jaac.2014.12.011. PMID: 25721184.
30. Hughes CW, Barnes S, Barnes C, et al. Depressed Adolescents Treated with Exercise (DATE): a pilot randomized controlled trial to test feasibility and establish preliminary effect sizes. *Ment Health Phys Act*. 2013 Jun;6(2):119-31. doi: 10.1016/j.mhpa.2013.06.006. PMID: 24244220.
31. Rickhi B, Kania-Richmond A, Moritz S, et al. Evaluation of a spirituality informed e-mental health tool as an intervention for major depressive disorder in adolescents and young adults - a randomized controlled pilot trial. *BMC Complement Altern Med*. 2015 Dec 24;15:450. doi: 10.1186/s12906-015-0968-x. PMID: 26702639.
32. Barthow C, Wickens K, Stanley T, et al. The Probiotics in Pregnancy Study (PiP Study): rationale and design of a double-blind randomised controlled trial to improve maternal health during pregnancy and prevent infant eczema and allergy. *BMC Pregnancy Childbirth*. 2016 Jun 3;16(1):133. doi: 10.1186/s12884-016-0923-y. PMID: 27255079.
33. Findling RL, Robb A, Bose A. Escitalopram in the treatment of adolescent depression: a randomized, double-blind, placebo-controlled extension trial. *J Child Adolesc Psychopharmacol*. 2013 Sep;23(7):468-80. doi: 10.1089/cap.2012.0023. PMID: 24041408.
34. Vitiello B, Rohde P, Silva S, et al. Functioning and quality of life in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1419-26. doi: 10.1097/01.chi.0000242229.52646.6e. PMID: 17135987.
35. Curry J, Rohde P, Simons A, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1427-39. doi: 10.1097/01.chi.0000240838.78984.e2. PMID: 17135988.
36. Kratochvil CJ, May DE, Silva SG, et al. Treatment response in depressed adolescents with and without co-morbid attention-deficit/hyperactivity disorder in the Treatment for Adolescents with Depression Study. *J Child Adolesc Psychopharmacol*. 2009 Oct;19(5):519-27. doi: 10.1089/cap.2008.0143. PMID: 19877976.
37. Barbe RP, Bridge J, Birmaher B, et al. Suicidality and its relationship to treatment outcome in depressed adolescents. *Suicide Life Threat Behav*. 2004 Spring;34(1):44-55. PMID: 15106887.
38. Rohde P, Seeley JR, Kaufman NK, et al. Predicting time to recovery among depressed adolescents treated in two psychosocial group interventions. *J Consult Clin Psychol*. 2006 Feb;74(1):80-8. doi: 10.1037/0022-006X.74.1.80. PMID: 16551145.
39. Fristad MA, Vesco AT, Young AS, et al. Pilot randomized controlled trial of Omega-3 and individual-family psychoeducational psychotherapy for children and adolescents with depression. *J Clin Child Adolesc Psychol*. 2019;48(sup1):S105-s18. doi: 10.1080/15374416.2016.1233500. PMID: 27819485.

40. Kennard B, Silva S, Vitiello B, et al. Remission and residual symptoms after short-term treatment in the Treatment of Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1404-11. doi: 10.1097/01.chi.0000242228.75516.21. PMID: 17135985.
41. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002 Oct;41(10):1205-15. doi: 10.1097/00004583-200210000-00010. PMID: 12364842.
42. Emslie GJ, Prakash A, Zhang Q, et al. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014 May;24(4):170-9. doi: 10.1089/cap.2013.0096. PMID: 24815533.
43. Atkinson SD, Prakash A, Zhang Q, et al. A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014 May;24(4):180-9. doi: 10.1089/cap.2013.0146. PMID: 24813026.
44. Wagner KD, Robb AS, Findling RL, et al. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry*. 2004 Jun;161(6):1079-83. doi: 10.1176/appi.ajp.161.6.1079. PMID: 15169696.
45. Emslie GJ, Wagner KD, Kutcher S, et al. Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2006 Jun;45(6):709-19. doi: 10.1097/01.chi.0000214189.73240.63. PMID: 16721321.
46. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997 Nov;54(11):1031-7. PMID: 9366660.
47. Forest Laboratories. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of citalopram in children and adolescents with depression. Forest Laboratories - Clinical Study Register. 2001(1). PMID: CN-00763823.
48. Emslie GJ, Ventura D, Korotzer A, et al. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry*. 2009 Jul;48(7):721-9. doi: 10.1097/CHI.0b013e3181a2b304. PMID: 19465881.
49. Berard R, Fong R, Carpenter DJ, et al. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2006 Feb-Apr;16(1-2):59-75. doi: 10.1089/cap.2006.16.59. PMID: 16553529.
50. Le Noury JL, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *Br Med J*. 2015;351. PMID: 2016-20242-001.
51. Le Noury J, Nardo JM, Healy D, et al. Study 329 continuation phase: safety and efficacy of paroxetine and imipramine in extended treatment of adolescent major depression. *Int J Risk Saf Med*. 2016 Sep 17;28(3):143-61. doi: 10.3233/jrs-160728. PMID: 27662279.
52. Durgam S, Chen C, Migliore R, et al. A phase 3, double-blind, randomized, placebo-controlled study of vilazodone in adolescents with major depressive disorder. *Paediatr Drugs*. 2018 Aug;20(4):353-63. doi: 10.1007/s40272-018-0290-4. PMID: 29633166.
53. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2001 Jul;40(7):762-72. doi: 10.1097/00004583-200107000-00010. PMID: 11437014.

54. Emslie GJ, Heiligenstein JH, Hoog SL, et al. Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 2004 Nov;43(11):1397-405. doi: 10.1097/01.chi.0000140453.89323.57. PMID: 15502599.
55. Emslie GJ, Kennard BD, Mayes TL, et al. Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. *Am J Psychiatry*. 2008 Apr;165(4):459-67. doi: 10.1176/appi.ajp.2007.07091453. PMID: 18281410.
56. Atkinson S, Lubaczewski S, Ramaker S, et al. Desvenlafaxine versus placebo in the treatment of children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2018;28(1):55-65. doi: 10.1089/cap.2017.0099. PMID: 2018-03285-007.
57. Emslie GJ, Findling RL, Yeung PP, et al. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry*. 2007 Apr;46(4):479-88. doi: 10.1097/chi.0b013e31802f5f03. PMID: 17420682.
58. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006 Mar;63(3):332-9. doi: 10.1001/archpsyc.63.3.332. PMID: 16520440.
59. Kennard BD, Mayes TL, Chahal Z, et al. Predictors and moderators of relapse in children and adolescents with major depressive disorder. *J Clin Psychiatry*. 2018 Mar/Apr;79(2). doi: 10.4088/JCP.15m10330. PMID: 29474007.
60. Hirschtritt ME, Pagano ME, Christian KM, et al. Moderators of fluoxetine treatment response for children and adolescents with comorbid depression and substance use disorders. *J Subst Abuse Treat*. 2012 Jun;42(4):366-72. doi: 10.1016/j.jsat.2011.09.010. PMID: 22116008.
61. GlaxoSmithKline. A double-blind, multicentre placebo controlled study of paroxetine in adolescents with unipolar major depression. 1998. <http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/038/CN-00497038/frame.html>.
62. Emslie G, Kratochvil C, Vitiello B, et al. Treatment for Adolescents with Depression Study (TADS): safety results. *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1440-55. doi: 10.1097/01.chi.0000240840.63737.1d. PMID: 17135989.
63. Kratochvil C, Emslie G, Silva S, et al. Acute time to response in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1412-8. doi: 10.1097/01.chi.0000237710.73755.14. PMID: 17135986.
64. Bernstein GA, Borchardt CM, Perwien AR, et al. Imipramine plus cognitive-behavioral therapy in the treatment of school refusal. *J Am Acad Child Adolesc Psychiatry*. 2000 Mar;39(3):276-83. doi: 10.1097/00004583-200003000-00008. PMID: 10714046.
65. Bernstein GA, Anderson LK, Hektner JM, et al. Imipramine compliance in adolescents. *J Am Acad Child Adolesc Psychiatry*. 2000 Mar;39(3):284-91. doi: 10.1097/00004583-200003000-00009. PMID: 10714047.
66. Iftene F, Predescu E, Stefan S, et al. Rational-emotive and cognitive-behavior therapy (REBT/CBT) versus pharmacotherapy versus REBT/CBT plus pharmacotherapy in the treatment of major depressive disorder in youth; a randomized clinical trial. *Psychiatry Res*. 2015 Feb 28;225(3):687-94. doi: 10.1016/j.psychres.2014.11.021. PMID: 25500320.
67. Wilkinson PO, Goodyer IM. The effects of cognitive-behavioural therapy on mood-related ruminative response style in depressed adolescents. *Child Adolesc Psychiatry Ment Health*. 2008 Jan 29;2(1):3. doi: 10.1186/1753-2000-2-3. PMID: 18230146.

68. Kim SM, Han DH, Lee YS, et al. Combined cognitive behavioral therapy and bupropion for the treatment of problematic on-line game play in adolescents with major depressive disorder. *Comput Human Behav.* 2012;28(5):1954-9. PMID: CN-00853199.
69. Foster S, Mohler-Kuo M, Tay L, et al. Estimating patient-specific treatment advantages in the 'Treatment for Adolescents with Depression Study'. *J Psychiatr Res.* 2019 May;112:61-70. doi: 10.1016/j.jpsychires.2019.02.021. PMID: 30856378.
70. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA.* 2008 Feb 27;299(8):901-13. doi: 10.1001/jama.299.8.901. PMID: 18314433.
71. Brent DA, Emslie GJ, Clarke GN, et al. Predictors of spontaneous and systematically assessed suicidal adverse events in the treatment of SSRI-resistant depression in adolescents (TORDIA) study. *Am J Psychiatry.* 2009 Apr;166(4):418-26. doi: 10.1176/appi.ajp.2008.08070976. PMID: 19223438.
72. Asarnow JR, Emslie G, Clarke G, et al. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. *J Am Acad Child Adolesc Psychiatry.* 2009 Mar;48(3):330-9. doi: 10.1097/CHI.0b013e3181977476. PMID: 19182688.
73. American Psychological Association. Guideline development panel for the treatment of depressive disorders. Clinical practice guideline for the treatment of depression across three age cohorts. Washington, DC: American Psychological Association; 2019. <https://www.apa.org/depression-guideline/guideline.pdf>. Accessed on August 12 2019.
74. National Institute for Health and Care Excellence. Depression in children and young people: identification and management. NICE guideline [NG134]. United Kingdom: National Institute for Health and Care Excellence; 2019. <https://www.nice.org.uk/guidance/ng134/chapter/Recommendations>. Accessed on August 12 2019.
75. Cheung AH, Zuckerbrot RA, Jensen PS, et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): part II. treatment and ongoing management. *Pediatrics.* 2018 Feb 26;141(3). doi: 10.1542/peds.2017-4082. PMID: 29483201.
76. Zuckerbrot RA, Cheung A, Jensen PS, et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): part I. practice preparation, identification, assessment, and initial management. *Pediatrics.* 2018 Feb 26;141(3). doi: 10.1542/peds.2017-4081. PMID: 29483200.



# Chapter 1. Introduction

## Background

Depressive disorders (DDs) can affect long-term mental and physical health conditions, lead to poor functional status, and increase risk of suicide.<sup>1-6</sup> The potential for lasting negative effects of child-onset depression underscores the importance of its early identification, diagnosis, and subsequent treatment.<sup>7</sup> Despite evidence that several effective treatments for depression exist, one 2016 national survey indicated that only 40.9 percent of adolescents ages 12 to 17 years who experienced a major depressive episode in the prior 12 months reported receiving depression treatment during the same time period.<sup>8</sup>

Several nonpharmacological, pharmacological, and combined treatment options for childhood depression are available to clinicians with varying levels of evidence behind their use and efficacy. In general, the evidence base for individual treatment types is inconsistent for use in pediatric populations,<sup>9-16</sup> and the evidence base is much weaker for younger children than for adolescents. Although some evidence exists for benefits, particularly from nonpharmacological treatments, very few studies report associated harms. The 2013 review published for the U.S. Preventive Services Task Force (USPSTF) recommendation on screening for major depressive disorder (MDD) among children and adolescents in primary care indicated that, with one exception (the Treatment for Adolescents with Depression Study<sup>17</sup>), no psychotherapy intervention efficacy trial reported harms as an outcome. The absence of information on harms associated with nonpharmacological interventions precludes making an informed recommendation that adequately weighs the benefits and harms of these treatments.

Substantial concern surrounds the use of pharmacological interventions to treat childhood depression. Although the Food and Drug Administration (FDA) has approved two types of selective serotonin reuptake inhibitors (SSRIs) to treat MDD (fluoxetine for children age 8 or older and escitalopram for adolescents ages 12 to 17), FDA issued several warnings in the early 2000s. These warnings stemmed from reports of possible increased risk of suicidal ideation and suicide attempts associated with one SSRI, paroxetine, as well as the possibility of increased risk of suicidality in some children and adolescents treated with antidepressants.<sup>18</sup> FDA requires a boxed warning on these medications about the potential danger of suicidality with a recommendation to closely monitor for worsening of depression, agitation or withdrawal, and increased suicidal thoughts or behaviors.

Practice patterns are typically complex and may include single therapy or combination therapy.<sup>19</sup> Some clinicians combine interventions, particularly when a single treatment type has failed. Specific interventions may be started concurrently or staggered (e.g., one treatment followed by another new intervention 4 weeks later). Some evidence suggests differential effects of combination therapy when compared with psychotherapy or pharmacotherapy alone in studies conducted on children and adolescents.<sup>17, 20, 21</sup>

Recently, clinical care of children with depression has increasingly used healthcare teams to deliver a collaborative care model of intervention delivery involving the healthcare system. Similar interventions focused on a team providing coordinated care may be referenced as co-managed care, colocated care, integrated care, integrative care, and stepped care. Frequently, primary care providers and mental health specialists work together to deliver collaborative care interventions with the support of a case manager to identify and treat patients in need.

Table 1 describes several guidelines for treating child and adolescent depression, including details on the scope and applicability. Treatments can vary by age of the patient, diagnosis,

severity of disorder, and response to therapy. Not all guidelines address all potential topics. Two of the three most recent guidelines (American Psychological Association [APA], 2019,<sup>22</sup> National Institution for Health and Care Excellence [NICE], 2019,<sup>23</sup> and the Guidelines for Adolescent Depression in Primary Care [GLAD-PC, 2018<sup>24, 25</sup>]) address options for children and adolescents, although both guidelines (APA and NICE) note the paucity of evidence for children. The GLAD-PC guidelines are specific to MDD; the others are not specific to MDD but do not specify treatment options by disorder. Two guidelines (GLAD-PC and NICE) recommend treatments depending on level of severity (mild, moderate, severe). GLAD-PC and NICE recommend either active support and monitoring or psychotherapy for patients with mild DDs. NICE and GLAD-PC guidelines recommend SSRI medications or a combination of psychotherapy and SSRIs for patients with moderate or severe disorders. The NICE guideline suggests that patients with at least moderate levels of depression severity may benefit from starting psychotherapy and an SSRI concurrently; the GLAD-PC guideline is not as specific in this regard. The APA guidelines only offer recommendations for initial treatment. The NICE guidelines call out the paucity of evidence on psychotherapy as second-line treatments and offer cautious support for sertraline or citalopram as a second-line treatment if fluoxetine is not effective. For those not responding within 6 to 8 weeks of initial treatment, the GLAD-PC guidelines suggest consulting with mental health specialists and adding (or maximizing the dose of) pharmacotherapy or psychotherapy. Across these recent guidelines, significant areas of uncertainty persist in treating children, disorders other than MDD, and partial or no response to initial therapy.

**Table 1. Current clinical practice guidelines for the treatment of child and adolescent DDs**

Guideline (Year of Publication)	Process Used To Produce Guideline	Population	Treatment Recommendations
APA, 2019 <sup>22</sup>	Systematic reviews (SRs), meta-analyses, expert consensus	Children and adolescents with DDs (minor depression, major depression, PDD [formerly called “dysthymia”], intermittent depression, or having depression symptoms at or above a prespecified level based on a validated measure of depression severity)	For children, there was insufficient evidence to recommend psychotherapy (behavioral therapy, cognitive therapy, CBT, family therapy, play therapy, problem-solving therapy, psychodynamic therapy, supportive therapy) or pharmacotherapy.  For adolescents, initial treatment with CBT or IPT-A; fluoxetine as a first-line medication with MDD; insufficient evidence to recommend either psychotherapy or fluoxetine over the other for MDD.
GLAD-PC, 2018 <sup>24, 25</sup> (supported by AAP and CPS)	SRs, expert consensus, input from youth and families with lived experience	Patient: Adolescents ages 10 to 21 with MDD differentiated by severity level (mild, moderate, severe) <sup>a</sup>	Active support and monitoring for 6-8 weeks for patients with mild MDD; referral to mental health specialists for patients with moderate to severe MDD and those who do not improve with active support and monitoring.  Advocates for the use of psychotherapies (CBT or IPT), SSRI medications, or both.

<b>Guideline (Year of Publication)</b>	<b>Process Used to Produce Guideline</b>	<b>Population</b>	<b>Treatment Recommendations</b>
USPSTF, 2016 <sup>26</sup>	SRs, expert consensus	Adolescents with MDD (insufficient evidence to make a recommendation for children)	Guideline did not state explicit treatment recommendations because it focuses on screening for depression in pediatric primary care settings; however, part of the chain of indirect evidence used to make the recommendation included efficacy of CBT, collaborative care, fluoxetine, CBT combined with fluoxetine, and escitalopram among adolescents.
NICE, 2019 <sup>23</sup>	SR and consideration of cost-effectiveness	Children and adolescents with depression (unspecified type) with recommendations made according to severity	Several psychological therapies have shown efficacy but no clear evidence of superiority of one over another in comparative effectiveness studies; adolescents with depression of at least moderate severity may benefit from starting psychological and pharmacotherapy concurrently; antidepressants are not recommended for adolescents with mild depression; children with moderate to severe depression should be offered family IPT, family therapy, psychodynamic psychotherapy, or individual CBT; adolescents with moderate to severe depression should be offered at least 3 months of CBT; when pharmacotherapy is indicated, the guidelines call for vigilant, active monitoring for adverse drug reactions.
NICE, 2019 <sup>23</sup>	SR and consideration of cost-effectiveness	Children and adolescents with depression (unspecified type) with recommendations made according to severity	Several psychological therapies have shown efficacy but no clear evidence of superiority of one over another in comparative effectiveness studies; adolescents with depression of at least moderate severity may benefit from starting psychological and pharmacotherapy concurrently; antidepressants are not recommended for adolescents with mild depression; children with moderate to severe depression should be offered family IPT, family therapy, psychodynamic psychotherapy, or individual CBT; adolescents with moderate to severe depression should be offered at least 3 months of CBT; when pharmacotherapy is indicated, the guidelines call for vigilant, active monitoring for adverse drug reactions.
AACAP, 2007 <sup>27</sup>	Rigorous review of empirical evidence and clinical consensus	Children and adolescents with DDs (unspecified) with recommendations varying by severity, duration, history of prior depressive episodes, and complications	Depression of short duration with no complications or with mild impairment can be treated with education, support, and case management; nonresponse to these initial strategies or those with complicated or depression symptoms accompanied by moderate to severe functional impairment should be followed by a trial of psychotherapy or antidepressants; treatment should be continued for 6-12 months and, to prevent recurrence, longer if possible for some youth who might have a history of relapse/recurrence after treatment, chronic or severe types of depression, or long prior periods of recovery.

<sup>a</sup> Authors mention that recommendations can be applied to adolescents with PDD and premenstrual dysphoric disorder as well.

AACAP = American Academy of Child and Adolescent Psychiatry; AAP = American Academy of Pediatrics; APA = American Psychological Association; CBT = cognitive behavioral therapy; CPS = Canadian Pediatric Society; DD = depressive disorder; GLAD-PC = Guidelines for Adolescent Depression in Primary Care; IPT = interpersonal therapy; IPT-A = interpersonal therapy for adolescents; MDD = major depressive disorder; NICE = National Institute for Health and Care Excellence; PDD = persistent

depressive disorder; SR = systematic review; SSRI = selective serotonin reuptake inhibitor; USPSTF = United States Preventive Services Task Force.

All guidelines suggest that the treatment phase should last for an adequate amount of time (6 to 12 months<sup>27, 28</sup> after resolution of symptoms) with active monitoring for potential adverse events.

Clinicians contend with numerous challenges in treating childhood depression appropriately. Perhaps most importantly, clinicians need to account for developmental changes over the course of childhood and adolescence that likely have widespread impacts on outcomes. Adolescents and younger children may experience differential benefits and harms depending on treatment type.<sup>29</sup> In addition, differences in outcomes may vary by severity and type of DD (e.g., MDD, persistent depressive disorder [PDD, previously termed dysthymia] or DD not otherwise specified [DD NOS]). Although the evidence on PDD is relatively sparse, PDD can be a gateway to MDD and signal high risk of recurrent mood disorders. Other clinical uncertainty persists regarding how the harms may vary according to dose of medication or how the efficacy of treatments may vary by frequency or intensity of the nonpharmacological intervention. Moreover, few nonpharmacological studies have systematically collected and reported harms data (e.g., re-experiencing trauma, suicidality),<sup>30</sup> which leads to uncertainty about weighing the risks and benefits of different types of treatment. Treatment recommendations also need to account for patient and family preferences<sup>31, 32</sup> and prior experience with depression that has not responded to treatment.<sup>33</sup> Comparatively little is known about these issues that influence treatment selection. Finally, the evidence base on comparative effectiveness of depression interventions in childhood is sparse.<sup>34</sup> These uncertainties obscure best practices in selecting a treatment most likely to benefit each individual patient.

## Scope and Key Questions

### Scope of the Review

This systematic review (SR) addresses the efficacy, comparative effectiveness and harms of commonly used types of nonpharmacological and pharmacological treatments, as listed in Tables 2 and 3.

**Table 2. Nonpharmacological interventions used to treat child and adolescent depression**

Intervention Type	Interventions
Psychological/ psychosocial	CBT, rational emotive behavior therapy, behavioral activation, other behavioral therapy, IPT, directive counseling, Katathym-imaginative psychotherapy, family therapy, parent education, self-help groups, problem-solving therapy, autonomic training, combined-modality therapy, psychological adaptation therapies
Lifestyle	Exercise (physical activity), diet therapy, mindfulness (including mindfulness-based stress reduction), meditation (including mindfulness meditation), relaxation therapy, massage therapy, music therapy, art therapy, integrative restoration, visualization, tai-chi, yoga, spirituality, acupuncture
Supplements	St. John's wort, SAME, fish oil, melatonin, L-tryptophan, folic acid, 5-HTP, zinc, chromium, ginkgo biloba, vitamin E, omega-3 fatty acids, hypericum, inositol, selenium
Other	Electroconvulsive therapy, transcranial magnetic stimulation, light therapy (phototherapy), hypnotherapy (including self-hypnotherapy), neurofeedback, deep brain stimulation, biofeedback

5-HTP = 5-hydroxytryptophan; CBT = cognitive behavioral therapy; IPT = interpersonal therapy; SAME = S-adenosyl-L-methionine.

**Table 3. Pharmacological agents used to treat child and adolescent depression**

<b>Class</b>	<b>Drugs</b>
SSRIs	Fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, vilazodone
SNRIs	Duloxetine, venlafaxine
Tricyclic antidepressants (TCAs)	Amitriptyline, desipramine, imipramine, nortriptyline, doxepin, clomipramine
Monoamine oxidase inhibitors (MAOIs)	Rasagiline, selegiline, isocarboxazid, phenelzine, tranylcypromine
Atypical antidepressants	Bupropion, mirtazapine, nefazodone, trazodone, vortioxetine

MAOI = monoamine oxidase inhibitor; SNRI = selective serotonin reuptake inhibitor; SSRI = serotonin and norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

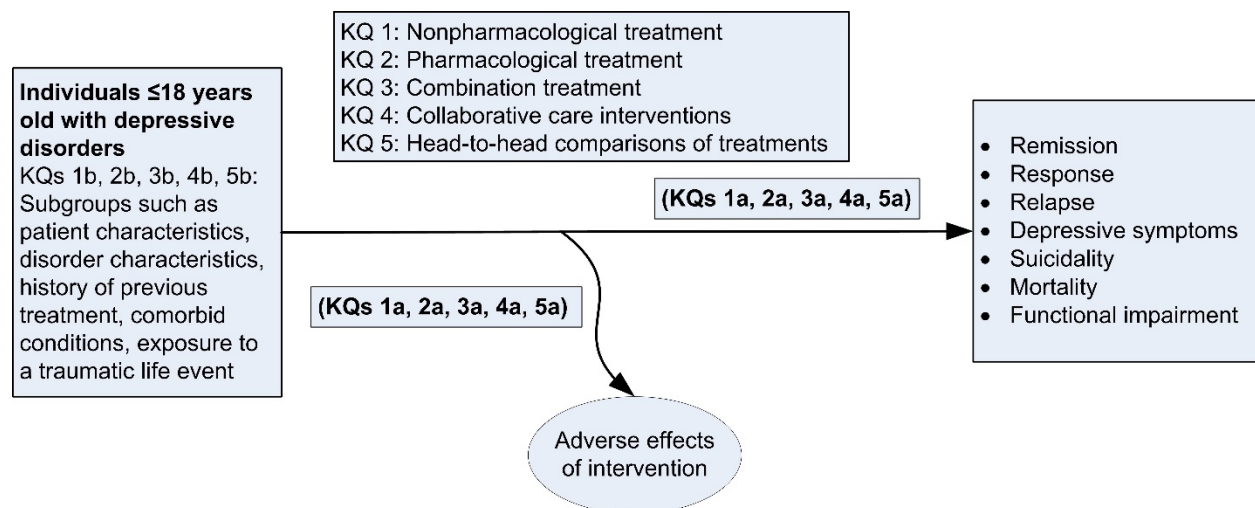
## Key Questions and Analytic Framework

Multiple Key Informants and members of a Technical Expert Panel helped finalize the following Key Questions (KQs). We developed an analytic framework to guide the SR (Figure 1). Table 4 lists the related PICOTS (population, interventions, comparators, outcomes, timing, and setting).

- KQ 1a.** In adolescents and children, what are the benefits and harms of nonpharmacological interventions for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?
- KQ 1b.** How do the benefits and harms vary by subpopulation (e.g., patient characteristics, parent/caregiver characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?
- KQ 2a.** In adolescents and children, what are the benefits and harms of pharmacological interventions for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?
- KQ 2b.** How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?
- KQ 3a.** In adolescents and children, what are the benefits and harms of combination interventions for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?
- KQ 3b.** How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?

- KQ 4a.** In adolescents and children, what are the benefits and harms of collaborative care interventions for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?
- KQ 4b.** How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?
- KQ 5a.** In adolescents and children, what are the comparative benefits and harms of treatments (pharmacological, nonpharmacological, combined, collaborative care interventions) for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?
- KQ 5b.** How do the benefits and harms vary by subpopulation (e.g., patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?

**Figure 1. Analytic framework for depression in children and adolescents**



KQ = Key Question.

**Table 4. Inclusion/exclusion criteria**

<b>PICOTS</b>	<b>Inclusion</b>	<b>Exclusion</b>
Population	<p>Children and adolescents (<math>\leq 18</math> years old) with a DD (MDD or PDD/DYS) as indicated by a diagnosis made from an established taxonomy (e.g., DSM, ICD) via administration of a structured or semistructured clinical interview (CIDI, DISC, SCID, PRIME-MD, Kinder-DIPS, K-SADS, DICA, CAS, SADS, DAWBA, SCAN), use of a cut point indicative of clinical MDD or PDD/DYS as measured by a clinically validated depression scale (BDI, CDI, CESD, PHQ, MFQ, ChildD-S)<sup>a</sup> or via a clinician diagnosis</p> <p>Subgroups of interest (KQs 1b, 2b, 3b, 4b, 5b) include those distinguished by patient characteristics (e.g., developmental age—child or adolescent, gender, race/ethnicity), parent/caregiver characteristics, disorder characteristics (e.g., type, severity), history of previous treatment, comorbid condition, and exposure to a traumatic life event</p>	All other children and adolescents ( $\leq 18$ years old), all adults $>18$ years old
Intervention	<p>Nonpharmacological interventions:</p> <p><u>Psychological/psychosocial</u>: Cognitive behavioral therapy, rational emotive behavior therapy, behavioral activation, other behavioral therapy, IPT, directive counseling, Katathym-imaginative psychotherapy, family therapy, parent education, self-help groups, problem-solving therapy, autonomic training, combined-modality therapy, psychological adaptation therapies</p> <p><u>Lifestyle</u>: Exercise (physical activity), diet therapy, mindfulness (including mindfulness-based stress reduction), meditation (including mindfulness meditation), relaxation therapy, massage therapy, music therapy, art therapy, integrative restoration, visualization, tai-chi, yoga, spirituality, acupuncture</p> <p><u>Supplements</u>: St. John's wort, SAMe, fish oil, melatonin, L-tryptophan, folic acid, 5-HTP, zinc, chromium, ginkgo biloba, vitamin E, omega-3 fatty acids, hypericum, inositol, selenium</p> <p><u>Other</u>: Electroconvulsive therapy, transcranial magnetic stimulation, light therapy (phototherapy), hypnotherapy (including self-hypnotherapy), neurofeedback, deep brain stimulation, biofeedback</p> <p>Pharmacological interventions: <u>SSRIs</u>: Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, vilazodone</p> <p><u>SNRIs</u>: Duloxetine, venlafaxine</p> <p><u>TCAs</u>: Amitriptyline, desipramine, imipramine, nortriptyline, doxepin, clomipramine</p> <p><u>MAOIs</u>: Rasagiline, selegiline, isocarboxazid, phenelzine, tranylcypromine</p> <p><u>Atypical antidepressants</u>: Bupropion, mirtazapine, nefazodone, trazodone, vortioxetine</p> <p>Combination interventions: Any combined treatment that includes two or more types of nonpharmacological, pharmacological, and/or collaborative care interventions, either started together or given as augments to initial treatment types</p> <p>Collaborative care interventions: Collaborative care, integrated care, integrative care, stepped care, coordinated care, comanaged care, colocated care</p>	All other interventions

PICOTS	Inclusion	Exclusion
Comparator	KQ 1: Treatment as usual, sham, attention control, wait-list control KQ 2: Placebo, treatment as usual, attention control, wait-list control KQ 3: Treatment as usual, placebo, sham, attention control, wait-list control KQ 4: Treatment as usual, placebo, sham, attention control, wait-list control KQ 5: Any nonpharmacological, pharmacological, or collaborative care intervention alone or in combination	All other comparators
Outcomes	Benefits: Remission Response Relapse Depressive symptoms Suicidality Mortality Functional impairment Harms: Any AEs of intervention (e.g., death, SAEs)	All other outcomes
Time frame	Any publication dates At least 6 weeks of treatment	Less than 6 weeks of treatment
Settings	Outpatient care in countries with a very high Human Development Index <sup>b</sup>	Inpatient care, studies conducted in countries without a very high Human Development Index
Study design	For benefits: <ul style="list-style-type: none"> <li>• Adolescents (sample age &gt;12 and ≤18): RCTs</li> <li>• Children (sample age ≤12): RCTs or CCTs</li> </ul> For harms: <ul style="list-style-type: none"> <li>• RCTs, CCTs, and observational studies</li> </ul> Reference lists of relevant systematic reviews published in 2013 or later used to ensure search strategies captured all relevant studies.	All other designs and studies using included designs that do not meet the sample size criterion
Language	Studies published in English	Studies published in languages other than English

<sup>a</sup> We excluded studies that used a screener rather than a clinical diagnosis based on our finding of lack of consistency in the use of cut points on screeners. Studies may use different cut points for the same instrument because of lack of consensus on appropriate cut points or to increase sample size.

<sup>b</sup> <http://hdr.undp.org/en/content/human-development-index-hdi>

5-HTP = 5-hydroxytryptophan; AE = adverse event; BDI = Beck Depression Inventory; CAS = Child Assessment Schedule; CCT = controlled clinical trial; CDI = Children's Depression Inventory; CES-D = Center for Epidemiological Studies Depression Scale; ChildD-S = Children's Depression Screener; CIDI = Composite International Diagnostic Interview; DAWBA = Development and Wellbeing Assessment; DD = depressive disorder; DICA = Diagnostic Interview for Children and Adolescents; DISC = Diagnostic Interview Schedule for Children; DSM = *Diagnostic and Statistical Manual*; DYS = dysthymia; ICD = International Statistical Classification of Diseases and Related Health Problems; IPT = interpersonal therapy; Kinder-DIPS = Diagnostic Interview for Psychiatric Disorders in Children and Adolescents; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; KQ = Key Question; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; PDD = persistent depressive disorder; PHQ = Patient Health Questionnaire; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; PRIME-MD = The Primary Care Evaluation of Mental Disorders; RCT = randomized controlled trial; SADS = Schedule for Affective Disorders and Schizophrenia; SAmE = S-adenosyl-L-methionine; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; SCID = Structured Clinical Interview for DSM disorders; SAE = serious adverse event; SNRI = selective serotonin reuptake inhibitor; SOE = strength of evidence; SR = systematic review; SSRI = serotonin and norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TEP = Technical Expert Panel.



## Chapter 2. Methods

We followed established methodologies of systematic reviews (SRs) as outlined in the Agency for Healthcare Quality and Research (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>35</sup> The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements. A Key Informant panel gave feedback on the initial proposed Key Questions (KQs); these KQs were posted on AHRQ's Effective Health Care website for public comment in February 2018 for 3 weeks and revised in response to comments. We then drafted a protocol for the SR and recruited a panel of technical experts to provide high-level content and methodological expertise throughout the development of the review. The study protocol is registered in the international prospective register of systematic reviews (PROSPERO #: CRD42018112150) and published on AHRQ's website at <https://effectivehealthcare.arq.gov/topic/childhood-depression/protocol>.

### Literature Search Strategy

To identify articles relevant to each KQ, we conducted a focused MEDLINE<sup>®</sup> search using a variety of terms, medical subject headings (MeSH), and major headings. The search included studies published from inception to May 29, 2019 and was limited to English-language and human-only studies. We also searched the Cochrane Library, the Cochrane Central Trials Registry, the Cumulative Index to Nursing and Allied Health Literature<sup>®</sup>, and PsycINFO<sup>®</sup> by using analogous search terms. In addition, we searched gray literature for unpublished studies relevant to this review and included studies that met all the inclusion criteria and contained enough methodological information for assessing internal validity/quality. Sources of gray literature included ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, HSRProj, pharmaceutical companies' dossiers (for pharmacotherapies of interest), and scientific evidence.

Relevant SRs and meta-analysis, as well as reference mining of relevant publications, were used to identify additional existing and new literature. An experienced librarian with inputs from the study investigators developed the search strategy (Appendix A). An independent experienced librarian peer-reviewed the search strategy.

### Inclusion and Exclusion Criteria

Eligible studies had to meet all the following criteria: (1) children and adolescents 18 years or younger with a confirmed diagnosis of major depressive disorder (MDD), persistent depressive disorder (PDD or dysthymia, as previously defined), or depression not otherwise specified (NOS); (2) study participants received any nonpharmacotherapy, pharmacotherapy, alone or combined, including interventions delivered in collaborative care systems that consisted of at least 6 weeks of treatment; and (3) study participants reported outcomes of interest (standardized depression or functional impairment benefit measures or harms outcomes). We included randomized controlled trials (RCTs) for benefits and RCTs or observational studies for harms. We further restricted the studies to those conducted in countries with a very high Human Development Index (HDI; at least one country in multiple-country studies had to be on the very high HDI list) and those published in English. We did not restrict publication time. Appendix B lists detailed inclusion and exclusion criteria.

## Study Selection

We imported all citations identified through searches and other sources into EndNote v.7. Independent reviewers screened the titles and abstracts of all citations using the inclusion and exclusion criteria using Covidence (a systematic review software).<sup>36</sup> Studies included by either reviewer were retrieved for full-text screening. Independent reviewers then screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus. If consensus was not reached, a third reviewer helped resolve differences. Excluded studies are listed in Appendix C.

## Data Abstraction

We developed and pilot tested a standardized data extraction form to extract study characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, interventions, comparisons, outcomes, settings, study design, and related items for assessing study quality and applicability). Trained reviewers abstracted the relevant data from each included article into the evidence tables; a second member of the team reviewed all data abstractions for completeness and accuracy. For the studies that addressed the subgroup KQs (KQs 1b, 2b, 3b, 4b, 5b), we only included studies that directly compared the efficacy or effectiveness between subgroups of interest.

## Assessment of Methodological Risk of Bias of Individual Studies

Our assessment of methodological risk of bias was guided by the criteria set forth by AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. To assess the risk of bias (i.e., internal validity), we used the ROBINS-1<sup>37</sup> tool for observational studies and the Cochrane RCT tool<sup>38</sup> for RCTs. For both observational studies and RCTs, risk-of-bias assessment included questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias; concepts covered include those about adequacy of randomization (for RCTs only), similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity.<sup>35</sup>

Two independent reviewers assigned risk-of-bias ratings for each study, with disagreements resolved by discussion and consensus. Reviewers assigned a rating of low risk of bias (study met all criteria), some concerns (study met some criteria), high risk of bias (methodological shortcomings leading to high risk of bias in one or more categories), or unclear risk of bias (methods not reported clearly).

## Data Synthesis

We summarized all included studies in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, setting (including geographic location), and results. When relevant (the evidence included studies with high risk of bias and without high risk of bias), we conducted qualitative or quantitative sensitivity analyses to gauge the difference in conclusions upon including and excluding high risk-of-bias studies. For bodies of evidence with meta-analyses, we reported effect sizes with and without high risk-of-bias studies.

If we found three or more studies with low levels of heterogeneity (similar populations, interventions, comparators, outcomes), we considered meta-analysis. For all analyses, we used random effects models to estimate pooled or comparative effects; unlike a fixed-effects model, this approach allowed for the likelihood that the true population effect may vary from study to study. To determine whether quantitative analyses were appropriate for bodies of evidence that contained three or more similar studies, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance.<sup>39</sup> We calculated standardized differences (relative risks or standardized mean differences) for outcomes; when we graded the strength-of-evidence (SOE) grade as higher than insufficient, we also presented absolute differences in effect, when possible, in the detailed results to aid with interpretation of results.

We assessed statistical heterogeneity in effects between studies included in meta-analyses by calculating the chi-square statistic and the  $I^2$  statistic (the proportion of variation in study estimates due to heterogeneity). The importance of the observed value of  $I^2$  depends on the magnitude and direction of effects and on the SOE for heterogeneity (e.g., p-value from the chi-square test or a confidence interval for  $I^2$ ).

When possible, for each intervention/comparator grouping, we present findings clustered by age of sample. We elected to use age categories as defined by study authors (adolescents as defined by study authors [typically age 11 or 12 years or older], children as defined by study authors [typically age 10 or 11 years or younger], and mixed adolescent and child samples [typically age 7 or 8 to 17 or 18 years]) rather than our own a priori definitions (adolescents [sample age >12 and ≤18]: RCTs, children [sample age ≤12]) to capture all available evidence. In addition, we present findings clustered by the sample's required depressive disorder (DD) diagnoses for inclusion—MDD only or a wider spectrum of DDs (i.e., MDD, PDD/dysthymic disorders, or other DDs like DD NOS). We generally use the same diagnostic term as the original study (e.g., PDD or dysthymia). We also note special characteristics of the sample required for study inclusions such as females only, those with treatment-resistant depression, those with a comorbid disorder like substance use disorder, or those with exposure to a traumatic life event. Studies that test different delivery systems of similar interventions (e.g., in person versus online or targeting adolescents only versus adolescents and parents) or different aspects of DDs (e.g., acute episodes versus relapse after successful treatment) are reported separately as well. We present end-of-treatment data for all studies; these vary widely from weeks to months. We also present longer-term outcomes when available. We synthesized the data qualitatively when quantitative analyses were not appropriate (e.g., due to heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting).

Harms reported in text included mortality, suicidal ideation or behaviors, suicide attempts, serious adverse events, and withdrawals due to adverse events. Appendix tables list other types of harms (e.g., pooled adverse events not deemed as serious or individual adverse events such as stomach- or headaches, dry mouth, dizziness). For suicidal ideation or behavior, we generally graded studies on the most comprehensive available measure; in some studies, this measure also included suicide attempts. When studies reported suicide attempts separately, we also graded that outcome separately.

## Grading the Strength of Evidence

We graded the SOE based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group guidance<sup>40</sup> and guidance established for the Evidence-

based Practice Center Program.<sup>41</sup> Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: risk of bias (includes study design and aggregate quality), consistency, directness, precision of the evidence, and reporting bias. This approach requires looking beyond statistical significance alone, even when studies are consistent and of high quality and outcomes are direct and clinically relevant. It emphasizes the adequacy of the sample size to rule out spurious associations and results that are not clinically relevant. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect).

Table 5 describes the grades of evidence that could be assigned. Grades reflect the strength of the body of evidence to answer KQs on the comparative effectiveness, efficacy, and harms of the interventions included in this review. Two reviewers assessed each domain for each key outcome with differences resolved by consensus. If the volume of evidence was large, we focused the SOE for the outcomes deemed to be of greatest importance to decision-makers and those most commonly reported in the literature. Based on input thus far from Key Informants, we chose these to include depression symptom reduction, remission, relapse, recovery, functional impairment, suicidality, and serious AEs. Because these are direct outcomes, the evidence was not downgraded for indirectness; the strength of evidence tables do not explicitly grade for directness as a result.

**Table 5. Definitions of the grades of overall SOE<sup>41</sup>**

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

SOE = strength of evidence.

For bodies of evidence for which we could conduct sensitivity analyses, we based the final SOE grade on the evidence base without high risk-of-bias studies for benefits. For harms, if the results continued to be consistent, we retained the overall SOE from the entire evidence base, in order to capture the potential for a signal of harms. We appended a footnote to SOE tables to indicate when sensitivity analyses changed the SOE grade.

The evidence on variations in benefits and harms in subgroups generally came from post-hoc analyses and could potentially be attributed to chance. Outcomes for subgroup analyses were not graded.

## Assessing Applicability

We assessed the applicability of individual studies as well as the applicability of a body of evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>42</sup> For individual studies, we examined conditions that may limit applicability based on the PICOTS (population, interventions, comparators, outcomes, timing, and setting) structure. Some factors identified a priori that may limit the applicability of evidence include the following: age of the sample (adolescent vs. younger children), comorbid conditions, exposure to a traumatic life event, severity or type of DD, history of previous depressive

episodes or depression treatment, or setting (primary care vs. specialty care). We analyzed populations separately that were characterized by having a comorbid condition or exposure to traumatic life events. We indicated age and type of DD in the analysis and otherwise call out characteristics of the study populations that might limit applicability.

## Chapter 3. Results

In this chapter, we present the yield from literature searches first, followed by a brief description of the characteristics of included studies. The remainder of the chapter presents results organized by Key Question (KQ) and then by intervention and comparator for benefits and harms. Within each intervention and comparator cluster, we first present key points followed by detailed results. The detailed results present evidence separately for subpopulations of interest (children, adolescents, major depressive disorder [MDD] only, or a wider spectrum of depression diagnoses [MDD, persistent depressive disorder (PDD), depressive disorders not otherwise specified (DD NOS)]). Appendixes D, E, F, G, H, and I are organized by the intervention comparison groups for each of the KQs. Appendix D presents individual study characteristics. Appendixes E, F, and G provide the outcome data on benefits (E), harms (F), and subpopulations (G). Appendix H details our risk-of-bias assessments for the randomized controlled trials, and Appendix I provides the risk-of-bias details for the single nonrandomized study. Appendix J contains our meta-analyses results. Appendix K lists references.

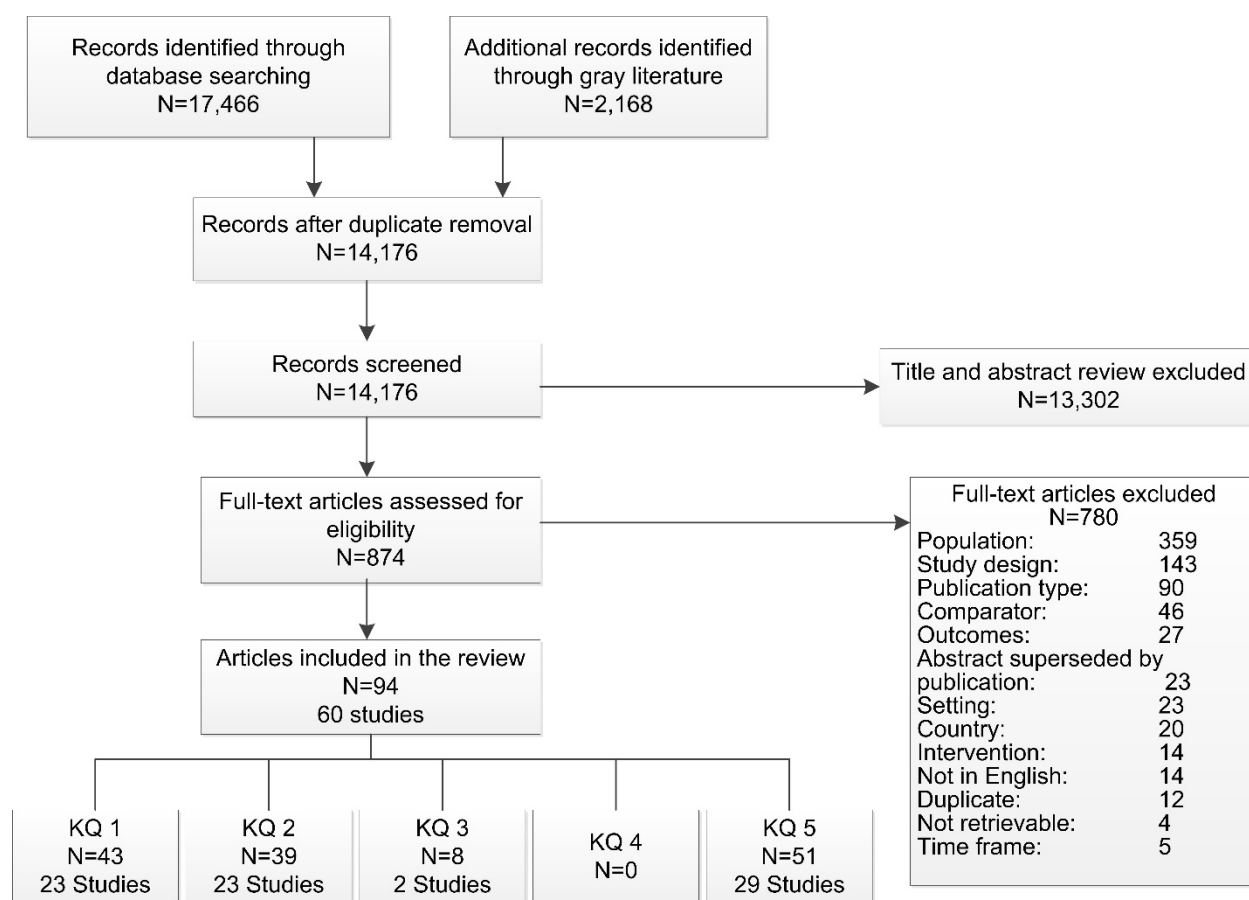
### Literature Searches and Study Characteristics

The electronic search, gray literature, and reference mining identified 14,176 citations. After title and abstract screening, we retrieved 874 studies for full-text review. A total of 60 studies (94 articles) met eligibility criteria and were included in the analyses (Figure 2). For KQ 1, we identified 23 randomized controlled trials (RCTs) of nonpharmacological treatments.<sup>43-65</sup>

Five RCTs compared cognitive behavioral therapy (CBT) with pill placebo,<sup>53</sup> wait-list,<sup>59</sup> usual care, or treatment as usual (TAU).<sup>45, 49, 56</sup> Three RCTs compared CBT with an active control.<sup>44, 54, 60</sup> Two RCTs compared relapse prevention CBT plus continued antidepressant medication with continued medication management alone.<sup>48, 51</sup> Eleven trials addressed other psychotherapy approaches (i.e., interpersonal therapy [IPT],<sup>57, 58</sup> family-based IPT,<sup>47</sup> attachment-based family therapy,<sup>55, 63</sup> family therapy,<sup>43, 60, 64, 65</sup> Parent-Child Interaction Therapy [PCIT],<sup>50</sup> and psychoanalytic therapy<sup>44</sup>) compared with wait-list, TAU, or active controls. Two trials address omega-3 versus pill placebo.<sup>52, 65</sup> Single RCTs compared exercise with an active control<sup>62</sup> and spirituality with wait-list.<sup>46</sup> One omega-3 fatty acid and family therapy RCT,<sup>65</sup> one family therapy RCT,<sup>43</sup> and three CBT RCTs provided subpopulation evidence.<sup>53, 54, 60</sup>

For KQ 2, we identified 23 RCTs comparing pharmacological approaches.<sup>34, 53, 66-84</sup> Fourteen RCTs examined selective serotonin reuptake inhibitors (SSRIs) compared with placebo.<sup>34, 53, 67-70, 72, 75, 76, 79, 81, 82, 84-92</sup> Two RCTs compared relapse prevention with fluoxetine compared with placebo.<sup>80, 93</sup> Five RCTs (one publication reported on two studies<sup>94</sup>) compared serotonin and norepinephrine reuptake inhibitors (SNRIs) with placebo.<sup>67, 76, 77, 94</sup> Four RCTs compared tricyclic antidepressants (TCAs) with placebo,<sup>71, 74, 78</sup> One RCT examined monoamine oxidase inhibitors (MAOIs) with placebo<sup>66</sup> and one RCT of venlafaxine plus active control versus placebo plus active control.<sup>73</sup> Seven RCTs of SSRIs and TCAs compared with placebo provided evidence on subpopulations.<sup>53, 69, 72, 80, 82, 91, 95-98</sup> For KQ 3, we identified one RCT comparing fluoxetine plus CBT with placebo<sup>53</sup> and one RCT comparing omega-3 plus family therapy with placebo.<sup>65</sup> Both provided evidence on subpopulations. We found no studies for KQ 4. For KQ 5, we found 29 studies including 28 RCTs<sup>44, 53, 57, 59-61, 65, 67, 68, 75-77, 91, 99-113</sup> and one nonrandomized trial<sup>114</sup> addressing comparative effectiveness. Three RCTs compared CBT with other psychotherapy.<sup>44, 57, 60</sup> Seven RCTs compared the delivery methods of psychotherapy.<sup>59, 61, 100, 106-108, 110</sup> Three RCTs compared psychotherapy and pharmacotherapy<sup>53, 99, 101</sup>; six compared

**Figure 2. Article flow diagram**



KQ = Key Question; N = number.

psychotherapy plus pharmacotherapy and psychotherapy<sup>53, 99, 101, 111, 113, 114</sup>; seven compared psychotherapy plus pharmacotherapy and pharmacotherapy.<sup>53, 99, 101, 103-105, 112</sup> One RCT compared omega-3 with other therapies.<sup>65</sup> Two RCTs each compared SSRIs with SNRIs,<sup>67, 68</sup> SSRIs with TCAs,<sup>76, 83</sup> and interventions for treatment resistant depression.<sup>109</sup> Three RCTs were dose comparison studies.<sup>67, 75, 77</sup> Seven studies addressed subpopulations for comparative effectiveness.<sup>33, 53, 61, 76, 77, 83, 86, 90, 91, 97, 98, 109, 115, 116</sup>

Table 6 below presents key characteristics of our included studies. A majority of the studies (56.7%) had some concerns for risk of bias for benefits, and 41.7 percent had high risk of bias. We rated one RCT as low. For those studies reporting on harms, 23 of 39 studies were assessed as some concern for risk of bias, 14 of 39 studies as high risk of bias, one study as low risk of bias, and one as uncertain. The tables in Appendix H include additional details of the risk-of-bias assessments for these trials.

A minority (33.3%) of studies offered an active comparator: most compared treatments with placebo, usual care, or wait-list controls. Usual care participants were free to initiate or continue nonstudy mental health or other healthcare services.<sup>56, 103, 117</sup> For pharmacotherapy studies, usual care participants may have received the index medication.<sup>103</sup> For psychotherapy studies, therapists offered treatment that they believed to be effective.<sup>49</sup> Usual care could include therapy, medications, or combined therapy and medications.<sup>63</sup>

**Table 6. Key characteristics of included studies**

Study Characteristics	Subcharacteristics	Number of Studies	Percent
Study quality for benefits	Low risk-of-bias studies	1	1.7
	Some concerns for risk-of-bias studies	34	56.7
	High risk-of-bias studies	25	41.7
Study quality for harms	Low risk-of-bias studies	1	1.7
	Some concerns for risk-of-bias studies	23	38.3
	High risk-of-bias studies	14	23.3
	Unclear risk of bias	1	1.7
	Not applicable (did not report on harms)	21	35.0
Population characteristics: Child or adolescent	Child (mean age <13, ages range from 5 to 12)	5	8.3
	Adolescent (mean age ≥13, ages range from 11 to 18)	30	50.0
	Both (mean age varies, age ranges from 7 to 18)	25	41.7
Population characteristics: Gender	Mostly female	40	66.7
	Mostly male	20	33.3
Population characteristics: Race	Mostly white	40	66.7
	Mostly nonwhite	4	6.7
	Not reported	16	26.7
Population characteristics: Diagnosis	MDD	46	76.7
	MDD, PDD, DD NOS, combinations	14	23.3
Intervention characteristics: Types of interventions	Nonpharmacological	27	45.0
	Pharmacological	24	40.0
	Both	9	15.0
Comparator	Active comparator	20	33.3
	Placebo comparator	27	45.0
	Usual care comparator	13	21.7
Geographic setting	United States of America	43	71.7
	United Kingdom	3	5.0
	Canada	1	1.7
	Australia	2	3.3
	Multiple countries	7	11.7
	Israel	1	1.7
	Norway	1	1.7
	Romania	1	1.7
	South Korea	1	1.7
KQ 1: Benefits and harms of nonpharmacological interventions	Cognitive behavioral therapy	10	NA <sup>a</sup>
	Other therapies (IPT, family-based IPT, attachment-based family therapy, family therapy, parent-child interaction therapy)	11	NA <sup>a</sup>
	Omega-3	2	NA <sup>a</sup>
	Exercise	1	NA <sup>a</sup>
	Spirituality	1	NA <sup>a</sup>
KQ 2: Benefits and harms of pharmacological interventions	SSRIs	14	NA <sup>a</sup>
	SNRIs	5	NA <sup>a</sup>
	TCAs	4	NA <sup>a</sup>
	Relapse prevention with fluoxetine versus placebo	2	NA <sup>a</sup>
	MAOIs	1	NA <sup>a</sup>
	Venlafaxine plus active control versus placebo plus active control	1	NA <sup>a</sup>
KQ 3: Benefits and harms of combined interventions	Cognitive behavioral therapy + fluoxetine	1	NA <sup>a</sup>
	Omega-3 + family therapy	1	NA <sup>a</sup>



Study Characteristics	Subcharacteristics	Number of Studies	Percent
KQ 4: Benefits and harms of collaborative care interventions	Collaborative care interventions	0	NA <sup>a</sup>
KQ 5: Benefits and harms from head-to-head comparisons of interventions	CBT versus other psychotherapy	3	NA <sup>a</sup>
	Comparison of psychotherapy delivery methods	7	NA <sup>a</sup>
	Psychotherapy versus pharmacotherapy	3	NA <sup>a</sup>
	Psychotherapy plus pharmacotherapy versus psychotherapy	6	NA <sup>a</sup>
	Psychotherapy plus pharmacotherapy versus pharmacotherapy	7	NA <sup>a</sup>
	Omega-3 versus other therapies	1	NA <sup>a</sup>
	SSRIs vs SNRIs	2	NA <sup>a</sup>
	SSRIs vs TCAs	2	NA <sup>a</sup>
	Dose comparison	3	NA <sup>a</sup>
	Interventions for treatment-resistant depression	2	NA <sup>a</sup>

<sup>a</sup> The number of studies sum to more than 100% because studies may address multiple Key Questions.

CBT = cognitive behavioral therapy; DD = depressive disorder; DD NOS = depressive disorder not otherwise classified; IPT = interpersonal therapy; KQ = Key Question; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; NA = not applicable; PCIT = parent child interaction therapy; PDD = persistent depressive disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; vs = versus.

We generally used study-defined categorizations of outcomes and footnoted exceptions (e.g., one study reported a common measure of remission (a score of 28 or more on the Children's Depression Rating Scale—Revised, or CDRS<sub>≤</sub>28) as response;<sup>118</sup> we reclassified this outcome as remission but footnoted the decision. Studies did not report suicidal ideation or behavior consistently. We generally relied on the most comprehensive available measure; in some studies, this measure also included suicide attempts. Studies that defined serious adverse events generally used the Food and Drug Administration's (FDA's) definition, that is, events resulting in death, life-threatening events, new or prolonged hospitalization, disability or permanent damage, congenital anomalies, or other serious events.<sup>48, 53, 76</sup> In some instances, authors did not specify serious adverse events (SAEs).

## KQ 1a: Benefits and Harms of Nonpharmacological Interventions

### CBT Versus Pill Placebo: Benefits

#### Key Points

- The evidence was insufficient to judge the benefits (depressive symptoms, response, remission, loss of diagnosis, or functional impairment) of CBT when compared with pill placebo.

#### Detailed Results

One RCT with medium risk of bias with three companion publications compared benefits between CBT (n=111) and pill placebo (n=112)<sup>53, 85-87</sup> among adolescents with MDD in a 12-week study (Table 7). Additional details about the Treatment among Adolescents with Depression (TADS) trial can be found in Appendix Tables D-1 and E-1.

The evidence from a single study was insufficient to judge the effectiveness of CBT versus placebo for depressive symptoms, response, remission, or functional impairment.

**Table 7. Strength of evidence for benefits of CBT versus pill placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. pill placebo	Depressive symptoms, clinician report	SMD (CDRS-R), 0.03; 95% CI, -0.23 to 0.30	1 RCT (n=223) <sup>53</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (CGI-I of 1 or 2, very much improved or much improved): 0.88; 95% CI, 0.72 to 1.09	1 RCT (n=223) <sup>53</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Remission (loss of diagnosis)	RR (loss of K-SAD P/L MDD diagnosis): 0.99; 95% CI, 0.69 to 1.44	1 RCT (n=176) <sup>85</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Remission	RR (CDRS-R of 28 or less): 1.01; 95% CI, 0.90 to 1.13	1 RCT (n=223) <sup>85</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional impairment, clinician report	SMD (CGAS): 0.06; 95% CI, -0.20 to 0.32	1 RCT (n=223) <sup>87</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions Scale; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SAD P/L MDD = schedule for affective disorders present/lifetime major depressive disorder; SMD = standardized mean difference; vs. = versus.

## CBT Versus Pill Placebo: Harms

### Key Points

- The evidence was insufficient to judge the harms of CBT when compared with pill placebo for any examined harms (mortality from suicide, suicide-related or harms-related adverse events (AEs), suicide attempts, or worsening suicidal ideation).

### Detailed Results

One RCT with one companion publication that had medium risk of bias compared harms between CBT (n=111) and pill placebo (n=112)<sup>53, 119</sup> among adolescents with MDD in a 12-week study (Table 8). Additional details about the TADS trial can be found in Appendix Tables D-1 and F-1.

**Table 8. Strength of evidence for harms of CBT versus pill placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. pill placebo	Mortality from suicide	No suicides in either group	1 RCT (n=223) <sup>53</sup>	Serious imprecision (few events, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicide-related AEs	RR, 1.65; 95% CI, 0.41 to 6.70	1 RCT (n=185) <sup>119</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Harms-related AEs	RR, 0.83; 95% CI, 0.26 to 2.65	1 RCT (n=223) <sup>53</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicide attempts	RR, 2.97; 95% CI, 0.12 to 71.93	1 RCT (n=185) <sup>119</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Worsening suicidal ideation	RR (SIQ-Jr of 31 or greater): 0.28; 95% CI, 0.06 to 1.32	1 RCT (n=185) <sup>119</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

AE = adverse event; CBT = cognitive behavioral therapy; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SIQ-Jr = Suicide Ideation Questionnaire-Junior High School; vs. = versus.

The evidence was insufficient to evaluate the harms of CBT when compared with pill placebo for any examined harms (mortality from suicide, suicide-related or harms-related AEs, suicide attempts, or worsening suicidal ideation). The study reported the total number of SAEs that met the FDA's definition of an adverse event (N=23) but did not report results by study arm; separately it reported suicide-related AEs. Not all these adverse events are SAEs.

## CBT Versus Wait-List Control: Benefits

### Key Points

- When compared with wait-list control, CBT had greater improvements in self-reported depressive symptoms and clinician-reported functional impairment at 8 weeks of treatment among adolescents with MDD or dysthymia (strength of evidence [SOE] low for benefit).
- The evidence was insufficient to judge improvements in clinician- or parent-reported depressive symptoms, response, or recovery.

## Detailed Results

Table 9 presents two RCTs,<sup>57, 59</sup> one with high risk of bias<sup>57</sup> and one with medium risk of bias,<sup>59</sup> compared CBT with wait-list control among adolescents with dysthymia or MDD or both. The duration of the intervention spanned 8<sup>59</sup> to 12 weeks.<sup>57</sup> Compared with wait-list control, CBT improved self-reported depressive symptoms (mean difference [Beck Depression Inventory (BDI)], -5.90; 95% confidence interval (CI), -10.89 to -0.92) and improved clinician-reported functional impairment (mean difference [Global Assessment of Functioning (GAF)], 6.5; 95% CI, 0.68 to 12.32) (SOE low for benefit). The evidence was insufficient to judge whether there were improvements noted in clinician- or parent-reported depressive symptoms, recovery, or response. Additional details can be found in Appendix Tables D-2 and E-2.

**Table 9. Strength of evidence for benefits of CBT versus wait-list control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. wait-list control	Depressive symptoms, clinician reported	SMD (HAM-D and CDI): -0.53 and -0.35 across two studies  CI crosses the null in one study	2 RCTs (n=103) <sup>57, 59</sup>	Imprecision (wide CIs, small sample size), inconsistency of overlap in CIs, 1 with high risk of bias <sup>57</sup>	Insufficient	Adolescents with MDD or dysthymia
	Depressive symptoms, self-reported	SMD (BDI): -0.59, 95% CI, -1.09 to -0.08 <sup>a</sup>	1 RCT (n=64) <sup>59</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit	Adolescents with MDD or dysthymia
	Depressive symptoms, parent reported	SMD (CBCL-Depression): 0.48, 95% CI, -0.03 to 0.98	1 RCT (n=64) <sup>59</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Response	RR (CDI<17): 0.58, 95% CI, 0.22 to 1.51	1 RCT (n=48) <sup>57</sup>	Imprecision (wide CIs, small sample size), high risk of bias, <sup>57</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or both
	Recovery	RR (no longer meeting criteria for depression diagnosis): 1.35; 95% CI, 0.85 to 2.13	1 RCT (n=64) <sup>59</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Functional impairment, clinician reported	SMD (GAF): 0.55; 95% CI, 0.05 to 1.05	1 RCT (n=64) <sup>59</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD or dysthymia

BDI = Beck Depression Inventory; CBCL-Depression = Child Behavior Checklist- depression; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CI = confidence interval; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## CBT Versus Wait-List Control: Harms

### Key Points

- No studies reported on harms.

### Detailed Results

Two RCTs,<sup>57, 59</sup> one with high risk of bias<sup>57</sup> and one with medium risk of bias,<sup>59</sup> compared CBT to wait-list control and did not report harms.

## CBT (Delivered to Adolescent and Parent) Versus Wait-List Control: Benefits

### Key Points

- The evidence was insufficient to evaluate the effect of CBT delivered to the adolescent and parent on depressive symptoms as reported by the clinician, self-reported, or by parent, recovery or functional impairment as reported by clinician, when compared with wait-list control.

### Detailed Results

One RCT,<sup>59</sup> with medium risk of bias, compared CBT delivered to both adolescent and parents with wait-list control in an 8-week study of adolescents with MDD or dysthymia (Table 10). The evidence was insufficient to determine whether CBT, when delivered to adolescents and parents, improved clinician-, self-reported, or parent-reported depressive symptoms, recovery, or clinician-reported functional impairments when compared with wait-list control. Additional details can be found in Appendix Tables D-3 and E-3.

## CBT (Delivered to Adolescent and Parent) Versus Wait-List Control: Harms

### Key Points

- No studies reported harms.

**Table 10. Strength of evidence for benefits of CBT (delivered to adolescents and parents) versus wait-list control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT (delivered to adolescent and parent) vs. wait-list control	Depressive symptoms, clinician-reported	SMD (HAM-D), 0.14; 95% CI, -0.66 to 0.37	1 RCT (n=69) <sup>59</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT (delivered to adolescent and parent) vs. wait-list control (continued)	Depressive symptoms, self-reported	SMD (BDI), -0.24; 95% CI, -0.76 to 0.27	1 RCT (n=69) <sup>59</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with dysthymia
	Depressive symptoms, parent-reported	SMD (CBCL-Depression), 0.43; 95% CI, -0.02 to 0.88	1 RCT (n=79) <sup>59</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Recovery	RR (no longer meeting depression diagnosis criteria), 1.43; 95% CI, 0.91 to 2.25	1 RCT (n=79) <sup>59</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Functional impairment, clinician-reported	SMD (GAF), 0.40; 95% CI, -0.12 to 0.92	1 RCT (n=69) <sup>59</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia

BDI = Beck Depression Inventory; CBCL-Depression = child behavior checklist- depression; CBT = cognitive behavioral therapy; CI = confidence interval; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; n = number; MDD = major depressive disorder; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## Detailed Results

One RCT<sup>59</sup> with medium risk of bias compared CBT delivered to adolescents and parents with wait-list control. No harms were reported.

## CBT + TAU Versus TAU/UC: Benefits

### Key Points

- For adolescents with MDD, CBT plus TAU improved end-of-treatment clinician-reported depressive symptoms; time to recovery; and short- -term recovery, response, and clinician-reported functional status (low for benefit for all outcomes).
- For adolescents with MDD, the evidence was insufficient to determine if CBT plus TAU improved long-term recovery, response, or functional impairment.
- For adolescents with MDD or dysthymia, the evidence was insufficient to determine whether CBT plus TAU improved clinician, self- or parent-reported depressive symptoms, time to recovery response, or clinician-reported functional impairment.

## Detailed Results

Two RCTs<sup>45, 56</sup> with medium risk of bias compared CBT plus TAU to TAU/usual care (UC) in adolescents with MDD<sup>45</sup> and adolescents with mixed depression diagnoses (MDD and dysthymia)<sup>56</sup> offered in a primary care or a health maintenance organization setting (Table 11).

In the MDD trial, participants self-selected TAU and were randomly assigned to CBT, for two four-session modules (participants received seven sessions on average). The adolescents in the RCT with MDD or dysthymia<sup>56</sup> were depressed adolescent offspring of depressed parents. The intervention lasted for 8 weeks.<sup>56</sup> Among adolescents with MDD, CBT<sup>45</sup> improved clinician-reported depressive symptoms when compared with TAU/UC (mean difference [Children's Depression Rating Scale (CDRS)], -7.11; 95% CI, -10.3 to -3.90) (SOE low for benefit). Adolescents receiving CBT also showed improved short-term recovery (risk difference [RD], 192/1,000; 95% CI, 80 more to 3043 more cases), improved time to recovery (mean difference [weeks], -7.40; 95% CI, -13.4 to -1.42), improved short-term response (risk difference, 212/1,000; 95% CI, 78 more to 346 more cases) and improved clinician-reported functional status (mean difference [Children's Global Assessment Scale (CGAS)], 5.32; 95% CI, 2.73 to 7.91) (SOE low for benefit).

**Table 11. Strength of evidence for benefits of CBT + TAU versus TAU/UC**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT + TAU vs. TAU/UC	Depressive symptoms, clinician-reported	SMD (HAM-D), -0.10; 95% CI, -0.52 to 0.32	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Depressive symptoms, clinician-reported	SMD (CDRS), -0.60; 95% CI, -0.87 to -0.32	1 RCT (n=212) <sup>45</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Depressive symptoms, clinician-reported (96 weeks)	SMD (HAM-D), -0.06; 95% CI, -0.48 to 0.35	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Depressive symptoms, clinician-reported (104 weeks)	SMD (CDRS), -0.10; 95% CI, -0.37 to 0.17	1 RCT (n=212) <sup>45</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, self-reported	SMD (CES-D), -0.20; 95% CI, -0.62 to 0.22	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT + TAU vs. TAU/UC (continued)	Depressive symptoms, self-reported (96 weeks)	SMD (CES-D), -0.16; 95% CI, -0.58 to 0.26	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Depressive symptoms, parent-reported	SMD (CBCL-Depression), 0.24; 95% CI, -0.18 to 0.66	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Depressive symptoms, parent-reported (96 weeks)	SMD (CBCL-Depression), 0.06; 95% CI, -0.36 to 0.48	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Weeks to recovery	SMD (time in weeks to at least 8 weeks of no or minimal depressive symptoms), -0.349, 5% CI, -0.60 to -0.06	1 RCT (n=212) <sup>45</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Recovery	RR (no longer having a depression diagnosis), 1.10; 95% CI, 0.76 to 1.60	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Recovery	RR (at least 8 weeks of no or minimal depressive symptoms), 2.59; 95% CI, 1.41 to 4.74	1 RCT (n=212) <sup>45</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Recovery (96 weeks)	RR (no longer having a depression diagnosis), 0.97; 95% CI, 0.85 to 1.10	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Recovery (104 weeks)	RR (at least 8 weeks of <5 depressive symptoms), 1.13; 95% CI, 1.00 to 1.28	1 RCT (n=212) <sup>45</sup>	Imprecision (small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (at least 8 weeks of <5 depressive symptoms), 1.45; 95% CI, 1.13 to 1.85	1 RCT (n=212) <sup>45</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD



Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT + TAU vs. TAU/UC (continued)	Response (104 weeks)	RR (at least 8 weeks of no or minimal depressive symptoms), 1.02; 95% CI, 0.95 to 1.10	1 RCT (n=212) <sup>45</sup>	Serious imprecision (small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional impairment, clinician reported	SMD (GAF), 0; 95% CI, -0.42 to 0.42	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Functional status, clinician reported	SMD (CGAS), 0.56; 95% CI, 0.28 to 0.83	1 RCT (n=212) <sup>45</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Functional impairment, clinician reported (96 weeks)	SMD (GAF), -0.21; 95% CI, -0.63 to 0.21	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Functional impairment, clinician reported (104 weeks)	SMD (CGAS), 0.04; 95% CI, -0.23 to 0.31	1 RCT (n=212) <sup>45</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

CBCL-Depression = child behavior checklist - depression; CBT = cognitive behavioral therapy; CDRS = Children's Depression Rating Scale; CES-D = Center for Epidemiologic Studies Depression Scale; CGAS = Children's Global Assessment Scale; CI = confidence interval; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; RCT = randomized controlled trial; n = number; RR = relative risk; SMD = standardized mean difference; TAU = treatment as usual; UC = usual care; vs. = versus.

Among adolescents with MDD or dysthymia,<sup>56</sup> no improvements were noted for CBT plus TAU when compared with TAU/UC in a 16-week intervention (insufficient SOE). No improvements were noted in either population for rates of adequate clinical depression response for CBT plus TAU when compared with TAU/UC. Additional details can be found in Appendix Tables D-4 and E-4.

## CBT + TAU Versus TAU/UC: Harms

### Key Points

- Among adolescents with MDD only or with MDD or dysthymia, the evidence was insufficient to judge the effect of CBT plus TAU on suicidality, when compared with TAU or UC, across a range of followup periods.

### Detailed Results

Two RCTs<sup>45, 56</sup> with medium risk of bias examined harms of CBT plus TAU when compared with TAU/UC in adolescents with MDD<sup>45</sup> and adolescents with MDD or dysthymia<sup>56</sup> offered in a primary care or a health maintenance organization setting (Table 12). Among adolescents with

MDD or dysthymia, the evidence was insufficient to judge differences in suicidality.<sup>56</sup> Among adolescents with MDD, the evidence, comprising one study,<sup>45</sup> the evidence was insufficient to judge differences in suicidality at 12 or 104 weeks. Additional details can be found in Appendix Tables D-4 and F-2.

**Table 12. Strength of evidence for harms of CBT + TAU versus TAU/UC**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT + TAU vs. TAU/UC	Suicidality	SMD (K-SADS suicide items total score), 0.17; 95% CI, -0.25 to 0.52	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Suicidality (12 weeks)	Reported OR (K-SADS), 1.21; 95% CI, 0.32 to 3.78 <sup>a</sup>	1 RCT (n=212) <sup>45</sup>	Serious imprecision (small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicidality (96 weeks)	SMD (K-SADS suicide items total score), 0; 95% CI, -0.41 to 0.41	1 RCT (n=88) <sup>56</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Suicidality (104 weeks)	RR (K-SADS), 1.00; 95% CI, 0.06 to 15.8	1 RCT (n=212) <sup>45</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

<sup>a</sup> The RR cannot be calculated independently because of an error in the reported results

CBT = cognitive behavioral therapy; CI = confidence interval; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; MDD = major depressive disorder; n = number; R = odds ratio; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; TAU = treatment as usual; UC = usual care; vs. = versus.

## CBT (Modified) Versus UC: Benefits

### Key Points

- The evidence comparing modified CBT with UC was insufficient to evaluate improvements in self-reported depressive symptoms or remission of depression diagnosis.

### Detailed Results

One RCT<sup>49</sup> with medium risk of bias compared modified CBT with UC in a 12-week study in adolescents (Table 13), diagnosed with MDD, dysthymic disorder, or unspecified DD, and all had experienced interpersonal trauma. CBT was modified to address cognitions related to the experience of interpersonal trauma. The evidence comparing modified CBT with UC was insufficient to compare CBT with UC for self-reported depressive symptoms or remission of depression. Additional details can be found in Appendix Tables D-5 and E-5.

**Table 13. Strength of evidence for benefits of CBT (modified) versus UC**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT (modified) vs. UC: benefits	Depressive symptoms, self-reported	SMD (BDI-II), 0.16; 95% CI, -0.44 to 0.76	1 RCT (n=43) <sup>49</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD, dysthymic disorder, or unspecified DD
	Remission	RR (No longer meeting depression diagnosis), 1.05; 95% CI, 0.57 to 1.93	1 RCT (n=43) <sup>49</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD, dysthymic disorder, or unspecified DD

BDI-II = Beck Depression Inventory-II; CBT = cognitive behavioral therapy; CI = confidence interval; DD = depressive disorder; n = number; RR = relative risk; SMD = standardized mean difference; UC = usual care; vs. = versus.

## CBT (Modified) Versus UC: Harms

### Key Points

- No harms reported harms.

### Detailed Results

One RCT<sup>49</sup> with medium risk of bias compared modified CBT to UC in a 12-week study in adolescents with MDD, dysthymia, or DD NOS but did not report harms.

## CBT Versus Active Control: Benefits

### Key Points

- The evidence was insufficient to judge the effectiveness of CBT when compared with active control.

### Detailed Results

Three RCTs,<sup>44, 54, 60, 120</sup> one with high risk of bias<sup>60</sup> and two studies<sup>44, 54</sup> with medium risk of bias, compared CBT delivered to adolescents with MDD with active control (Table 14). Study length varied between 8 weeks,<sup>54</sup> 12-16 weeks,<sup>60</sup> and 36 weeks.<sup>44</sup> The evidence was insufficient to judge the effectiveness of CBT when compared with active control. Additional details can be found in Appendix Tables D-6 and E-6.

**Table 14. Strength of evidence for benefits of CBT versus active control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. active control	Depressive symptoms, clinician reported	SMD (HDRS), -0.39; 95% CI, -0.81 to 0.02	1 RCT (n=91) <sup>54</sup> 8 weeks	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, clinician reported (48 weeks)	SMD (HDRS), 0.26; 95% CI, -0.16 to 0.68	1 RCT (n=87) <sup>54</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, self-reported	SMD (BDI-II and MFQ), -0.41, -0.40, -0.17 across 3 studies  2 CIs cross the null	3 RCTs (n=402) <sup>44, 54, 60</sup>	Serious imprecision (wide CIs, small sample size), inconsistency of overlap in CIs, high risk of bias <sup>60</sup>	Insufficient	Adolescents with MDD
	Depressive symptoms, self-reported (48 weeks)	SMD (BDI-II), 0.26; 95% CI, -0.16 to 0.68	1 RCT (n=87) <sup>54</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, self-reported (86 weeks)	SMD, -1.30; 95% CI, -5.37 to 2.77	1 RCT (n=239) <sup>44</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response	RR, 1.58; 95% CI, 1.01 to 2.46	1 RCT (n=72) <sup>60</sup>	Imprecision (small sample size), high risk of bias <sup>60</sup> , unknown consistency	Insufficient	Adolescents with MDD
	Response	RR, 1.00; 95% CI, 0.81 to 1.23	1 RCT (n=209) <sup>44</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response (86 weeks)	RR, 1.04; 95% CI, 0.86 to 1.26	1 RCT (n=239) <sup>44</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Remission	RR (no longer meeting MDD criteria), 1.47 and 1.92 across 2 studies, CIs span the null, , one study reports no statistically significant differences (details NR)	3 RCTs (n=402) <sup>44, 54, 60</sup>	Serious imprecision (wide CIs, small sample size), inconsistency of overlap in CIs, high risk of bias <sup>60</sup>	Insufficient	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. active control (continued)	Remission, no longer meeting MDD criteria (48 weeks)	RR, 0.94; 95% CI, 0.54 to 1.65	1 RCT (n=87) <sup>54</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Remission, no longer meeting MDD criteria (86 weeks)	RR, 1.03; 95% CI, 0.87 to 1.22	1 RCT (n=239) <sup>44</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Relapse (86 weeks)	RR, 1.40; 95% CI, 0.50 to 3.97	1 RCT (n=92) <sup>120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional impairment, clinician-reported	SMD (CGAS), 0.13; 95% CI, -0.29 to 0.54	1 RCT (n=91) <sup>54</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional impairment, clinician-reported	RR (CGAS<60), 0.79; 95% CI, 0.39 to 1.59	1 RCT (n=72) <sup>60</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>60</sup> , unknown consistency	Insufficient	Adolescents with MDD
	Functional impairment, clinician-reported (48 weeks)	SMD, 0.01; 95% CI, -0.41 to 0.43	1 RCT (n=87) <sup>54</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional impairment, self-reported	SMD, -0.30; 95% CI, -0.72 to 0.11	1 RCT (n=91) <sup>54</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional impairment, self-reported (48 weeks)	SMD, -0.06; 95% CI, -0.48 to 0.36	1 RCT (n=87) <sup>54</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

BDI-II = Beck Depression Inventory-II; CBT = cognitive behavioral therapy; CGAS = Children's Global Assessment Scale; CI = confidence interval; HDRS = Hamilton Depression Rating Scale; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## CBT Versus Active Control: Harms

### Key Points

- The evidence was insufficient to judge the harms of CBT when compared with active control for suicide attempts.

## Detailed Results

Two RCTs that had medium<sup>44, 120-122</sup> and high<sup>60</sup> risk of bias compared harms between CBT and active control among adolescents with MDD at 12-16 weeks and at 86 weeks (Table 15). The evidence was insufficient to judge the harms of CBT when compared with active control. Additional details can be found in Appendix Tables D-6 and F-3.

**Table 15. Strength of evidence for harms of CBT versus active control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. active control	Suicide attempt	1 per arm, denominator not provided	1 RCT (n not reported) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicide attempts (86 weeks)	No recent suicide attempts in either group	1 RCT (n not reported) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Dropout	32% vs, 36%, no evidence of difference in chi-square test, RR not calculable	1 RCT (n by arm not reported) <sup>121, 122</sup>	Unknown imprecision, unknown consistency	Insufficient	Adolescents with MDD

CBT = cognitive behavioral therapy; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; vs. = versus.

## Relapse Prevention CBT + Continued Antidepressant Medication Management Versus Continued Medication Management: Benefits

### Key Points

- When compared with continued medication management alone, relapse prevention CBT plus continued antidepressant medication management showed lower risk of relapse throughout the 78-week followup period.
- The evidence was insufficient to judge the effectiveness of relapse prevention CBT plus continued antidepressant medication management when compared with continued medication management alone on clinician reported depressive symptoms, remission or functional impairment.

## Detailed Results

Two RCTs<sup>48, 51</sup> and a long-term followup<sup>123</sup> compared relapse prevention CBT combined with continued antidepressant medication management to continued medication management alone (Table 16). One RCT with medium risk of bias examined differences in adolescents with MDD in an 8- to 11-week study of continuation phase CBT. A second RCT with medium risk of bias examined differences in adolescents and children with MDD in a 30-week study<sup>48</sup> followed by long-term followup<sup>123</sup> for an additional 6 months. The evidence was insufficient to judge the effectiveness of relapse prevention CBT plus continued antidepressant medication management

when compared with medication management alone for clinician-reported depressive symptoms, remission, or functional impairment. When compared with medication management alone, CBT combined with medication showed lower risk of relapse throughout the 78-week followup period (risk difference, -260/1,000; 95% CI, 433 fewer cases to 87 fewer cases) (SOE low for benefit).<sup>48, 123</sup> Additional details can be found in Appendix Tables D-7 and E-7.

**Table 16. Strength of evidence for benefits of relapse prevention CBT + continued antidepressant medication management versus continued medication management**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Relapse prevention CBT + continued antidepressant medication management vs. continued medication management	Depressive symptoms, clinician-reported	SMD (CDRS-R), -0.52; 95% CI, -1.10 to 0.07	1 RCT (n=46) <sup>51</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Remission	RR (CDRS-R of 28 or less), 1.08; 95% CI, 0.95 to 1.22	1 RCT (n=144) <sup>48, 123</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Remission (78 weeks)	RR (CDRS of 28 or less), 1.05; 95% CI, 0.96 to 1.15	1 RCT (n=144) <sup>48, 123</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Relapse	RR (CDRS of 40 or more), 0.36; 95% CI, 0.16 to 0.80	1 RCT (n=115) <sup>48, 123</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents and children with MDD
	Relapse	RR (CDRS-R of 40 or more), 0.36; 95% CI, 0.11 to 1.17	1 RCT (n=46) <sup>51</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Relapse (78 weeks)	RR (CDRS-R of 40 or more), 0.55; 95% CI, 0.40 to 0.85	1 RCT (n=121) <sup>48, 123</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents and children with MDD
	Functional impairment, clinician-reported	SMD (CGAS), 0.13; 95% CI, -0.45 to 0.71	1 RCT (n=46) <sup>51</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

CBT = cognitive behavioral therapy; CDRS = Children's Depression Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

# Relapse Prevention CBT + Continued Antidepressant Medication Management Versus Continued Medication Management: Harms

## Key Points

- The evidence was insufficient to judge the harms of relapse prevention CBT combined with continued antidepressant medication management when compared with continued medication management alone.

## Detailed Results

Two RCTs<sup>48, 51</sup> and a long-term followup<sup>123</sup> examined harms when comparing relapse prevention CBT combined with medication management to medication management alone (Table 17). The evidence was insufficient to evaluate the examined harms (suicidal ideation, suicide attempts, or withdrawal due to adverse effects or serious adverse effects) of continued medication management alone when compared with CBT combined with medication management. Additional details can be found in Appendix Tables D-7 and F-4.

**Table 17. Strength of evidence for harms of relapse prevention CBT + continued antidepressant medication management versus continued medication management**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Relapse prevention CBT + continued antidepressant medication management vs. continued medication management	Suicidal ideation not leading to hospitalization	RR, 0.13; 95% CI, 0.01 to 2.50	1 RCT (n=144) <sup>48</sup>	Serious imprecision (wide CIs, small, sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Suicidal ideation leading to hospitalization	RR, 0.31; 95% CI, 0.01 to 7.41	1 RCT (n=144) <sup>48</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Suicidal behavior not leading to hospitalization	RR, 2.76; 95% CI, 0.11 to 66.7	1 RCT (n=144) <sup>48</sup>	Serious imprecision (wide CIs, small, sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Suicide attempt	RR, 0.55; 95% CI, 0.05 to 5.60	1 RCT (n=46) <sup>51</sup>	Serious imprecision (wide CIs, small, sample size), unknown consistency	Insufficient	Adolescents with MDD



Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Relapse prevention CBT + continued antidepressant medication management vs. continued medication management (continued)	Suicide attempt leading to hospitalization	RR, 0.31; 95% CI, 0.01 to 7.41	1 RCT (n=144) <sup>48</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs	RR, 0.61; 95% CI, 0.11 to 3.56	1 RCT (n=144) <sup>48</sup>	Serious imprecision (wide CIs, small, sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs	RR, 0.36; 95% CI, 0.02 to 8.46	1 RCT (n=46) <sup>51</sup>	Serious imprecision (wide CIs, small, sample size), unknown consistency	Insufficient	Adolescents with MDD
	SAEs	RR, 1.18; 95% CI, 0.47 to 3.00	1 RCT (n=144) <sup>48</sup>	Serious imprecision (wide CIs, small, sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	SAEs	RR, 1.09; 95% CI, 0.17 to 7.10	1 RCT (n=46) <sup>51</sup>	Serious imprecision (wide CIs, small, sample size), unknown consistency	Insufficient	Adolescents with MDD

AE = adverse event; CBT = cognitive behavioral therapy; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; vs. = versus.

## IPT Versus Wait-List Control: Benefits

### Key Points

- The evidence was insufficient to judge the effectiveness of IPT when compared with wait-list control for improving depressive symptoms or response to treatment.

### Detailed Results

One RCT<sup>57</sup> with high risk of bias compared benefits of IPT with wait-list control in adolescents with MDD, dysthymia, or both in an 8-week intervention (Table 18). Compared with wait-list control, IPT showed improved self-reported depressive symptoms but imprecision and high risk of bias limited the grade to insufficient. The evidence was not sufficient to judge the effectiveness of IPT on depression response when compared with wait-list control. Additional details can be found in Appendix Tables D-8 and E-8.

**Table 18. Strength of evidence for benefits of IPT versus wait-list control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
IPT vs. wait-list control	Depressive symptoms, self-reported	SMD (CDI), -0.76; 95% CI, -1.35 to -0.16	1 RCT (n=46) <sup>57</sup>	Imprecision (small sample size), high risk of bias, <sup>57</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or both
	Response	RR (no longer severely depressed), 1.83; 95% CI, 0.82 to 4.12	1 RCT (n=46) <sup>57</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>57</sup> , unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or both

CDI = Children's Depression Inventory; CI = confidence interval; IPT = interpersonal psychotherapy; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## IPT Versus Wait-List Control: Harms

### Key Points

- No evidence exists on the harms of IPT when compared with wait-list control.

### Detailed Results

One RCT of adolescents with MDD in an 8-week intervention with high risk of bias did not report on harms of IPT when compared with wait-list control.

## IPT Versus Active Control: Benefits

### Key Points

- The evidence was insufficient to judge the effectiveness of IPT when compared with active control for clinician- or self-reported depressive symptoms, depression response, remission, or clinician- or self-reported functional impairment.

### Detailed Results

One RCT<sup>58</sup> with high risk of bias compared IPT with active control in a 12-week trial of interpersonal psychotherapy for adolescents with MDD (Table 19). The evidence was insufficient to judge the benefits of IPT when compared with active control for clinician- and self-reported depressive symptoms, depression response, remission, and clinician- and self-reported functional impairment. Additional details can be found in Appendix Tables D-9 and E-9.

**Table 19. Strength of evidence for benefits of IPT versus active control (clinical monitoring)**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
IPT vs. active control (clinical monitoring)	Depressive symptoms, clinician report	SMD (HDRS), -0.66; 95% CI, -1.24 to -0.08	1 RCT (n=48) <sup>58</sup>	Imprecision (small sample size), high risk of bias, <sup>58</sup> unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, self-report	SMD (BDI), -0.66; 95% CI, -1.24 to -0.08	1 RCT (n=48) <sup>58</sup>	Imprecision (small sample size), high risk of bias, <sup>58</sup> unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (HDRS of 6 or less and BDI of 9 or less, 1.64; 95% CI, 1.00 to 2.68	1 RCT (n=48) <sup>58</sup>	Imprecision (small sample size), high risk of bias, <sup>58</sup> unknown consistency	Insufficient	Adolescents with MDD
	Remission	RR (loss of MDD diagnosis), 1.50; 95% CI, 1.04 to 2.17	1 RCT (n=48) <sup>58</sup>	Imprecision (small sample size), high risk of bias, <sup>58</sup> unknown consistency	Insufficient	Adolescents with MDD
	Functional impairment, clinician report	SMD (CGI), -1.31; 95% CI, -1.93 to -0.69	1 RCT (n=48) <sup>58</sup>	Imprecision (small sample size), high risk of bias, <sup>58</sup> unknown consistency	Insufficient	Adolescents with MDD
	Functional impairment, self-report	SMD (SAS-SR), -0.45; 95% CI, -1.02 to 0.12	1 RCT (n=48) <sup>58</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>58</sup> unknown consistency	Insufficient	Adolescents with MDD

BDI = Beck Depression Inventory; CGI = Clinical Global Impressions Scale; CI = confidence interval; HDRS = Hamilton Depression Rating Scale; IPT = interpersonal psychotherapy; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SAS-SR = Social Adjustment Scale-Self Report; SMD = standardized mean difference; vs. = versus.

## IPT Versus Active Control: Harms

### Key Points

- The evidence was insufficient to judge the risks of suicidality of IPT when compared with active control.

### Detailed Results

One RCT<sup>58</sup> of adolescents with MDD compared IPT with active control. SOE was insufficient to judge the harms of IPT when compared with active control (Table 20). Additional details can be found in Appendix Tables D-9 and F-5.

**Table 20. Strength of evidence for harms of IPT versus active control (clinical monitoring)**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
IPT vs. active control (clinical monitoring)	Suicidality	RR (ideation, plan, or attempt measured by SADS-E), 0.88; 95% CI, 0.72 to 1.09	1 RCT (n=48) <sup>58</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>58</sup> unknown consistency	Insufficient	Adolescents with MDD

CI = confidence interval; IPT = interpersonal psychotherapy; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SADS-E = Schedule for Affective Disorders and Schizophrenia for School-Aged Children; vs. = versus.

## Family-Based IPT Versus Active Control: Benefits

### Key Points

- Family-based IPT improved clinician-, parent-, and self-reported depressive symptoms when compared with active control (SOE low for benefit).
- The evidence was insufficient to judge the effectiveness of family-based IPT on remission when compared with active control.

### Detailed Results

One RCT<sup>47</sup> with medium risk of bias compared family-based IPT for active control in children with MDD, dysthymia, or DD NOS in a 14-week intervention (Table 21). Family-based IPT improved clinician-, self-, and parent-reported depressive symptoms (low SOE for benefit). The mean difference on the clinician-reported scale (CDRS-R) was -0.50; 95% CI, -2.48 to -0.10. The mean difference on the self-reported Mood and Feelings Questionnaire for children (MFQ-C) was -6.50; 95% CI, -7.85 to -5.15. The mean difference on the parent-reported Mood and Feelings Questionnaire (MFQ-P) was -5.60; 95% CI, -6.49 to -4.71. The evidence was insufficient to judge the effectiveness of family-based IPT when compared with active control for remission. Additional details can be found in Appendix Tables D-10 and E-10.

## Family-Based IPT Versus Active Control: Harms

### Key Points

- No evidence exists on the harms of family-based IPT when compared with wait-list control.

### Detailed Results

One RCT<sup>47</sup> with medium risk of bias compared family-based IPT with active control in children with MDD, dysthymia, or DD NOS in a 14-week intervention but did not report harms.

**Table 21. Strength of evidence for benefits of family-based IPT versus active control (child-centered therapy)**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Family-based IPT vs. active control (child-centered therapy)	Depressive symptoms, clinician report	SMD (CDRS-R), -4.22; 95% CI, -5.38 to -3.06	1 RCT (n=38) <sup>47</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Children with MDD, dysthymia, DD NOS
	Depressive symptoms, self-report	SMD (MFQ-C), -3.35; 95% CI, -4.36 to -2.34 <sup>a</sup>	1 RCT (n=38) <sup>47</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Children with MDD, dysthymia, DD NOS
	Depressive symptoms, parent report	SMD (MFQ-P), -4.35; 95% CI, -5.53 to -3.16	1 RCT (n=38) <sup>47</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Children with MDD, dysthymia, DD NOS
	Remission	RR (CDRS-R of 28 or less), 2.08; 95% CI, 0.87 to 4.95	1 RCT (n=38) <sup>47</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Children with MDD, dysthymia, DD NOS

CDRS = Children's Depression Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; CI = confidence interval; DD = depressive disorder; IPT = interpersonal psychotherapy; MDD = major depressive disorder; MFQ-C = Mood and Feelings Questionnaire-Child; MFQ-P = Mood and Feelings Questionnaire-Parent; NOS = not otherwise specified; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## Attachment-Based Family Therapy Versus Wait-List Control: Benefits

### Key Points

- The evidence was insufficient to judge the effectiveness of attachment-based family therapy when compared with wait-list control for clinician-reported depressive symptoms, response, or remission of depression diagnosis.

### Detailed Results

One RCT<sup>55</sup> with high risk of bias compared attachment-based family therapy with wait-list control and found improved depression response in a 12-week intervention with adolescents with MDD (Table 22); imprecision and high risk of bias limited the grade to insufficient. Evidence was insufficient to judge the effectiveness of attachment-based family therapy versus wait-list control for clinician-reported depressive symptoms or for remission of depression diagnosis. Additional details can be found in Appendix Tables D-11 and E-11.

**Table 22. Strength of evidence for benefits of attachment-based family therapy versus wait-list control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Attachment-based family therapy vs. wait-list control	Depressive symptoms, clinician report	SMD (HAM-D), -0.64; 95% CI, -1.35 to 0.07	1 RCT (n=32) <sup>55</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>55</sup> unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (BDI of 9 or less), 3.33; 95% CI, 1.12 to 9.90	1 RCT (n=32) <sup>55</sup>	Imprecision (small sample size), high risk of bias, <sup>55</sup> unknown consistency	Insufficient	Adolescents with MDD
	Remission	RR (no longer meeting MDD criteria), 1.74; 95% CI, 0.97 to 3.14	1 RCT (n=32) <sup>55</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>55</sup> unknown consistency	Insufficient	Adolescents with MDD

BDI = Beck Depression Inventory; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## Attachment-Based Family Therapy Versus Wait-List Control: Harms

### Key Points

- The evidence was insufficient to judge the risks of suicidal ideation of attachment-based family therapy when compared with wait-list control.

### Detailed Results

One RCT<sup>55</sup> with high risk of bias compared suicidal ideation in adolescents with MDD receiving attachment-based family therapy to wait-list control in a 12-week intervention (Table 23). The evidence was insufficient to judge the harms of attachment-based family therapy when compared with wait-list control. Additional details can be found in Appendix Tables D-11 and F-6.

**Table 23. Strength of evidence for harms of attachment-based family therapy versus wait-list control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Attachment-based family therapy vs. wait-list control	Suicidal ideation (SIQ)	SMD (SIQ score), -0.37; 95% CI, -1.07 to 0.32	1 RCT (n=32) <sup>55</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>55</sup> unknown consistency	Insufficient	Adolescents with MDD

CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; SIQ = Suicidal Ideation Questionnaire; SMD = standardized mean difference; vs. = versus.

## Attachment-Based Family Therapy Versus TAU: Benefits

### Key Points

- The evidence was insufficient to judge the effectiveness of attachment-based family therapy when compared with TAU.

### Detailed Results

One RCT<sup>63</sup> with high risk of bias compared benefits of attachment-based family therapy (n=11) with TAU (n=9) among adolescents 13 to 17 years with MDD in a 12-week intervention. Evidence was insufficient to judge the effectiveness of attachment-based therapy when compared with TAU for improved clinician- and self-reported depression symptoms. Evidence was not sufficient to judge the effectiveness of attachment-based family therapy when compared with TAU. Results of attachment-based family therapy are presented in Table 24. Additional details can be found in Appendix Tables D-12 and E-12.

**Table 24. Strength of evidence for benefits of attachment-based family therapy versus TAU**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Attachment-based family therapy vs. TAU	Depressive symptoms, clinician report	SMD (HAM-D), -1.08; 95% CI, -2.02 to -0.14	1 RCT (n=20) <sup>63</sup>	Imprecision, (small sample size), high risk of bias, <sup>63</sup> unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, self-report	SMD (BDI), 1.42; 95% CI, -2.40 to -0.43)	1 RCT (n=20) <sup>63</sup>	Imprecision, (small sample size), high risk of bias, <sup>63</sup> unknown consistency	Insufficient	Adolescents with MDD
	Recovery	RR (HAM-D <9), 2.45 95% CI, 0.31 to 19.7	1 RCT (n=20) <sup>63</sup>	Serious imprecision, (wide CIs, small sample size), high risk of bias, <sup>63</sup> unknown consistency	Insufficient	Adolescents with MDD

BDI = Beck Depression Inventory; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; TAU = treatment as usual; vs. = versus.

## Attachment-Based Family Therapy Versus TAU: Harms

### Key Points

- No evidence exists on the harms of attachment-based family therapy compared with TAU.

### Detailed Results

One RCT<sup>63</sup> with high risk of bias compared benefits of attachment-based family therapy (n=11) with TAU (n=9) among adolescents 13 to 17 years with MDD in a 12-week intervention but did not report harms.

## Family Therapy Versus Pill Placebo: Benefits

### Key Points

- The evidence comparing family therapy with pill placebo was insufficient for depression symptoms and remission for adolescents and children with MDD, dysthymia, or DD NOS.

### Detailed Results

One RCT with some risk-of-bias concerns<sup>65</sup> compared family therapy, specifically psychoeducation plus CBT, (n=18) with pill placebo (n=18) over 12 weeks duration (Table 25). Evidence was insufficient to evaluate the effectiveness of family therapy compared with pill placebo for clinician-reported depressive symptoms and remission. Additional details can be found in Appendix Tables D-13 and E-13.

**Table 25. Strength of evidence for benefits of family therapy versus pill placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Family therapy vs. pill placebo	Depressive symptoms, clinician report	SMD (CDRS-R), -0.10; 95% CI, -0.75 to 0.55	1 RCT (n=36) <sup>65</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS
	Remission	RR (CDRS-R≤28), 1.10; 95% CI, 0.63 to 1.91	1 RCT (n=36) <sup>65</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS

CDRS-R = Children's Depression Rating Scale-Revised; DD = depressive disorders; MDD = major depressive disorder; n = number; NOS = not otherwise specified; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.



## Family Therapy Versus Pill Placebo: Harms

### Key Points

- No study reported on harms.

### Detailed Results

One RCT with some risk-of-bias concerns<sup>65</sup> of adolescents and children ages 7 to 14 years compared family therapy with placebo over 12 weeks duration but did not report on harms.

## Family Therapy Versus Active Control: Benefits

### Key Points

- For adolescents or children with MDD, dysthymia, or DD NOS, family therapy improved depression response when compared with active control (low SOE of benefit).
- The evidence comparing family therapy with active control was insufficient for depression symptoms, response, and remission.

### Detailed Results

Three RCTs,<sup>43, 60, 64, 124, 125</sup> two with some risk-of-bias concerns,<sup>43, 64, 125</sup> and a third with high risk of bias,<sup>60</sup> compared family therapy (n=103) with active control (n=138) in studies that were 8 to 16 weeks long (Table 26). Compared with active control, one study<sup>43</sup> found that family therapy showed higher rates of adequate clinical depression response with a 50 percent reduction in CDRS-R scores from baseline to posttreatment (risk difference, 179/1,000; 95% CI, 25 more cases to 333 more cases). Evidence was insufficient to evaluate the effectiveness of family therapy and active control for clinician- or self-reported depressive symptoms, depression response, remission, recurrence, and clinician- or self-reported functional impairment. Additional details can be found in Appendix Tables D-14 and E-14.

**Table 26. Strength of evidence for benefits of family therapy versus active control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Family therapy vs. active control	Depressive symptoms, clinician report	SMD (CDRS-R), -0.30; 95% CI, -0.67 to 0.07	1 RCT (n=99) <sup>43</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents or children with MDD, dysthymia, or DD NOS
	Depressive symptoms, self-report	SMD (CDI-CR, SMFQ) ranges from -0.28 to -0.01 with both 95% CIs crossing the null	2 RCTs (n=163) <sup>43, 64, 125</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, minor depression, dysthymia, or DD NOS

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Family therapy vs. active control (continued)	Depressive symptoms, self-report (5 months)	SMD (SMFQ), 0.18; 95% CI, -0.31 to 0.67	1 RCT (n=64) <sup>64</sup> <sup>125</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD, minor DD, or dysthymic disorder
	Depressive symptoms, self-report	SMD (BDI), -0.07; 95% CI, -0.54 to 0.40	1 RCT (n=107) <sup>60</sup>	Serious imprecision, (wide CIs, small sample size), high risk of bias, <sup>60</sup> unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, parent report	SMD (CDI-PR), -0.19; 95% CI, -0.56 to 0.17	1 RCT (n=99) <sup>43</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents or children with MDD, dysthymia, or DD NOS
	Response	RR (CDRS-R decrease of 50% or more), 1.30; 95% CI, 1.03 to 1.64	1 RCT (n=99) <sup>43</sup>	Imprecision, (small sample size), unknown consistency	Low for benefit	Adolescents or children with MDD, dysthymia, or DD NOS
	Response	RR (BDI<9), 0.93; 95% CI, 0.53 to 1.63	1 RCT (n=107) <sup>60</sup>	Serious imprecision, (wide CIs, small sample size), inconsistent high risk of bias, <sup>60</sup> unknown consistency	Insufficient	Adolescents with MDD
	Remission	RR (CDRS-R<28), 1.40; 95% CI, 0.95 to 2.06	1 RCT (n=99) <sup>43</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents or children with MDD, dysthymia, or DD NOS
	Remission	RR (no MDD and BDI<9 for at least 3 consecutive sessions), 0.83; 95% CI, 0.42 to 1.67	1 RCT (n=107) <sup>60</sup>	Serious imprecision, (wide CIs, small sample size), high risk of bias, <sup>60</sup> unknown consistency	Insufficient	Adolescents with MDD
	Recurrence	Recurrence was relatively rare but was more common among youths receiving IP (details NR)	1 RCT (n=134) <sup>124</sup>	Unknown imprecision, unknown consistency	Insufficient	Adolescents or children with MDD, minor depression, or dysthymia

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Family therapy vs. active control (continued)	Functional impairment, clinician report	SMD (CGAS), -0.09; 95% CI, -0.46 to 0.27	1 RCT (n=99) <sup>43</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS
	Functional impairment, clinician report	RR (calculated for CGAS<60 yes vs. no), 1.09 95% CI, 0.56 to 2.13	1 RCT (n=107) <sup>60</sup>	Serious imprecision, (wide CIs, small sample size), high risk of bias, <sup>60</sup> unknown consistency	Insufficient	Adolescents with MDD
	Functional impairment, self-report	SMD (SAS-SR), -0.29 95% CI, -0.66 to 0.08	1 RCT (n=99) <sup>43</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or DD NOS

BDI = Beck Depression Inventory; CDI-CR = Children's Depression Inventory-Child Report; CDI-PR = Children's Depression Inventory-Parent Report; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CI = confidence interval; DD = depressive disorders; MDD = major depressive disorder; n = number; NOS = not otherwise specified; NR = not reported; RCT = randomized controlled trial; RR = relative risk; SAS-SR = Social Adjustment Scale for Children-Self-Report; SMD = standardized mean difference; SMFQ = Short Moods and Feelings Questionnaire; vs. = versus.

## Family Therapy Versus Active Control: Harms

### Key Points

- The evidence was insufficient to judge the risks of suicidality of family therapy when compared with active control.

### Detailed Results

One RCT<sup>60</sup> with high risk of bias did not provide sufficient evidence to judge the risks of suicidality of family therapy when compared with active control (Table 27). Additional details can be found in Appendix Tables D-14 and F-7.

**Table 27. Strength of evidence for harms of family therapy versus active control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Family therapy vs. active control	Suicidality	RR (ideation with a plan or attempt as measured by K-SADS-P/E), 0.40; 95% CI, 0.08 to 1.93	1 RCT (n=107) <sup>60</sup>	Serious imprecision (wide CIs, small sample size, high risk of bias, <sup>60</sup> unknown consistency)	Insufficient	Adolescents with MDD

CI = confidence interval; K-SADS-P/E - School Age Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Versions; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; vs. = versus.

## PCIT Versus Active Control: Benefits

### Key Points

- The evidence was insufficient to judge the benefits of PCIT when compared with active control for depressive symptoms or functional impairment.

### Detailed Results

One RCT<sup>50</sup> with high risk of bias compared benefits of PCIT (n=25) with active control (n=18) in preschool children (ages 3 to 7 years) in a 12-week intervention (Table 28). The evidence was insufficient to judge the effectiveness of PCIT when compared with active control on depressive symptoms or parent-reported functional impairment. Additional details can be found in Appendix Tables D-15 and E-15.

**Table 28. Strength of evidence for benefits of PCIT versus active control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
PCIT vs. active control	Depressive symptoms, clinician reported	SMD (PAPA), -0.02; 95% CI, -0.58 to 0.63	1 RCT (n=43) <sup>50</sup>	Serious imprecision (wide CIs, small sample size, high risk of bias, <sup>50</sup> unknown consistency)	Insufficient	Children with MDD
	Depressive symptoms, parent reported	SMD (PFC-S), -0.33; 95% CI, -0.94 to 0.28	1 RCT (n=43) <sup>50</sup>	Serious imprecision (wide CIs, small sample size, high risk of bias, <sup>50</sup> unknown consistency)	Insufficient	Children with MDD
	Functional impairment, parent reported	SMD (HBQ), -0.07; 95% CI, -0.54 to 0.67	1 RCT (n=43) <sup>50</sup>	Serious imprecision (wide CIs, small sample size, high risk of bias, <sup>50</sup> unknown consistency)	Insufficient	Children with MDD

CI = confidence interval; HBQ = Health and Behavior Questionnaire; MDD = major depressive disorder; n = number; PAPA = Preschool Age Psychiatric Assessment; PCIT = Parent-Child Interaction Therapy; PFC-S = Preschool Feelings Checklist-Scale Version; RCT = randomized controlled trial; SMD = standardized mean difference; vs. = versus.

## PCIT Versus Active Control: Harms

### Key Points

- The evidence was insufficient to judge the harms of PCIT when compared with active control on AEs.

### Detailed Results

One RCT<sup>50</sup> with high risk of bias examined PCIT and active control and noted there were no adverse events; however, the study did not mention assessment of adverse effects or data

supporting absence of adverse effects. Evidence was insufficient to judge harms of PCIT when compared with active control. Additional details can be found in Appendix Tables D-15 and F-8.

## Short-Term Psychoanalytic Therapy Versus Active Control: Benefits

### Key Points

- Evidence was insufficient to judge the effectiveness of psychoanalytic therapy when compared with active control for self-reported depressive symptoms, response, remission, or relapse.

### Detailed Results

One RCT<sup>44, 120</sup> with some risk-of-bias concerns compared short-term psychoanalytic therapy (n=157) with active control (n=158) in adolescents ages 11 to 17 years (Table 29). Treatment was delivered in up to 28 sessions with an average of 30 weeks of intervention. The evidence was insufficient to evaluate effectiveness at 36 weeks (end-of-treatment) or 86 weeks. Evidence was also insufficient to evaluate depression response or remission when assessed at 36 weeks and again at 86 weeks. Additional details can be found in Appendix Tables D-16 and E-16.

**Table 29. Strength of evidence for benefits of short-term psychoanalytic therapy versus active control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychoanalytic therapy vs. active control	Depressive symptoms, self-report	SMD (MFQ), -0.25; 95% CI, -0.51 to 0.02	1 RCT (n=214) <sup>44</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, self-report (86 weeks)	SMD (MFQ), -0.11; 95% CI, -0.37 to 0.14	1 RCT (n=237) <sup>44</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (reduction of 5 points of the MFQ), 1.03; 95% CI, 0.89 to 1.20	1 RCT (n=311) <sup>44</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response (86 weeks)	RR (reduction of 5 points of the MFQ), 1.03; 95% CI, 0.86 to 1.11	1 RCT (n=311) <sup>44</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychoanalytic therapy vs. active control (continued)	Presence of MDD	RR (one or more antisocial behavior symptoms (self-reported) and met clinical diagnostic criteria for MDD), 0.81; 95% CI, 0.57 to 1.15	1 RCT (n=193) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Presence of MDD (86 weeks)	RR (one or more antisocial behavior symptoms (self-reported) and met clinical diagnostic criteria for MDD), 0.56; 95% CI, 0.31 to 0.99	1 RCT (n=191) <sup>44, 120</sup>	Imprecision (small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Remission	No significant difference (data not reported)	1 RCT (n=191) <sup>44, 120</sup>	Serious imprecision (small sample size, unknown CIs), unknown consistency	Insufficient	Adolescents with MDD
	Relapse (among those who remitted at the end of treatment at 36 weeks, measured at 86 weeks of followup)	RR (K-SADS), 0.36; 95% CI, 0.07 to 1.75	1 RCT (n=91) <sup>44</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

CI = confidence interval; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## Short-Term Psychoanalytic Therapy Versus Active Control: Harms

### Key Points

- The evidence was insufficient to judge the harms of short-term psychoanalytic therapy when compared with active control for mortality from suicide, suicide-related AEs, suicide attempts, or worsening suicidal ideation.

### Detailed Results

One RCT<sup>44, 120-122</sup> with some risk-of-bias concerns compared short-term psychoanalytic therapy (n=157) with active control (n=158) in adolescents ages 11 to 17 years (Table 30). Evidence was insufficient to judge the harms of short-term psychoanalytic psychotherapy when

compared with active control for recent suicide attempts. Additional details can be found in Appendix Tables D-16 and F-9.

**Table 30. Strength of evidence for harms of short-term psychoanalytic therapy versus active control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychoanalytic therapy vs. active control	Suicide attempt	1 per arm, denominator not provided	1 RCT (n not reported) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicide attempts (86 weeks)	No recent suicide attempts in either group	1 RCT (n not reported) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Dropout	43% vs, 36%, no evidence of difference in chi-square test, RR not calculable	1 RCT (n by arm not reported) <sup>121, 122</sup>	Unknown imprecision, unknown consistency	Insufficient	Adolescents with MDD

CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; vs. = versus.

## Exercise Versus Active Control: Benefits

### Key Points

- When compared with active control (nonstrenuous exercise group), aerobic exercise improved response (low for benefit) for adolescents with MDD.
- The evidence was insufficient to judge the effectiveness of exercise on depression symptoms, response or remission.

### Detailed Results

One RCT<sup>62</sup> with some risk-of-bias concerns compared aerobic exercise (n=16) with active control (n=14) among adolescents ages 12 to 18 years with MDD in a 12-week intervention (Table 31). Compared with active control, aerobic exercise demonstrated improved response rate when compared with active control at 12 weeks but not at 52 weeks (risk difference, 333/1,000; 95% CI, 59 more cases to 607 more cases) (low for benefit SOE). The evidence was not sufficient to judge whether exercise improved clinician-, self-, or parent-reported depressive symptoms or remission of depression. Additional details can be found in Appendix Tables D-17 and E-17.

**Table 31. Strength of evidence for benefits of exercise versus active control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Exercise vs. active control	Depressive symptoms, clinician report	SMD (CDRS-R), -0.66; 95% CI, -1.45 to 0.14	1 RCT (n=26) <sup>62</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, self-report	SMD (CGI), 0.70 95% CI, 0.05 to 1.35	1 RCT (n=26) <sup>62</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, parent report	SMD (QIDS-PR), 1.10 95% CI, -1.54 to 3.74	1 RCT (n=26) <sup>62</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (CGI of 2 or less and at least a 50% reduction in CDRS), 1.48 95% CI, 0.99 to 2.22	1 RCT (n=26) <sup>62</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Response (52 weeks)	RR (CGI of 2 or less and at least a 50% reduction in CDRS), 1.09 95% CI, 0.92 to 1.29	1 RCT (n=26) <sup>62</sup>	Serious imprecision (small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Remission	RR (no residual symptoms, CDRS of 28 or less and CGI of 2 or less), 1.71 95% CI, 0.94 to 3.14 95% CI,	1 RCT (n=26) <sup>62</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Remission (52 weeks)	RR (no residual symptoms, CDRS of 28 or less and CGI of 2 or less), 1.09 95% CI, 0.92 to 1.29	1 RCT (n=26) <sup>62</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

CDRS = Children's Depression Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; CGI = Clinical Global Impressions Scale; CI = confidence interval; MDD = major depressive disorder; n = number; QIDS-PR = Quick Inventory for Depressive Symptomatology-Adolescent Version; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.



## Exercise Versus Active Control: Harms

### Key Points:

- No harms were reported for aerobic exercise when compared with nonstrenuous exercise.

### Detailed Results

One RCT<sup>62</sup> with some risk of bias examined aerobic exercise (n=16) with active control (n=14) among adolescents ages 12 to 18 years in a 12-week intervention but did not report on harms.

## Spirituality-Informed Online Sessions Versus Wait-List: Benefits

### Key Points

- The evidence on online weekly sessions based on spirituality-informed principles showed an improvement in clinician-reported depressive symptoms (low SOE for benefit).

### Detailed Results

One RCT (some risk-of-bias concerns)<sup>46</sup> of adolescents with MDD compared online weekly sessions based on spirituality-informed principles (n=18) with wait-list control (n=13) in an 8-week intervention (Table 32). Spirituality-based intervention demonstrated improvement in clinician-reported depressive symptoms (mean difference [CDRS-R], -13.99; 95% CI, -22.65 to -5.33) (low for benefit). Additional details can be found in Appendix Tables D-18 and E-18.

**Table 32. Strength of evidence for benefits of spirituality versus wait-list control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Spirituality vs. wait-list	Depressive symptoms, clinician report	SMD (CDRS-R), -1.15 95% CI, -1.92 to -3.20	1 RCT (n=25) <sup>46</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD

CDRS-R = Children's Depression Rating Scale-Revised; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; SMD = standardized mean difference; vs. = versus.

## Spirituality-Informed Online Sessions Versus Wait-List: Harms

### Key Points

- No study reported on harms.

### Detailed Results

One RCT<sup>46</sup> of adolescents ages 13 to 24 years with some risk-of-bias concerns compared online weekly sessions based on spirituality-informed principles (n=18) with wait-list control (n=13) in an 8-week intervention but did not report on harms.

## Omega-3 Versus Pill Placebo: Benefits

### Key Points

- The evidence is insufficient to judge the effectiveness of omega-3 when compared with pill placebo for depressive symptoms, response, and remission.

### Detailed Results

Two RCTs (one with some risk of bias concerns<sup>65</sup> and one high risk of bias<sup>52</sup>) of adolescents and children ages 6 to 14 years compared omega-3 with placebo over 12 to 16 weeks duration, but evidence was insufficient for clinician-reported depressive symptoms, response, or remission (Table 33). Additional details can be found in Appendix Tables D-19 and E-19.

**Table 33. Strength of evidence for benefits of omega-3 versus pill placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Omega-3 vs. pill placebo	Depressive symptoms, clinician report	SMD (CDRS) cannot be calculated but authors report that mean difference is -20.72, $p=0.03$ at the end of treatment	1 RCT (n=20) <sup>52</sup>	Imprecision (small sample size), high risk of bias, <sup>52</sup> unknown consistency	Insufficient	Children with MDD
	Depressive symptoms, clinician report	SMD (CDRS): 0, 95% CI, -0.67 to 0.67	1 RCT (n=34) <sup>65</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS
	Response	RR (CDRS score of <29), 15.0 95% CI, 0.97 to 1.85	1 RCT (n=20) <sup>52</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>52</sup> unknown consistency	Insufficient	Children with MDD
	Remission (loss of diagnosis)	RR (more than 50% reduction in CDRS score), 9.00 95% CI, 0.55 to 147.96	1 RCT (n=20) <sup>52</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>52</sup> unknown consistency	Insufficient	Children with MDD
	Remission	RR (CDRS score $\leq$ 28), 0.79, 95% CI, 0.39 to 1.57	1 RCT (n=34) <sup>65</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS

CDRS = Children's Depression Rating Scale; CI = confidence interval; DD = depressive disorders; MDD = major depressive disorder; NOS = not otherwise specified; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## **Omega-3 Versus Pill Placebo: Harms**

### **Key Points**

- No study reported on harms.

### **Detailed Results**

Two RCTs (one with some risk-of-bias concerns<sup>65</sup> and one high risk of bias<sup>52</sup>) of adolescents and children ages 6 to 14 years compared omega-3 with placebo over 12 to 16 weeks duration<sup>52</sup> but did not report on harms.

## **KQ 1b: Benefits and Harms of Nonpharmacological Interventions by Subpopulation**

### **CBT Versus Pill Placebo: Subpopulations**

#### **Key Points**

- The efficacy of CBT versus placebo did not differ by depressive symptom severity.
- When compared with pill placebo, CBT resulted in greater improvements in functional impairment among those with higher family income levels. No differences between CBT and pill placebo were found in functional impairment among those in the low to middle family income levels.
- When compared with pill placebo, CBT resulted in greater improvements in depressive symptoms among those with attention deficit hyperactivity disorder (ADHD). No differences between CBT and pill placebo were found in depressive symptoms among those without ADHD.

#### **Detailed Results**

Two companion publications<sup>97, 98</sup> to one RCT with medium risk of bias<sup>53</sup> examined subgroup differences in benefits between CBT (n=111) and pill placebo (n=112) among adolescents with MDD in a 12-week study. Additional details about the TADS trial can be found in Appendix Tables D-20 and G-1.

No significant differences between CBT and pill placebo groups in functional impairment were found across depressive symptom severity subgroups.<sup>97</sup> In the second study, adolescents with ADHD in the CBT group had significantly greater improvements in depressive symptoms than those with ADHD in the placebo group; those without ADHD did not have any differences in depressive symptoms between CBT and placebo groups at the end of treatment.<sup>98</sup> Subgroup differences in functional impairment improvements between those in the CBT and pill placebo groups also were found by family income status. In the lower income group, there were no significant differences in functional impairment at the end of treatment, but in the higher income group, those in CBT had better improvements in functional impairment than pill placebo adolescents at the end of treatment.

## **CBT Versus Wait-List Control: Subpopulations**

### **Key Points**

- Studies comparing CBT and wait-list control did not evaluate differences by subgroups of interest to this review.

## **CBT (Delivered to Adolescent and Parent) Versus Wait-List Control: Subpopulations**

### **Key Points**

- Studies compared CBT delivered to adolescent and parent with wait-list control did not evaluate differences by subgroups of interest to this review.

## **CBT + TAU Versus TAU/UC: Subpopulations**

### **Key Points**

- Studies comparing CBT plus TAU with TAU did not evaluate differences by subgroups of interest to this review.

## **CBT (Modified) Versus UC: Subpopulations**

### **Key Points**

- Studies comparing modified CBT with UC did not evaluate differences by subgroups of interest to this review.

## **CBT Versus Active Control: Subpopulations**

### **Key Points**

- Lifetime suicidality was not associated with treatment response among adolescents in the CBT or systematic-behavior family therapy groups, but for those in the active control group, the response of subjects with suicidal history was less favorable than for nonsuicidal subjects.<sup>126</sup>
- Among white adolescents, those in the CBT group recovered faster than those in the active control group. No differences in recovery were found across treatment groups among nonwhite adolescents.<sup>127</sup>
- Among adolescents with prior MDD episodes, those in the CBT group recovered faster than those in the active control group. No differences across treatment groups were found among those with first-episode MDD.<sup>127</sup>
- Among adolescents with high levels of positive coping skills, those in the CBT group recovered faster than those in the active control group. No differences were found across treatment groups among those with poor levels of positive coping skills.<sup>127</sup>

## **Detailed Results**

One companion publication<sup>126</sup> to an RCT with high risk of bias<sup>60</sup> examined subgroup differences in benefits between CBT (n=37), systematic-behavior family therapy (n=35), and a nondirective supportive therapy active comparator (n=35) among adolescents with MDD in a 12- to 16-week study. One companion publication<sup>127</sup> to an RCT with medium risk of bias<sup>54</sup> examined subgroup differences in benefits between CBT (n=56) and a life skills/tutoring active comparator group (n=58) among adolescents with MDD in an 8-week study.

In the first study, lifetime suicidality was found to moderate treatment response in the active control group.<sup>126</sup> participants with suicidal history were less likely to respond to treatment than nonsuicidal participants. In the second study, when compared with the active control, CBT was found to improve recovery time better than active control among adolescents who were white, had experienced prior MDD episodes, or had high levels of positive coping skills. However, no differences across treatment groups were found for adolescents who were nonwhite, experiencing their first MDD episode, or had poor positive coping skills.<sup>127</sup> Additional details can be found in Appendix Tables D-21 and G-2.

## **Relapse Prevention CBT + Continued Antidepressant Medication Management Versus Continued Medication Management: Subpopulations**

### **Key Points**

- Studies comparing modified CBT plus continued antidepressant medication management with continued medication management did not evaluate differences by subgroups of interest to this review.

## **IPT Versus Wait-List Control: Subpopulations**

### **Key Points**

- Studies comparing IPT with wait-list control did not evaluate differences by subgroups of interest to this review.

## **IPT Versus Active Control: Subpopulations**

### **Key Points**

- Studies comparing IPT when compared with active control did not evaluate differences by subgroups of interest to this review.

## **Family-Based IPT Versus Active Control: Subpopulations**

### **Key Points**

- Studies comparing family-based IPT with active control did not evaluate differences by subgroups of interest to this review.

## **Attachment-Based Family Therapy Versus Wait-List Control: Subpopulations**

### **Key Points**

- Studies comparing attachment-based family therapy with wait-list control did not evaluate differences by subgroups of interest to this review.

## **Attachment-Based Family Therapy Versus TAU: Subpopulations**

### **Key Points**

- Studies comparing attachment-based family therapy with TAU did not evaluate differences by subgroups of interest to this review.

## **Family Therapy Versus Pill Placebo: Subpopulations**

### **Key Points**

- One study comparing family therapy (psychoeducation plus CBT) with pill placebo found declines in depression severity in the intervention arm but not in the placebo arm in families with more psychosocial stressors.
- The same study found no moderating effects of maternal depression.

### **Detailed Results**

One RCT with some risk-of-bias concerns<sup>65</sup> examined the effect of history of maternal depression and found a decline in depression severity associated with the number of psychosocial stressors in the intervention arm but not in the placebo arm. The study found that when families reported fewer psychosocial stressors, the intervention arm had a significant decline in depression severity and little impact in the placebo arm. The same study found no moderating effects associated with history of maternal depression. Additional details can be found in Appendix Tables D-22 and G-3.

## **Family Therapy Versus Active Control: Subpopulations**

### **Key Points**

- Studies comparing family therapy with active control did not find differences by subgroups of interest to this review.

### **Detailed Results**

One RCT<sup>43</sup> found no effects of demographic age group, gender, race, family composition, family income) or clinical variables (syndromal vs. subsyndromal depression, baseline CDRS score, comorbid anxiety disorder, comorbid disruptive behavior disorder, chronicity, current antidepressant medication) on treatment response. Additional details can be found in Appendix Tables D-23 and G-4.

## **PCIT Versus Active Control: Subpopulations**

### **Key Points**

- Studies comparing PCIT with active control did not evaluate differences by subgroups of interest to this review.

## **Psychoanalytic Therapy Versus Active Control: Subpopulations**

### **Key Points**

- Studies comparing psychoanalytic therapy with active control did not evaluate differences by subgroups of interest to this review.

## **Exercise Versus Active Control: Subpopulations**

### **Key Points**

- Studies comparing exercise with active control did not evaluate differences by subgroups of interest to this review.

## **Spirituality Versus Wait-List: Subpopulations**

### **Key Points**

- Studies comparing spirituality with wait-list control did not evaluate differences by subgroups of interest to this review.

## **Omega-3 Versus Pill Placebo: Subpopulations**

### **Key Points**

- One study comparing omega-3 with pill placebo found declines in depression severity in the intervention arm but not in the placebo arm in families with more psychosocial stressors.
- The same study found no moderating effects of maternal depression.

### **Detailed Results**

One RCT with some risk-of-bias concerns<sup>65</sup> examined the effect of history of maternal depression and found a decline in depression severity associated with the number of psychosocial stressors in the intervention arm but not in the placebo arm. The study found that when families reported fewer psychosocial stressors, the intervention arm had a significant decline in depression severity and little impact in the placebo arm. The same study found no moderating effects associated with history of maternal depression. Additional details can be found in Appendix Tables D-24 and G-5.

## KQ 2a: Benefits and Harms of Pharmacological Interventions

### SSRIs Versus Placebo: Benefits

#### Key Points

- Fluoxetine improves clinician-rated depressive symptoms, and response among adolescents with MDD (low SOE of benefit) when compared with placebo; for other populations including both adolescents and children with MDD, children with MDD, or adolescents and children with MDD, dysthymia, or DD NOS, the evidence for fluoxetine versus placebo is insufficient.
- Escitalopram improves long-term depressive symptoms (low SOE), long-term remission rates (low SOE), and functional status (low SOE) for adolescents with MDD when compared with placebo, but the evidence was insufficient for response or end-of-treatment depressive symptoms or remission.
- The evidence is insufficient to judge the efficacy of citalopram, vilazodone, or paroxetine versus placebo for symptoms, response, remission, and functional status.
- The evidence for SSRIs as a class was mixed. For adolescents and children with MDD, the evidence was insufficient to judge clinician-reported depressive symptoms and remission but suggested benefit for response and functional status (low for benefit). The evidence for adolescent-only populations with MDD was heterogeneous. Fluoxetine demonstrated benefit for symptoms and response. For SSRIs other than fluoxetine, the evidence was generally insufficient to judge benefit for depressive symptoms, remission, or response.
- The evidence for SSRIs as a class suggested no benefit for remission among adolescents with MDD.

#### Detailed Results

Fourteen RCTs compared SSRIs (specifically, fluoxetine, citalopram, escitalopram, paroxetine, and vilazodone) with pill placebo.<sup>34, 53, 67-70, 72, 75, 76, 79, 81, 82, 84-92</sup> Risk-of-bias ratings ranged from “some concerns” to “high risk” across all studies.

For paroxetine, the original results for one trial (“Study 329”) were published in 2001<sup>83</sup> and reported that “paroxetine was generally well tolerated and effective for major depression in adolescents” (p. 762). Subsequent critiques of the original trial led to the release of the unpublished study report<sup>91</sup> and a re-analysis to address several flaws (under an initiative termed “restoring invisible and abandoned trials” [RIAT] for the acute phase in 2015<sup>90</sup> and for the continuation phase in 2016).<sup>92</sup> Specifically, the RIAT analysis addressed several selective outcome and analysis reporting flaws. The original protocol specified two primary outcomes (change in total Hamilton Depression Rating Scale [HAM-D] score and proportion of responders) and six secondary outcomes and found no statistically significant differences for any of the prespecified outcomes. Before and after breaking the blind, several new outcomes were added to the list of outcomes,<sup>90</sup> and the 2001 results focused on statistically significant results from outcomes that had not been prespecified.<sup>128</sup> Because the RIAT analysis sought to avoid these issues (the possibility of “hypothesis after the fact known,”<sup>90, p. 5</sup> the authors limited the re-analysis to variables that had been prespecified in the protocol. The current analysis relies on the RIAT analysis of the acute phase<sup>90</sup> and the continuation phase.<sup>92</sup> The RIAT analysis



presented results for the last-observation-carried-forward data, as planned in Study 329, but additionally provided results for multiple imputation methods of addressing missing values.

Examining SSRIs individually among adolescents and children with MDD, the evidence for fluoxetine for clinician-rated symptoms (standardized mean difference [SMD], -0.23; 95% CI, -0.46 to 0.00;  $I^2=69.7$ ) was graded as insufficient due to imprecision, inconsistency, and high risk of bias (four of five studies had a high risk of bias). Without the high risk-of-bias studies, the results are imprecise (SMD, -0.14; 95% CI, -0.4 to 0.1;  $N=224$ ); the SOE did not change as a result of the sensitivity analysis. The evidence for the remainder of the outcomes for adolescents and children with MDD for fluoxetine was rated as insufficient. For an adolescent-only population with MDD, the evidence from one study<sup>53</sup> suggested improved clinician-rated depression symptoms (mean difference [CDRS-R], -7.98; 95% CI, -10.12 to -5.84) and response rates for adolescents for fluoxetine when compared with placebo (risk difference, 258/1,000 cases; 95% CI, 131 more cases to 385 more cases) (low SOE).<sup>85</sup>

The evidence for escitalopram versus placebo from a single study<sup>88</sup> suggested improvement over the long term (24 weeks) for depressive symptoms (mean difference [CDRS-R], -4.40; 95% CI, -8.15 to -0.65) (low SOE), response (risk difference, 130/1,000; 95% CI, 21 more cases to 239 more cases) (low SOE), remission rates (risk difference, 149/1,000; 95% CI, 40 more cases to 258 more cases) (low SOE). The study also suggested improvement in end-of-treatment functional status (mean difference [CGAS], 3.60; 95% CI, 0.13 to 7.07) (low SOE) for adolescents with MDD, but the evidence was insufficient end-of-treatment depressive symptoms, response, or remission. The evidence for the remainder of outcomes for citalopram, paroxetine, and vilazodone was graded as insufficient.<sup>34, 69, 70, 75, 81, 90-92</sup>

As a class, the evidence for SSRIs compared with pill placebo on clinician-rated depressive symptoms for adolescents and children with MDD was insufficient. Notably, the results when inclusive of high risk-of-bias studies suggest benefit (SMD, -0.19; 95% CI, -0.35 to -0.03;  $I^2=60\%$ ); a sensitivity analysis without these studies indicates that the CIs for the effect size span the null (SMD without high risk-of-bias studies, -0.14; 95% CI, -0.29 to 0.12;  $I^2=28\%$ ,  $N=869$ ).

Among adolescents only, the underlying heterogeneity across drugs within the drug class, risk of bias of included studies, and concerns about potential harms arising from paroxetine complicate the interpretation of the evidence. A meta-analysis that includes all drugs and high risk-of-bias studies suggests benefit (SMD, -0.24; 95% CI, -0.45 to -0.04;  $I^2=75\%$ ;  $N=1,501$ ) but is characterized by heterogeneity that can be explained by the single fluoxetine study. Fluoxetine, as described above, does suggest benefit for clinician-rated depression symptoms among adolescents with depression. A meta-analysis without fluoxetine also suggests benefit (SMD, -0.12; 95% CI, -0.22 to -0.02;  $I^2=0\%$ ;  $N=1,280$ ) but includes two high risk-of-bias studies, both on paroxetine. Given concerns about prescribing paroxetine in adolescents with depression, a more clinically relevant evaluation would exclude paroxetine studies. Excluding the two high risk-of-bias paroxetine studies and the fluoxetine study results in imprecise results: confidence intervals span the null for the remaining drugs (escitalopram and vilazodone). As a result, we rated the evidence for clinician-rated depression symptoms among adolescents as insufficient because of imprecision, inconsistency, and high risk of bias.

Response rates improved for adolescents and children with MDD (risk difference, 72/1,000; 95% CI, 2 to 124;  $I^2=9\%$ ; low SOE). Without the high risk-of-bias studies, the results continue to be consistent and precise (risk difference, 80/1,000; 95% CI, 16 more to 143 more cases,  $I^2=0\%$ ); the sensitivity analysis does not change the SOE.

Among adolescents only, the results for response rates mirror the results for clinician-rated depression symptoms. The interpretation of the evidence is complicated by underlying heterogeneity, risk of bias, and the inclusion of paroxetine. The results for the entire evidence base suggest benefit (relative risk [RR], 1.16; 95% CI, 1.01 to 1.35;  $I^2=61\%$ ) but a single fluoxetine study that demonstrates benefit drives these results and underpins the heterogeneity of the evidence base. Excluding the fluoxetine study reduces heterogeneity but also results in a lower estimate of benefit, with greater uncertainty (the confidence intervals span the null). Excluding the high risk-of-bias studies (both paroxetine) similarly results in imprecise results. Results that exclude both fluoxetine and paroxetine (that is, results for just escitalopram and vilazodone) span the null. Given these factors, we rated the evidence as insufficient because of imprecision, consistency, and high risk of bias.

The evidence for the drug class in terms of improving remission rates for adolescents and children with MDD were inconsistent in addition to being imprecise and having high risk of bias.<sup>67, 68, 72, 82</sup> Without the high risk-of-bias studies, the results continued to be imprecise and inconsistent; the SOE did not change as a result of the sensitivity analysis. The results for adolescents with MDD, by contrast, suggested no benefit (low SOE): without the high risk-of-bias study,<sup>90</sup> the results continued to be consistent; the SOE did not change as a result of the sensitivity analysis.<sup>75, 79</sup>

The evidence regarding SSRIs and functional status for adolescents and children with MDD was graded as low for benefit (SMD, 0.16; 95% CI, 0.03 to 0.29,  $I^2=0\%$ ). Without the high risk-of-bias studies, the evidence continued to suggest benefit (SMD, 0.17; 95% CI, 0.02 to 0.33;  $I^2=0\%$ ); the SOE did not change as a result of the sensitivity analysis. Results of the individual SSRI drug and the SSRI class comparisons with pill placebo are presented in Table 34. Additional details about these studies can be found in Appendix Tables D-26 and E-20.

**Table 34. Strength of evidence for benefits of SSRIs versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Fluoxetine	Depressive symptoms, clinician report	SMD for all studies (CDRS-R), -0.23; 95% CI, -0.46 to 0.00, $I^2=70$ (Appendix J, Figure J-1)	5 RCTs (n=979) <sup>67, 68, 72, 76, 82</sup>	Imprecision (wide CIs), inconsistency high risk of bias <sup>67, 68, 72, 82</sup>	Insufficient	Adolescents and children with MDD
	Depressive symptoms, clinician report	SMD (CDRS-R), -0.68; 95% CI, -0.95 to -0.41)	1 RCT (n=221) <sup>53</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Depressive symptoms, clinician report	Between-group mean difference (CDRS-R), -4.23; 95% CI, -12.95 to 4.49	1 RCT (n=34) <sup>84</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or other DDs plus a comorbid substance-related disorder

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Fluoxetine (continued)	Depressive symptoms, self-report	SMD (CDI/BDI), -0.19; 95% CI, -0.59 to 0.21	1 RCT (n=96) <sup>72</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>72</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	Depressive symptoms, self-report	SMD (BDI), 0.09; 95% CI, -0.18 to 0.35	1 RCT (n=97) <sup>82</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>82</sup> unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, self-report	SMD (CDI), 0.05; 95% CI, -0.35 to 0.45	1 RCT (n=122) <sup>82</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>82</sup> unknown consistency	Insufficient	Children with MDD
	Depressive symptoms, self-report	Between-group mean difference (BDI), 4.70; 95% CI, -5.23 to 14.63	1 RCT (n=34) <sup>84</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with (MDD) or other DDs plus a comorbid substance-related disorder
	Response	RR (probability of response w/CGI/CDRS-R), 1.15; 95% CI, 0.99 to 1.34, I <sup>2</sup> =50% (Appendix J, Figure J-2)	4 RCTs (n=878) <sup>67, 68, 76, 82</sup>	Imprecision (wide CIs), inconsistency, high risk of bias <sup>67, 68, 76, 82</sup>	Insufficient	Adolescents and children with MDD
	Response	RR (CGI-I), 1.74; 95% CI, 1.30 to 2.34	1 RCT (n=221) <sup>53</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Response	RR (CGI-I), 1.30; 95% CI, 0.96 to 1.76	1 RCT (n=34) <sup>84</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or other DDs plus a comorbid substance-related disorder
	Remission	RR (remission: CDRS-R), 1.24; 95% CI, 0.78 to 1.92, I <sup>2</sup> =75% (Appendix J, Figure J-3)	4 RCTs (n=774) <sup>67, 68, 72, 82</sup>	Imprecision (wide CIs, inconsistency, high risk of bias <sup>67, 68, 72, 82</sup> )	Insufficient	Adolescents and children with MDD
	Remission	RR (remission: CDRS-R), 1.35; 95% CI, 0.79 to 2.31	1 RCT (n=221) <sup>85</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional status, clinician report	SMD (GAF, CGAS) range from 0.08 to 0.27 Both 95% CIs cross the null	2 RCTs (n=280) <sup>72, 82</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>72, 82</sup>	Insufficient	Adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Fluoxetine (continued)	Functional status, clinician report	SMD (CGAS), 0.23; 95% CI, -0.04 to 0.49	1 RCT (n=221) <sup>87</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional status, clinician report	Between group mean difference (CGAS), 1.85; 95% CI, -8.67 to 12.37)	1 RCT (n=30) <sup>84</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with (MDD) or other DDs plus a comorbid substance-related disorder
SSRI: Escitalopram	Depressive symptoms, clinician report	SMD (CDRS-R), -0.21; 95% CI, -0.44 to 0.01	1 RCT (n=311) <sup>79</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, clinician report (24-week followup)	SMD (CDRS-R), -0.26; 95% CI, -0.48 to -0.04	1 RCT (n=311) <sup>88</sup>	Imprecision (wide CIs), unknown consistency	Low for benefit	Adolescents with MDD
	Response	RR (CDRS-R), 1.21; 95% CI, 1.00 to 1.46	1 RCT (n=311) <sup>79</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response (24 weeks)	RR (CDRS-R), 1.25; 95% CI, 1.03 to 1.51	1 RCT (n=311) <sup>79</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Remission	RR (CDRS-R), 1.17; 95% CI, 0.74 to 1.84	1 RCT (n=311) <sup>79</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Remission (24 weeks)	RR (CDRS-R), 1.50; 95% CI, 1.09 to 1.84	1 RCT (n=311) <sup>88</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Functional status, clinician report (24 weeks)	SMD (CGAS), 0.23; 95% CI, 0.08 to 0.46	1 RCT (n=301) <sup>88</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
SSRI: Citalopram	Depressive symptoms, clinician report	SMD (CDRS-R) ranges from -0.12 to -0.37 with 1 of 2 95% CIs crossing the null	2 RCTs (n=446) <sup>34, 81</sup>	Imprecision (wide CIs), inconsistency in CIs crossing the null	Insufficient	Adolescents and children with MDD
	Response	RR (CGI-I) ranges from 1.04 to 1.21 with both 95% CIs crossing the null.	2 RCTs (n=446) <sup>34, 81</sup>	Serious imprecision (wide CIs, OIS likely not met)	Insufficient	Adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Citalopram (continued)	Remission <sup>a</sup>	RR (CDRS-R), 1.50; 95% CI, 0.94 to 2.39	1 RCT (n=178) <sup>81</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Functional status, clinician report	SMD (CGAS) ranges from 0.18 to 0.21 with both 95% CIs crossing the null	2 RCTs (n=439) <sup>34, 89</sup>	Serious imprecision (wide CIs, OIS likely not met)	Insufficient	Adolescents and children with MDD
SSRI: Paroxetine	Depressive symptoms, clinician report	Reported adjusted mean difference (CDRS-R), 0.80; 95% CI, -3.09 to 4.69	1 RCT (n=203) <sup>69</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Depressive symptoms, clinician report	SMD (HAM-D, K-SADS-L), ranges from -0.06 to -0.23 across 2 studies with both 95% CIs crossing the null	2 RCTs (n=436) <sup>70, 90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>70, 90</sup>	Insufficient	Adolescents with MDD
	Depressive symptoms, self-report	MD (MFQ), -0.74; 95% CI, -4.27 to 2.80	1 RCT (n=268) <sup>70</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>70</sup> unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (CGI-I), 1.16; 95% CI, 0.66 to 2.03	1 RCT (n=206) <sup>69</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Response	RR (HAM-D, MADRS) of 1.05 in both studies; 95% CI crossed the null in both studies	2 RCTs (n=445) <sup>70, 90</sup>	Imprecision (wide CIs), high risk of bias <sup>70, 90</sup>	Insufficient	Adolescents with MDD
	Response (sustained)	RR (reported), 1.38; 95% CI, 0.95 to 2.02	1 RCT (n=180) <sup>91</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>91</sup> unknown consistency	Insufficient	Adolescents with MDD
	Remission	RR (CDRS-R<28), 0.81; 95% CI, 0.51 to 1.31	1 RCT (n=206) <sup>69</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Remission	RR (HAM-D), 1.21; 95% CI, 0.95 to 1.55	1 RCT (n=180) <sup>92</sup>	Serious imprecision (wide CIs, small sample size) high risk of bias, <sup>92</sup> unknown consistency	Insufficient	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Paroxetine (continued)	Relapse	RR (HAM-D), 1.93; 95% CI, 1.03 to 3.61	1 RCT (n=108) <sup>92</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>92</sup> unknown consistency	Insufficient	Adolescents with MDD
	Functional status, clinician report	Median difference (GAF), 1.33; 95% CI, -2.19 to 4.86, p=0.46	1 RCT (n=187) <sup>69</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Functional status, self-report	SMD (AFC), 0.24; 95% CI, -0.11 to 0.60	1 RCT (n=122) <sup>90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>90</sup> unknown consistency	Insufficient	Adolescents with MDD
	Functional status, parent report	SMD (AFC), 0.25; 95% CI, -0.11 to 0.61	1 RCT (n=122) <sup>91</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>91</sup> unknown consistency	Insufficient	Adolescents with MDD
SSRI: Vilazodone	Depressive symptoms, clinician report	RR (CDRS-R), -0.07; 95% CI, -0.25 to 0.11	1 RCT (n=524) <sup>75</sup>	Imprecision (wide CIs), unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (CDRS-R), 1.07; 95% CI, 0.86 to 1.35	1 RCT (n=524) <sup>75</sup>	Imprecision (wide CIs), unknown consistency	Insufficient	Adolescents with MDD
	Remission	RR (CDRS-R), 1.04; 95% CI, 0.82 to 1.32	1 RCT (n=524) <sup>75</sup>	Imprecision (wide CIs), unknown consistency	Insufficient	Adolescents with MDD
SSRIs: Pooling two or more SSRIs, including fluoxetine, citalopram, escitalopram, paroxetine, or vilazodone	Depressive symptoms, clinician report	SMD (HAM-D, CDRS-R, MADRS), -0.19; 95% CI, -0.35 to -0.03, I <sup>2</sup> =60%, (Appendix J, Figure J-4)  SMD without high risk-of-bias studies, -0.14; 95% CI, -0.29 to 2.12, I <sup>2</sup> =28%, N=869	8 RCTs (n=1624) <sup>34, 67-69, 72, 76, 81, 82</sup>	High risk of bias, <sup>67, 68, 72, 82</sup> inconsistency, imprecision (wide CIs) without high risk-of-bias studies	Insufficient <sup>b</sup>	Adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRIs: Pooling two or more SSRIs, including fluoxetine, citalopram, escitalopram, paroxetine, or vilazodone (continued)	Depressive symptoms, clinician report	SMD (HAM-D, CDRS, MADRS), -0.24; 95% CI, -0.45 to -0.04, $I^2=75\%$ , (Appendix J, Figure J-5)	5 RCTs (n=1,501) <sup>53, 70, 75, 79, 90</sup>	Imprecision (wide CIs), inconsistency with fluoxetine study, high risk of bias <sup>70, 90</sup>	Insufficient <sup>b</sup>	Adolescents with MDD
		SMD without high risk-of-bias studies (both paroxetine), -0.30; 95% CI, -0.64 to 0.03, $I^2=86\%$ , N=1,056				
		SMD without fluoxetine, -0.12; 95% CI, -0.23 to -0.02, N=1,280				
	Response	SMD without fluoxetine or paroxetine, -0.21; 95% CI, -0.44 to 0.01, N=311 for escitalopram and -0.07, 95% CI, -0.22 to 0.08), N = 524 for vilazodone	7 RCTs (n=1,525) <sup>34, 67-69, 76, 81, 82</sup>	Imprecision (wide CIs), high risk of bias <sup>67, 68, 82</sup>	Low for benefit	Adolescents and children with MDD
		RR (HAM-D, MADRS, CGI-I), 1.15; 95% CI, 1.04 to 1.26, $I^2=9\%$ , (Appendix J, Figure J-6)				
		RR without high risk-of-bias studies, 1.19; 95% CI, 1.06 to 1.36, $I^2=0\%$ , N=847				

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRIs: Pooling two or more SSRIs, including fluoxetine, citalopram, escitalopram, paroxetine, or vilazodone (continued)	Response	RR (CDRS-R, CGI-I, HAM-D, MADRS), 1.16; 95% CI, 1.01 to 1.35, $I^2=61\%$ , (Appendix J, Figure J-7)  RR without high risk-of-bias studies, 1.27; 95% CI, 1.00 to 1.62, $I^2=74\%$ , N=986  RR without fluoxetine study, 1.09; 95% CI, 0.99 to 1.20, $I^2=0\%$ , N=1,210  RR without fluoxetine or paroxetine, 1.21; 95% CI, 1.00 to 1.46, N=311 for escitalopram and 1.07; 95% CI, 0.86 to 1.35, N = 524 for vilazodone	5 RCTs (n= 1,431) <sup>53, 70, 75, 79, 90</sup>	Imprecision (wide CIs), inconsistency with fluoxetine study, high risk of bias <sup>70, 90</sup>	Insufficient <sup>b</sup>	Adolescents with MDD
	Remission <sup>a</sup>	RR (CDRS-R, CGI-I), 1.19; 95% CI, 0.86 to 1.64, $I^2=68\%$ , (Appendix J, Figure J-8)  Without high risk-of-bias studies (all fluoxetine), CIs span the null, but point estimates continue to be inconsistent	6 RCTs (n=1153) <sup>67-69, 72, 81, 82</sup>	Imprecision (wide CIs), inconsistency, high risk of bias <sup>67, 68, 72, 82</sup>	Insufficient	Adolescents and children with MDD



Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRIs: Pooling two or more SSRIs, including fluoxetine, citalopram, escitalopram, paroxetine, or vilazodone (continued)	Remission	RR (HAM-D, CDRS-R), 1.15; 95% CI, 0.98 to 1.33, I <sup>2</sup> =0%, (Appendix J, Figure J-9)  RR without high risk-of-bias studies, 1.10; 95% CI, 0.91 to 1.34, I <sup>2</sup> =0%, N=870	4 RCTs (n=1,050) <sup>75, 79, 85, 92</sup>	Imprecision, (wide CIs), high risk of bias <sup>92</sup>	Low for no benefit	Adolescents with MDD
	Functional status, clinician report	SMD (GAF, CGAS), 0.16; 95% CI, 0.03 to 0.29, I <sup>2</sup> =0%, (Appendix J, Figure J-10)  Without high risk-of-bias studies, SMD, 0.17; 95% CI, 0.02 to 0.33, I <sup>2</sup> =0%, N=626	5 RCTs (n=941) <sup>34, 69, 72, 82, 89</sup>	Imprecision (wide CIs), high risk of bias <sup>72, 82</sup>	Low for benefit	Adolescents and children with MDD

<sup>a</sup> One study<sup>81</sup> reported CDRS≤28 as response. Because this outcome is typically evaluated as remission, we recategorized this outcome as remission.

<sup>b</sup> In the absence of sensitivity analyses accounting for high risk of bias and heterogeneity, this evidence would not have been downgraded for imprecision; the grade would have been low for benefit.

AFC = Autonomous Functioning Checklist; BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CGI = Clinical Global Impressions Scale; CGI-I = Clinical Global Impressions Scale-Improvement; CI = confidence interval; DD = depressive disorders; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; K-SADs-L = Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children; MADRS = Montgomery-Asberg Depression Rating Scale; MD = mean difference; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n = number; OIS = optimal information size; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitors.

## SSRIs Versus Placebo: Harms

### Key Points

- The evidence was insufficient to judge the harms of fluoxetine compared with placebo for suicidal ideation or behaviors, SAEs, or withdrawal due to AEs.
- Paroxetine was associated with a higher risk of suicidal ideation or behavioral and withdrawals due to AEs than placebo (low SOE for harms).
- The evidence for escitalopram, paroxetine, and vilazodone for all other outcomes was insufficient to judge the risk of harms.
- SSRIs as a class were associated with a higher risk of serious adverse events in studies with adolescents or adolescents and children with MDD (low risk of harms).

- SSRIs as a class were associated with a higher risk of withdrawals for adverse events in studies with adolescents with MDD (low risk of harms).
- Across a broad range of other populations, the evidence was insufficient to judge the risk of suicidal ideation or behaviors, SAEs, or withdrawals with SSRIs as a class, but the insufficient grade reflects uncertainty, primarily because of rare outcomes rather than the absence of harms.

## Detailed Results

Eleven RCTs compared SSRIs, including fluoxetine, citalopram, escitalopram, paroxetine, and vilazodone, with pill placebo and reported AEs.<sup>53, 67-70, 72, 75, 76, 79, 81-84, 88, 89, 90, 92, 119</sup> Overall characteristics of these studies are described in the benefits section. Mortality was reported in two studies of fluoxetine, and no deaths were reported in either group from any cause including suicide.

In broadly defined populations (adolescents or children, MDD or other DDs), the evidence for the effects of fluoxetine versus placebo was insufficient for suicidal ideation or behaviors, SAEs, or withdrawal due to AEs because of serious imprecision and high risk of bias. Removing the high risk-of-bias studies<sup>67, 68</sup> continued to yield seriously imprecise results; the SOE did not change as a result of the sensitivity analysis. This conclusion also held for a more narrowly defined population of adolescents and children with MDD with or without high risk-of bias studies.<sup>67, 68</sup>

A pooled analysis of all paroxetine studies indicates uncertainty because of confidence intervals spanning the null, but two of three included studies have a high risk of bias. The results from the single study without critical risk-of-bias concerns spans the null and would be insufficient to judge the harms of suicidal ideation or behaviors. We judged the evidence to be low for harms, despite the inclusion of high risk-of-bias studies to convey the signal for a risk of harm. Specifically the harm reported in one study (n=180) indicates a substantial risk difference of 95/1,000, 95% CI, 22 to 168.<sup>90</sup> The evidence for paroxetine suggested a higher risk of withdrawal due to AEs (risk difference, 60/1,000; 95% CI, 19 more cases to 101 more cases) (low SOE of harms). The evidence for escitalopram, paroxetine, and vilazodone for all other outcomes was insufficient to judge the risk of harms.

When SSRIs were examined as a class for suicidal ideation or behaviors, the analyses in broadly defined populations (adolescents, children, MDD, other DDs) and more narrowly defined populations (adolescents only, MDD only) had high risk of bias and serious imprecision, leading to a judgment of insufficient evidence. Without the high risk-of-bias studies (which included the paroxetine study that demonstrated a higher risk of suicidal ideation or behavior), these results continued to demonstrate serious imprecision; the SOE was not changed as a result of the sensitivity analysis. In other words, although we judged paroxetine to have an increased risk of suicidal ideation for adolescents, we did not find evidence for increased risk of suicidal ideation for the entire class of SSRIs.

Our inclusion criteria requiring study-level data and our lack of access to some data resulted in the exclusion of some potentially relevant results from the meta-analysis. These criteria also reduced the power of the analysis. After looking at published studies, we then examined the effect of our exclusions in comparison with the FDA meta-analysis<sup>129</sup> that prompted the boxed warning on all antidepressants. The sensitivity analyses described below are cumulative; that is, we retained the data from each analysis as we moved to the next to maximize the power of the analyses.

First, we added data to which we did not have access. One study of citalopram did not report suicidal behavior or outcomes in the publication<sup>81</sup> or in the FDA clinical review,<sup>130</sup> but the FDA meta-analysis included results indicating one event in the drug arm and two in the placebo arm.<sup>129</sup> Adding these results, using the FDA meta-analysis as a source, did not change the direction or statistical significance of the results (RR, 1.11; 95% CI, 0.89 to 1.38).

Second, we added data for which we did not have sufficient information to attribute causality. One escitalopram study reported one “potential suicide-related event” in the drug arm and two in the placebo arm and judged that only one of the placebo events was possibly related to the study medication.<sup>34</sup> Assuming the worst-case scenario and including all these events as potential harms, as in the FDA meta-analysis, did not change the direction or statistical significance of the effect (RR, 1.09; 95% CI, 0.89 to 1.33). The FDA meta-analysis found one study of mirtazapine with one event in the treatment and none in the placebo arm.<sup>129</sup> Adding these results, using the FDA meta-analysis as a source, did not change the direction or statistical significance of the results (RR, 1.09; 95% CI, 0.89 to 1.33).

Third, we added pooled studies for which we were unable to extract study-level data. One such study pooled two trials for sertraline.<sup>131</sup> The FDA meta-analysis had access to study-level results and reported three events in the drug arm and none in the placebo arm in one study (A0501001) and two in each arm in the second study (A0501017). Adding these results, using the FDA meta-analysis as a source, did not change the direction or statistical significance of the results (RR, 1.10; 95% CI, 0.90 to 1.34).

Fourth, we added studies for which we used different data values than the FDA meta-analysis: for the TADS trial,<sup>119</sup> we relied on published reports suggesting 10 events in the fluoxetine arm and 3 in the placebo arm using the Columbia Classification system yielding a higher but not statistically significant difference between the arms (RR, 3.43; 95% CI, 0.97 to 12.11); the FDA meta-analysis reported 9 and 2, yielding a statistically significant difference between the arms (RR, 4.62; 95% CI, 1.02 to 20.92).<sup>129</sup> Using the numbers in the FDA meta-analysis for the TADS also did not change the direction or statistical significance of the results (RR, 1.10; 95% CI, 0.90 to 1.34).

Finally, we tested whether pooling SSRIs along with all other drugs (venlafaxine, desvenlafaxine, amitriptyline, imipramine, duloxetine, MAOIs), as in the FDA meta-analysis, would alter the results. This broader analysis also did not change the direction or statistical significance of the results (RR, 1.07; 95% CI, 0.90 to 1.27).

The FDA meta-analysis included other populations and settings from our review; we did not attempt sensitivity analyses to address these populations because they are outside the scope of this review. Specifically, we excluded studies with inpatient populations.<sup>132, 133</sup> One of the excluded studies was judged in the FDA meta-analysis<sup>129</sup> as having more events in the drug arm than in the placebo arm (9 vs. 5),<sup>132</sup> and the other had no events in the drug arm and one in the placebo arm.<sup>133</sup> We also excluded studies of populations with disorders other than depression. In these populations, the potential adverse effects of antidepressants on suicidality may be more apparent because there is no mitigating benefit from improved symptom response. The evidence for SAEs for adolescents only or adolescents and children with MDD demonstrated higher risk (RR, 20/1,000; 95% CI, 1 more case to 40 more cases), but was marked by very few events (68 events), leading to seriously imprecise results and a judgment of low for harms. Without high risk-of-bias studies, the results continued to be imprecise with confidence intervals that span the null (risk difference, 20/1,000; 95% CI, 1 less case to 33 more cases;  $I^2=0\%$ ;  $N=1,180$ ). We

judged the evidence to be low for harms, despite the inclusion of high risk-of-bias studies. The evidence from studies of adolescents and children was insufficient.

The evidence suggests an increased risk of withdrawals with SSRIs as a class for adolescents with depression (risk difference, 26/1,000; 95% CI, 6 fewer cases to 45 more cases). Without high risk-of-bias studies, these results span the null. We judged the evidence to be low for harms, despite the inclusion of high risk-of-bias studies. The results in other populations (adolescents and children with MDD, adolescents or children with MDD) had high risk of bias and serious imprecision, leading to a judgment of insufficient evidence. Without the high risk-of-bias studies, these results continued to demonstrate serious imprecision; the SOE was not changed as a result of the sensitivity analysis.

Results of the individual SSRI drug and the class comparisons with pill placebo for harms are presented in Table 35. Additional details can be found in Appendix Tables D-26 and F-10.

**Table 35. Strength of evidence for harms of SSRIs versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Fluoxetine	Mortality	No deaths in either group	1 RCT (n=224) <sup>76</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Mortality	No mortality from completed suicides in either group	1 RCT (n=221) <sup>53</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicidal ideation or behaviors	RR (C-SSRS/discontinuation due to SI), 1.05; 95% CI, 0.70 to 1.58, I <sup>2</sup> =0%, (Appendix J, Figure J-11)  CIs for RR without high risk-of-bias studies span the null	4 RCTs (n=701) <sup>67, 68, 76, 84</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents and children with MDD or adolescents with MDD or other DDs with a comorbid substance-abuse disorder
	Suicidal ideation or behaviors	RR (C-SSRS/discontinuation due to SI), 1.06; 95% CI, 0.70 to 1.60, I <sup>2</sup> =0%, (Appendix J, Figure J-12)  CIs for RR without high risk-of-bias studies span the null	3 RCTs (n=667) <sup>67, 68, 76</sup>	Imprecision (wide CIs, few events), high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Fluoxetine (continued)	Suicide-related AEs	RR (C-CASA), 1.74; 95% CI, 0.43 to 7.12	1 RCT (n=219) <sup>119</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicide attempts	RR (number with attempts), 5.41; 95% CI, 0.25 to 105.7)	1 RCT (n=221) <sup>53</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	SAEs	RR, 2.15; 95% CI, 0.93 to 4.96; I <sup>2</sup> , 19%, (Appendix J, Figure J-13)  CIs for RR without high risk-of-bias studies span the null	5 RCTs (n=1,113) <sup>53, 67, 68, 76, 82</sup>	Imprecision (few events), high risk of bias <sup>67, 68, 82</sup>	Insufficient <sup>a</sup>	Adolescents or adolescents and children with MDD
	SAEs	RR, 2.08; 95% CI, 0.53 to 8.17; I <sup>2</sup> , 39% (Appendix J, Figure J-14)  CIs for RR without high risk-of-bias studies span the null	4 RCTs (n=892) <sup>67, 68, 76, 82</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>67, 68, 82</sup>	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs	RR, 0.88; 95% CI, 0.41 to 1.88; I <sup>2</sup> , 12% (Appendix J, Figure J-15)  CIs for RR without high risk-of-bias studies span the null	5 RCTs (n=998) <sup>67, 68, 72, 76, 82</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>67, 68, 72, 82</sup>	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs (extension phase)	RR ranged from 0.42 (95% CI, 0.11 to 1.56) to 1.87 (95% CI, 0.58 to 5.99)  CIs for RR without high risk-of-bias studies span the null	2 RCTs (n=344) <sup>67, 68</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Escitalopram	Suicidal ideation or behaviors	RR (C-SSRS, SIQ-JR), 0.99; 95% CI, 0.46 to 2.11	1 RCT (n=258) <sup>79</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicidal ideation or behaviors (24 weeks)	RR (C-SSRS, SIQ-JR), 1.33; 95% CI, 0.70 to 2.53	1 RCT (n=259) <sup>88</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	SAEs (24 weeks)	RR, 0.99 95% CI, 0.14 to 6.85	1 RCT (n=165) <sup>79</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Withdrawal due to AEs	RR, 4.05; 95% CI, 0.46 to 35.84	1 RCT (n=312) <sup>79</sup>	Serious imprecision (wide CIs, OIS likely not met), unknown consistency	Insufficient	Adolescents with MDD
	Withdrawal due to AEs (24 weeks)	RR, 8.89; 95% CI, 0.49 to 162.6	1 RCT (n=165) <sup>79</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
SSRI: Citalopram	SAEs	RR, 0.31; 95% CI, 0.01 to 7.39	1 RCT (n=178) <sup>89</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs	RR, 0.96; 95% CI, 0.29 to 3.18	1 RCT (n=174) <sup>89</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
SSRI: Paroxetine	Suicidal ideation or behaviors	RR, 3.06; 95% CI, 1.16 to 8.07 I <sup>2</sup> =0%, (Appendix J, Figure J-16)  RR without high risk-of-bias studies, 1.96; 95% CI, 0.18 to 21.30, N=206 <sup>69</sup>	3 RCTs (n=662) <sup>69, 70, 90</sup>	Imprecision (wide CIs), high risk of bias <sup>70, 90</sup>	Low for harms <sup>b, c</sup>	Adolescents or adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Paroxetine (continued)	Suicidal ideation or behaviors	RR ranged from 2.12 (95% CI, 0.46 to 9.78) to 5.15 (95% CI, 1.17 to 22.56)	2 RCTs (n=466) <sup>70, 90</sup>	Serious imprecision (wide CIs), high risk of bias <sup>70, 90</sup>	Low for harms <sup>b</sup>	Adolescents with MDD
	Suicidal ideation or behaviors	RR, 1.96; 95% CI, 0.18 to 21.30	1 RCT (n=206) <sup>69</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Suicidal ideation or behaviors, 6 months continuation	RR (RIAT), 5.30; 95% CI 1.72 to 10.8	1 RCT (n=180) <sup>92</sup>	Imprecision (small sample size), high risk of bias <sup>92</sup> , unknown consistency	Low for harms <sup>b</sup>	Adolescents with MDD
	Suicide attempts	RR (reported), 0.78; 95% CI, 0.13 to 4.77	1 RCT (n=276) <sup>70</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>70</sup> unknown consistency	Insufficient	Adolescents with MDD
	SAEs	RR, 5.15; 95% CI, 1.17 to 22.56	1 RCT (n=180) <sup>83</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>83</sup> , unknown consistency	Insufficient	Adolescents with MDD
	SAEs	RR, 5.89; 95% CI, 0.72 to 48.02	1 RCT (n=206) <sup>69</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs	RR, 2.00; 95% CI, 1.14 to 3.53; I <sup>2</sup> =0%, (Appendix J, Figure J-17)  RR without high risk-of-bias study, 4.55; 95% CI, 1.01 to 20.52, N=203 <sup>69</sup>	3 RCTs (n=658) <sup>69, 70, 90</sup>	Imprecision (wide CIs), high risk of bias <sup>70, 90</sup>	Low for harms	Adolescents or adolescents and children with MDD
	Withdrawal due to AEs (continuation phase)	RR (RIAT), 0.73; 95% CI, 0.22 to 2.36	1 RCT (n=49) <sup>92</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>92</sup> , unknown consistency	Insufficient	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Vilazodone	Suicidal ideation or behaviors	RR (C-SSRS), 0.99; 95% CI, 0.77 to 1.28	1 RCT (n=526) <sup>75</sup>	Serious imprecision (wide CIs, few events), unknown consistency	Insufficient	Adolescents with MDD
	Suicidal attempts	RR (C-SSRS), 0.48, 95% CI, 0.07 to 3.39	1 RCT (n=526) <sup>75</sup>	Serious imprecision (wide CIs, few events), unknown consistency	Insufficient	Adolescents with MDD
	SAEs	RR, 2.41; 95% CI, 0.28 to 20.45	1 RCT (n=526) <sup>75</sup>	Serious imprecision (wide CIs, few events), unknown consistency	Insufficient	Adolescents with MDD
	Withdrawal due to AEs	RR, 2.08; 95% CI, 0.71 to 6.10	1 RCT (n=529) <sup>75</sup>	Serious imprecision (wide CIs, few events), unknown consistency	Insufficient	Adolescents with MDD
SSRIs: Pooling two or more SSRIs, including fluoxetine, escitalopram, paroxetine, and vilazodone	Suicidal ideation or behaviors	RR, 1.14; 95% CI, 0.89 to 1.45; I <sup>2</sup> , 8% (Appendix J, Figure J-18)  RR without high risk-of-bias studies (two paroxetine studies and two fluoxetine studies), 1.08; 95% CI, 0.86 to 1.36; I <sup>2</sup> =0%; N=1,467	10 RCTs (n=2,368) <sup>67-70, 75, 76, 79, 84, 90, 119</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>67, 68, 70, 90</sup>	Insufficient <sup>a</sup>	Adolescents or adolescents and children with MDD or adolescents with MDD or other DDs with a comorbid substance-abuse disorder
	Suicidal ideation or behaviors	RR, 1.07; 95% CI, 0.71 to 1.62; I <sup>2</sup> , 0% (Appendix J, Figure J-19)  CIs for RR without high risk-of-bias studies span the null	4 RCTs (n=873) <sup>67-69, 76</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents and children with MDD



Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRIs: Pooling two or more SSRIs, including fluoxetine, escitalopram, paroxetine, and vilazodone (continued)	Suicidal ideation or behaviors	RR, 1.46; 95% CI, 0.87 to 2.47; $I^2=41\%$ , (Appendix J, Figure J-20)  RR without high risk-of-bias studies (both paroxetine), 1.10; 95% CI, 0.76 to 1.58; $I^2=15\%$ ; N=1,039	6 RCTs (n=1,495) <sup>70, 75, 79, 84, 90, 119</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>70, 90</sup>	Insufficient	Adolescents with MDD or adolescents with MDD or other DDs with a comorbid substance-abuse disorder
	SAEs	RR, 2.52; 95% CI, 1.40 to 4.54; $I^2$ , 4% (Appendix J, Figure J-21)  RR without high risk-of-bias studies (three fluoxetine studies and one paroxetine studies), 2.38; 95% CI, 1.13 to 5.01; $I^2=0\%$ ; N=1,358	9 RCTs (n=2,206) <sup>53, 67-69, 75, 76, 82, 83, 89</sup>	Imprecision (wide CIs, few events), high risk of bias <sup>67, 68, 82, 83</sup>	Low for harms <sup>a,b</sup>	Adolescents and children with MDD, adolescents with MDD
	SAEs	RR, 2.09; 95% CI, 0.69 to 6.28; $I^2$ , 31% (Appendix J, Figure J-22)  RR without high risk-of-bias studies (three fluoxetine studies), 2.70; 95% CI, 0.48 to 15.13; $I^2=19\%$ ; N= 608	6 RCTs (n=1,276) <sup>67-69, 76, 82, 89</sup>	High risk of bias <sup>67, 68, 82</sup>	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs	RR, 1.49; 95% CI, 0.98 to 2.25; $I^2$ , 12% (Appendix J, Figure J-23)  RR without high risk-of-bias studies, 1.84; 95% CI, 0.94 to 3.60; $I^2=5\%$ ; N=1,442	11 RCTs (n=2,671) <sup>67-70, 72, 75, 76, 79, 82, 89, 90</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>67, 68, 70, 72, 82, 90</sup>	Insufficient	Adolescents with MDD, adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRIs: Pooling two or more SSRIs, including fluoxetine, citalopram, escitalopram, paroxetine, and vilazodone (continued)	Withdrawal due to AEs	RR, 1.15; 95% CI, 0.58 to 2.28, I <sup>2</sup> , 29% (Appendix J, Figure J-24)  RR without high risk-of-bias studies, 1.47; 95% CI, 0.44 to 4.96; I <sup>2</sup> =42%; N=601	7 RCTs (n=1,375) <sup>67-69, 72, 76, 82, 89</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>67, 68, 72, 82</sup>	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs	RR, 1.91; 95% CI, 1.14 to 3.20; I <sup>2</sup> , 0% (Appendix J, Figure J-25)  CIs for RR without high risk-of-bias studies span the null	4 RCTs (n=1,296) <sup>70, 75, 79, 90</sup>	Serious imprecision, high risk of bias <sup>70, 90</sup>	Low for harms <sup>b</sup>	Adolescents with MDD

<sup>a</sup> One study<sup>53</sup> reported the total number of SAEs that met FDA's definition for an adverse event (N=23) but did not report results by study arm; this estimate of effect draws from harm-related adverse events, which were reported by study arm. Not all harm-related adverse events are SAEs.

<sup>b</sup> Without high risk-of-bias studies, the grade would have been rated as insufficient for imprecision. With high risk-of-bias studies, the evidence suggests increased risk of harms. We have retained the high risk-of-bias in these ratings to communicate the potential for a signal of harm.

<sup>c</sup> One high risk-of-bias study (n=180) reported a substantial risk (relative risk: 5.15, 95% CI, 1.17 to 22.56; risk difference: 95, 95% CI, 22 to 168).<sup>90</sup>

AE = adverse event; C-CASA = Columbia Classification Algorithm of Suicide Assessment; CI = confidence interval; C-SSRS = Columbia-Suicide Severity Rating Scale; FDA = Food and Drug Administration; MDD = major depressive disorder; n/N = number; OIS = optimal information size; RCT = randomized controlled trial; RIAT = restoring invisible and abandoned trials; RR = relative risk; SAE = serious adverse event; SI = suicidal ideation; SIQ-JR = Suicide Ideation Questionnaire-Junior High School; SSRI = selective serotonin reuptake inhibitor.

## Fluoxetine for Relapse Prevention Versus Placebo: Benefits

### Key Points

- Fluoxetine for relapse prevention improves relapse among children and adolescents.
- The evidence was insufficient to judge the efficacy of relapse prevention strategies on symptoms and time to relapse.

### Detailed Results

Two studies of fluoxetine versus placebo focused on relapse prevention.<sup>80, 93</sup> These studies evaluated 208 adolescents and children. The evidence from two studies suggested insufficient evidence on relapse; without the high risk-of-bias study, evidence from one study indicated benefit for relapse (risk difference, -272/1,000; 95% CI, 458 fewer cases to 86 fewer cases) (low SOE of benefit). The evidence for depressive symptoms and increased time to relapse was

insufficient to allow for conclusions. Results of the fluoxetine relapse prevention studies are presented in Table 36. Additional details can be found in Appendix Tables D-27 and E-21.

**Table 36. Strength of evidence for benefits of relapse prevention of fluoxetine versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Relapse prevention fluoxetine	Depressive symptoms, clinician report	SMD (CDRS-R), -0.48; 95% CI, -1.11 to 0.15	1 RCT (n=40) <sup>93</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>93</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	Depressive symptoms, self-report	SMD (BDI), -0.95; 95% CI, -1.98 to 0.08	1 RCT (n=18) <sup>93</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>93</sup> unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, self-report	SMD (CDI), -0.34; 95% CI, -1.23 to 0.54	1 RCT (n=21) <sup>93</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>93</sup> unknown consistency	Insufficient	Children with MDD
	Relapse	CIs for one of two studies span the null Without high risk of bias, RR (CDRS-R), 0.61; 95% CI, 0.42 to 0.88	2 RCTs (n=142) <sup>80, 93</sup>	Serious imprecision (wide CIs, small sample size), inconsistency, high risk of bias <sup>93</sup>	Low for benefit <sup>a</sup>	Adolescents and children with MDD
	Time to relapse	SMD (CDRS-R), 1.82; 95% CI, 1.09 to 2.56 <sup>a</sup>	1 RCT (n=40) <sup>93</sup>	Imprecision (small sample size, high risk of bias, <sup>93</sup> unknown consistency)	Insufficient	Adolescents and children with MDD
	Functional status, clinician report	SMD (GAF), 0.06; 95% CI, -0.58 to 0.70	1 RCT (n=38) <sup>93</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>93</sup> unknown consistency	Insufficient	Adolescents and children with MDD

<sup>a</sup> With the high risk-of-bias studies, the evidence would have been downgraded for inconsistency and imprecision and would have been downgraded to insufficient.

BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CI = confidence interval; GAF = Global Assessment of Functioning; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitors.

## Fluoxetine for Relapse Prevention Versus Placebo: Harms

### Key Points

- The evidence was insufficient to judge the harms from relapse strategies for suicidal ideation or behaviors, SAEs, and withdrawal due to AEs.

### Detailed Results

The evidence on relapse prevention comparing fluoxetine to placebo<sup>80, 93</sup> was insufficient to judge harms related to suicidal ideation or behaviors, SAEs, or withdrawal due to AEs. Results of the individual fluoxetine relapse study comparisons with pill placebo for harm are presented in Table 37. Additional details can be found in Appendix Tables D-27 and F-11.

**Table 37. Strength of evidence for harms of relapse prevention of fluoxetine versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Relapse prevention fluoxetine	Suicidal ideation or behaviors	RR, 0.33; 95% CI, 0.01 to 7.72	1 RCT (n=40) <sup>93</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>93</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	SAEs	RR, 0.52; 95% CI, 0.05 to 5.56	1 RCT (n=102) <sup>80</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs (continuation phase)	RR, 3.12; 95% CI, 0.13 to 74.8	1 RCT (n=102) <sup>80</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs	RR, 3.00; 95% CI, 0.13 to 69.5	1 RCT (n=40) <sup>93</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>93</sup> unknown consistency	Insufficient	Adolescents and children with MDD

AE = adverse event; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SSRI = selective serotonin reuptake inhibitors.

## SNRIs Versus Placebo: Benefits

### Key Points

- SNRIs did not improve primary depressive symptoms for adolescents and children with MDD when compared with pill placebo (low SOE of no benefit).
- The evidence suggests low SOE for no benefit for depressive symptoms or response for desvenlafaxine.
- The evidence for duloxetine and venlafaxine is insufficient to judge efficacy for depressive symptoms, remission, or response.

## Detailed Results

Five RCTs (two reported in one publication)<sup>94</sup> compared SNRIs to pill placebo including venlafaxine, desvenlafaxine and duloxetine.<sup>67, 76, 77, 94</sup> All studies included children and adolescents and no studies included adolescents only or children only. All studies focused on patients with MDD and no studies focused on a wider range of DDs. Three studies were rated high risk of bias,<sup>67, 94</sup> one was rated uncertain<sup>76</sup> and one was rated as having some concerns.<sup>77</sup>

As a class, SNRIs did not improve depressive symptoms (mean difference in CDRS-R, -1.48; 95% CI, -2.90 to -0.06), when compared with pill placebo (low SOE of no benefit). Without the high risk-of-bias study (duloxetine),<sup>67</sup> the results spanned the null; the SOE did not change as a result of the sensitivity analysis. The sensitivity analysis results for SNRIs, without the high risk-of-bias duloxetine study, were limited to desvenlafaxine studies alone; as a result, the SOE for desvenlafaxine for depressive symptoms also low for no benefit. The relative risk for response for all SNRIs suggests a modest benefit when including all studies (RR, 1.13; 95% CI, 1.03 to 1.23;  $I^2$ , 0%), but without high risk-of-bias studies, the results are imprecise and the strength of evidence is insufficient.

The evidence for duloxetine was insufficient to judge efficacy for remission or response. Results of the individual SNRI drug and the SNRI class comparisons with pill placebo are presented in Table 38. Additional details about these studies can be found in Appendix Tables D-28 and E-22.

**Table 38. Strength of evidence for benefits of SNRIs versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SNRI: Venlafaxine	Depressive symptoms, clinician report	SMD (CDRS-R) of -0.15 and -0.14, CIs of both studies cross the null	2 RCTs (n=334) <sup>94</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>94</sup>	Insufficient	Adolescents and children with MDD
	Response	RR (CDRS-R) of 1.25 and 1.13 Both 95% CIs cross the null.	2 RCTs (n=334) <sup>94</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>94</sup>	Insufficient	Adolescents and children with MDD
SNRI: Desvenlafaxine	Depressive symptoms, clinician report	SMD (CDRS-R) of -0.11 and 0.04, CIs of both studies cross the null	2 RCTs (n=590) <sup>76, 77</sup>	Inconsistency (direction of effect)	Low for no benefit	Adolescents and children with MDD
	Response	RR (CGI-I) of 1.06 and 1.10 Both 95% CIs cross the null.	2 RCTs (n=511) <sup>76, 77</sup>	Imprecision (wide CIs)	Low for no benefit	Adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SNRI: Duloxetine	Depressive symptoms, clinician report	SMD (CDRS-R, pooled for high and low dose), -0.22; 95% CI, -0.45 to 0.01	1 RCT (n=336) <sup>67</sup>	Imprecision (wide CIs), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	Response	RR (CDRS-R, pooled for high and low dose), 1.15; 95% CI, 0.97 to 1.36	1 RCT (n=346) <sup>67</sup>	Imprecision (wide CIs), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	Remission	RR (CDRS-R, pooled for high and low dose), 1.43; 95% CI, 1.05 to 1.95	1 RCT (n=346) <sup>67</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD
SNRIs: venlafaxine, desvenlafaxine and duloxetine	Depressive symptoms, clinician report	SMD (CDRS-R), -0.12; 95% CI, -0.23 to 0.000; I <sup>2</sup> =0%, I <sup>2</sup> , 8% (Appendix J, Figure J-26)  CIs for RR without high risk-of-bias studies span the null	5 RCTs (n=1,260) <sup>67, 76, 77, 94</sup>	Inconsistency (direction of effect), high risk of bias <sup>67, 94</sup>	Low for no benefit	Adolescents and children with MDD
	Response	RR (CDRS-R), 1.13; 95% CI, 1.03 to 1.23, I <sup>2</sup> , 0% (Appendix J, Figure J-27)  CIs for RR without high risk-of-bias studies span the null	5 RCTs (n=1,191) <sup>67, 76, 77, 94</sup>	Imprecise (wide CIs), high risk of bias, <sup>67, 94</sup> unknown consistency	Insufficient <sup>a</sup>	Adolescents and children with MDD

CDRS-R = Children's Depression Rating Scale-Revised; CGI-I = Clinical Global Impressions Scale- Improvement; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; SNRI = serotonin and norepinephrine reuptake inhibitor.

<sup>a</sup> In the absence of sensitivity analyses accounting for high risk of bias and heterogeneity, this evidence would not have been downgraded for imprecision; the grade would have been low for benefit.

## SNRIs Versus Placebo: Harms

### Key Points

- High-dose duloxetine (60 mg) is associated with a higher risk of withdrawals from SAEs when compared with placebo (low SOE of harms).
- The evidence was insufficient to judge the harms of mortality from desvenlafaxine.

- The evidence was insufficient to judge the harms from desvenlafaxine or duloxetine when compared with placebo for suicidal ideation or behaviors, SAEs, and withdrawals due to AEs.
- The evidence was insufficient to judge the harms from SNRIs as a class when compared with placebo for suicidal ideation or behaviors and withdrawals due to AEs.
- The FDA reported higher rates of hostility and suicide-related events in the venlafaxine arm when compared with placebo.

## Detailed Results

Three RCTs (one high risk of bias<sup>67</sup>) of SNRIs versus placebo were examined for harms.<sup>67, 76, 77</sup> The evidence for desvenlafaxine was insufficient to judge the risks of harms for mortality, suicidal ideation or behaviors, SAEs, or withdrawals due to AEs. One trial of duloxetine compared high dose (60 mg) and low dose (30 mg) with placebo. Although the evidence was insufficient to judge the risk of withdrawals for SAEs in the low-dose arm, it suggested a high risk in the high-dose arm (risk difference, 78/1,000; 95% CI, 11 more cases to 145 more cases) (low SOE of harms). The evidence was insufficient to judge the risks of harms for suicidal ideation or behaviors and SAEs for duloxetine.<sup>67</sup> The two venlafaxine studies reported in a single publication offered pooled results only.<sup>94</sup> While the publication did not provide study-level data on harm, study event rates were reported in the FDA meta-analysis.<sup>129</sup> The results indicate higher rates of hostility and suicide-related events in the venlafaxine arm when compared with placebo:<sup>94</sup> specifically, three events in the drug arm and none in the placebo arm in one study (Study 382) and five events in the drug arm and none in the placebo arm in the second study (Study 394). The FDA pooled analyses suggest an RR of 8.84 (95% CI, 1.12 to 69.51) for MDD populations.<sup>129</sup>

The harm outcomes of interest reported and examined include suicidal ideation or behaviors, SAEs, and withdrawal due to AEs. The evidence was sufficient to allow for meta-analysis in regard to suicidal ideation or behaviors and withdrawal due to AEs but was imprecise for these two outcomes of interest after removing the high risk-of-bias study. When drugs were examined individually, the evidence was rated as insufficient for the two drugs and the harm outcomes of interest. Additionally, mortality was reported in one RCT, and no deaths were reported, but this evidence was rated as insufficient. Results of the individual SNRI drug and class comparisons with pill placebo for harms are presented in Table 39. Additional details can be found in Appendix Tables D-28 and F-12.

**Table 39. Strength of evidence for harms of SNRIs versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SNRI: Desvenlafaxine	Mortality	No deaths in either group	1 RCT (n=227) <sup>76</sup>	Imprecision (no events, small sample size), high risk of bias, <sup>76</sup> unknown consistency	Insufficient	Adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SNRI: Desvenlafaxine (continued)	Suicidal ideation or behaviors	RR across 2 studies ranged from 0.71 to 1.10 with both CIs crossing the null	2 RCTs (n=587) <sup>76, 77</sup>	Serious imprecision (wide CIs, few events), inconsistency (in direction of effect)	Insufficient	Adolescents and children with MDD
	SAEs	RR, 6.82; 95% CI, 0.36 to 130.5	1 RCT (n=227) <sup>76</sup>	Serious imprecision (wide CIs, small sample size, few events), unknown consistency	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs	RR ranged from 0.49 to 0.97 with both CIs crossing the null	2 RCTs (n=590) <sup>76, 77</sup>	Serious imprecision (wide CIs, few events)	Insufficient	Adolescents and children with MDD
SNRI: Duloxetine	Suicidal ideation or behaviors	RR (C-SSRS), 0.99; 95% CI, 0.55 to 1.78	1 RCT (n=337) <sup>67</sup>	Serious imprecision (wide CIs, few events), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	SAEs	RR (pooled for both duloxetine groups), 3.72; 95% CI, 0.86 to 16.1	1 RCT (n=336) <sup>67</sup>	Serious imprecision (wide CIs, few events), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	Withdrawal due to AEs	RR (high-dose duloxetine), 3.39; 95% CI, 1.13 to 10.2  RR (low-dose duloxetine), 1.84; 95% CI, 0.55 to 6.12	1 RCT (n=346) <sup>67</sup>	Imprecision (wide CIs), high risk of bias, <sup>67</sup> unknown consistency	Insufficient for low dose, low for harms for high dose	Adolescents and children with MDD
SNRIs: desvenlafaxine and duloxetine	Suicidal ideation or behaviors	RR, 0.88; 95% CI, 0.60 to 1.29 I <sup>2</sup> , 0% (Appendix J, Figure J-28)  CIs for RR without high risk-of-bias studies span the null	3 RCTs (n=924) <sup>67, 76, 77</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>67</sup>	Insufficient	Adolescents and children with MDD



Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SNRIs: desvenlafaxine and duloxetine (continued)	Withdrawal due to AEs	RR, 1.20; 95% CI, 0.47 to 3.06, $I^2=45\%$ , (Appendix J, Figure J-29)  CIs for RR without high risk-of-bias studies span the null	3 RCTs (n=933) <sup>67, 76, 77</sup>	Serious imprecision (wide CIs, few events), high risk of bias <sup>67</sup>	Insufficient	Adolescents and children with MDD

AE = adverse event; CI = confidence interval; C-SSRS = Columbia-Suicide Severity Rating Scale; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SNRI = serotonin and norepinephrine reuptake inhibitors.

## TCAs Versus Placebo: Benefits

### Key Points

- The evidence for children with MDD was insufficient to judge the effectiveness of TCAs as a class or as individual drugs (imipramine, desipramine, amitriptyline, and nortriptyline) for depressive symptoms, response rates, remission, relapse, and functional status.

### Detailed Results

Four RCTs compared TCAs, including imipramine, desipramine, amitriptyline, and nortriptyline, with pill placebo.<sup>71, 74, 78, 83, 90-92, 134</sup> Three studies included adolescents only and one study (evaluating nortriptyline) included children only.<sup>78, 134</sup> None of the studies examined combined child/adolescent populations. All studies focused on patients with MDD, and no studies focused on a wider range of DDs. Risk-of-bias ratings ranged from “some concerns” to “high risk” across all studies.

One study, comparing imipramine, paroxetine, and placebo, was labeled “Study 329.” As noted previously in the section on paroxetine, the original results for Study 329 were published in 2001;<sup>83</sup> a reanalysis (RIAT) addressed several flaws for the acute phase in 2015<sup>90</sup> and for the continuation phase in 2016.<sup>92</sup> The current analysis relies on the RIAT analysis of the acute phase<sup>90</sup> and the continuation phase.<sup>92</sup>

The evidence for TCAs, when analyzed individually or as a class, is insufficient to judge efficacy for depressive symptoms, remission rates, response rates, and functional status. Results of the individual TCA drug and the TCA class comparisons with pill placebo are presented in Table 40. Additional details about these studies can be found in Appendix Tables D-29 and E-23.

**Table 40. Strength of evidence for benefits of TCAs versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
TCA: Imipramine	Depressive symptoms, clinician report	SMD (HAM-D), -0.05; 95% CI, -0.34 to 0.24	1 RCT (n=182) <sup>90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>90</sup> unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (HAM-D), 1.00; 95% CI, 0.83 to 1.21	1 RCT (n=181) <sup>90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>90</sup> unknown consistency	Insufficient	Adolescents with MDD
	Remission	RR (HAM-D), 1.11; 95% CI, 0.86 to 1.43	1 RCT (n=182) <sup>92</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>92</sup> unknown consistency	Insufficient	Adolescents with MDD
	Relapse	RR (HAM-D), 1.24; 95% CI, 0.61 to 2.49	1 RCT (n=104) <sup>92</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>92</sup> unknown consistency	Insufficient	Adolescents with MDD
	Functional status, self-report	SMD (AFC), 0.22; 95% CI, -0.07 to 0.51	1 RCT (n=119) <sup>90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>90</sup> unknown consistency	Insufficient	Adolescents with MDD
	Functional status, parent report	SMD (AFC), 0.10; 95% CI, -0.26 to 0.46	1 RCT (n=119) <sup>91</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>91</sup> unknown consistency	Insufficient	Adolescents with MDD
TCA: Desipramine	Depressive symptoms, clinician report	SMD (HAM-D), -0.38; 95% CI, -0.97 to 0.21	1 RCT (n=36) <sup>71</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms, self-report	SMD (BDI), -0.41; 95% CI, -1.11 to 0.29	1 RCT (n=30) <sup>71</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
TCA: Desipramine (continued)	Remission	RR (K-SADS), 1.39; 95% CI, 0.85 to 2.29	1 RCT (n=36) <sup>71</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional status, clinician report	SMD (CGAS), -0.08; 95% CI, -0.78 to 0.61	1 RCT (n=34) <sup>71</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
TCA: Amitriptyline	Depressive symptoms, clinician report	SMD (HAM-D), -0.17; 95% CI, -0.88 to 0.55	1 RCT (n=31) <sup>74</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>74</sup> unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (HAM-D), 3.61; 95% CI, 0.95 to 13.8	1 RCT (n=31) <sup>74</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>74</sup> unknown consistency	Insufficient	Adolescents with MDD
TCA: Nortriptyline	Depressive symptoms, clinician report	SMD(CDRS), 0.08; 95% CI, -0.48 to 0.63	1 RCT (n=50) <sup>134</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Children with MDD
	Response	RR (CDRS), 1.85; 95% CI, 0.64 to 5.35	1 RCT (n=50) <sup>78, 134</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Children with MDD
	Functional status, clinician report	SMD (CGAS), -0.15; 95% CI, -0.71 to 0.40	1 RCT (n=50) <sup>134</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Children with MDD
TCAs: imipramine, desipramine, amitriptyline	Depressive symptoms, clinician report	SMD (CDRS, HAM-D), -0.11; 95% CI, -0.36 to 0.14, I <sup>2</sup> , 0% (Appendix J, Figure J-30)	3 RCTs (n=252) <sup>71, 74, 90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>74, 90</sup>	Insufficient	Adolescents with MDD

AFC = Autonomous Functioning Checklist ; BDI = Beck Depression Inventory; CDRS = Children's Depression Rating Scale; CGAS = Children's Global Assessment Scale; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; TCA = tricyclic antidepressants.

## TCAs Versus Placebo: Harms

### Key Points

- When TCAs were examined individually or as a class, evidence related to harm outcomes of interest was rated as insufficient.

### Detailed Results

Three RCTs of TCAs versus pill placebo in 258 adolescents reported harm outcomes of interest.<sup>71, 74, 90-92</sup> The TCAs studied include imipramine, desipramine, and amitriptyline. The harm outcomes reported and examined included mortality, suicidal ideation or behaviors, SAEs, and withdrawal due to AEs. As noted above, one study was labeled “Study 329.” As noted previously, the original results for Study 329 were published in 2001;<sup>83</sup> a reanalysis (RIAT) addressed several flaws for the acute phase in 2015<sup>90</sup> and for the continuation phase in 2016.<sup>92</sup>

One RCT regarding imipramine reported on mortality, and no deaths were reported in either treatment group, but this evidence was graded as insufficient.<sup>91</sup> Examined individually, the evidence for harm for suicidal ideation and behavior, SAEs, and withdrawal due to AEs was graded insufficient for the three drugs. The evidence was sufficient to allow for pooled results for one harm outcome: withdrawal due to AEs. The evidence for harm from this meta-analysis was rated as insufficient.<sup>71, 74, 90</sup> Results of the individual TCA drug and class comparisons with pill placebo for harms are presented in Table 41. Additional details can be found in Appendix Tables D-29 and F-13.

**Table 41. Strength of evidence for harms of TCAs versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
TCA: Imipramine	Mortality	There were no deaths reported during treatment or 30 days following treatment completion in either group	1 RCT (n=182) <sup>91</sup>	Serious imprecision (small sample size), high risk of bias, <sup>91</sup> unknown consistency	Insufficient	Adolescents with MDD
	Suicidal ideation or behaviors	RR, 1.87; 95% CI, 0.35 to 9.96	1 RCT (n=182) <sup>90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>90</sup> unknown consistency	Insufficient	Adolescents with MDD
	Suicide-related AEs (6 months)	RR, 2.01; 95% CI, 0.73 to 5.57	1 RCT (n=182) <sup>92</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>92</sup> unknown consistency	Insufficient	Adolescents with MDD
	SAEs	RR, 2.29; 95% CI, 0.46 to 11.5	1 RCT (n=182) <sup>83</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>83</sup> unknown consistency	Insufficient	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
TCA: Imipramine (continued)	Withdrawal due to AEs	RR, 4.73; 95% CI, 2.08 to 10.79	1 RCT (n=182) <sup>90</sup>	Imprecision (small sample size), high risk of bias, <sup>90</sup> unknown consistency	Insufficient	Adolescents with MDD
	Withdrawal due to AEs (6 months)	RR, 2.06; 95% CI, 0.66 to 6.45	1 RCT (n=182) <sup>92</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>92</sup> unknown consistency	Insufficient	Adolescents with MDD
TCA: Desipramine	Withdrawal due to AEs	RR, 0.48; 95% CI, 0.05 to 4.91	1 RCT (n=45) <sup>71</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
TCA: Amitriptyline	Suicidal ideation or behaviors	RR, 0.25; 95% CI, 0.01 to 5.59	1 RCT (n=31) <sup>74</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>74</sup> unknown consistency	Insufficient	Adolescents with MDD
	Withdrawal due to AEs	RR, 0.96; 95% CI, 0.26 to 3.59	1 RCT (n=31) <sup>74</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>74</sup> unknown consistency	Insufficient	Adolescents with MDD
TCAs: imipramine, desipramine, amitriptyline	Withdrawal due to AEs	RR, 1.66; 95% CI, 0.41 to 6.75; I <sup>2</sup> , 68% (Appendix J, Figure J-31)	3 RCTs (n=258) <sup>71, 74, 90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>74, 90</sup>	Insufficient	Adolescents with MDD

AE = adverse event; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; TCA = tricyclic antidepressants.

## MAOIs Versus Placebo: Benefits

### Key Points

- The evidence comparing selegiline in the transdermal system (STS) with placebo for depressive symptoms and response rates for adolescents with MDD was graded as insufficient.

### Detailed Results

One RCT of the MAOI selegiline in the STS form compared the treatment with patch placebo and included 304 adolescents with MDD.<sup>66</sup> The study was rated as having some risk-of-bias concerns. Evidence for depressive symptoms and response rates for adolescents with MDD was graded as insufficient. Results of the individual STS drug and the comparison with patch placebo

are presented in Table 42. Additional details about these studies can be found in Appendix Tables D-30 and E-24.

**Table 42. Strength of evidence for benefits of MAOIs versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
STS	Depressive symptoms, clinician report	SMD (CDRS-R), 0.01; 95% CI, -0.55 to 0.56	1 RCT (n=304) <sup>66</sup>	Serious imprecision (wide CIs, small sample), unknown consistency	Insufficient	Adolescents with MDD
	Response	RR (CGI), 0.98; 95% CI, 0.81 to 1.19	1 RCT (n=304) <sup>66</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

CDRS-R = Children's Depression Rating Scale-Revised; CGI = Clinical Global Impressions Scale; CI = confidence interval; MDD = major depressive disorder; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; STS = selegiline transdermal system.

## MAOIs Versus Placebo: Harms

### Key Points

- The evidence was insufficient to judge harms of selegiline STS versus placebo.

### Detailed Results

One RCT of the MAOI selegiline in STS form versus patch placebo of 308 adolescents with MDD reported harms. The evidence for suicidal ideation or behaviors and withdrawal due to AEs was rated insufficient.<sup>66</sup> Results of the analysis of STS comparison with patch placebo for harms are presented in Table 43. Additional details can be found in Appendix Tables D-30 and F-14.

**Table 43. Strength of evidence for harms of MAOIs versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
STS	Suicidal ideation or behaviors	RR, 1.03; 95% CI, 0.26 to 4.03	1 RCT (n=308) <sup>66</sup>	Serious imprecision (wide CIs, few events), unknown consistency	Insufficient	Adolescents with MDD
	Withdrawal due to AEs	RR, 2.05; 95% CI, 0.72 to 5.87	1 RCT (n=308) <sup>66</sup>	Serious imprecision (wide CIs, few events), unknown consistency	Insufficient	Adolescents with MDD

AE = adverse event; CI = confidence interval; MDD = major depressive disorder; n = number; RR = relative risk; STS = selegiline transdermal system.

## Venlafaxine + Active Control Versus Placebo + Active Control: Benefits

### Key Points

- In a population of adolescents and children with MDD, when comparing venlafaxine with active control versus placebo with active control, the evidence for benefit was rated as insufficient regarding depressive symptoms.

### Detailed Results

One RCT compared venlafaxine with an active psychotherapy control versus placebo with active psychotherapy control in the treatment of MDD in 33 adolescents and children.<sup>73</sup> The evidence for depressive symptoms from clinician, self, or parent report was rated as insufficient. Details of the analysis of the benefits and harms outcomes are presented in Table 44. Additional details about these studies can be found in Appendix Tables D-31 and E-25.

**Table 44. Strength of evidence for benefits of venlafaxine plus active control versus placebo plus active control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Venlafaxine + active control vs. placebo + active control	depressive symptoms, clinician report	SMD (CDRS) data not provided but authors report between-group differences not significant (p=0.47)	1 RCT (n=33) <sup>73</sup>	Serious imprecision (unknown CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Depressive symptoms, self-report	SMD (CDI) data not provided but authors report between-group differences not significant (p=0.37)	1 RCT (n=33) <sup>73</sup>	Serious imprecision (unknown CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Depressive symptoms, parent report	SMD (CBCL) data not provided but authors report between-group differences not significant (p=0.08)	1 RCT (n=33) <sup>73</sup>	Serious imprecision (unknown CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD

CBCL = Child Behavior Checklist; CDI = Children's Depression Inventory; CDRS = Children's Depression Rating Scale; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; SMD = standardized mean difference; vs. = versus.

## Venlafaxine + Active Control Versus Placebo + Active Control: Harms

### Key Points

- In a population of adolescents and children with MDD, when comparing venlafaxine with active control versus placebo with active control, the evidence for harm was rated as insufficient regarding withdrawal due to AEs.

## Detailed Results

One RCT compared venlafaxine with an active psychotherapy control versus placebo with active psychotherapy control in the treatment of MDD in 33 adolescents and children.<sup>73</sup> The evidence for harms in terms of withdrawal due to AEs was rated as insufficient. Details of the analysis of the benefits and harms outcomes are presented in Table 45. Additional details can be found in Appendix Tables D-31 and F-15.

**Table 45. Strength of evidence for harms of venlafaxine plus active control versus placebo plus active control**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Venlafaxine + active control vs. placebo + active control	Withdrawal due to AEs	RR, 3.00; 95% CI, 0.13 to 68.8	1 RCT (n=33) <sup>73</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD

AE = adverse event; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; vs. = versus.

## KQ 2b: Benefits and Harms of Pharmacological Interventions by Subpopulation

### SSRIs Versus Placebo: Subpopulations

#### Key Points

- A few trials examined potential moderators of the efficacy of fluoxetine versus placebo and of paroxetine versus placebo.
- For fluoxetine, statistically significant moderators included sex (in one of three studies only), depression severity (in one of two studies), and chronic depression, comorbid ADHD, alcohol consumption, and family income in one study each.
- For paroxetine, most moderators did not influence the effect of the drug on benefits. Studies suggested varying results by age. In one study of children and adolescents, age did not moderate outcomes. In another, depression symptoms and response were better in older adolescents than younger adolescents. The difference in the incidence of harms between paroxetine and placebo patients was more pronounced in older adolescents than in younger adolescents.
- No evidence exists on the moderators of mortality, suicidality, SAEs, or withdrawal due to AEs of SSRIs compared with placebo.

## Detailed Results

- **Age:** Age group (defined as children ages 8 to 12 years versus adolescents ages 13 to 17 years in two of three studies,<sup>72, 82</sup> undefined in third study<sup>95</sup>) did not significantly affect change in depressive symptoms,<sup>72, 82</sup> response,<sup>82</sup> or relapse in fluoxetine studies that examined potential moderators.<sup>95</sup> A paroxetine study, found no statistically significant differences in depressive symptoms between children and adolescents.<sup>69</sup> A



study of adolescents found improved symptoms and response in older adolescents when compared with younger adolescents.<sup>70</sup> The same study found that the magnitude of the difference in adverse events in the paroxetine group when compared with placebo was more pronounced among older adolescents when compared with younger adolescents.

- **Sex:** Two studies found that the effect of fluoxetine versus placebo on change in depressive symptoms did not significantly differ by sex,<sup>72, 82</sup> and one study found the same as it relates to response.<sup>82</sup> However, in one study, females who remained on fluoxetine after the end of treatment (12 months) were almost 9 times more likely to relapse than males who remained on fluoxetine as compared to placebo.<sup>95</sup>
- **Race:** Race (Caucasian versus non-Caucasian) did not moderate the effect of fluoxetine versus placebo on relapse.<sup>95</sup>
- **Depression Severity:** Depressive symptom severity (mild/moderate versus marked/severe) did not moderate clinician-reported functional impairment in one study of fluoxetine versus placebo.<sup>97</sup> In a different study, those with higher baseline and higher end of acute phase treatment depression severity on the CDRS-R who remained on fluoxetine after the end of treatment (12 weeks) were more likely to relapse than those with lower levels of depression severity.<sup>95</sup>
- **Depression Chronicity:** In a sample with comorbid depression and substance use disorder, those with “chronic” depression (defined as episodes lasting 9 months or longer) showed significant decreases in depressive symptoms in the fluoxetine versus placebo group when compared with those with “transient” depression (episodes lasting less than 9 months).<sup>96</sup> However, the number of prior depressive episodes did not moderate the efficacy of fluoxetine versus placebo on relapse in two studies.<sup>91, 95</sup>
- **Age of Onset:** The age of onset of depression (11 years or younger versus 12 years or older) did not affect response rate in a trial of paroxetine versus placebo.<sup>91</sup>
- **Family History of Depression:** The effect of fluoxetine versus placebo on change in depressive symptoms did not significantly differ by family history of depression in one study.<sup>82</sup>
- **Features of Depression:** The effect of paroxetine versus placebo on response did not significantly differ by the presence of atypical depression features or melancholic features of depression.<sup>91</sup>
- **Comorbid Conditions:** Adolescents with ADHD in the fluoxetine group had significantly greater improvements in depressive symptoms than those with ADHD in the placebo group; those without ADHD did not have significant differences in depressive symptoms between fluoxetine and placebo groups at the end of treatment.<sup>98</sup> In a sample with comorbid depression and substance use disorder, those with moderate use of alcohol or less (as compared with heavy use) showed significantly greater response rates and significantly greater decreases in depressive symptoms in the fluoxetine versus placebo groups.<sup>96</sup> In the same study, however, the effect of fluoxetine versus placebo on change in depressive symptoms did not significantly differ by level of marijuana consumption.<sup>96</sup> In a different study, the presence of comorbid dysthymia or comorbid anxiety did not moderate the effect of fluoxetine versus placebo on relapse.<sup>95</sup> The effect of paroxetine versus placebo on response did not significantly differ by the presence of anxiety disorder or any comorbid disorder.<sup>91</sup>

- **Family Income:** In a study of fluoxetine versus placebo, fluoxetine was more effective in terms of clinician-reported functional impairment than placebo for families making less than \$75,000/year. In families making more than \$75,000, effectiveness did not significantly differ from that of placebo.<sup>97</sup>
- **Parent Characteristics:** Age of parents did not moderate the effect of fluoxetine versus placebo on relapse.<sup>95</sup>
- **Harms:** No evidence exists on moderators of key harms. One trial did, however, examine age, sex, and family history as potential moderators of other types of harms, as reported in the evidence tables.<sup>82</sup>

Additional details about these studies can be found in Appendix Tables D-32 and G-6.

## Fluoxetine for Relapse Prevention Versus Placebo: Subpopulations

### Key Points

- Participants with no residual symptoms who were switched to placebo for continuation treatment were more likely to relapse than those on fluoxetine.

### Detailed Results

One study<sup>80</sup> (N=102, children and adolescents) evaluated the effect of residual symptoms on relapse. The study found that the odds of relapse in the placebo arm was 6.3 (95% CI, 1.8 to 22.9) compared with the odds of relapse with residual symptoms (2.1; 95% CI, 0.7 to 6.6). Additional details about these studies can be found in Appendix Tables D-33 and G-7.

## SNRIs Versus Placebo: Subpopulations

### Key Points

- Studies comparing SNRIs with placebo did not evaluate differences by subgroups of interest to this review.

## TCAs Versus Placebo: Subpopulations

### Key Points

- The efficacy of imipramine versus placebo did not differ by any of the examined moderators in one study.

### Detailed Results

- **Age of Onset:** The age of onset of depression (11 years or younger versus 12 years or older) did not affect response rate in a trial of imipramine versus placebo.<sup>91</sup>
- **Features of Depression:** The effect of imipramine versus placebo on response did not significantly differ by the presence of atypical depression features or melancholic features of depression.<sup>91</sup>
- **Comorbid Conditions:** The effect of imipramine versus placebo on response did not significantly differ by the presence of anxiety disorder or any comorbid disorder.<sup>91</sup>

Additional details about these studies can be found in Appendix Tables D-34 and G-8.

## **MAOIs Versus Placebo: Subpopulations**

### **Key Points**

- Studies comparing MAOIs with placebo did not evaluate differences by subgroups of interest to this review.

## **Venlafaxine + Active Control Versus Placebo + Active Control: Subpopulations**

### **Key Points**

- Studies comparing venlafaxine plus active control with placebo plus active control did not evaluate differences by subgroups of interest to this review.

## **KQ 3a: Benefits and Harms of Combination Interventions**

### **Fluoxetine + CBT Versus Placebo: Benefits**

#### **Key Points**

- The evidence from one RCT on the combination of fluoxetine plus CBT when compared with placebo suggests improved depressive symptoms, response, remission, functional impairment, and time to first response (low SOE).

#### **Detailed Results**

One RCT compared the combination of fluoxetine plus CBT (n=107) with pill placebo (n=112)<sup>53, 85-87, 97, 98, 119, 135</sup> among adolescents with MDD in a 12-week study.

When compared with pill placebo, the combination of fluoxetine and CBT improved depressive symptoms (mean difference [CDRS-R], -7.98; 95% CI, -10.13 to -5.83), response (risk difference, 362/1,000; 95% CI, 239 more cases to 485 more cases), remission (risk difference, 200/1,000; 95% CI, 85 more cases to 315 more cases), and functional impairment (mean difference [CGAS], 7.3; 95% CI, -15.37 to 14.58) (low SOE). Time to first response was  $\geq 5$  weeks for adolescents treated with fluoxetine plus CBT compared with  $\geq 11$  weeks for adolescents treated with placebo.<sup>135</sup> The study reported loss of diagnosis but we could not independently calculate relative risk. Table 46 includes a summary of the results and assessment of SOE. Additional details about the TADS trial can be found in Appendix Tables D-35 and E-26.

**Table 46. Strength of evidence for benefits of fluoxetine + CBT versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Fluoxetine plus CBT vs. placebo	Depressive symptoms, clinician report	SMD (CDRS-R), -0.98; 95% CI, -1.26 to -0.70	1 RCT (n=219) <sup>53</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Response	RR (CGI-I of 1 or 2 indicating very much improved or improved), 2.04 95% CI, 1.54 to 2.70	1 RCT (n=219) <sup>53</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Remission	RR (CDRS of 28 or lower at the end of treatment), 2.18; 95% CI, 1.35 to 3.51	1 RCT (n=219) <sup>85</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
	Functional status clinician report	SMD (CGAS), 0.59 95% CI, 0.32 to 0.86	1 RCT (n=219) <sup>87</sup>	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD

CBT = cognitive behavioral therapy; CDRS = Children's Depression Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions Scale; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## Fluoxetine + CBT Versus Placebo: Harms

### Key Points

- The evidence was insufficient to judge the harms of fluoxetine plus CBT when compared with placebo on mortality due to suicide, suicide-related or harms-related AEs, suicide attempts, or worsening suicidal ideation.

### Detailed Results

One RCT compared harms between fluoxetine plus CBT (n=107) and pill placebo (n=112)<sup>53, 119</sup> among adolescents with MDD in a 12-week study (Table 47). Additional details about the TADS trial can be found in Appendix Tables D-5 and F-16.

When compared with pill placebo, the rates of suicide-related or harms-related AEs, suicide attempts, or worsening suicidal ideation were not different in the fluoxetine plus CBT group, but the SOE is limited because of the small sample size and wide CIs.<sup>119</sup>

**Table 47. Strength of evidence for harms of fluoxetine + CBT versus placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Fluoxetine plus CBT vs. pill placebo	Mortality from suicide	No suicides in either group	1 RCT (n=219) <sup>53</sup>	Serious imprecision (no events, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicide-related AEs	RR, 1.74 95% CI, 0.43 to 7.12	1 RCT (n=219) <sup>119</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Harms-related AEs	RR, 1.56; 95% CI, 0.57 to 4.21	1 RCT (n=219) <sup>53</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicide attempts	RR, 5.23 95% CI, 0.25 to 107.7	1 RCT (n=219) <sup>119</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Worsening suicidal ideation	RR (SIQ-Jr of 31 or greater), 0.28; 95% CI, 0.06 to 1.32	1 RCT (n=219) <sup>119</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

AE = adverse event; CBT = cognitive behavioral therapy; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SIQ-Jr = Suicide Ideation Questionnaire-Junior High School; vs. = versus.

## Omega-3 + Family Therapy Versus Placebo: Benefits

### Key Points

- The evidence comparing omega-3 plus family therapy with pill placebo was insufficient for depression symptoms and remission for adolescents and children with MDD, dysthymia, or DD NOS.

### Detailed Results

One RCT with some risk-of-bias concerns<sup>65</sup> compared omega-3 plus family therapy, specifically psychoeducation plus CBT, (n=17) with pill placebo (n=18) over 12 weeks duration (Table 48). Evidence was insufficient to evaluate the effectiveness of omega-3 plus family therapy compared with pill placebo for clinician-reported depressive symptoms and remission. Additional details can be found in Appendix Tables D-36 and E-27.

**Table 48. Strength of evidence for benefits of family therapy versus pill placebo**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Omega-3 plus family therapy vs. placebo	Depressive symptoms, clinician report	SMD (CDRS-R), -0.48; 95% CI, -1.15 to 0.20	1 RCT (n=35) <sup>65</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS
	Remission	RR (CDRS-R≤28), 1.38; 95% CI, 0.84 to 2.25	1 RCT (n=35) <sup>65</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS

CDRS-R = Children's Depression Rating Scale-Revised; DD = depressive disorders; n = number; NOS = not otherwise specified; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## Omega-3 + Family Therapy Versus Placebo: Harms

### Key Points

- No study reported on harms.

### Detailed Results

One RCT (with some risk-of-bias concerns)<sup>65</sup> of adolescents and children ages 7 to 14 years compared omega-3 plus family therapy with placebo over 12 weeks duration but did not report on harms.

## KQ 3b: Benefits and Harms of Combination Interventions by Subpopulation

### Fluoxetine + CBT Versus Placebo: Subpopulations

### Key Points

- We found no clear evidence that family income, depression severity, or ADHD moderated outcomes for combination therapy when compared with placebo.

### Detailed Results

Two companion publication<sup>97, 98</sup> to one RCT<sup>53</sup> examined subgroup differences between fluoxetine plus CBT (n=107) and pill placebo (n=112) among adolescents with MDD in a 12-week study. One companion publication<sup>98</sup> examined variations in depressive symptoms by ADHD diagnosis, and the other companion publication<sup>97</sup> examined variations in functional impairment by family income status and depressive symptom severity. Additional details about the TADS trial can be found in Appendix Tables D-35 and G-9.

In the first companion publication, adolescents in the fluoxetine plus CBT group had significantly greater improvements in depressive symptoms when compared with placebo across both ADHD diagnosis subgroups.<sup>98</sup> In the second companion publication, adolescents in the

fluoxetine plus CBT group had improved functional impairment when compared with those in placebo at the end of treatment across the various subgroups of family income status and the various subgroups separated by depressive symptom severity.<sup>97</sup>

## **Omega-3 + Family Therapy Versus Pill Placebo: Subpopulations**

### **Key Points**

- One study comparing omega-3 plus family therapy with pill placebo found declines in depression severity in the intervention arm but not in the placebo arm in families with more psychosocial stressors or history of maternal depression.

### **Detailed Results**

One RCT with some risk-of-bias concerns<sup>65</sup> examined the effect of history of maternal depression and found a decline in depression severity associated with the number of psychosocial stressors in the intervention arm but not in the placebo arm. The study found that when families reported fewer psychosocial stressors, the intervention arm had a significant decline in depression severity and little impact in the placebo arm. The same study found similar effects for families without a history of maternal depression: significant declines in depression severity in the combined arm and no change in the placebo arm. Additional details on these trials can be found in Appendix Tables D-36 and G-10.

## **KQ 4a: Benefits and Harms of Collaborative Care Interventions**

We found no studies of collaborative care interventions that met our inclusion and exclusion criteria.

## **KQ 4b: Benefits and Harms of Collaborative Care Interventions by Subpopulation**

We found no studies of collaborative care interventions that met our inclusion and exclusion criteria.

## **KQ 5a: Comparative Benefits and Harms of Treatments**

### **CBT Versus Other Psychotherapy: Benefits**

#### **Key Points**

- Insufficient evidence exists to support conclusions on comparisons of CBT and other psychotherapies on depression diagnosis, depressive symptoms, response, remission, and relapse.

#### **Detailed Results**

Three RCTs (one with some risk-of-bias concerns,<sup>44, 120</sup> two with high risk of bias<sup>57, 60, 126, 136-138</sup>) compared benefits between CBT and IPT,<sup>57</sup> systematic behavior family therapy,<sup>60, 126, 136-138</sup> and short-term psychoanalytical therapy (Table 49).<sup>44, 120</sup> All studies were conducted on

adolescents. Two were conducted on MDD samples; one included MDD or dysthymia.<sup>57</sup> The duration of the interventions ranged from 12 to 36 weeks. Additional details on these trials can be found in Appendix Tables D-37 and E-28.

**Table 49. Strength of evidence for benefits of CBT versus other psychotherapies**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. other psychotherapies (IPT, systematic behavior family therapy, short-term psychoanalytical therapy)	Presence of MDD episode (clinician reported)	RR, 0.53; 95% CI, 0.22 to 1.29	1 RCT (n=66) <sup>60, 126, 136-138</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>60, 126, 136-138</sup> unknown consistency	Insufficient	Adolescents with MDD, CBT vs. systematic behavior family therapy
	Presence of MDD	RR (one or more antisocial behavior symptoms (self-reported) and met clinical diagnostic criteria for MDD), 0.86; 95% CI, 0.57 to 1.29	1 RCT (n=187) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD, CBT vs. short-term psychoanalytical therapy
	Presence of MDD at 52 weeks (16 weeks after end of treatment)	RR (one or more antisocial behavior symptoms (self-reported) and met clinical diagnostic criteria for MDD), 0.96; 95% CI, 0.59 to 1.57	1 RCT (n=177) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD, CBT vs. short-term psychoanalytical therapy
	Presence of MDD at 86 weeks (50 weeks after end of treatment)	RR, 1.67; 95% CI, 0.92 to 3.03	1 RCT (n=187) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD, CBT vs. short-term psychoanalytical therapy



Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. other psychotherapies (IPT, systematic behavior family therapy, short-term psychoanalytical therapy) (continued)	Depressive symptoms (self-reported)	SMD (BDI), -0.39; 95% CI, -0.88 to 0.11	1 RCT (n=277) <sup>60, 126, 136-138</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>60, 126, 136-138</sup> unknown consistency	Insufficient	Adolescents with MDD, CBT vs. systematic behavior family therapy
	Depressive symptoms (self-reported)	SMD (MFQ), -0.16; 95% CI, -0.42 to 0.1	2 RCTs (n=213) <sup>44, 60, 120, 126, 136-138</sup>	Serious imprecision (wide CIs, small sample size)	Insufficient	Adolescents with MDD, CBT vs. CBT vs. short-term psychoanalytical therapy
	Depressive symptoms (self-reported) at 52 weeks (16 weeks after end of treatment)	SMD (MFQ), 0.77; 95% CI, 0.49 to 1.04	2 RCTs (n=221) <sup>44, 60, 120, 126, 136-138</sup>	Serious imprecision (wide CIs, small sample size)	Insufficient	Adolescents with MDD, CBT vs. CBT vs. short-term psychoanalytical therapy
	Depressive symptoms (self-reported) at 86 weeks (50 weeks after end of treatment)	SMD (MFQ), 0.03; 95% CI, -0.22 to 0.29	2 RCTs (n=237) <sup>44, 60, 120, 126, 136-138</sup>	Serious imprecision (wide CIs, small sample size)	Insufficient	Adolescents with MDD, CBT vs. CBT vs. short-term psychoanalytical therapy
	Depressive symptoms (self-reported)	SMD (based on CDI), 0.35; 95% CI, -0.28 to 0.98	1 RCT (n=40) <sup>57</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>57</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or both
	Depressive symptoms (self-reported) at 36 weeks (24 weeks after end of treatment)	SMD (based on CDI), -0.59; 95% CI, -1.43 to 0.24	1 RCT (n=23) <sup>57</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>57</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or both

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. other psychotherapies (IPT, systematic behavior family therapy, short-term psychoanalytical therapy) (continued)	Response	RR, 0.97; 95% CI, 0.81 to 1.16	1 RCT (n=213) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response at 52 weeks (16 weeks after end of treatment)	RR, 1.01; 95% CI, 0.86 to 1.20	1 RCT (n=221) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response at 86 weeks (50 weeks after end of treatment)	RR, 1.10; 95% CI, 0.95 to 1.26	1 RCT (n=237) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Response	RR, 0.72; 95% CI, 0.49 to 1.05	1 RCT (n=48) <sup>57</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>57</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or both
	Remission	RR, 1.6; 95% CI, 1.11 to 2.31 in one study <sup>60, 126, 136-138</sup> ) No significant differences in another (details NR) <sup>44, 120</sup>	2 RCTs (n=381) <sup>44, 60, 120, 126, 136-138</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>60, 126, 136-138</sup> inconsistent	Insufficient	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. other psychotherapies (IPT, systematic behavior family therapy, short-term psychoanalytical therapy) (continued)	Relapse at 86 weeks (50 weeks after end of treatment)	RR, 3.88; 95% CI, 0.87 to 17.27	1 RCT (n=97) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CI = confidence interval; IPT = interpersonal therapy; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

CBT was not significantly different than other psychotherapies in improving depression diagnosis, depressive symptoms, response, or relapse. The exclusion of the high risk-of-bias study when evaluating clinician-rated depression symptoms continued to result in insufficient ratings because of the serious imprecision of the remaining studies.

## CBT Versus Other Psychotherapy: Harms

### Key Points

- Insufficient evidence exists to support conclusions on comparisons of CBT and other psychotherapies on harms.

### Detailed Results

One RCT (with some risk-of-bias concerns) compared AE scores and dropout rates<sup>121, 122</sup> between CBT and short-term psychoanalytical therapy (Table 50).<sup>44, 120</sup> The study was conducted on adolescents with MDD, and the intervention lasted for 36 weeks. Additional details on this trial can be found in Appendix Tables D-37 and F-17.

AE scores did not vary by study arm. The study also reported suicides (1 per arm at 36 weeks) but did not report denominators for each arm; as a result, we could not calculate risk ratios. A second study reported on "Suicide>4" but did not define the measure; the results are not discussed further.<sup>60, 126, 136-138</sup>

**Table 50. Strength of evidence for harms of CBT versus other psychotherapies**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
CBT vs. other psychotherapies (short-term psychoanalytical therapy)	Suicide attempt	1 per arm, denominator not provided	1 RCT (n not reported) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicide attempt (86 weeks)	No recent suicide attempts in either group	1 RCT (n not reported) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	AEs score	SMD, 0.00 (95% CI, -0.27 to 0.27)	1 RCT (n=213) <sup>44, 120</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Dropout	32% vs, 43%, no evidence of difference in chi-square test, RR not calculable	1 RCT (n by arm not reported) <sup>121, 122</sup>	Unknown imprecision, unknown consistency	Insufficient	Adolescents with MDD

CBT = cognitive behavioral therapy; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## Psychotherapy Within-Type Comparisons of Delivery Methods or Approaches: Benefits

### Key Points

- Insufficient evidence exists to support conclusions on comparisons of CBT and other psychotherapies on depressive symptoms, remission, and functional impairment.

### Detailed Results

Six RCTs (two with some risk-of-bias concerns,<sup>59, 108</sup> four with high risk of bias<sup>100, 106, 107, 110, 139</sup>) compared benefits between delivery methods or approaches for different types of psychotherapy (Table 51). Three trials tested the involvement of parents (parent-adolescent CBT vs. adolescent-only CBT,<sup>100</sup> CBT with separate parent sessions vs. adolescent-only CBT,<sup>59</sup> and high vs. low intensity of engagement with parents in two IPT arms).<sup>108</sup> Two studies evaluated variants of CBT (enhanced CBT vs. CBT<sup>106</sup> and CBT over interactive televideo vs. face-to-face).<sup>107</sup> One evaluated focused individual psychodynamic psychotherapy (FIPP) compared with time-limited systems integrative family therapy (SIFT).<sup>110, 139</sup> All studies were conducted on adolescents; in addition, two studies also included children.<sup>59, 110, 139</sup> One study was conducted in overweight or obese children.<sup>90</sup> Depression types varied across the studies: some limited the studies to MDD only, while others included dysthymia. The duration of the interventions ranged from 8 weeks to 9 months. Additional details on these trials can be found in Appendix Tables D-39 and E-29.

**Table 51. Strength of evidence for comparative benefits of psychotherapy interventions comparing varying delivery methods or approaches**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Parent involvement in psychotherapy vs. no or reduced involvement in therapy	Depressive symptoms (clinician reported)	SMD (HAM-D), 0.35; 95% CI, -0.13 to 0.83	1 RCT (n=69) <sup>59</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Depressive symptoms (clinician reported)	SMD (CDRS-R), 0.14; 95% CI, -0.90 to 1.17	1 RCT (n=15) <sup>108</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD, dysthymia, DD NOS, adjustment disorder with depressed mood
	Depressive symptoms (self-reported)	No difference between treatment arms based on BDI, <sup>100</sup> RR, -0.32; 95% CI, -0.16 to 0.80 <sup>59</sup>	2 RCTs (n=93) <sup>59, 100</sup>	Serious imprecision (wide CIs, small sample size)	Insufficient	Adolescents with MDD
	Remission	RR, 1.06 (95% CI, 0.76 to 1.48)	1 RCT (n=69) <sup>59</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Functional status	SMD (GAF), -0.08 (95% CI, -0.56 to 0.39)	1 RCT (n=69) <sup>59</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD or dysthymia
Enhanced CBT vs. CBT	Depressive symptoms (self-rated)	SMD (BDI), 0.21; 95% CI, -0.61 to 1.03	1 RCT (n=28) <sup>106</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>106</sup> unknown consistency	Insufficient	Adolescents with MDD or dysthymia
	Depressive symptoms (self-rated) at 48 weeks (24 weeks after end of treatment)	SMD (BDI), 0.34; 95% CI, -0.49 to 1.18	1 RCT (n=26) <sup>106</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>106</sup> unknown consistency	Insufficient	Adolescents with MDD or dysthymia

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Televideo vs. face-to-face CBT	Depressive symptoms (self-rated)	No statistically significant effects reported for treatment arm for BDI or CDI (based on reported p-values)	1 RCT (n=28) <sup>107</sup>	Serious imprecision (small sample size), high risk of bias, <sup>107</sup> unknown consistency	Insufficient	Adolescents or children with MDD
Individual psychodynamic psychotherapy vs. family therapy	Diagnosis of depression or dysthymia (clinician reported)	RR (MDD), 0.79 (95% CI, 0.31 to 2.05)  RR (dysthymia), 0.90 (95% CI, 0.34 to 2.43)	1 RCT (n=72) <sup>110, 139</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>110, 139</sup> unknown consistency	Insufficient	Adolescents or children with MDD, dysthymia, or both
	Diagnosis of depression or dysthymia (clinician reported) at 15 months (9 months after end of treatment)	RR (MDD), 0.07; 95% CI, 0.00 to 1.19  RR (dysthymia), 0.12; 95% CI, 0.01 to 2.10	1 RCT (n=72) <sup>110, 139</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>110, 139</sup> unknown consistency	Insufficient	Adolescents or children with MDD, dysthymia, or both
	Depressive symptoms (self-reported)	SMD (based on CDI and MFQ) ranges from 0.29 to 0.52; CIs cross the null for MFQ	1 RCT (n=72) <sup>110, 139</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>110, 139</sup> unknown consistency	Insufficient	Adolescents or children with MDD, dysthymia, or both
	Depressive symptoms (self-reported) at 15 months (6 months after end of treatment)	SMD (based on CDI and MFQ) ranges from 0.09 to 0.13; CIs cross the null	1 RCT (n=72) <sup>110, 139</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>110, 139</sup> unknown consistency	Insufficient	Adolescents or children with MDD, dysthymia, or both
	Functional impairment	SMD (CGAS), 1.10; 95% CI, 0.95 to 1.26	1 RCT (n=72) <sup>110, 139</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>110, 139</sup> unknown consistency	Insufficient	Adolescents or children with MDD, dysthymia, or both

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Individual psychodynamic psychotherapy vs. family therapy (continued)	Functional impairment at 15 months (6 months after end of treatment)	SMD (CGAS), 0.30; 95% CI, -0.16 to 0.77	1 RCT (n=72) <sup>110, 139</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>110, 139</sup> unknown consistency	Insufficient	Adolescents or children with MDD, dysthymia, or both

BDI = Beck Depression Inventory; CGAS = Children's Global Assessment Scale; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CI = confidence interval; DD = depressive disorder; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n = number; NOS = not otherwise specified; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

The evidence does not support conclusions of differences in depression diagnosis, depressive symptoms, remission, or functional status with and without parent involvement in CBT or IPT (insufficient). The evidence was also insufficient to judge the comparative effectiveness of enhanced CBT versus standard CBT, televideo versus face-to-face CBT, and individual psychodynamic psychotherapy versus family therapy. Excluding the high risk-of-bias studies continued to result in insufficient ratings because of the serious imprecision of the remaining studies.

## Psychotherapy Within-Type Comparisons of Delivery Methods or Approaches: Harms

### Key Points

- No studies reported on harms.

### Detailed Results

Six RCTs (two with some risk-of-bias concerns,<sup>59, 108</sup> four with high risk of bias<sup>100, 106, 107, 110, 139</sup>) compared delivery methods or approaches for different types of psychotherapy, none evaluated harms.

## Psychotherapy Versus Pharmacotherapy: Benefits

### Key Points

- Fluoxetine is superior to CBT in improving clinician-reported depression scores in adolescents with MDD (low for benefit).
- Insufficient evidence exists to support conclusions on comparisons of CBT and other psychotherapies on self-reported depression scores, response, remission, and functional status.

### Detailed Results

Three RCTs compared benefits between CBT and pharmacotherapy (two with some risk-of-bias concerns<sup>53, 85-87, 97-99, 119, 135</sup> and one high risk-of-bias<sup>101</sup>). One of the three studies

offered group therapy (Table 52).<sup>99</sup> One study included participants with dysthymic disorder and DD NOS, in addition to MDD,<sup>101</sup> and the others were restricted to MDD only. All studies focused on adolescents. The duration of the interventions ranged from 12 to 16 weeks. Additional details on these three trials can be found in Appendix Tables D-40 and E-30.

**Table 52. Strength of evidence for benefits of psychotherapy versus pharmacotherapy**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy vs. pharmacotherapy	Depression (clinician rated)	SMD (CDRS-R), 0.66; 95% CI, 0.39 to 0.93	1 RCT (n=220) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Imprecision (small sample size), unknown consistency	Low (benefit for pharmacotherapy)	Adolescents with MDD
	Depressive symptoms (self-rated)	SMD (CDI, RADS), 0.07 to 0.54, CIs cross the null in one study <sup>99</sup>	2 RCTs (n=281) <sup>53, 85, 87, 97-99, 119, 135</sup>	Imprecision (small sample size), inconsistency in overlap of CIs	Insufficient	Adolescents with MDD
	Depressive symptoms (self-rated)	SMD (RADS), -0.42; 95% CI, -1.00 to 0.15	1 RCT (n=46) <sup>101</sup>	Imprecision (wide CIs, small sample size), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or DD NOS
	Response	RRs range from 1.12 to 1.24, CIs span the null in both studies	2 RCTs (n=284) <sup>53, 85, 87, 97-99, 119, 135</sup>	Serious imprecision (wide CIs, small sample size)	Insufficient	Adolescents with MDD
	Presence of MDD after treatment	OR (medication vs. CBT), 6.86; 95% CI, 1.12 to 41.48	1 RCT (n=46) <sup>101</sup>	Imprecision (wide CIs, small sample size), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or DD NOS
	Remission from MDD	RR, 0.70; 95% CI, 0.40 to 1.20	1 RCT (n=220) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Remission from dysthymia or DD not otherwise specified	OR (medication vs. CBT), OR = 1.6; 95% CI, 0.23 to 11.27	1 RCT (n=46) <sup>101</sup>	Imprecision (wide CIs, small sample size), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD dysthymia, or DD NOS



Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy vs. pharmacotherapy (continued)	Functional status	SMD (CGAS), -0.18; 95% CI, -0.47 to 0.11	1 RCT (n=220) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Imprecision (small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional status	SMD (CGAS), -0.18; 95% CI, -0.47 to 0.11	1 RCT (n=46) <sup>101</sup>	Imprecision (wide CIs, small sample size), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or DD NOS

CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CI = confidence interval; DD = depressive disorder; MDD = major depressive disorder; n = number; NOS = not otherwise specified; OR = odds ratio; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

One of two studies<sup>53, 85, 87, 97, 98, 119, 135</sup> reported that fluoxetine was superior to CBT in improving patient-reported depression scores (SMD, 0.54; 95% CI, 0.27 to 0.81); confidence intervals in the second study crossed the null. Given the imprecision, the findings are insufficient to judge the comparative effectiveness of the two treatments. The evidence was insufficient to support conclusions of differences in response or functional status.

Evidence from one study (TADS) suggests benefit for pharmacotherapy in reducing clinician-reported depression scores (mean difference [CDRS-R], 5.76; 95% CI, 3.46 to 8.06) when compared with CBT (low SOE) in adolescents with MDD.

## Psychotherapy Versus Pharmacotherapy: Harms

### Key Points

- Evidence from one study suggests fewer harms for psychotherapy than pharmacotherapy for treatment-emergent psychiatric AEs (low SOE) for adolescents with MDD.
- The evidence was insufficient to judge the comparative effectiveness of psychotherapy versus pharmacotherapy for improving suicidal ideation in adolescents with MDD, dysthymia, or DDs NOS.
- The evidence was insufficient to judge the comparative harms from psychotherapy versus pharmacotherapy on suicide attempts or SAEs.
- No deaths were reported.

### Detailed Results

Table 53 presents three RCTs compared harms between CBT and pharmacotherapy (two with some risk-of-bias concerns<sup>53, 85, 87, 97-99, 119, 135</sup> and one high risk of bias<sup>101</sup>). One study included participants with dysthymic disorder and DD NOS in addition to MDD,<sup>101</sup> and the other two were restricted to MDD only. All studies focused on adolescents. The duration of the interventions was 12 weeks for all studies. Additional details on these trials can be found in Appendix Tables D-40 and F-18.

**Table 53. Strength of evidence for harms of psychotherapy versus pharmacotherapy**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy vs. pharmacotherapy	Mortality	No suicides reported	1 RCT (n=220) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (small sample size, no events), unknown consistency	Insufficient	Adolescents with MDD
	Suicidality (self-reported score)	SMD (SIQR-Jr), -0.28; 95% CI, -0.55 to -0.02, suicidal ideation based on one item in the CDI was not statistically significant (p>0.05)	2 RCTs (n=279) <sup>53, 85, 87, 97-99, 119, 135</sup>	Imprecision (small sample size), inconsistency	Insufficient	Adolescents with MDD
	Suicidality (self-reported score)	SMD (SIQR-Jr), -0.20; 95% CI, -0.77 to 0.37	1 RCT (n=48) <sup>101</sup>	Imprecision (small sample size), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, or DD NOS
	Suicide attempts	RR, 0.49; 95% CI, 0.05 to 5.34  Suicide-related AEs, 0.55; 95% CI, 0.19 to 1.58	1 RCT (n=220) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicide-related AEs	RR, 0.33; 95% CI, 0.01 to 7.95	1 RCT (n=220) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (few events, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Harms-related AEs	RR, 0.38; 95% CI, 0.14 to 1.03	1 RCT (n=220) <sup>53</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Treatment-emergent psychiatric AEs	RR, 0.08; 95% CI, 0.01 to 0.62	1 RCT (n=220) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Imprecision (small sample size), consistency unknown	Low (benefit for psychotherapy)	Adolescents with MDD

AE = adverse event; CDI = Children's Depression Inventory; CI = confidence interval; MDD = major depressive disorder; n = number; NOS = not otherwise specified; RCT = randomized controlled trial; RR = relative risk; SIQR-Jr = Suicide Ideation Questionnaire-Junior High School; SMD = standardized mean difference; vs. = versus.

Results reported in one (TADS) study in adolescents with MDD suggest greater benefit for the CBT arm in reducing suicidal ideation than fluoxetine (calculated SMD for Suicide Ideation

Questionnaire-Junior High School (SIQR-Jr), -0.28; 95% CI, -0.55 to -0.02). These results, however, are not consistent with the authors' interpretation of their results: they report that "fluoxetine alone was not significantly different from CBT alone ( $P = 0.22$ )" (p. 814) with no further details. The other study on adolescents with MDD did not find significant differences in suicidal ideation by treatment arm. In adolescents with MDD, dysthymia, or DD NOS, the evidence was insufficient to evaluate comparative risks of suicidal ideation.

Evidence from one study<sup>85, 87, 97, 98, 119, 135</sup> suggests greater benefit for CBT for treatment-emergent psychiatric AEs when compared with pharmacotherapy (risk difference, -100/1,000, 160 fewer cases to 40 fewer cases) (low SOE) but is insufficient to judge comparative risks of suicide-related or harms-related AEs in adolescents with MDD.

## **Psychotherapy Plus Pharmacotherapy Versus Psychotherapy: Benefits**

### **Key Points**

- Combination therapy (psychotherapy plus pharmacotherapy) is superior to psychotherapy alone in improving clinician-reported depression scores, remission, and functional status in adolescents with MDD (low SOE).
- Combination therapy (psychotherapy plus pharmacotherapy) is superior to psychotherapy alone in improving clinician-reported depression scores in school-refusing adolescents with MDD and comorbid anxiety (low SOE).
- The evidence was insufficient to judge the comparative effectiveness of combined therapy when compared with psychotherapy alone for other populations and outcomes.

### **Detailed Results**

Five RCTs<sup>53, 85, 87, 97-99, 101, 111, 113, 119, 135, 140</sup> and one observational study<sup>114</sup> compared benefits between combined psychotherapy and pharmacotherapy and psychotherapy alone (one with low risk of bias,<sup>113</sup> three with some risk-of-bias concerns,<sup>53, 85, 87, 97-99, 111, 119, 135, 140</sup> and two with high risk of bias<sup>101, 114</sup>) (Table 54). Three studies offered sertraline,<sup>99, 101, 113</sup> one offered fluoxetine,<sup>53, 85, 87, 97, 98, 119, 135</sup> one offered imipramine in a group of school-refusing adolescents,<sup>111, 140</sup> and one did not specify the pharmacotherapy other than to state the adolescents elected to take SSRIs.<sup>114</sup> Regarding psychotherapy, five studies offered CBT (two offered group therapy<sup>99, 113</sup> and three offered individual therapy<sup>53, 85, 87, 97, 98, 101, 111, 119, 135, 140</sup>) and one offered IPT.<sup>114</sup> All except one study<sup>114</sup> were limited to adolescents. Two studies included participants with dysthymic disorder and DD NOS in addition to MDD,<sup>101, 114</sup> a second focused on adolescents with a primary DD and a comorbid alcohol use disorder,<sup>113</sup> a third focused on adolescents with one or more anxiety disorders and MDD,<sup>111, 140</sup> and the other two were restricted to MDD only.<sup>53, 85, 87, 97-99, 119, 135</sup>

The duration of the interventions ranged from 8 to 16 weeks. Additional details on these studies can be found in Appendix Tables D-41 and E-31.

**Table 54. Strength of evidence for benefits of psychotherapy plus pharmacotherapy versus psychotherapy**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. pharmacotherapy	Depression (clinician rated)	SMD (CBT + fluoxetine vs. CBT) (CDRS-R), -0.95; 95% CI, -1.23 to -0.67	1 RCT (n=218) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Imprecision (small sample size), unknown consistency	Low for benefit for combination therapy	Adolescents with MDD
	Depression (clinician rated)	SMD (IPT + SSRIs vs. IPT) (CDRS), -0.72; 95% CI, -1.76 to 0.32	1 study (n=16) <sup>114</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, unknown consistency	Insufficient	Children with MDD, dysthymic disorder, or DD NOS
	Depression (clinician rated)	SMD (CBT + imipramine vs. CBT) (CDRS), -0.83; 95% CI, -1.35 to -0.32	1 RCT (n=63) <sup>111, 140</sup>	Imprecision (small sample size), unknown consistency	Low for benefit for combination therapy	School-refusing adolescents with comorbid anxiety and MDD
	Depression (clinician rated)	SMD (CBT + sertraline vs. CBT) (HAM-D), 0.37; 95% CI, -0.88 to 1.62	1 RCT (n=10) <sup>113</sup>	Serious imprecision (wide CI, small sample size), unknown consistency	Insufficient	Adolescents with comorbid substance use disorders and MDD
	Depressive symptoms (self-rated)	SMD (CBT + fluoxetine or sertraline vs. CBT) (CDI, RADS) ranges from -0.83 to 0.11, CI, span the null in one study	2 RCTs (n=280) <sup>53, 85, 87, 97-99, 119, 135</sup>	Serious imprecision (wide CIs, small sample size), inconsistency	Insufficient	Adolescents with MDD
	Depressive symptoms (self-rated)	SMD (CBT + sertraline vs. CBT) (RADS), 0.33; 95% CI, -0.25 to 0.90	1 RCT (n=47) <sup>101</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>101</sup>	Insufficient	Adolescents with MDD, dysthymic disorder, or DD NOS
	Depressive symptoms (self-rated)	SMD (CBT + imipramine vs. CBT), -0.42; 95% CI, -0.92 to 0.08	1 RCT (n=63) <sup>111, 140</sup>	Serious imprecision (wide CIs, small sample size)	Insufficient	School-refusing adolescents with comorbid anxiety and MDD
	Presence of MDD after treatment	OR (CBT vs. combined therapy) 0.19; 95% CI, 0.03 to 1.16	1 RCT (n=47) <sup>101</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymic disorder, or DD NOS

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. pharmacotherapy (continued)	Remission from MDD	RR (CBT + fluoxetine vs. CBT), 2.31; 95% CI, 1.41 to 3.79	1 RCT (n=218) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Imprecision (small sample size), unknown consistency	Low for benefit for combination therapy	Adolescents with MDD
	Remission from MDD	OR (CBT vs. CBT + sertraline), 2.7; 95% CI, 0.60 to 12.14 <sup>101</sup>	1 RCT (n=47) <sup>101</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymic disorder, or DD NOS
	Remission from dysthymia, DD not otherwise specified	OR (CBT vs. CBT + sertraline), 0.71; 95% CI, 0.10 to 5.12 <sup>101</sup>	1 study (n=47) <sup>101</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymic disorder, or DD NOS
	Response	RR ranges from 0.78 to 1.64  CIs in 1 of 2 studies crosses the null	2 RCTs (n=270) <sup>53, 85, 87, 97-99, 119, 135</sup>	Serious imprecision (wide CIs, small sample size), inconsistency	Insufficient	Adolescents with MDD
	Remission from MDD	RR (CBT + imipramine vs. CBT), 1.65; 95% CI, 0.89 to 3.06 <sup>111, 140</sup>	1 RCT (n=63) <sup>111, 140</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	School-refusing adolescents with comorbid anxiety and MDD
	Functional status	SMD (CBT + fluoxetine vs. CBT) (CGAS), 0.56; 95% CI, 0.27 to 0.86	1 RCT (n=185) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Imprecision (small sample size), unknown consistency	Low for benefit for combined therapy	Adolescents with MDD
	Functional status	SMD (IPT + SSRIs vs. IPT), 0.42; 95% CI, -0.60 to 1.44	1 study (n=16) <sup>114</sup>	Serious imprecision (small sample size, wide confidence intervals), high risk of bias, <sup>114</sup> unknown consistency	Insufficient	Children with MDD, dysthymic disorder, or DD NOS

CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS = Children's Depression Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CI = confidence interval; DD = depressive disorder; HAM-D = Hamilton Depression Rating Scale; IPT = interpersonal psychotherapy; MDD = major depressive disorder; n = number; NOS = not otherwise specified; OR = odds ratio; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

The evidence indicates that in adolescents with MDD a combined approach of CBT plus fluoxetine results in greater improvement in clinician-rated depression (mean difference [CDRS-R], -8.27; 95% CI, -10.59 to 5.95), remission (risk difference, 210/1,000; 95% CI, 96 more cases to 324 more cases), and functional status (mean difference [CGAS], 6.60; 95% CI, 3.23 to 9.97) when compared with CBT alone (low SOE). In school-refusing adolescents with comorbid anxiety and MDD, the evidence also suggests greater effectiveness of combination therapy (CBT plus imipramine) than CBT alone on clinician-rated depression scores (mean difference [CDRS], -11.1; 95% CI, -17.68 to -4.52) (low SOE). In other populations, the evidence was not sufficient to judge the comparative benefit of a combined approach on clinician-rated depression scores. The evidence was not sufficient to judge the comparative effectiveness of combined psychotherapy plus pharmacotherapy versus psychotherapy on other outcomes.

## **Psychotherapy Plus Pharmacotherapy Versus Psychotherapy: Harms**

### **Key Points**

- The evidence was insufficient to judge the comparative harms from combination therapy or psychotherapy on suicidal ideation, suicide attempts, treatment-emergent psychiatric AEs, suicide-related AEs, or SAEs.
- No deaths were reported.

### **Detailed Results**

Three RCTs compared harms between CBT and pharmacotherapy (one with some risk-of-bias concerns<sup>53, 85, 87, 97-99, 119, 135</sup> and one high risk of bias<sup>101</sup>) (Table 55). One study included participants with dysthymic disorder and DD NOS in addition to MDD,<sup>101</sup> and the other two were restricted to MDD only. All studies focused on adolescents. The duration of the interventions was 12 weeks for all trials. Additional details of these trials can be found in Appendix Tables D-41 and F-19.

**Table 55. Strength of evidence for harms of psychotherapy plus pharmacotherapy versus psychotherapy**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. psychotherapy	Mortality	No suicides reported	1 RCT (n=218) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (small sample size, no events), unknown consistency	Insufficient	Adolescents with MDD
	Suicidality (self-reported score)	SMD (SIQR-Jr) 0.04; 95% CI, -0.23 to 0.30, suicidal ideation based on one item in the CDI was not statistically significant (p>0.05)	2 RCTs (n=270) <sup>53, 85, 87, 97-99, 119, 135</sup>	Serious imprecision (small sample size, wide CIs)	Insufficient	Adolescents with MDD
	Suicidality (self-reported score)	SMD (SIQR-Jr); 0.19; 95% CI, -0.38 to 0.76	1 RCT (n=47) <sup>101</sup>	Serious imprecision (small sample size, wide confidence intervals), high risk of bias, unknown consistency	Insufficient	Adolescents with MDD, dysthymic disorder, or DD NOS
	Suicide attempts	RR, 4.15; 95% CI, 0.47 to 36.53	1 RCT (n=218) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Psychiatric-related AEs	No events	1 RCT (n=218) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (no events, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Harms-related AEs	RR, 1.87; 95% CI, 0.65 to 5.39	1 RCT (n=218) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (no events, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Suicide-related AEs	RR, 1.25; 95% CI, 0.39 to 3.96	1 RCT (n=218) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (no events, small sample size), unknown consistency	Insufficient	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. psychotherapy (continued)	Treatment-emergent psychiatric AEs	RR, 6.22; 95% CI, 0.76 to 50.84	1 RCT (n=218) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

AE = adverse event; CDI = Children's Depression Inventory; CI = confidence interval; MDD = major depressive disorder; n = number; NOS = not otherwise specified; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SIQR-Jr = Suicide Ideation Questionnaire-Junior High School; SMD = standardized mean difference; vs. = versus.

The evidence was insufficient to rate the comparative effectiveness of the two treatments on suicidal ideation because of serious imprecision. The evidence from a single study is insufficient to rate the SOE on mortality, suicide attempts, psychiatric, suicide-related, or harms-related AEs, and treatment-emergent psychiatric AEs.

## Psychotherapy Plus Pharmacotherapy Versus Pharmacotherapy: Benefits

### Key Points

- Insufficient evidence exists to support conclusions on comparisons of combined therapy versus pharmacotherapy alone on clinician-rated depressive symptoms, response, recovery, relapse, and functional status.
- Not all combined therapy is effective. Adding CBT (brief, group, or individual) to pharmacotherapy (fluoxetine, sertraline, or unspecified SSRIs) does not appear to improve self-rated depression scores (low for no benefit), whereas adding CBT to bupropion appears to improve self-rated depression scores (low for benefit) as does adding fluoxetine to CBT compared with fluoxetine alone.
- Adding CBT to pharmacotherapy (fluoxetine) improves remission in MDD-only samples (low for benefit) but not in studies with a wider range of DDs (insufficient).
- Insufficient evidence exists to support conclusions on self-rated repression scores, presence of MDD, or remission for adding CBT to SSRIs, based on studies with a wider range of DDs.

### Detailed Results

Six RCTs (two high risk of bias<sup>101, 104</sup> and four with some concerns<sup>53, 85, 87, 97-99, 103, 105, 119, 135</sup>) compared benefits between combined pharmacotherapy and psychotherapy (specifically CBT) and pharmacotherapy alone (Table 56). Pharmacotherapy included sertraline (two studies),<sup>99, 101</sup> fluoxetine (one study<sup>53, 85, 87, 97, 98, 119, 135</sup>), SSRIs (two studies),<sup>103, 104</sup> and bupropion (one study<sup>105</sup>). One offered group therapy,<sup>99</sup> and others offered individual therapy. One study included participants with dysthymic disorder and DD NOS in addition to MDD,<sup>101</sup> and the others were restricted to MDD only. All studies focused on adolescents. The duration of the interventions ranged from 8 weeks to 28 weeks. Additional details of these trials can be found in Appendix Tables D-42 and E-32.



Evidence from two studies with varying intensity of CBT suggests mixed results for clinician-rated depression symptoms (insufficient). One study<sup>53, 85, 87, 97, 98, 119, 135</sup> with more intense CBT interventions demonstrated benefit in clinician-rated depression symptoms (SMD for CDRS-R, -0.31; 95% CI, -0.57 to -0.04), while the other with less intense CBT did not.<sup>103</sup>

For patient-rated depression symptoms, the results vary based on the comparisons. The pooled analysis comparing the benefits of CBT (group, individual, brief) plus SSRIs (sertraline, fluoxetine, unspecified SSRIs) versus SSRIs in MDD-only samples suggests low SOE for no benefit based on evidence spanning the null in three of four studies (SMD, -0.15; 95% CI, -0.34 to 0.03, N=450,  $I^2=0\%$ ).<sup>53, 85, 87, 97-99, 103, 104, 119, 135</sup> One study suggested benefit from adding fluoxetine to CBT (individual sessions) compared with fluoxetine alone. Without the high risk-of-bias study,<sup>104</sup> the results continued to suggest no benefit (SMD, -0.14; 95% CI, -0.36 to 0.08, N=427,  $I^2=22\%$ ); the SOE did not change as a result of the sensitivity analysis. Evidence from one study in an MDD-only sample suggests benefit for adding CBT to bupropion when compared with bupropion alone (mean difference [BDI], -5.2; 95% CI, -9.31 to -1.09) (low SOE).<sup>105</sup> Evidence for samples with a wider range of diagnoses (MDD, dysthymic disorder, or DD NOS) from one high risk-of-bias study<sup>101</sup> is insufficient to determine whether adding CBT to SSRIs is superior to CBT alone.

**Table 56. Strength of evidence for benefits of psychotherapy plus pharmacotherapy versus pharmacotherapy**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. pharmacotherapy	Depressive symptoms (clinician-rated)	SMD (MDD only, CBT + SSRIs vs. SSRIs), based on CDRS-R and HAM-D, ranges from -0.31 to -0.03, CIs span the null in one study	2 RCTs (n=368) <sup>53, 85, 87, 97, 98, 103, 119, 135</sup>	Imprecision (wide CIs), inconsistency	Insufficient	Adolescents with MDD
	Depressive symptoms (clinician-rated) at 52 weeks (40 weeks after treatment)	SMD for MDD-only sample, CBT + SSRI vs. SSRI (HAM-D), -0.23; 95% CI, -0.55 to 0.09	1 RCT (n=152) <sup>103</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms (self-rated)	SMD for MDD-only sample, CBT + SSRI vs. SSRI (based on CDI, RADS, CES-D, and MFQ), -0.15; 95% CI, -0.34 to 0.03, $I^2=0\%$ (Appendix J, Figure J-32)	4 RCTs (n=450) <sup>53, 85, 87, 97-99, 104, 105, 119, 135</sup>	Imprecision (wide CIs), inconsistent, high risk of bias <sup>104</sup>	Low for no benefit of adding CBT to SSRIs	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. pharmacotherapy (continued)	Depressive symptoms (self-rated) (continued)	SMD without high risk-of-bias studies, -0.14; 95% CI, -0.36 to 0.31, N=427, $I^2=22\%$				
	Depressive symptoms (self-rated) at 52 weeks (40 weeks after treatment)	SMD for MDD-only sample, CBT + SSRI vs. SSRI (CES-D), -0.3; 95% CI, -0.64 to 0.00	1 RCT (n=152) <sup>103</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Depressive symptoms (self-rated)	SMD (CBT + SSRIs vs. SSRIs) (RADs), -0.07; 95% CI, -0.62 to 0.48	1 RCT (n=51) <sup>101</sup>	Imprecision (wide CIs), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, DD NOS
	Depressive symptoms (self-rated)	SMD for MDD-only sample, CBT + bupropion vs. bupropion (based on BDI) -0.62; 95% CI, -1.11 to -0.12 <sup>105</sup>	1 RCT (n=65) <sup>105</sup>	Imprecision (small sample size), unknown consistency	Low for benefit of adding CBT to bupropion	Adolescents with MDD
	Presence of MDD after treatment	OR (combination vs. medication), 1.31; 95% CI, 0.31 to 5.48)	1 RCT (n=51) <sup>101</sup>	Imprecision (wide CIs), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, DD NOS
	Response	RR (based on improvement against CDI threshold) ranges from 0.89 to 1.17, CIs cross the null in both studies	2 RCTs (n=275) <sup>53, 85, 87, 97-99, 119, 135</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Recovery	RR for recovery from index diagnosis, 0.82; 95% CI, 0.48 to 1.42	1 RCT (n=152) <sup>103</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Recovery at 52 weeks (40 weeks after end of treatment)	RR for recovery from index diagnosis, 0.82; 95% CI, 0.48 to 1.42	1 RCT (n=152) <sup>103</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. pharmacotherapy (continued)	Remission from MDD	RR (combination vs. medication), 1.61; 95% CI, 1.05 to 2.46)	1 RCT (n=216) <sup>85</sup>	Imprecision (wide CIs, small sample size), unknown consistency	Low for benefit for fluoxetine plus CBT vs. fluoxetine	Adolescents with MDD
	Remission from MDD	OR (medication vs. combination), OR, 3.0; 95% CI, 0.68 to 13.31	1 RCT (n=51) <sup>101</sup>	Imprecision (wide CIs), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, DD NOS
	Remission from dysthymia or DD not otherwise specified	OR (combination vs. medication), 0.71; 95% CI, 0.10 to 5.12	1 RCT (n=51) <sup>101</sup>	Imprecision (wide CIs), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, DD NOS
	Relapse	Evenly split between the two condition, p=.76	1 RCT (n=135) <sup>103</sup>	Serious imprecision (based on reported p- values, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Functional status	SMD (CGAS) ranges from 0.18 to 0.38, CIs span the null in one study	2 RCTs (n=368) <sup>53, 85, 87, 97, 98, 103, 119, 135</sup>	Imprecision (wide CIs), inconsistency	Insufficient	Adolescents with MDD
	Functional status at 52 weeks (40 weeks after end of treatment)	SMD (CGAS), 0.37; 95% CI, 0.05 to 0.69	1 RCT (n=152) <sup>103</sup>	Imprecision (small sample size), unknown consistency	Insufficient	Adolescents with MDD

BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CES-D = Center for Epidemiologic Studies Depression Scale; CGAS = Children's Global Assessment Scale; CI = confidence interval; DD = depressive disorder; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n/N = number; NOS = not otherwise specified; OR = odds ratio; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Evidence on remission varies based on condition. One high risk-of-bias study<sup>101</sup> with participants with MDD, dysthymic disorder, or DD NOS suggests no difference between treatment arms for remission (insufficient evidence), while the other study in an MDD-only sample (some risk-of-bias concerns)<sup>53, 85, 87, 97, 98, 119, 135</sup> demonstrated that combined treatment (fluoxetine plus CBT) is superior to fluoxetine alone (risk difference, 140/1,000; 95% CI, 19 more cases to 261 more cases) (low evidence of benefit for combined treatment).<sup>85</sup>

Evidence from two studies with different intensity of treatment suggests mixed results for functional status (insufficient). One study<sup>53, 85, 87, 97, 98, 119, 135</sup> with more intense CBT interventions demonstrated improved functional status (SMD for CGAS, 0.38; 95% CI, 0.09 to 0.66), while the other with less intense CBT did not.<sup>103</sup> The study evaluating less intense CBT reported no difference in functional outcomes at any point,<sup>103</sup> but our calculated SMD for CGAS

scores at 52 weeks suggest a difference between arms (based on an assumption of intention-to-treat analysis). Given the lack of clarity in the sample size for the long-term outcome, we graded the functional status outcome as insufficient, despite a statistically significant difference between study arms.

## Psychotherapy Plus Pharmacotherapy Versus Pharmacotherapy: Harms

### Key Points

- The evidence was insufficient to judge the comparative harms of combined therapy versus pharmacotherapy.
- No deaths were reported.

### Detailed Results

Four RCTs (two with some risk-of-bias concerns<sup>53, 85, 87, 97-99, 119, 135</sup> and two with high risk of bias<sup>101, 112</sup>) compared harms between combined therapy with pharmacotherapy alone (Table 57). All included CBT (one offered group therapy<sup>99</sup>). All were conducted in adolescents. One study included a mixed sample of MDD, dysthymia, and DD NOS.<sup>101</sup> The duration of the interventions ranged from 12 to 28 weeks. Additional details on these trials can be found in Appendix Tables D-42 and F-20.

The evidence on suicidal ideation or suicidal events is marked by serious imprecision and high risk of bias and is insufficient to make conclusions. One study reported no suicides.

**Table 57. Strength of evidence for harms of psychotherapy plus pharmacotherapy versus pharmacotherapy**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. pharmacotherapy	Mortality	No suicides reported	1 RCT (n=216) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (small sample size, no events), unknown consistency	Insufficient	Adolescents with MDD
	Suicidal ideation	SMD (SIQR-Jr), -0.23; 95% CI, -0.50 to 0.04, suicidal ideation based on one item in the CDI was not statistically significant (p>0.05)	2 RCTs (n=275) <sup>53, 85, 87, 97-99, 119, 135</sup>	Serious imprecision (small sample size, wide CIs)	Insufficient	Adolescents with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. pharmacotherapy (continued)	Suicidal ideation	SMD (SIQR-Jr), -0.04; 95% CI, -0.59 to 0.51	1 RCT (n=51) <sup>101</sup>	Serious imprecision (small sample size, wide CIs), high risk of bias, <sup>101</sup> unknown consistency	Insufficient	Adolescents with MDD, dysthymia, DD NOS
	Suicide attempts	RR range from 1.01 to 2.04, CIs span the null	2 RCTs (n=380) <sup>53, 85, 87, 97, 98, 112, 119, 135</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias for suicide events	Insufficient	Adolescents with MDD
	Suicide-related AEs	Suicide-related AEs, 0.68; 95% CI, 0.25 to 1.84	1 RCT (n=216) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD
	Harms-related AEs	Harms-related AEs, 0.71; 95% CI, 0.32 to 1.58	1 RCT (n=216) <sup>53, 85, 87, 97, 98, 119, 135</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents with MDD

AE = adverse event; CDI = Children's Depression Inventory; CI = confidence interval; DD = depressive disorder; MDD = major depressive disorder; n = number; NOS = not otherwise specified; RCT = randomized controlled trial; RR = relative risk; SIQR-Jr = Suicide Ideation Questionnaire-Junior High School; SMD = standardized mean difference; vs. = versus.

## Omega-3 Versus Other Therapies: Benefits

### Key Points

- The evidence comparing a combination of omega-3 and family or these therapies individually was insufficient for depression symptoms and remission for adolescents and children with MDD, dysthymia, or DD NOS.

### Detailed Results

One RCT with some risk-of-bias concerns<sup>65</sup> compared omega-3 (n=18), family therapy, specifically psychoeducation plus CBT, (n=19), or their combination (n=17) over 12 weeks duration (Table 58). Evidence was insufficient to evaluate the effectiveness of family therapy compared with pill placebo for clinician-reported depressive symptoms and remission. Additional details can be found in Appendix Tables D-43 and E-33.

**Table 58. Strength of evidence for benefits of omega 3, family therapy, and combined therapy**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Omega-3 vs. family therapy	Depressive symptoms, clinician report	SMD (CDRS-R), 0.11; 95% CI, -0.56 to 0.79	1 RCT (n=34) <sup>65</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS
	Remission	RR (CDRS-R≤28), 0.72; 95% CI, 0.37 to 1.40	1 RCT (n=34) <sup>65</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS
Omega-3 versus omega-3 plus family therapy	Depressive symptoms, clinician report	SMD (CDRS-R), 0.53; 95% CI, -0.17 to 1.22	1 RCT (n=33) <sup>65</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS
	Remission	RR (CDRS-R≤28), 0.57; 95% CI, 0.31 to 1.06	1 RCT (n=33) <sup>65</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS
Omega 3 plus family therapy versus family therapy	Depressive symptoms, clinician report	SMD (CDRS-R), -0.42; 95% CI, -1.09 to 0.25	1 RCT (n=35) <sup>65</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS
	Remission	RR (CDRS-R≤28), 1.25; 95% CI, 0.79 to 1.96	1 RCT (n=35) <sup>65</sup>	Serious imprecision, (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD, dysthymia, or DD NOS

CDRS-R = Children's Depression Rating Scale-Revised; DD = depressive disorders; MDD = major depressive disorder; n = number; NOS = not otherwise specified; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

## Omega-3 Versus Other Therapies: Harms

### Key Points

- No study reported on harms.

### Detailed Results

One RCT with some risk-of-bias concerns<sup>65</sup> of adolescents and children ages 7 to 14 years compared omega-3, family therapy, and their combination over 12 weeks duration but did not report on harms.

## SSRIs Versus SNRIs: Benefits

### Key Points

- Insufficient evidence exists to support conclusions on comparisons of duloxetine versus fluoxetine on depressive symptoms, response, and remission.

### Detailed Results

Two high risk-of-bias RCTs compared benefits between SSRIs and SNRIs (two with some risk-of-bias concerns<sup>67, 68</sup>) (Table 59). One tested fixed doses of duloxetine (60 mg vs. 30 mg) compared with fixed doses of fluoxetine (20 mg),<sup>67</sup> and the second tested flexible doses of duloxetine (30 mg to 120 mg) compared with flexible doses of fluoxetine (10 mg to 40 mg).<sup>68</sup> All studies were conducted on adolescents and children with MDD. The duration of the interventions was 10 weeks. Additional details on these trials can be found in Appendix Tables D-44 and E-34.

The evidence does not support conclusions of differences in depressive symptoms, response, or remission for duloxetine versus fluoxetine, primarily because of serious imprecision: CIs spanned the null and the studies were not powered to test for equivalence.

**Table 59. Strength of evidence for benefits of SSRIs versus SNRIs**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Duloxetine vs. fluoxetine	Depressive symptoms (clinician rated)	Differences in CDRS-R not statistically significant, CIs not calculable (SDs not reported)	2 RCTs (n=531) <sup>67, 68</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents or children with MDD
	Response	RR (50% improvement in CDRS-R total score from baseline at week 10) ranges from 1.06 to 1.13, CIs span the null	2 RCTs (n=531) <sup>67, 68</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents or children with MDD
	Remission	RR for 30 mg duloxetine vs. 20 fluoxetine, 1.44; 95% CI, 1.03 to 2.00, <sup>67</sup> RR for other comparisons range from 1.24 to 1.25 and CIs span the null	2 RCTs (n=531) <sup>67, 68</sup>	Serious imprecision (wide CIs, small sample size), inconsistent high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents or children with MDD

CDRS-R = Children's Depression Rating Scale—Revised; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SD = standard deviation; vs. = versus.

## SSRIs Versus SNRIs: Harms

### Key Points

- The evidence is insufficient to support conclusions for suicidal behavior, suicidal ideation, or discontinuation due to AEs or SAEs.

### Detailed Results

Two studies, previously discussed under benefits, reported on harms of duloxetine versus fluoxetine (Table 60).<sup>67, 68</sup> The comparisons included 60 mg or 30 mg of duloxetine versus 20 mg of fluoxetine<sup>67</sup> and flexible dosing of duloxetine and fluoxetine.<sup>68</sup> Additional details on these trials can be found in Appendix Tables D-44 and F-21.

**Table 60. Strength of evidence for harms of SSRIs versus SNRIs**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Duloxetine vs. fluoxetine	Suicide behavior	Events range from 0 to 1 per arm, RR ranges 0.32 to 1.00, CIs span the null	2 RCTs (n=531) <sup>67, 68</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents or children with MDD
	Suicidal ideation	RR ranges from 0.83 to 1.40, CIs span the null	2 RCTs (n=531) <sup>67, 68</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents or children with MDD
	Discontinuation due to AEs	RR for flexible dose duloxetine vs. fluoxetine, 8.56; 95% CI, 1.16 to 63.36, <sup>68</sup> RRs for other comparisons range from 1.18 to 2.18 and span the null	2 RCTs (n=531) <sup>67, 68</sup>	Serious imprecision (wide CIs, small sample size), inconsistency, high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents or children with MDD
	Treatment-emergent AEs	RRs range from 0.94 to 1.19, CIs span the null	2 RCTs (n=531) <sup>67, 68</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>67, 68</sup>	Insufficient	Adolescents or children with MDD

AE = adverse event; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SNRI = selective serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

The evidence does not support conclusions of differences in suicidal behavior, suicidal ideation, or discontinuation due to AEs or SAEs. One high risk-of-bias study demonstrated a higher risk of discontinuation due to AEs in the flexible duloxetine dosing arm when compared with the flexible fluoxetine dosing arm (8.56; 95% CI, 1.16 to 63.36), but the results are not consistent with other comparisons of the two drugs.



## SSRIs Versus TCAs: Benefits

### Key Points

- Insufficient evidence exists to support conclusions on pharmacotherapy dose comparisons on depressive symptoms, response, remission, relapse, and functional impairment.

### Detailed Results

Two RCTs compared benefits between SSRIs and TCAs. One high risk-of-bias trial (“Study 329”) compared the effectiveness of paroxetine and imipramine in adolescents with MDD (Table 61).<sup>83, 90-92</sup> A second trial (uncertain risk of bias) compared fluoxetine with desvenlafaxine in children and adolescents with MDD.<sup>76</sup> The duration of the intervention was 8 weeks in both trials, although Study 329 provided sustained treatment to responders alone over the course of 6 months. As noted previously, the original results for Study 329 were published in 2001;<sup>83</sup> a reanalysis (RIAT) addressed several flaws for the acute phase in 2015<sup>90</sup> and for the continuation phase in 2016.<sup>92</sup> The current analysis relies on the RIAT analysis of the acute phase<sup>90</sup> and the continuation phase.<sup>92</sup>

**Table 61. Strength of evidence for benefits of SSRIs versus TCAs**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Paroxetine vs. imipramine	Depressive symptoms (clinician reported)	SMD for change in HAM-D, -0.17; 95% CI, -0.46 to 0.12 <sup>a</sup>	1 RCT (n=184) <sup>90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>83, 91</sup> unknown consistency	Insufficient	Adolescents, MDD
	Remission	“Response at some point”, 1.09; 95% CI, 0.88 to 1.36	1 RCT (n=192) <sup>92</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>83, 91</sup> unknown consistency	Insufficient	Adolescents, MDD
	Relapse	RR for relapse in acute or continuation phase, 1.56; 95% CI, 0.92 to 2.64	1 RCT (n=118) <sup>92</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>83, 91</sup> unknown consistency	Insufficient	Adolescents, MDD
	Functional impairment (parent reported)	SMD (change in AFC), 0.02; 95% CI, -0.34 to 0.38 <sup>a</sup>	1 RCT (n=184) <sup>90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>83, 91</sup> unknown consistency	Insufficient	Adolescents, MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Fluoxetine vs. desvenlafaxine	Depression symptoms (clinician rated)	SMD (CDRS-R), -0.18; 95% CI, -0.44 to 0.09	1 RCT (n=225) <sup>76</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Response	RR (CGI of 1 [very much improved] or 2 [much improved]), 1.14; 95% CI, 0.96 to 1.35	1 RCT (n=200) <sup>76</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD

<sup>a</sup> Assumes a pre-post correlation of 0.5; CI continues to be span the null; with higher or lower pre-post correlations. AFC =Autonomous Functioning Checklist; CDRS-R = Children's Depression Rating Scale-Revised; CGI = Clinical Global Impressions Scale; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; vs. = versus.

Based on the results of the RIAT analyses, evidence was insufficient to indicate a difference between paroxetine and imipramine for any outcome. Similarly, the evidence was insufficient to judge the comparative effectiveness of fluoxetine and desvenlafaxine. Additional details for these studies can be found in Appendix Tables D-45 and E-35.

## SSRIs Versus TCAs: Harms

### Key Points

- Insufficient evidence exists to support conclusions on the comparative harms of SSRIs and TCAs.

### Detailed Results

As noted previously, two RCTs compared benefits between SSRIs and TCAs. One trial (Study 329, high risk of bias) compared the effectiveness of paroxetine and imipramine in adolescents with MDD (Table 62).<sup>83, 90-92</sup> A second trial (uncertain risk of bias) compared fluoxetine with desvenlafaxine in children and adolescents with MDD.<sup>76</sup> The flaws in the original analysis included recategorizing suicidal ideation and behavior as “emotional lability,” restriction of reporting to events occurring above a given frequency, coding outcomes, coding events under different headings for different patients, failing to transcribe all AEs, and so on.<sup>90</sup> As reported for benefits, this synthesis relies on the RIAT analysis of the acute and continuation phases of the review. Additionally, we report mortality and SAEs from the original trial report.<sup>91</sup>

The evidence was not sufficient to judge the comparative harms of paroxetine versus imipramine or fluoxetine versus desvenlafaxine. Additional details on these trials can be found in Appendix Tables D-45 and F-22.

**Table 62. Strength of evidence for harms of SSRIs versus TCAs**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Paroxetine vs. imipramine	Mortality	No events in either arm	1 RCT (n=188) <sup>90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>83, 91</sup> unknown consistency	Insufficient	Adolescents, MDD
	Suicidal ideation or behavior	RR, 2.81; 95% CI, 0.93 to 8.51	1 RCT (n=188) <sup>90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>83, 91</sup> unknown consistency	Insufficient	Adolescents, MDD
	SAEs	RR, 2.25; 95% CI, 0.81 to 6.22	1 RCT (n=188) <sup>92</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>83, 91</sup> unknown consistency	Insufficient	Adolescents, MDD
	Withdrawal due to AEs in the acute phase	RR, 0.46; 95% CI, 0.26 to 0.81	1 RCT (n=188) <sup>92</sup>	Imprecision (small sample size), high risk of bias, <sup>83, 91</sup> unknown consistency	Insufficient	Adolescents, MDD
	Withdrawal due to AEs in the continuation phase	RR, 0.48; 95% CI, 0.18 to 1.27	1 RCT (n=58) <sup>90</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias <sup>83, 91</sup>	Insufficient	Adolescents, MDD
Fluoxetine vs. desvenlafaxine	Mortality	No events in either arm	1 RCT (n=228) <sup>76</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Treatment-emergent suicidal ideation or behavior	RR, 1.29; 95% CI, 0.61 to 3.18	1 RCT (n=225) <sup>76</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	SAEs	RR, 0.68; 95% CI, 0.12 to 3.98	1 RCT (n=228) <sup>76</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Fluoxetine vs. desvenlafaxine (continued)	Withdrawal due to AEs	RR, 0.52; 95% CI, 0.05 to 5.68	1 RCT (n=225) <sup>76</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD

AE = adverse event; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; vs. = versus.

## Pharmacotherapy Dose Comparisons: Benefits

### Key Points

- Insufficient evidence exists to support conclusions on pharmacotherapy dose comparisons on depressive symptoms, response, and remission.

### Detailed Results

Three RCTs compared benefits between pharmacotherapy doses (two with some risk-of-bias concerns<sup>75, 77</sup> and one with high risk of bias<sup>67</sup>) (Table 63). All tested doses of different drugs (60 mg vs. 30 mg of duloxetine,<sup>67</sup> 15 mg vs. 30 mg of vilazodone,<sup>75</sup> and low- vs. high-dose venlafaxine).<sup>77</sup> All studies were conducted on adolescents; in addition, two studies also included children.<sup>67, 77</sup> All focused on MDD. The duration of the interventions was 8 to 10 weeks. Additional details on these trials can be found in Appendix Tables D-46 and E-36.

The evidence does not support conclusions of differences in depressive symptoms, response, or remission for any of the dose comparisons, primarily because of serious imprecision: CIs spanned the null, and the studies were not powered to test for equivalence.

**Table 63. Strength of evidence for benefits of pharmacotherapy dose comparisons**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Duloxetine 60 mg vs. duloxetine 30 mg	Depressive symptoms (clinician rated)	Differences in CDRS-R not statistically significant, CIs not calculable (SDs not reported)	1 RCT (n=219) <sup>67</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	Response	RR (50% improvement in CDRS-R total score from baseline at week 10), 1.0; 95% CI, 0.84 to 1.19	1 RCT (n=219) <sup>67</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Duloxetine 60 mg vs. duloxetine 30 mg (continued)	Remission	RR (based on CDRS-R), 0.8; 95% CI, 0.641 to 1.18	1 RCT (n=219) <sup>67</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD
Vilazodone 15 mg vs. vilazodone 30 mg	Depressive symptoms (clinician rated)	SMD (CDRS-R), 0.11; 95% CI, 0.10 to 0.32	1 RCT (n=354) <sup>75</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents, MDD
	Response	RR (CDRS-R), 0.89; 95% CI, 0.75 to 1.05	1 RCT (n=354) <sup>75</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents, MDD
	Remission	RR (CDRS-R), 0.95; 95% CI, 0.75 to 1.20	1 RCT (n=354) <sup>75</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents, MDD
Desvenlafaxine low dose (20, 30, or 35 mg/day based on baseline weight) vs. desvenlafaxine high dose (25, 35, or 50 mg/day based on baseline weight)	Depressive symptoms (clinician rated)	Difference in mean change in CDRS-R, 1.52; 95% CI, -1.56 to 4.61	1 RCT (n=241) <sup>77</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Response	RR (based on CGI score of 1 [very much improved] or 2 [much improved]), 0.90; 95% CI, 0.70 to 1.13	1 RCT (n=241) <sup>77</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD

CDRS-R = Children's Depression Rating Scale-Revised; CGI = Clinical Global Impressions Scale; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SD = standard deviation; SMD = standardized mean difference; vs. = versus.

## Pharmacotherapy Dose Comparisons: Harms

### Key Points

- Insufficient evidence exists to support conclusions on pharmacotherapy dose comparisons on suicidal behavior, suicidal ideation, or discontinuation due to AEs or SAEs.

## Detailed Results

Three studies, previously discussed under benefits, reported on harms of different pharmacotherapy doses (Table 64).<sup>67, 75, 77</sup> The comparisons included 60 mg versus 30 mg of duloxetine,<sup>67</sup> 15 mg versus 30 mg of vilazodone,<sup>75</sup> and low- versus high-dose venlafaxine.<sup>77</sup> Additional details on these trials can be found in Appendix Tables D-46 and F-23.

The evidence does not support conclusions of differences in suicidal behavior, suicidal ideation, or discontinuation due to AEs or SAEs. One high risk-of-bias study demonstrated a higher risk of treatment-emergent AEs in the 60 mg duloxetine arm when compared with the 30 mg duloxetine arm (RR, 1.26; 95% CI, 1.04 to 1.53), but we judged the evidence to be insufficient because of imprecision and high risk of bias.

**Table 64. Strength of evidence for harms of pharmacotherapy dose comparisons**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Duloxetine 60 mg vs. duloxetine 30 mg	Suicide behavior	No events in either arm	1 RCT (n=219) <sup>67</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	Suicidal ideation	RR, 1.69; 95% CI, 0.83 to 3.43	1 RCT (n=219) <sup>67</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	Discontinuation due to AEs	RR, 1.85; 95% CI, 0.75 to 4.53	1 RCT (n=219) <sup>67</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD
	Treatment-emergent AEs	RR, 1.26; 95% CI, 1.04 to 1.53	1 RCT (n=219) <sup>67</sup>	Imprecision (small sample size), high risk of bias, <sup>67</sup> unknown consistency	Insufficient	Adolescents and children with MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Vilazodone 15 mg vs. vilazodone 30 mg	Suicide attempt	RR, 1.03; 95% CI, 0.06 to 16.32	1 RCT (n=354) <sup>75</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents, MDD
	Suicidal ideation	RR, 1.16; 95% CI, 0.86 to 1.55	1 RCT (n=354) <sup>75</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents, MDD
	SAEs	RR, 0.65; 95% CI, 0.11 to 3.88	1 RCT (n=354) <sup>75</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents, MDD
	Treatment-emergent AEs	RR, 0.93; 95% CI, 0.82 to 1.06	1 RCT (n=354) <sup>75</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents, MDD
	Discontinuation due to AEs	RR, 1.16; 95% CI, 0.46 to 2.95	1 RCT (n=354) <sup>75</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents, MDD
Desvenlafaxine low dose (20, 30, or 35 mg/day based on baseline weight) vs. desvenlafaxine high dose (25, 35, or 50 mg/day based on baseline weight)	Treatment-emergent suicidal ideation or behavior	RR, 0.65; 95% CI, 0.29 to 1.44	1 RCT (n=241) <sup>77</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
	Discontinuation due to AEs	RR, 2.28; 95% CI, 0.61 to 8.59	1 RCT (n=241) <sup>77</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD

AE = adverse event; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; vs. = versus.

# Treatment-Resistant Depression Interventions: Benefits

## Key Points

- Insufficient evidence exists to support conclusions on the effects of treatment-resistant depression interventions on depressive symptoms (clinician and self-reported), response, and functional impairment.

## Detailed Results

Two RCTs compared benefits between different types of treatment-resistant depression interventions (one trial with some risk-of-bias concerns<sup>102</sup> and one trial with two companion publications with high risk-of-bias concerns<sup>33, 109, 116</sup>) (Table 65). One tested different doses of fluoxetine (increasing to 40 mg or 60 mg versus staying on 20 mg) on children and adults with MDD, and the other tested four groups of adolescents with MDD: 1) switching to a new SSRI, 2) switching to a new SSRI plus CBT, 3) switching to venlafaxine, and 4) switching to venlafaxine plus CBT. This trial reported pooled results of switching to another SSRI (with or without CBT) versus switching to venlafaxine (with or without CBT) and also CBT (plus switching to another SSRI or venlafaxine) versus no CBT (switching to another SSRI or venlafaxine alone). The first sample included 14 to 16 2-hour sessions for adolescents and 7 2-hour sessions for parents. The second sample included 16 2-hour sessions for adolescents and 7 to 9 2-hour sessions for parents. The authors did not specify the duration of the interventions. Additional details on these trials can be found in Appendix Tables D-47 and E-37.

**Table 65. Strength of evidence for benefits of treatment-resistant depression intervention comparisons**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Switch to new SSRI (with or without CBT) vs. switch to venlafaxine (with or without CBT)	Depressive symptoms (clinician rated)	SMD (based on CDRS-R), 0.07; 95% CI, -0.15 to 0.28	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>109, 116, 141</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to CBT (with switch to new SSRI or to venlafaxine) vs. no CBT (with switch to new SSRI or to venlafaxine)	Depressive symptoms (clinician rated)	SMD (based on CDRS-R), 0.09; 95% CI, -0.13 to 0.30	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>109, 116, 141</sup> unknown consistency	Insufficient	Adolescents, MDD
Increased dose of fluoxetine vs. continued dose of fluoxetine 20 mg	Depressive symptoms (clinician rated)	SMD (based on CDRS-R), -0.26; 95% CI, -0.99 to 0.47	1 RCT (n=29) <sup>102</sup>	Imprecision (wide CIs, small sample size), <sup>102</sup> unknown consistency	Insufficient	Adolescents and children with MDD



Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Switch to new SSRI (with or without CBT) vs. switch to venlafaxine (with or without CBT)	Depressive symptoms (self-rated)	SMD (based on CDRS-R), 0.15; 95% CI, -0.07 to 0.36	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>109, 116, 141</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to CBT (with switch to new SSRI or to venlafaxine) vs. no CBT (with switch to new SSRI or to venlafaxine)	Depressive symptoms (self-rated)	SMD (based on CDRS-R), -0.05; 95% CI, -0.26 to 0.17	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>109, 116, 141</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to new SSRI (with or without CBT) vs. switch to venlafaxine (with or without CBT)	Response	RR (CGI-I score $\leq$ 2 and CDRS-R decline $\geq$ 50% from baseline at week 12), 0.03; 95% CI, -0.26 to 0.21	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>109, 116, 141</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to CBT (with switch to new SSRI or to venlafaxine) vs. no CBT (with switch to new SSRI or to venlafaxine)	Response	RR (CGI-I score $\leq$ 2 and CDRS-R decline $\geq$ 50% from baseline at week 12), -0.32; 95% CI, -0.56 to -0.08	1 RCT (n=254) <sup>33, 109, 116</sup>	Imprecision (small sample size), high risk of bias, <sup>109, 116, 141</sup> unknown consistency	Insufficient	Adolescents, MDD
Increased dose of fluoxetine vs. continued dose of fluoxetine 20 mg	Response	RR (based on decrease in total CDRS-R score $\geq$ 30% from 10 weeks—end of acute treatment with no response—to 19 weeks), 0.89; 95% CI, 0.02 to 1.76	1 RCT (n=29) <sup>102</sup>	Serious imprecision (wide CIs, small sample size), unknown consistency	Insufficient	Adolescents and children with MDD
Switch to new SSRI (with or without CBT) vs. switch to venlafaxine (with or without CBT)	Functional impairment (clinician rated)	SMD (based on CGAS), -0.13; 95% CI, -0.35 to 0.08	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>109, 116, 141</sup> unknown consistency	Insufficient	Adolescents, MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Switch to CBT (with switch to new SSRI or to venlafaxine) vs. no CBT (with switch to new SSRI or to venlafaxine)	Functional impairment (clinician rated)	SMD (based on CGAS), -0.18; 95% CI, -0.40 to 0.03	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>109, 116, 141</sup> unknown consistency	Insufficient	Adolescents, MDD

CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions Scale; CI = confidence interval; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

The evidence does not support conclusions of differences in depressive symptoms, response, or remission for any of the dose comparisons, primarily because of serious imprecision: CIs spanned the null, and the studies were not powered to test for equivalence. One study did indicate that participants engaging in CBT (plus a switch to either a new SSRI or venlafaxine) were less likely to respond (Clinical Global Impressions Scale [CGI-I] score  $\leq 2$  and CDRS-R decline  $\geq 50\%$ ) by end of treatment than those taking medication alone (a switch to either a new SSRI or venlafaxine alone (RR, -0.32; 95% CI, -0.56 to -0.08), but the SOE was limited by imprecision and high risk of bias.<sup>33, 109, 116</sup>

## Treatment-Resistant Depression Interventions: Harms

### Key Points

- The evidence does not support conclusions for mortality, suicidal attempts, events, or ideation or discontinuation due to SAEs or AEs.

### Detailed Results

Two trials, one with two companion publications as previously discussed under benefits, reported on harms of different treatment-resistant depression interventions (Table 66).<sup>33, 102, 109, 116</sup> The comparisons included increasing the dose of fluoxetine to 40 mg or 60 mg versus remaining on 20 mg<sup>102</sup> and comparing a switch to a new SSRI (with or without CBT) versus a switch to venlafaxine (with or without CBT) or a switch to a new medication plus CBT versus a new medication only (no CBT).<sup>33, 109, 116</sup> Additional details of these trials can be found in Appendix Tables D-47 and F-24.

The evidence does not support conclusions of differences in mortality, suicide attempts, behaviors, or ideation or in discontinuation due to SAEs or AEs.

**Table 66. Strength of evidence for harms of treatment-resistant depression intervention comparisons**

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Switch to new SSRI (with or without CBT) vs. switch to venlafaxine (with or without CBT)	Mortality	No completed suicides	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>33, 109, 116</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to CBT (with switch to new SSRI or to venlafaxine) vs. no CBT (with switch to new SSRI or to venlafaxine)	Mortality	No completed suicides	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>33, 109, 116</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to new SSRI (with or without CBT) vs. switch to venlafaxine (with or without CBT)	Suicide attempts	RR, -0.36; 95% CI, -0.92 to 0.20	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>33, 109, 116</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to CBT (with switch to new SSRI or to venlafaxine) vs. no CBT (with switch to new SSRI or to venlafaxine)	Suicide attempts	RR, -0.21; 95% CI, -0.75 to 0.34	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>33, 109, 116</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to new SSRI (with or without CBT) vs. switch to venlafaxine (with or without CBT)	Suicidal events (new, or worsening suicidal ideation, a suicidal threat, or a suicide attempt)	RR, 0.15; 95% CI, -0.19 to 0.49	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>33, 109, 116</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to CBT (with switch to new SSRI or to venlafaxine) vs. no CBT (with switch to new SSRI or to venlafaxine)	Suicidal events (new, or worsening suicidal ideation, a suicidal threat, or a suicide attempt)	RR, -0.01; 95% CI, -0.34 to 0.33	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>33, 109, 116</sup> unknown consistency	Insufficient	Adolescents, MDD

Comparison	Outcome	Conclusion	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Switch to new SSRI (with or without CBT) vs. switch to venlafaxine (with or without CBT)	Suicidal ideation	SMD (based on SIQ-Jr), 0.01; 95% CI, -0.21 to 0.22	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>33, 109, 116</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to CBT (with switch to new SSRI or to venlafaxine) vs. no CBT (with switch to new SSRI or to venlafaxine)	Suicidal ideation	SMD (based on SIQ-Jr), -0.02; 95% CI, -0.23 to 0.20	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>33, 109, 116</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to new SSRI (with or without CBT) vs. switch to venlafaxine (with or without CBT)	Withdrawal due to SAEs	RR, 0.03; 95% CI, -0.39 to 0.45	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>33, 109, 116</sup> unknown consistency	Insufficient	Adolescents, MDD
Switch to CBT (with switch to new SSRI or to venlafaxine) vs. no CBT (with switch to new SSRI or to venlafaxine)	Withdrawal due to SAEs	RR, -0.30; 95% CI, -0.74 to 0.13	1 RCT (n=254) <sup>33, 109, 116</sup>	Serious imprecision (wide CIs, small sample size), high risk of bias, <sup>33, 109, 116</sup> unknown consistency	Insufficient	Adolescents, MDD
Increased dose of fluoxetine vs. continued dose of fluoxetine 20 mg	Withdrawal due to AEs	RR, N/A because IG1 had 0 out of 14 and IG2 had 3 out of 15	1 RCT (n=29) <sup>102</sup>	Serious imprecision (few events, small sample size), <sup>102</sup> unknown consistency	Insufficient	Adolescents and children with MDD

AE = adverse event; CBT = cognitive behavioral therapy; IG1 = intervention group 1; IG2 = intervention group 2; MDD = major depressive disorder; n = number; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SIQR-Jr = Suicide Ideation Questionnaire-Junior High School; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

## KQ 5b: Comparative Benefits and Harms of Treatments by Subpopulation

### CBT Versus Other Psychotherapy: Subpopulations

#### Key Points

- Studies comparing CBT and other psychotherapy did not evaluate differences by subgroups of interest to this review.

## **Psychotherapy Within-Type Comparisons of Delivery Methods or Approaches: Subpopulations**

### **Key Points**

- Insufficient evidence exists to support conclusions on the comparative effectiveness of types of CBT in populations with high versus low severity of MDD.

### **Detailed Results**

One study (with some risk-of-bias concerns) compared outcomes of CBT group therapy for adolescents with a separate group for parents with CBT group therapy for adolescents with high versus low severity of MDD.<sup>61</sup> The study included two randomized samples; the intervention was modified between the 2 samples to facilitate learning and retention. The first sample included 14 to 16 2-hour sessions for adolescents and 7 2-hour sessions for parents. The second sample included 16 2-hour sessions for adolescents and 7 to 9 2-hour sessions for parents. The authors did not specify the duration of the interventions. Additional details of this trials can be found in Appendix Tables D-48 and G-11. The study found no differences in outcomes by severity of MDD.

## **Psychotherapy Versus Pharmacotherapy: Subpopulations**

### **Key Points**

- Family income, baseline depression symptom severity, and ADHD moderated the effect of the intervention: CBT was inferior to fluoxetine in groups with lower family income, marked or severe baseline depression symptoms, or ADHD.
- Other patient, caregiver, and study site characteristics had no moderating effect.

### **Detailed Results**

Three companion publications<sup>97, 98, 115</sup> to one RCT with medium risk of bias<sup>53</sup> examined subgroup differences in benefits between CBT (n=111) and fluoxetine (n=109) among adolescents with MDD in a 12-week study. Additional details about the TADS trial can be found in Appendix Tables D-49 and G-12.

Family income, baseline symptom severity, and ADHD all moderated the effect of the interventions. CBT was inferior to fluoxetine in groups with (1) lower income when compared with higher income, (2) marked or severe depression symptoms at baseline when compared with mild or moderate depression symptoms, and (3) ADHD when compared with the non-ADHD group. These results are based on small sample sizes from a study that was not powered to examine these differences.

Other patient demographic (age, race, gender), nonclinical (verbal intelligence, treatment expectations, conflict with caregiver), and clinical characteristics (Current episode duration, functional impairment, suicidal ideation, childhood trauma, melancholic features, number comorbid diagnoses, hopelessness, cognitive distortions, dysthymia, anxiety disorder); caregiver characteristics (caregiver depression, parent treatment expectations); and study characteristics (study site, referral source) had no moderating effect on the outcome.<sup>115</sup>

## **Psychotherapy Plus Pharmacotherapy Versus Psychotherapy: Subpopulations**

### **Key Points**

- Family income and ADHD moderate the effect of the intervention: CBT plus fluoxetine was superior to CBT in groups with lower family income or ADHD.
- Baseline depression symptom severity did not moderate the effects of the intervention.

### **Detailed Results**

Two companion publications<sup>97, 98</sup> to one RCT with medium risk of bias<sup>53</sup> examined subgroup differences in benefits between CBT plus fluoxetine (n=107) and CBT only (n=111) among adolescents with MDD in a 12-week study. Additional details about the TADS trial can be found in Appendix Tables D-50 and G-13.

Family income and ADHD moderated the effect of the interventions, but baseline symptom severity did not. CBT plus fluoxetine was superior to CBT (1) in groups with lower income when compared with higher income and (2) in the ADHD group when compared with the non-ADHD group. These results are based on small sample sizes from a study that was not powered to examine these differences.

## **Psychotherapy Plus Pharmacotherapy Versus Pharmacotherapy: Subpopulations**

### **Key Points**

- Baseline depression symptom severity and ADHD moderated the effect of the intervention: CBT plus fluoxetine was superior to fluoxetine in groups with ADHD, higher treatment expectations, or mild to moderate baseline depression symptoms.
- Family income did not moderate the effects of the intervention.
- Other patient, caregiver, and study site characteristics had no moderating effect.

### **Detailed Results**

Three companion publications<sup>97, 98, 115</sup> to one RCT with medium risk of bias<sup>53</sup> examined subgroup differences in benefits between CBT plus fluoxetine (n=107) and fluoxetine (n=109) among adolescents with MDD in a 12-week study. Additional details about the TADS trial can be found in Appendix Tables D-51 and G-14.

Baseline depression symptom severity and ADHD moderated the effect of the interventions, but family income did not. CBT plus fluoxetine was superior to fluoxetine (1) in groups with mild or moderate depression severity when compared with marked or severe baseline depression and (2) in the ADHD group when compared with the non-ADHD group. CBT plus fluoxetine outperformed fluoxetine in patients with higher treatment expectations, but the difference was reduced among patients with childhood trauma.<sup>115</sup> These results are based on small sample sizes from a study that was not powered to examine these differences.

Other patient demographic (age, race, gender), nonclinical (verbal intelligence, conflict with caregiver), and clinical characteristics (current episode duration, functional impairment, suicidal ideation, melancholic features, number comorbid diagnoses, hopelessness, cognitive distortions,

dysthymia, anxiety disorder); caregiver characteristics (caregiver depression, parent treatment expectations); and study characteristics (study site, referral source) had no moderating effect on the outcome.<sup>115</sup>

## **Omega-3 Versus Other Therapies: Subpopulations**

### **Key Points**

- Studies comparing omega-3, family therapy, and their combinations did not evaluate differences by subgroups of interest to this review.

## **SSRIs Versus SNRIs: Subpopulations**

### **Key Points**

- Studies comparing SSRIs and SNRIs did not evaluate differences by subgroups of interest to this review.

## **SSRIs Versus TCAs: Subpopulations**

### **Key Points**

- Insufficient evidence exists to support conclusions on the comparative effectiveness of SSRIs and TCA in adolescents.

### **Detailed Results**

Two RCTs compared benefits between SSRIs and TCAs. One trial (Study 329, high risk of bias) compared the effectiveness of paroxetine and imipramine in adolescents with MDD.<sup>83, 90-92</sup> A second trial (uncertain risk of bias) compared fluoxetine with desvenlafaxine in children and adolescents with MDD.<sup>76</sup> The duration of the intervention was 8 weeks in both trials, although Study 329 provided sustained treatment to responders alone over the course of 6 months. Additional details for these studies can be found in Appendix Tables D-52 and G-15.

As noted previously, we restricted the discussion of benefits to results from the RIAT analysis alone for Study 329. Neither publication for the RIAT analysis offers results for subgroups. The results from the original trial suggest no differences in response (defined a priori as 50% reduction or a score of 8 or less in the total HAM-D) by features of atypical depression, melancholic features, anxiety disorder, age at onset, and coexistence of anxiety or the other comorbid disorders. The SOE of these results is restricted by the high risk of bias of the source data.

## **Pharmacotherapy Dose Comparisons: Subpopulations**

### **Key Points**

- Insufficient evidence exists to support conclusions on the comparative effectiveness of desvenlafaxine in adolescents and children.

## Detailed Results

One RCT with some risk-of-bias concerns<sup>77</sup> compared low- versus high-dose desvenlafaxine<sup>77</sup> conducted on adolescents (12 to 17 years) and children (7 to 11 years) with MDD and found no differences by age group (no additional numerical details reported). Additional details for this study can be found in Appendix Tables D-53 and G-16.

## Treatment-Resistant Depression Interventions: Subpopulations

### Key Points

- Age, race, or baseline depression severity did not moderate the comparison of switching to a new medication (a new SSRI or venlafaxine) plus CBT versus switching to a new medication alone (with no CBT) on response to treatment.<sup>33, 109, 116</sup>
- When compared with no CBT plus new medication, CBT plus new medication increased response rates among those with no abuse history.<sup>33, 109, 116</sup>
- When compared to no CBT plus new medication, CBT plus new medication increased response rates among those with at least 1 comorbid condition, but there were no differences between groups among those with no comorbid conditions.<sup>33, 109, 116</sup>
- When compared with no CBT plus new medication, CBT plus new medication increased response rates among those with low levels of hopelessness, but there were no differences between groups among those high levels of hopelessness.<sup>33, 109, 116</sup>

## Detailed Results

One companion publication<sup>33</sup> to an RCT<sup>109</sup> with high risk of bias examined moderators of the efficacy of CBT (with switch to a new medication) versus no CBT (switch to a medication only) among adolescents with MDD in a 12-week study. Additional details about this RCT and its companion publications can be found in Appendix D-54 and G-17.

No significant differences in response rates were found in the comparisons between study groups with respect to age, race, or baseline depression severity. Subgroup differences were found, however, by trauma history, number of comorbid disorders, and level of hopelessness (see Appendix Table G-17 for specific information). Participants in the CBT (plus switched medication) group had significantly greater response rates than participants in the no CBT (plus switched medication) group among those with no abuse history. Among those with a history of abuse, the study reported a p value of 0.06 in comparing efficacy between the no-CBT (plus switched medication) arm when compared with the CBT (plus switched medication) arm. There also were significantly higher response rates among those within the CBT + medication group than in the no-CBT + medication group among those with at least one comorbid disorder but no differences in efficacy between groups among those with no comorbid disorders. Finally, the authors reported significantly greater efficacy in the CBT + medication group than in the no-CBT + medication group among those with low levels of hopelessness but no differences in response rates among those in the CBT-medication and no-CBT + medication groups among those with high levels of hopelessness.



## Chapter 4. Discussion

We conducted a systematic review and meta-analysis to examine the effectiveness and safety of treatments for child and adolescent depressive disorders (DDs) (i.e., major depressive disorder [MDD], dysthymia/persistent depressive disorder (PDD), and/or depressive disorder not otherwise specified [DD NOS]). The systematic review examined efficacy and comparative effectiveness of nonpharmacological, pharmacological, and combination treatments as well as interventions delivered in collaborative care settings. Our review yielded 57 studies, including 23 randomized controlled trials (RCTs) of nonpharmacological efficacy, 21 RCTs of pharmacological efficacy, 1 RCT of combination efficacy, and 27 RCTs and 1 nonrandomized trial of comparative effectiveness.

Some psychotherapy studies examined similar interventions but different comparators and population groups (i.e., children, adolescent, or children and adolescents and/or those with MDD versus those with a wider range of DDs). Still others had low sample sizes or high risk of bias. The comparators also varied and could not be pooled: cognitive behavioral therapy (CBT), for example, is compared with pill placebo, wait-list control, usual care, and active control. Taken together, these issues precluded quantitative synthesis of many findings. Most evidence was insufficient because of imprecision, inconsistency or bias; only a few comparisons yielded low strength of evidence (SOE) of benefit. Table 67 offers numbers needed to treat and numbers needed to harm patients for a subset of these results, that is, for categorical outcomes of benefits or harms for which we judged the SOE to be at least low.

**Table 67. Numbers needed to treat to benefit and numbers needed to treat to harm for interventions for childhood depression<sup>a</sup>**

Population	Intervention Versus Comparator	Outcome	Intervention Events (n)/Sample (N) (%)	Comparison Events (n)/Sample (N) (%)	NNTB/ NNTH (CI)	Applicability
Adolescents with MDD (NNTB)	CBT + TAU vs. TAU/UC	Short-term recovery	31/99 (31.3%)	12/99 (12.1%)	5 (3 to 13)	Adolescents with MDD
	CBT + TAU vs. TAU/UC	Short-term response	68/99 (68.7%)	47/99 (47.5%)	5 (3 to 13)	Adolescents with MDD
	Exercise vs. active control	Response	14/14 (100.0%)	8/12 (66.7%)	3 (2 to 17)	Adolescents with MDD
	SSRI: fluoxetine vs. pill placebo	Response	66/109 (60.6%)	39/112 (34.8%)	4 (3 to 8)	Adolescents with MDD
	SSRI: escitalopram vs. placebo	Remission (24 weeks)	78/154 (50.6%)	56/157 (35.7%)	7 (4 to 25)	Adolescents with MDD
	SSRI: escitalopram vs. placebo	Response (24 weeks)	78/154 (50.6%)	56/157 (35.7%)	8 (4 to 48)	Adolescents with MDD
	Fluoxetine + CBT vs. placebo	Response	76/107 (71.0%)	39/112 (34.8%)	3 (2 to 4)	Adolescents with MDD
	Fluoxetine + CBT vs. placebo	Remission	40/107 (37.0%)	19/112 (17.0%)	5 (3 to 12)	Adolescents with MDD

Population	Intervention Versus Comparator	Outcome	Intervention Events (n)/Sample (N) (%)	Comparison Events (n)/Sample (N) (%)	NNTB/ NNTH (CI)	Applicability
Adolescents with MDD (NNTB) (continued)	Psychotherapy plus pharmacotherapy versus psychotherapy (CBT) plus fluoxetine vs. pharmacotherapy alone	Remission from MDD	40/107 (37.0%)	18/111 (16.0%)	5 (3 to 10)	Adolescents with MDD
	Psychotherapy plus pharmacotherapy versus psychotherapy (CBT) plus fluoxetine vs. pharmacotherapy alone	Remission from MDD	40/107 (37.0%)	25/109 (23.0%)	7 (4 to 53)	Adolescents with MDD
Adolescents and children with MDD (NNTB)	Relapse prevention CBT + continued antidepressant medication management vs. continued medication management	Relapse (78 weeks)	24/67 (36.0%)	33/54 (62.0%)	4 (2 to 11)	Adolescents and children with MDD
	All SSRIs (fluoxetine, escitalopram, paroxetine, and vilazodone) vs. placebo	Response	429/770 (55.7%)	365/755 (48.3%)	14 (8 to 500)	Adolescents and children with MDD
	All SSRIs (fluoxetine, escitalopram, paroxetine, and vilazodone) vs. placebo	Response	429/770 (55.7%)	365/755 (48.3%)	14 (8 to 500)	Adolescents and children with MDD
	SSRI: fluoxetine vs. placebo	Relapse (32 weeks)	21/50 (42.0%)	36/52 (69.2%)	4 (2 to 12)	Adolescents and children with MDD
Adolescents or children with MDD, dysthymia, or DD NOS (NNTB)	Family therapy vs. active control	Response	52/67 (77.6%)	40/67 (59.7%)	6 (3 to 40)	Adolescents or children with MDD, dysthymia, or DD NOS
Adolescents with MDD (NNTB)	All SSRIs (escitalopram, paroxetine, and vilazodone) vs. placebo	Withdrawal due to AEs	55/785 (7.0%)	18/511 (3.5%)	38 (22 to 167)	Adolescents with MDD
	Pharmacotherapy vs. psychotherapy (CBT)	Treatment-emergent psychiatric AEs	12/109 (11.0%)	1/111 (0.9%)	10 (6 to 25)	Adolescents with MDD
Adolescents and children with MDD (NNTB)	SNRI: duloxetine (high dose) vs. placebo	Withdrawal due to SAEs	12/108 (11.1%)	4/122 (3.3%)	13 (7 to 91)	Adolescents and children with MDD

Population	Intervention Versus Comparator	Outcome	Intervention Events (n)/Sample (N) (%)	Comparison Events (n)/Sample (N) (%)	NNTB/ NNTH (CI)	Applicability
Adolescents or adolescents and children with MDD (NNTH)	SSRI: paroxetine vs. placebo	Suicidal ideation or behaviors	21/378 (5.6%)	5/284 (1.8%)	31 (NNTH 14 to NNTB 125 <sup>b</sup> )	Adolescents or adolescents and children with MDD
	SSRI: paroxetine vs. placebo	Withdrawal due to AEs	43/376 (11.4%)	15/282 (5.3%)	17 (10 to 53)	Adolescents or adolescents and children with MDD
	All SSRIs (fluoxetine, citalopram, paroxetine, and vilazodone) vs. placebo	SAEs	50/1,205 (4.2%)	18/1,002 (1.8%)	50 (25 to 1,000)	Adolescents and children with MDD, adolescents with MDD

<sup>a</sup> This table is limited to outcomes for which authors reported a categorical response (yes/no), for which we judged the SOE to be at least low for benefit or for harm. We do not include outcomes for which the SOE is rated as low for no benefit because the confidence intervals for effect span the null.

<sup>b</sup> Without high risk-of-bias studies, the grade would have been rated as insufficient for imprecision. With high risk-of-bias studies, the evidence suggests increased risk of harms. We have retained the high risk-of-bias in these ratings to communicate the potential for a signal of harm. Specifically, one study in adolescents with MDD (n=180)<sup>90</sup> reported a substantial risk (relative risk: 5.15, 95% CI, 1.17 to 22.56; risk difference: 95, 95% CI, 22 to 168);<sup>90</sup> the NNTH is 10, 95% CI, 6 to 45; others do not report a statistically significant difference.

AE = adverse event; CBT = cognitive behavioral therapy; CI = confidence interval; DD NOS = depressive disorder not otherwise specified; MDD = major depressive disorder; N/n = number; NNTB = number needed to treat for an additional beneficial outcome; NNTH = number needed to treat for an additional harmful outcome; SAE = serious adverse event; SNRI = serotonin and norepinephrine reuptake inhibitor; SOE = strength of evidence; SSRI = selective serotonin reuptake inhibitor; TAU = treatment as usual; UC = usual care; vs. = versus.

All evidence of benefit of nonpharmacological interventions arises from single studies of interventions. For nonpharmacological interventions (Key Question [KQ] 1) among adolescents with MDD, interventions with evidence of benefit included the following: (1) CBT plus treatment as usual (TAU) versus TAU/usual care (UC) for depressive symptoms (clinician reported); weeks to recovery; and short-term recovery, response, and functional status; (2) exercise versus active control for response among adolescents with MDD; and (3) spirituality-informed online sessions versus wait-list on depressive symptoms (clinician rated).

For adolescents with MDD or dysthymia, interventions with evidence of benefit included CBT versus wait-list control for depressive symptoms (self-reported) and functional status. relapse prevention CBT plus continued antidepressant medication versus continued antidepressant medication management only for relapse at post-treatment and 78-week followup.

For children with MDD, dysthymia, or DD NOS, interventions with evidence of benefit included family-based interpersonal therapy (IPT) versus active control for depressive symptoms (clinician, self-, and parent reported).

For adolescents or children with MDD, dysthymia, or DD NOS, interventions with evidence of benefit included family therapy versus active control for response.

These findings, as noted above, are all low SOE. CBT, for example, offers benefits when compared with wait-list control or usual care, but the evidence is insufficient when compared with pill placebo or active control. Given the heterogeneity of comparators, we are unable to determine if the lack of consistency in demonstrating benefits of CBT arises from differences in

effect or differences in study size, design, and conduct. We found no eligible evidence on a range of other psychotherapies, including play therapy and psychodynamic therapy, and therefore cannot comment on their effectiveness. Family therapy and omega3 were superior to a pill placebo when families experienced more psychosocial stressors or had a history of maternal depression.

Exploratory subgroup analyses determined that the efficacy of CBT was higher for children and/or adolescents with higher family income levels, comorbid attention deficit hyperactivity disorder (ADHD), white race, less suicidality, fewer prior MDD episodes, and positive coping skills.

The evidence for pharmacological interventions includes more studies testing a common intervention (KQ 2). As a result, more studies could be pooled and examined quantitatively via meta-analyses. For adolescents with MDD, pharmacological interventions that yielded at least low strength of benefit or harms included the following: (1) fluoxetine versus placebo for depressive symptoms (clinician reported) and response; (2) escitalopram versus placebo for long-term depressive symptoms, long-term response, long-term remission rates, and functional status among adolescents with MDD; (3) paroxetine versus placebo for increased suicidal ideation or behavior and withdrawals due to adverse events (AEs) among adolescents with MDD; (4) selective serotonin reuptake inhibitors (SSRIs), as a class, versus placebo for improved response and functional status among children and adolescents with MDD; (5) SSRIs, as a class, for no benefit for remission among adolescents with MDD; and (6) SSRIs, as a class, versus placebo for withdrawal due to AEs in adolescents with MDD.

Among adolescents or children with MDD, pharmacological interventions with evidence of benefit or harm included the following: (1) SSRIs, as a class, versus placebo for increased risk of serious AEs; (2) relapse prevention fluoxetine versus placebo for relapse; (3) desvenlafaxine for no difference in depressive symptoms (clinician rated) and response as compared with placebo; (4) high-dose duloxetine for higher risk of withdrawal due to AEs; and (5) serotonin–norepinephrine reuptake inhibitors (SNRIs), as a class, for no difference in depressive symptoms (clinician rated) as compared with placebo.

Evidence for other age groups and DDs was insufficient.

Exploratory subgroup analyses determined that the efficacy of fluoxetine was higher for children and/or adolescents who were male or who had lower depressive symptom severity, chronic depression, comorbid ADHD, less frequent use of alcohol, and higher family incomes, and the efficacy of paroxetine was higher for children than adolescents. For fluoxetine as relapse prevention, one study found that participants with no residual symptoms who were switched to placebo for continuation treatment were more likely to relapse than those on fluoxetine.

Regarding combination therapy (KQ 3), one study examined a combination psychotherapy plus pharmacotherapy treatment versus control (i.e., CBT plus fluoxetine vs. placebo) and found low SOE of benefit for depressive symptoms (clinician reported), response, remission, and functional status among adolescents with MDD. One study compared omega-3 plus family therapy with pill placebo among adolescents or children with MDD, dysthymia, or DD NOS and found declines in depression severity in the intervention arm but not in the placebo arm in families with more psychosocial stressors or history of maternal depression.

No studies of collaborative care interventions (KQ 4) met the review inclusion and exclusion criteria.

Comparative effectiveness (KQ 5) studies that yielded low SOE of benefits or harms included, among adolescents with MDD, (1) fluoxetine over CBT for depressive symptoms

(clinician rated) D; (2) CBT for fewer treatment-emergent psychiatric AEs than fluoxetine; (3) combined CBT plus fluoxetine over CBT for depressive symptoms (clinician rated), remission, and functional status; (4) combined CBT (brief, group, or individual) plus SSRIs over SSRIs (fluoxetine, sertraline, or unspecified SSRIs) for no benefit for depression scores (self-rated); (5) combined CBT plus fluoxetine over fluoxetine for remission; and (6) combined CBT plus bupropion versus bupropion for depressive symptoms (self-reported). Among school-refusing adolescents with comorbid anxiety and MDD, combined CBT plus imipramine improved depressive symptoms (clinician rated) when compared with CBT.

Exploratory subgroup analyses determined that CBT was inferior to fluoxetine in groups with lower family income, marked/severe baseline depressive symptom severity, and comorbid ADHD. CBT plus fluoxetine was superior to fluoxetine in groups with ADHD, higher treatment expectations, or mild to moderate baseline depression symptoms. In addition, when compared with no CBT plus new medication, CBT plus new medication increased response rates among those with no abuse history, who had at least one comorbid condition, and those with low levels of hopelessness.

Notably, although the point estimates for improvement on continuous measures of symptom improvement and functional status for escitalopram and nonpharmacological interventions generally exceeded the distribution-based minimal clinically important differences [MCIDs] (0.5 of standard deviation (SD) of the control group, generally from baseline when available, for the studies contributing to strength-of-evidence results), the CIs did not. As a result, the clinical significance of the reported change is unclear.

## Findings in Relation to What Is Already Known

As noted in Chapter 1, treatments can vary by age of the patient, diagnosis, severity of disorder, and response to therapy. Three recent guidelines (American Psychological Association, 2019;<sup>22</sup> National Institution for Health and Care Excellence, 2019;<sup>23</sup> and the Guidelines for Adolescent Depression in Primary Care, 2018<sup>24, 25</sup>) continue to have uncertainty related to treating children, disorders other than MDD, and partial or no response to initial therapy. They do support CBT, fluoxetine, and combined therapies.

The findings of this review extend prior research that has demonstrated benefits of various nonpharmacological, pharmacological, and combination treatments for children and adolescents with DDs. The findings also confirm that little evidence exists for children, for those with DDs other than MDD, and for long-term outcomes. Of note, most benefits with low SOE were found for adolescents with MDD only. In fact, when examining the evidence for separate age groups (e.g., children, adolescents, or both), DDs (MDD or a wider range of DDs) and comparators (e.g., wait-list vs. active controls), the body of evidence yielded no more than low SOE for any outcomes examined. In addition, most benefits with low SOE were found for adolescents with MDD only.

Although our analysis does suggest an increased risk of suicidal ideation or behavior with paroxetine, studies included in this review provided insufficient evidence of associations between SSRIs as a drug class and suicidality.

In 2003, Food and Drug Administration (FDA) issued a public health advisory for paroxetine because of concerns about suicidal ideation.<sup>142</sup> FDA then extended the warning to all antidepressants in 2004,<sup>18</sup> based on a systematic review of 24 trials of participants with depression.<sup>129</sup> The FDA systematic review found an increased risk of suicidality as an AE for all antidepressants and all indications but also noted the lack of statistically significant differences

in MDD populations by drug, other than for venlafaxine extended release. Our results also suggest an increased but nonstatistically significant effect for populations with DDs.

Several differences between our analyses and those conducted by FDA are noteworthy. For example, the scope of FDA's analysis differed from that of the current review. FDA relied on a meta-analysis of 24 trials, 16 of which included depressed patients. Our review required all participants in all studies to have diagnosed DDs; we excluded studies of patients with other disorders. Suicidality as an AE may be easier to identify in patients with disorders other than depression, where the mitigating benefit of clinical improvement in depressive symptoms (including suicidal ideation) is not observed. We also excluded studies with inpatient populations.<sup>81, 133</sup> All these exclusions resulted in a smaller yield than FDA's analysis for all antidepressants and all indications for the corresponding time period, and the reduced power of the remaining trials lowered the precision of the estimate.

Another difference has to do with the time period covered. Our review included studies published after the issuance of the warnings more than a decade ago. These studies did not find evidence of increased suicidal ideation for the SSRI drug class as a whole, in part because some studies were not powered to detect differences.

Other variations in findings between our review and FDA's analysis might be the result of methodological differences. For example, our review relied on reported suicide ideation or behavior data, whereas FDA's review included analyses of text string data of AE reporting systems collected by drug manufacturers. In fact, reanalysis of the data from text strings that used a standardized approach to categorizing suicidality revealed high rates of discrepancies in suicidality determinations.

Of note, although none of the studies included in FDA's review reported any completed suicides in either the intervention or control group throughout the study period,<sup>143</sup> this fact points to the rarity of suicides and the low power of existing trials to adequately address this outcome. An added problem relates to documented instances of selective outcome reporting. As noted previously, the "restoring invisible and abandoned trials" [RIAT] analysis of a paroxetine trial found increased suicidal ideation for paroxetine.<sup>90</sup> Similar analyses for older trials may further alter the evidence base.

Clinical practice guidelines for providers treating depressed children and adolescents have included language careful to acknowledge that some increased suicide risk may occur but that the benefits of SSRIs outweigh potential harms.<sup>25, 28, 144</sup> Because the balance between risks and potential harms might differ by age group (i.e., because both benefits and harms might differ by age group), these guidelines typically separate out adolescent and younger children populations. Research in adults has also shown age-dependent effects: antidepressant use is associated with increased suicide risk among young adults, has no significant associations among middle-aged adults, and is inversely associated with suicide risk among older adults.<sup>145</sup> Careful study of differences in suicidality associated with antidepressant use in adolescents versus younger children is difficult because the sample sizes to conduct these analyses are further compromised in these studies. As we have noted in this review, there is a paucity of data available to study associations with antidepressant use among younger children. In any event, these recommendations offer support for treating adolescent depression, especially when the proximal time to the initial prescription includes vigilant monitoring for increases in suicidality to mitigate the excess risk. In general, the findings are consistent with current clinical practice guidelines by the Guidelines for Adolescent Depression in Primary Care that recommend the use of psychotherapies (specifically CBT), SSRI medications, or both for those age 10 or older<sup>24, 25</sup> and

the U.S. Preventive Services Task Force recommendation statement based on found efficacy of CBT, fluoxetine, escitalopram, and combined treatments among adolescents.<sup>26</sup> No other samples of children showed clear evidence of benefits.

In this review, few comparative effectiveness trials demonstrated a clear advantage of one type of treatment over another. The exceptions generally arose from single studies, which showed some benefit for SSRIs in combination with CBT when compared CBT or SSRIs alone. The finding of insufficient evidence for most comparators is consistent with the National Institute for Health and Care Excellence guidelines that found no clear evidence of superiority of one treatment over another.<sup>144</sup>

Finally, the review demonstrated some initial subgroup differences in efficacy and comparative effectiveness. Differences in efficacy and effectiveness based on depression severity and comorbid conditions support current guidelines that recommend different treatments based on such characteristics.<sup>24, 25, 27, 144</sup>

## Limitations

Despite the significant public health problem posed by depression in children and adolescents, with very high level of risk including significant functional impairments and high risk of early mortality from suicide, the body of evidence examining effective treatments is not large. We restricted inclusion to RCTs for benefits; the synthesis does not include data from observational studies and pooled analyses as a result. Many of the included trials were rated as having a high risk of bias; this rating limited our confidence in the conclusions regarding the effectiveness of the intervention. As noted previously, our inclusion criteria limiting the eligibility to studies of outpatients with DDs reduced the available power of the analysis and may have resulted in understated harms of antidepressants. A key concern, particularly with regard to harms of pharmacotherapy, is the documented instance of selective outcome reporting and the potential for publication bias.

In addition to the overall small number of good trials, the modalities of treatment were also limited. Of psychotherapy trials, several examined effectiveness of CBT; fewer trials examined IPT or family therapy, and still fewer trials examined effectiveness of other interventions for depression in children.

As noted previously, we found limited evidence on children. National estimates from 2017 suggest that 13.3 percent (3.2 million) of adolescents aged 12-17 have had one major depressive episode.<sup>146</sup> Estimates for younger children are less well understood; in one review, an aggregated estimate of 2.8 percent of children under 13 had depression.<sup>147, 148</sup> Our inclusion criteria required a diagnosed DD; the evidence base in this review is therefore not representative of interventions for children with clinically elevated symptoms but not mood disorders. The same inclusion criterion also limited our ability to synthesize the evidence on some treatments, including collaborative care.<sup>149</sup>

We found no studies examining effectiveness of newer approaches to treatment, including motivational interviewing or acceptance and commitment therapy.

Our findings on harms in treatment and placebo arms of studies are very limited. Studies that did report harms were generally not powered to do so, furthering limiting our conclusions on harms. In interpreting the available data on harms from treatment, clinicians also need to account for the profound harms of untreated depression.<sup>150-153</sup> Information on the rate of harms of untreated depression is particularly important in the context of rising suicidality following the boxed warning among depressed children and adolescents.

Another limitation relates to the heterogeneity and lack of specification regarding level of training of the individuals providing the intervention, as well as the frequency or dose of the intervention and the duration of treatment.

Limitations in medication trials include short durations of intervention and follow up, lack of generalizability of the study population, heterogeneity of assessment tools, and susceptibility to risk of bias.

Another limitation of the evidence on treatment of depression in children and adolescents is there was no uniformity of measures assessing for depression. This heterogeneity of assessment instruments used to diagnose depression likely affects variability of results. The evidence is also marked by inconsistency regarding how outcomes were measured with some studies using self-reports of depressive symptoms, and others using clinician reports or parent reports of depressive symptoms. Many trials had a small number of participants; this limitation influenced our judgment on the precision of the evidence and the consequent certainty.

## **Applicability**

The results of this review are generally applicable to a population of adolescents and children with MDD with limited psychiatric comorbidity, who have access to mental health professionals who can provide CBT or have access to psychiatrists or pediatricians able to prescribe SSRIs, SNRIs, tricyclic antidepressants, or monoamine oxidase inhibitors.

Studies were more likely to include adolescents than children. Additionally, patients with MDD are vastly more represented than those with other forms of depression such as dysthymia. When comorbidity was described, the most common comorbidities were anxiety disorders, ADHD, or disruptive behavior disorders. Most studies were in majority-white populations in North America or Europe. Baseline depression severity was generally in the mild to moderate range. It is difficult to determine how the results would apply to a more diverse, complicated, or impaired population.

## **Future Research Needs**

Table 68 presents a map of the evidence base across all KQs. It depicts uncertainties and gaps in the literature, along with evidence of signals of benefits, harms, or no benefits (although these signals may be specific to a narrow population or measure and be limited in their applicability). Broadly speaking, the evidence base is characterized by large areas of uncertainty or lack of information; these large gaps in the evidence occur more frequently in the nonpharmacological evidence base. The evidence on benefits of nonpharmacological interventions, when available, comes from single studies. More specifically, several issues stand out as gaps and may serve as areas for future research. First, we found insufficient evidence on many interventions and outcomes. Greater certainty in the estimate of effect will require more and better evidence for nearly all evaluated interventions. In some instances, we found no eligible evidence of benefits or harms in our specified populations, as with collaborative care. Second, we found very sparse evidence on children with MDD or a wider range of DDs. In the instances where we found signals for benefits, harms, or no harms, they often arose from studies of adolescents with MDD. We found few studies, comparatively speaking, of children and of children or adolescents with a mix of depressive diagnoses; the resulting evidence base offered limited indications of benefit or harm for these populations. These populations would benefit from well-designed trials. Third, we found limited information on moderators. These analyses, when available, were generally hypothesis generating. The studies were rarely designed to



measure differences in moderating variables. Some studies evaluated several demographic, clinical, caregiver, and study characteristics and found evidence of moderation for a subset of variables only. These findings could be explained by chance; we could not arrive at conclusions as a result. As an example, a single study found that monotherapy (CBT or fluoxetine) may offer benefits similar to combination therapy for those with ADHD, but monotherapy may not match combined therapy for those without ADHD<sup>98</sup> but these findings arise from small samples and post-hoc analyses and require confirmation from larger preplanned analyses. The paucity of evidence limits our ability to support recommendations tailored by underlying patient characteristics. A comprehensive clinical pathway would need to account for selecting and sequencing interventions to account for these characteristics. A robust trial focusing on sequencing treatments would help provide patient-centered evidence that accounts for underlying patient characteristics.

**Table 68. Evidence map for interventions for childhood depression<sup>a</sup>**

Population	Key Questions	Interventions and Comparators	Symptoms	Response	Recovery	Remission	Relapse	Functional Status	Mortality	Suicidal Ideation\Behavior	Suicide Attempts	Serious Adverse Events	Withdrawal due to AEs	Subgroup Analysis
			I	I	0	I	0	I	I	I	I	I	0	+
Adolescents, MDD	KQ 1 benefits and harms of nonpharmacological interventions	CBT vs. pill placebo	I	I	0	I	0	I	I	I	I	I	0	+
		CBT vs. active control	I	I	0	I	I	I	0	0	I	0	0	I
		CBT plus TAU vs. TAU/UC	+	+	+	0	0	+	0	I	0	0	0	0
		Attachment-based family therapy vs. wait-list	I	I	0	I	0	0	0	I	0	0	0	0
		Attachment-based family therapy vs. TAU	I	0	I	0	0	0	0	0	0	0	0	0
		Short-term psychoanalytic therapy vs. active	I	I	0	I	I	0	0	0	I	0	0	0
		Exercise vs. active control	I	+	0	I	0	0	0	0	0	0	0	0
		Spirituality vs. wait-list	+	0	0	0	0	0	0	0	0	0	0	0
		Family therapy vs. active control	I	I	0	I	0	I	0	I	0	0	0	I
		Relapse prevention CBT plus continued antidepressant medication management vs. continued medication management	I	0	0	0	I	I	0	0	I	I	I	0
		IPT vs. active control: benefits	I	I	0	I	0	I	0	I	0	0	0	0

Population	Key Questions	Interventions and Comparators	Symptoms	Response	Recovery	Remission	Relapse	Functional Status	Mortality	Suicidal Ideation\Behavior	Suicide Attempts	Serious Adverse Events	Withdrawal due to AEs	Subgroup Analysis
Adolescents, MDD (continued)	KQ 2 benefits and harms of pharmacological interventions	SSRI: Fluoxetine vs. placebo	+	+	0	1	0	1	1	0	1	1	0	+
		SSRI: Escitalopram vs. placebo	+	+	0	+	0	+	0	1	0	1	1	0
		SSRI: Paroxetine vs. placebo	1	1	0	1	1	1	0	-	1	1	1	+
		SSRI: Vilazodone vs. placebo	1	1	0	1	0	0	0	1	1	1	1	0
		SSRIs (fluoxetine) for relapse prevention vs. placebo	1	0	0	0	0	0	0	0	0	0	0	0
		TCA: Imipramine vs. placebo	1	1	0	1	1	1	1	1	0	1	1	1
		TCA: Desipramine vs. placebo	1	0	0	1	0	1	0	0	0	0	1	0
		TCA: Amitriptyline vs. placebo	1	1	0	0	0	0	0	1	0	0	1	0
		MAOIs vs. placebo	1	1	0	0	0	0	0	1	0	0	1	0
		Fluoxetine plus CBT vs. placebo	+	+	0	+	0	+	1	1	1	1	0	1
	KQ 3 benefits and harms of combination interventions	Collaborative care vs. usual care	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 4 benefits and harms of collaborative care interventions	SSRIs vs. TCAs	1	0	0	1	1	1	1	1	0	1	1	1
		CBT vs. other psychotherapy	1	1	0	1	1	0	0	0	1	1	0	0
		Treatment-resistant depression	1	1	0	0	0	1	1	1	1	1	1	+
		Psychotherapy vs. pharmacotherapy	+	1	0	1	0	1	1	1	1	+	0	+
		Psychotherapy plus pharmacotherapy vs. pharmacotherapy	-, +	1	1	+	1	1	1	1	1	1	0	+
		Psychotherapy plus pharmacotherapy vs. psychotherapy	+	1	0	+	0	+	1	1	1	1	0	+
		Psychotherapy within-type comparisons of delivery methods or approaches	1	0	0	0	0	0	0	0	0	0	0	1
		Pharmacotherapy dose comparisons	1	1	0	1	0	0	0	1	1	1	1	1

Population	Key Questions	Interventions and Comparators	Symptoms	Response	Recovery	Remission	Relapse	Functional Status	Mortality	Suicidal Ideation\Behavior	Suicide Attempts	Serious Adverse Events	Withdrawal due to AEs	Subgroup Analysis
			+			0	0	+	0	0	0	0	0	0
Adolescents, MDD, PDD, other DD, or DD NOS	KQ 1 benefits and harms of nonpharmacological interventions	CBT vs. wait-list control	+			0	0	+	0	0	0	0	0	0
		CBT (delivered to adolescent and parent) vs. wait-list control		0		0	0		0	0	0	0	0	0
		CBT plus TAU vs. TAU/UC		0		0	0		0		0	0	0	0
		CBT (modified) vs. UC		0	0		0	0	0	0	0	0	0	0
		IPT vs. wait-list control			0	0	0	0	0	0	0	0	0	0
	KQ 2 benefits and harms of pharmacological interventions	SSRI: Fluoxetine vs. placebo			0	0	0		0		0	0	0	
	KQ 3 benefits and harms of combination interventions	Any combination therapy vs. usual care or placebo	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 4 benefits and harms of collaborative care interventions	Collaborative care vs. usual care	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 5 comparative benefits and harms of treatments	CBT vs. other psychotherapy			0	0	0	0	0	0	0	0	0	0
		Psychotherapy vs. pharmacotherapy		0	0		0		0		0	0	0	0
		Psychotherapy plus pharmacotherapy vs. pharmacotherapy		0	0		0	0	0		0	0	0	0
		Psychotherapy plus pharmacotherapy vs. psychotherapy		0	0		0	0	0		0	0	0	0
		Psychotherapy within-type comparisons of delivery methods or approaches		0	0		0		0	0	0	0	0	
Adolescents and children, MDD	KQ 1 benefits and harms of nonpharmacological interventions	Relapse prevention CBT plus continued antidepressant medication management vs. continued medication management	0	0	0		+	0	0					0
	KQ 2 benefits and harms of pharmacological interventions	SSRI: Fluoxetine vs. placebo			0		0				0			+
		SSRI: Paroxetine vs. placebo			0		0		0		0			
		SSRI: Citalopram vs. placebo			0		0		0	0	0			0
		SSRIs (fluoxetine) for relapse prevention vs. placebo		0	0	0	+		0		0			+
		SNRI: Venlafaxine vs placebo			0	0	0	0	0	0	0	0	0	0

Population	Key Questions	Interventions and Comparators	Symptoms	Response	Recovery	Remission	Relapse	Functional Status	Mortality	Suicidal Ideation\Behavior	Suicide Attempts	Serious Adverse Events	Withdrawal due to AEs	Subgroup Analysis
Adolescents and children, MDD (continued)	KQ 2 benefits and harms of pharmacological interventions (continued)	SNRI: Desvenlafaxine vs. placebo	-	-	0	0	0	0	1	1	0	1	1	0
		SNRI: Duloxetine vs. placebo	1	1	0	1	0	0	0	1	0	1	-	0
		Venlafaxine plus active control vs. placebo plus active control	1	0	0	0	0	0	0	0	0	0	1	0
	KQ 3 benefits and harms of combination interventions	Any combination therapy vs. usual care or placebo	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 4 benefits and harms of collaborative care interventions	Collaborative care vs. usual care	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 5 comparative benefits and harms of treatments	SSRIs vs. SNRIs	1	1	0	1	0	0	0	1	0	1	1	0
		SSRIs vs. TCAs	1	1	0	0	0	0	1	1	0	1	1	0
		Pharmacotherapy dose comparisons	1	1	0	1	0	0	0	1	0	1	1	1
		Psychotherapy within-type comparisons of delivery methods or approaches	1	0	0	0	0	0	0	0	0	0	0	0
		Treatment-resistant depression interventions	1	1	0	0	0	0	0	0	0	0	1	0
Children, MDD	KQ 1 benefits and harms of nonpharmacological interventions	PCIT vs. active control	1	0	0	0	0	1	0	0	0	0	0	0
	KQ 2 benefits and harms of pharmacological interventions	SSRI: Fluoxetine vs. placebo	1	0	0	0	0	0	0	0	0	0	0	0
		SSRIs (fluoxetine) for relapse prevention vs. placebo	1	0	0	0	0	0	0	0	0	0	0	0
		TCA (nortriptyline) vs. placebo	1	1	0	0	0	1	0	0	0	0	0	0
	KQ 3 benefits and harms of combination interventions	Any combination therapy vs. usual care or placebo	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 4 benefits and harms of collaborative care interventions	Collaborative care vs. usual care	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 5 comparative benefits and harms of treatments	Any comparisons of active treatment	0	0	0	0	0	0	0	0	0	0	0	0
Children, MDD, PDD, or DD NOS	KQ 1 benefits and harms of nonpharmacological interventions	Family-based IPT vs. active control	+	0	0	1	0	0	0	0	0	0	0	0
	KQ 2 benefits and harms of pharmacological interventions	Any pharmacotherapy vs. placebo	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 3 benefits and harms of combination interventions	Any combination therapy vs. usual care or placebo	0	0	0	0	0	0	0	0	0	0	0	0

Population	Key Questions	Interventions and Comparators	Symptoms	Response	Recovery	Remission	Relapse	Functional Status	Mortality	Suicidal Ideation\Behavior	Suicide Attempts	Serious Adverse Events	Withdrawal due to AEs	Subgroup Analysis
			0	0	0	0	0	0	0	0	0	0	0	0
Children, MDD, PDD, or DD NOS (continued)	KQ 4 benefits and harms of collaborative care interventions	Collaborative care vs. usual care	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 5 comparative benefits and harms of treatments	Psychotherapy plus pharmacotherapy vs. psychotherapy	I	0	0	0	0	I	0	0	0	0	0	0
Adolescents or children, MDD, PDD, or DD NOS	KQ 1 benefits and harms of nonpharmacological interventions	Family therapy vs. active control	I	+	0	I	I	I	0	0	0	0	0	I
		Family therapy vs. pill placebo	I	0	0	I	0	0	0	0	0	0	0	I
		Omega-3 vs. pill placebo	I	0	0	I	0	0	0	0	0	0	0	I
	KQ 2 benefits and harms of pharmacological interventions	Any pharmacotherapy vs. placebo	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 3 benefits and harms of combination interventions	Omega-3 plus family therapy versus pill placebo	I	0	0	I	0	0	0	0	0	0	0	I
	KQ 4 benefits and harms of collaborative care interventions	Collaborative care vs. usual care	0	0	0	0	0	0	0	0	0	0	0	0
	KQ 5 comparative benefits and harms of treatments	Psychotherapy within-type comparisons of delivery methods or approaches	I	0	0	0	0	I	0	0	0	0	0	0
		Omega-3 vs. family therapy	I	0	0	I	0	0	0	0	0	0	0	0
		Omega-3 vs. omega-3 plus family therapy	I	0	0	I	0	0	0	0	0	0	0	0
		Omega-3 plus family therapy vs, family therapy	I	0	0	I	0	0	0	0	0	0	0	0

I = insufficient evidence, + = evidence of benefit, - = evidence of harm (for harms outcomes, specifically mortality, suicidal ideation or behavior, suicide attempts, SAEs, and withdrawals) or of no benefit (for benefits outcomes, specifically symptoms, response, recovery, remission, relapse, and functional status), +,- = evidence indicates both benefit and harm for specific populations or outcomes. 0 = no evidence

<sup>a</sup> “+” and “-” symbols indicate any evidence of benefit, harm, or no benefit across any measure and for any population: interpretation of these signals requires additional context. The evidence of benefit or harm for each outcome may be limited to a single measure or a single population.

AE = adverse event; CBT = cognitive behavioral therapy; DD = depressive disorder; IPT = interpersonal psychotherapy; KQ = Key Question; NOS = not otherwise specified; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; PCIT = Parent-Child Interaction Therapy Emotion Development; PDD = persistent depressive disorder; SAE = serious adverse event; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TAU = treatment as usual; TCA = tricyclic antidepressants; UC = usual care; vs. = versus.

Fourth, psychotherapy studies rarely reported on harms. Fifth, we had difficulty interpreting the clinical significance of some reported changes in continuous scales in the absence of evidence on anchor-based minimally important differences for patients (that is, the smallest amount an outcome must change to be meaningful to patients) on those scales.

The evidence base is marked by little or no replication, particularly for nonpharmacological therapies. The evidence for a given psychotherapeutic approach is generally represented by a single trial; as a result, even when studies found evidence of benefit, our judgment of the certainty regarding the benefits of the therapy was limited. Other reasons that limited the certainty of conclusions include small sample size and poor precision, flaws in study design, high and differential attrition, and at least some evidence of reporting bias. These issues point to a compelling need for rigorous and adequately powered studies.

Future research in this area should also focus on implementation. The mechanisms of action and conditions for success were generally not described in the primary studies, further limiting the clinical utility of our results.

## **Conclusion**

In summary, our results, when parsed by population and disorder, suggest that for adolescents with MDD, CBT, fluoxetine, escitalopram, and combined fluoxetine plus CBT may reduce depressive symptoms in the short term, although the clinical implication of improvement in continuous measures of depressive symptoms is unclear. SSRIs as a class may improve response and functional status among adolescents and children with MDD. However, they may be associated with a higher risk of serious AEs among adolescents and children with MDD and with a higher risk of withdrawal due to AEs among adolescents with MDD. Paroxetine may be associated with a higher risk of suicidal ideation or behaviors in adolescents with MDD. For adolescents and children with MDD, PDD, or DD NOS, CBT and family therapy may improve symptoms, response, and functional status. For adolescents and children with MDD, CBT plus medications may help prevent relapse. Evidence on children with MDD alone or with a wider range of DDs (MDD, PDD, or DD NOS) is sparse.

Across populations and disorders, the findings of this review indicate that several interventions may be associated with low SOE of benefits such as CBT, fluoxetine, escitalopram, and combined fluoxetine and CBT in the short term; we found insufficient evidence on harms for these individual interventions. As noted above, paroxetine had a higher risk of suicidal ideation or behaviors in adolescents with MDD, but the evidence was insufficient for other SSRIs as a drug class across populations and disorders, likely as a result of low power to detect these events.

## References

1. Bang KS, Chae SM, Hyun MS, et al. The mediating effects of perceived parental teasing on relations of body mass index to depression and self-perception of physical appearance and global self-worth in children. *J Adv Nurs*. 2012 Dec;68(12):2646-53. doi: 10.1111/j.1365-2648.2012.05963.x. PMID: 22384945.
2. Lewinsohn PM, Rohde P, Klein DN, et al. Natural course of adolescent major depressive disorder: I. Continuity into young adulthood. *J Am Acad Child Adolesc Psychiatry*. 1999 Jan;38(1):56-63. doi: 10.1097/00004583-199901000-00020. PMID: WOS:000077871100020.
3. Owens M, Stevenson J, Hadwin JA, et al. Anxiety and depression in academic performance: an exploration of the mediating factors of worry and working memory. *Sch Psychol Int*. 2012 Aug;33(4):433-49. doi: 10.1177/0143034311427433. PMID: WOS:000306230500004.
4. Pomerantz EM, Altermatt ER, Saxon JL. Making the grade but feeling distressed: gender differences in academic performance and internal distress. *J Educ Psychol*. 2002 Jun;94(2):396-404. doi: 10.1037//0022-0663.94.2.396. PMID: WOS:000176058300014.
5. Thapar A, Collishaw S, Potter R, et al. Managing and preventing depression in adolescents. *BMJ*. 2010 Jan 22;340:c209. doi: 10.1136/bmj.c209. PMID: 20097692.
6. Weissman MM, Wolk S, Goldstein RB, et al. Depressed adolescents grown up. *JAMA*. 1999 May 12;281(18):1707-13. PMID: 10328070.
7. Avenevoli S, Swendsen J, He JP, et al. Major depression in the national comorbidity survey-adolescent supplement: Prevalence, correlates, and treatment. *J Am Acad Child Adolesc Psychiatry*. 2015 Jan;54(1):37-44 e2. doi: 10.1016/j.jaac.2014.10.010. PMID: 25524788.
8. Center for Behavioral Health Statistics and Quality. 2016 National Study on Drug Use and Health: detailed tables. Substance Abuse and Mental Health Services Administration. Rockville, MD: 2017.
9. Tang A. A systematic review of combination antidepressant medication and psychotherapy in children and adolescents with unipolar depression. 2017. [http://www.crd.york.ac.uk/PROSPERO/display\\_record.php?ID=CRD42017060191](http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017060191).
10. Duffy F, Sharpe H, Schwannauer M. A systemic review and meta-analysis of the effectiveness of interpersonal psychotherapy for adolescents with depression. 2016. [https://www.crd.york.ac.uk/PROSPERO/display\\_record.php?RecordID=33888](https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=33888)
11. Weersing VR, Brent DA, Rozenman MS, et al. Brief behavioral therapy for pediatric anxiety and depression in primary care: a randomized clinical trial. *JAMA Psychiatry*. 2017 Jun 1;74(6):571-8. doi: 10.1001/jamapsychiatry.2017.0429. PMID: 28423145.
12. Locher C, Koechlin H, Zion SR, et al. Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2017 Oct 1;74(10):1011-20. doi: 10.1001/jamapsychiatry.2017.2432. PMID: 28854296.
13. Weersing VR, Jeffreys M, Do MT, et al. Evidence base update of psychosocial treatments for child and adolescent depression. *J Clin Child Adolesc Psychol*. 2017 Jan-Feb;46(1):11-43. doi: 10.1080/15374416.2016.1220310. PMID: 27870579.
14. Thabrew H, Stasiak K, Hetrick SE, et al. Psychological therapies for anxiety and depression in children and adolescents with long-term physical conditions. *Cochrane*; 2017. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012488/full>

15. Forti-Buratti MA, Saikia R, Wilkinson EL, et al. Psychological treatments for depression in pre-adolescent children (12 years and younger): systematic review and meta-analysis of randomised controlled trials. *Eur Child Adolesc Psychiatry*. 2016 Oct;25(10):1045-54. doi: 10.1007/s00787-016-0834-5. PMID: 26969618.
16. Weisz JR, Kuppens S, Ng MY, et al. What five decades of research tells us about the effects of youth psychological therapy: a multilevel meta-analysis and implications for science and practice. *Am Psychol*. 2017 Feb-Mar;72(2):79-117. doi: 10.1037/a0040360. PMID: WOS:000395718500001.
17. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004 Aug 18;292(7):807-20. doi: 10.1001/jama.292.7.807. PMID: 15315995.
18. U.S. Food and Drug Administration. Suicidality in children and adolescents being treated with antidepressant medications. Silver Spring, MD: U.S. Food and Drug Administration; 2004.  
<http://wayback.archive-it.org/7993/20170113164717/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161679.htm>. Accessed on February 25 2019.
19. Mojtabai R, Olfson M, Han B. National trends in the prevalence and treatment of depression in adolescents and young adults. *Pediatrics*. 2016 Dec;138(6). doi: 10.1542/peds.2016-1878. PMID: 27940701.
20. Pampallona S, Bollini P, Tibaldi G, et al. Combined pharmacotherapy and psychological treatment for depression: a systematic review. *Arch Gen Psychiatry*. 2004 Jul;61(7):714-9. doi: 10.1001/archpsyc.61.7.714. PMID: 15237083.
21. IsHak WW, Ha K, Kapitanski N, et al. The impact of psychotherapy, pharmacotherapy, and their combination on quality of life in depression. *Harv Rev Psychiatry*. 2011 Nov-Dec;19(6):277-89. doi: 10.3109/10673229.2011.630828. PMID: WOS:000297170100001.
22. American Psychological Association. Guideline development panel for the treatment of depressive disorders. Clinical practice guideline for the treatment of depression across three age cohorts. Washington, DC: American Psychological Association; 2019.  
<https://www.apa.org/depression-guideline/guideline.pdf>. Accessed on August 12 2019.
23. National Institute for Health and Care Excellence. Depression in children and young people: identification and management. NICE guideline [NG134]. United Kingdom: National Institute for Health and Care Excellence; 2019.  
<https://www.nice.org.uk/guidance/ng134/chapter/Recommendations>. Accessed on August 12 2019.
24. Cheung AH, Zuckerbrot RA, Jensen PS, et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): part II. treatment and ongoing management. *Pediatrics*. 2018 Feb 26;141(3). doi: 10.1542/peds.2017-4082. PMID: 29483201.
25. Zuckerbrot RA, Cheung A, Jensen PS, et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): part I. practice preparation, identification, assessment, and initial management. *Pediatrics*. 2018 Feb 26;141(3). doi: 10.1542/peds.2017-4081. PMID: 29483200.
26. Siu AL. Screening for depression in children and adolescents: US Preventive Services Task Force Recommendation Statement. *Pediatrics*. 2016;137(3):1-8. PMID: 2016-23950-015.
27. Birmaher B, Brent D, AACAP Work Group on Quality Issues, et al. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2007 Nov;46(11):1503-26. doi: 10.1097/chi.0b013e318145ae1c. PMID: 18049300.
28. Cheung AH, Zuckerbrot RA, Jensen PS, et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): II. Treatment and ongoing management. *Pediatrics*. 2007 Nov;120(5):e1313-26. doi: 10.1542/peds.2006-1395. PMID: 17974724.



29. Gordon MS, Tonge B, Melvin GA. Outcome of adolescent depression: 6 months after treatment. *Aust N Z J Psychiatry*. 2011 Mar;45(3):232-9. doi: 10.3109/00048674.2010.538838. PMID: 21128873.
30. Lilienfeld SO. Psychological treatments that cause harm. *Perspect Psychol Sci*. 2007 Mar;2(1):53-70. doi: 10.1111/j.1745-6916.2007.00029.x. PMID: WOS:000207450300005.
31. Jaycox LH, Asarnow JR, Sherbourne CD, et al. Adolescent primary care patients' preferences for depression treatment. *Administration and Policy in Mental Health and Mental Health Services Research*. 2006;33(2):198-207.
32. Bradley KL, McGrath PJ, Brannen CL, et al. Adolescents' attitudes and opinions about depression treatment. *Community Ment Health J*. 2010;46(3):242-51.
33. Asarnow JR, Emslie G, Clarke G, et al. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. *J Am Acad Child Adolesc Psychiatry*. 2009 Mar;48(3):330-9. doi: 10.1097/CHI.0b013e3181977476. PMID: 19182688.
34. Wagner KD, Jonas J, Findling RL, et al. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J Am Acad Child Adolesc Psychiatry*. 2006 Mar;45(3):280-8. doi: 10.1097/01.chi.0000192250.38400.9e. PMID: 16540812.
35. Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2014. [www.effectivehealthcare.ahrq.gov/methodsguide.cfm](http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm).
36. Covidence. Covidence systematic review software. Melbourne, Australia: Veritas Health Innovation; n.d. [www.covidence.org](http://www.covidence.org). Accessed on March 19 2019.
37. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919. PMID: 27733354.
38. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration; 2011. [www.handbook.cochrane.org](http://www.handbook.cochrane.org). Accessed on January 10 2017.
39. West SL, Gartlehner G, Mansfield AJ, et al. Comparative effectiveness review methods: clinical heterogeneity methods research report. (Prepared by RTI International-University of North Carolina Evidence-based Practice Center under Contract No. 290-2007-10056-I). AHRQ Publication No: 10-EHC070-EF. Rockville, MD: Agency for Healthcare Research and Quality; September 2010.
40. Akl E, Mustafa R, Wiercioch NSW, et al. 1. Overview of the GRADE approach. In: Schunemann H, Brozek J, Guyatt G, Oxman A, eds. GRADE handbook. The GRADE Working Group 2013.
41. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol*. 2015 Nov;68(11):1312-24. doi: 10.1016/j.jclinepi.2014.11.023. PMID: 25721570.
42. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011 Nov;64(11):1198-207. doi: 10.1016/j.jclinepi.2010.11.021. PMID: 21463926.
43. Thompson MC, Sugar CA, Langer DA, et al. A randomized clinical trial comparing family-focused treatment and individual supportive therapy for depression in childhood and early adolescence. *J Am Acad Child Adolesc Psychiatry*. 2017 Jun;56(6):515-23. doi: 10.1016/j.jaac.2017.03.018. PMID: 28545757.

44. Goodyer IM, Reynolds S, Barrett B, et al. Cognitive-behavioural therapy and short-term psychoanalytic psychotherapy versus brief psychosocial intervention in adolescents with unipolar major depression (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled trial. *Health Technol Assess*. 2017 Mar;21(12):1-94. doi: 10.3310/hta21120. PMID: 28394249.
45. Clarke G, DeBar LL, Pearson JA, et al. Cognitive behavioral therapy in primary care for youth declining antidepressants: a randomized trial. *Pediatrics*. 2016 May;137(5). doi: 10.1542/peds.2015-1851. PMID: 27244782.
46. Rickhi B, Kania-Richmond A, Moritz S, et al. Evaluation of a spirituality informed e-mental health tool as an intervention for major depressive disorder in adolescents and young adults - a randomized controlled pilot trial. *BMC Complement Altern Med*. 2015 Dec 24;15:450. doi: 10.1186/s12906-015-0968-x. PMID: 26702639.
47. Dietz LJ, Weinberg RJ, Brent DA, et al. Family-based interpersonal psychotherapy for depressed preadolescents: examining efficacy and potential treatment mechanisms. *J Am Acad Child Adolesc Psychiatry*. 2015 Mar;54(3):191-9. doi: 10.1016/j.jaac.2014.12.011. PMID: 25721184.
48. Kennard BD, Emslie GJ, Mayes TL, et al. Sequential treatment with fluoxetine and relapse--prevention CBT to improve outcomes in pediatric depression. *Am J Psychiatry*. 2014 Oct;171(10):1083-90. doi: 10.1176/appi.ajp.2014.13111460. PMID: 24935082.
49. Shirk SR, Deprince AP, Crisostomo PS, et al. Cognitive behavioral therapy for depressed adolescents exposed to interpersonal trauma: an initial effectiveness trial. *Psychotherapy (Chic)*. 2014 Mar;51(1):167-79. doi: 10.1037/a0034845. PMID: 24377410.
50. Luby J, Lenze S, Tillman R. A novel early intervention for preschool depression: findings from a pilot randomized controlled trial. *J Child Psychol Psychiatry*. 2012 Mar;53(3):313-22. doi: 10.1111/j.1469-7610.2011.02483.x. PMID: 22040016.
51. Kennard BD, Emslie GJ, Mayes TL, et al. Cognitive-behavioral therapy to prevent relapse in pediatric responders to pharmacotherapy for major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. 2008 Dec;47(12):1395-404. doi: 10.1097/CHI.0b013e31818914a1. PMID: 18978634.
52. Nemets H, Nemets B, Apter A, et al. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am J Psychiatry*. 2006 Jun;163(6):1098-100. doi: 10.1176/ajp.2006.163.6.1098. PMID: 16741212.
53. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004 Aug 18;292(7):807-20. doi: 10.1001/jama.292.7.807. PMID: 15315995.
54. Rohde P, Clarke GN, Mace DE, et al. An efficacy/effectiveness study of cognitive-behavioral treatment for adolescents with comorbid major depression and conduct disorder. *J Am Acad Child Adolesc Psychiatry*. 2004 Jun;43(6):660-8. doi: 10.1097/01.chi.0000121067.29744.41. PMID: 15167082.
55. Diamond GS, Reis BF, Diamond GM, et al. Attachment-based family therapy for depressed adolescents: a treatment development study. *J Am Acad Child Adolesc Psychiatry*. 2002 Oct;41(10):1190-6. doi: 10.1097/00004583-200210000-00008. PMID: 12364840.
56. Clarke GN, Hornbrook M, Lynch F, et al. Group cognitive-behavioral treatment for depressed adolescent offspring of depressed parents in a health maintenance organization. *J Am Acad Child Adolesc Psychiatry*. 2002 Mar;41(3):305-13. doi: 10.1097/00004583-200203000-00010. PMID: 11886025.
57. Rossello J, Bernal G. The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. *J Consult Clin Psychol*. 1999 Oct;67(5):734-45. PMID: 10535240.

58. Mufson L, Weissman MM, Moreau D, et al. Efficacy of interpersonal psychotherapy for depressed adolescents. *Arch Gen Psychiatry*. 1999 Jun;56(6):573-9. PMID: 10359475.
59. Clarke GN, Rohde P, Lewinsohn PM, et al. Cognitive-behavioral treatment of adolescent depression: efficacy of acute group treatment and booster sessions. *J Am Acad Child Adolesc Psychiatry*. 1999 Mar;38(3):272-9. doi: 10.1097/00004583-199903000-00014. PMID: 10087688.
60. Brent DA, Holder D, Kolko D, et al. A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. *Arch Gen Psychiatry*. 1997 Sep;54(9):877-85. PMID: 9294380.
61. Rohde P, Lewinsohn PM, Seeley JR. Response of depressed adolescents to cognitive-behavioral treatment: do differences in initial severity clarify the comparison of treatments? *J Consult Clin Psychol*. 1994 Aug;62(4):851-4. PMID: 7962890.
62. Hughes CW, Barnes S, Barnes C, et al. Depressed Adolescents Treated with Exercise (DATE): a pilot randomized controlled trial to test feasibility and establish preliminary effect sizes. *Ment Health Phys Act*. 2013 Jun;6(2):119-31. doi: 10.1016/j.mhpa.2013.06.006. PMID: 24244220.
63. Israel P, Diamond GS. Feasibility of attachment based family therapy for depressed clinic-referred Norwegian adolescents. *Clin Child Psychol Psychiatry*. 2013;18(3):334-50. doi: 10.1177/1359104512455811. PMID: 108668356. Language: English. Entry Date: 20160426. Revision Date: 20160426. Publication Type: Article.
64. Poole LA, Knight T, Toumbourou JW, et al. A randomized controlled trial of the impact of a family-based adolescent depression intervention on both youth and parent mental health outcomes. *J Abnorm Child Psychol*. 2018 Jan;46(1):169-81. doi: 10.1007/s10802-017-0292-7. PMID: 28374218.
65. Fristad MA, Vesco AT, Young AS, et al. Pilot randomized controlled trial of Omega-3 and individual-family psychoeducational psychotherapy for children and adolescents with depression. *J Clin Child Adolesc Psychol*. 2019;48(sup1):S105-s18. doi: 10.1080/15374416.2016.1233500. PMID: 27819485.
66. DelBello MP, Hochadel TJ, Portland KB, et al. A double-blind, placebo-controlled study of selegiline transdermal system in depressed adolescents. *J Child Adolesc Psychopharmacol*. 2014 Aug;24(6):311-7. doi: 10.1089/cap.2013.0138. PMID: 24955812.
67. Emslie GJ, Prakash A, Zhang Q, et al. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014 May;24(4):170-9. doi: 10.1089/cap.2013.0096. PMID: 24815533.
68. Atkinson SD, Prakash A, Zhang Q, et al. A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014 May;24(4):180-9. doi: 10.1089/cap.2013.0146. PMID: 24813026.
69. Emslie GJ, Wagner KD, Kutcher S, et al. Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2006 Jun;45(6):709-19. doi: 10.1097/01.chi.0000214189.73240.63. PMID: 16721321.
70. Berard R, Fong R, Carpenter DJ, et al. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2006 Feb-Apr;16(1-2):59-75. doi: 10.1089/cap.2006.16.59. PMID: 16553529.
71. Klein RG, Mannuzza S, Koplewicz HS, et al. Adolescent depression: controlled desipramine treatment and atypical features. *Depress Anxiety*. 1998;7(1):15-31. PMID: 9592629.

72. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997 Nov;54(11):1031-7. PMID: 9366660.
73. Mandoki MW, Tapia MR, Tapia MA, et al. Venlafaxine in the treatment of children and adolescents with major depression. *Psychopharmacol Bull*. 1997;33(1):149-54. PMID: 9133767.
74. Kye CH, Waterman GS, Ryan ND, et al. A randomized, controlled trial of amitriptyline in the acute treatment of adolescent major depression. *J Am Acad Child Adolesc Psychiatry*. 1996 Sep;35(9):1139-44. doi: 10.1097/00004583-199609000-00011. PMID: 8824057.
75. Durgam S, Chen C, Migliore R, et al. A phase 3, double-blind, randomized, placebo-controlled study of vilazodone in adolescents with major depressive disorder. *Paediatr Drugs*. 2018 Aug;20(4):353-63. doi: 10.1007/s40272-018-0290-4. PMID: 29633166.
76. Weihs KL, Murphy W, Abbas R, et al. Desvenlafaxine versus placebo in a fluoxetine-referenced study of children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2018 Feb;28(1):36-46. doi: 10.1089/cap.2017.0100. PMID: 29189044.
77. Atkinson S, Lubaczewski S, Ramaker S, et al. Desvenlafaxine versus placebo in the treatment of children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2018;28(1):55-65. doi: 10.1089/cap.2017.0099. PMID: 2018-03285-007.
78. Geller B, Cooper TB, McCombs HG, et al. Double-blind, placebo-controlled study of nortriptyline in depressed children using a "fixed plasma level" design. *Psychopharmacol Bull*. 1989;25(1):101-8. PMID: 2672066.
79. Emslie GJ, Ventura D, Korotzer A, et al. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry*. 2009 Jul;48(7):721-9. doi: 10.1097/CHI.0b013e3181a2b304. PMID: 19465881.
80. Emslie GJ, Kennard BD, Mayes TL, et al. Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. *Am J Psychiatry*. 2008 Apr;165(4):459-67. doi: 10.1176/appi.ajp.2007.07091453. PMID: 18281410.
81. Wagner KD, Robb AS, Findling RL, et al. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry*. 2004 Jun;161(6):1079-83. doi: 10.1176/appi.ajp.161.6.1079. PMID: 15169696.
82. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002 Oct;41(10):1205-15. doi: 10.1097/00004583-200210000-00010. PMID: 12364842.
83. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2001 Jul;40(7):762-72. doi: 10.1097/00004583-200107000-00010. PMID: 11437014.
84. Findling RL, Pagano ME, McNamara NK, et al. The short-term safety and efficacy of fluoxetine in depressed adolescents with alcohol and cannabis use disorders: a pilot randomized placebo-controlled trial. *Child Adolesc Psychiatry Ment Health*. 2009 Mar 19;3(1):11. doi: 10.1186/1753-2000-3-11. PMID: 19298659.
85. Kennard B, Silva S, Vitiello B, et al. Remission and residual symptoms after short-term treatment in the Treatment of Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1404-11. doi: 10.1097/01.chi.0000242228.75516.21. PMID: 17135985.
86. Foster S, Mohler-Kuo M. Treating a broader range of depressed adolescents with combined therapy. *J Affect Disord*. 2018 Dec 1;241:417-24. doi: 10.1016/j.jad.2018.08.027. PMID: 30145512.

87. Vitiello B, Rohde P, Silva S, et al. Functioning and quality of life in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1419-26. doi: 10.1097/01.chi.0000242229.52646.6e. PMID: 17135987.
88. Findling RL, Robb A, Bose A. Escitalopram in the treatment of adolescent depression: a randomized, double-blind, placebo-controlled extension trial. *J Child Adolesc Psychopharmacol*. 2013 Sep;23(7):468-80. doi: 10.1089/cap.2012.0023. PMID: 24041408.
89. Forest Laboratories. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of citalopram in children and adolescents with depression. Forest Laboratories - Clinical Study Register. 2001(1). PMID: CN-00763823.
90. Le Noury JL, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *Br Med J*. 2015;351. PMID: 2016-20242-001.
91. GlaxoSmithKline. A double-blind, multicentre placebo controlled study of paroxetine in adolescents with unipolar major depression. 1998. <http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/038/CN-00497038/frame.html>.
92. Le Noury J, Nardo JM, Healy D, et al. Study 329 continuation phase: safety and efficacy of paroxetine and imipramine in extended treatment of adolescent major depression. *Int J Risk Saf Med*. 2016 Sep 17;28(3):143-61. doi: 10.3233/jrs-160728. PMID: 27662279.
93. Emslie GJ, Heiligenstein JH, Hoog SL, et al. Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 2004 Nov;43(11):1397-405. doi: 10.1097/01.chi.0000140453.89323.57. PMID: 15502599.
94. Emslie GJ, Findling RL, Yeung PP, et al. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry*. 2007 Apr;46(4):479-88. doi: 10.1097/chi.0b013e31802f5f03. PMID: 17420682.
95. Kennard BD, Mayes TL, Chahal Z, et al. Predictors and moderators of relapse in children and adolescents with major depressive disorder. *J Clin Psychiatry*. 2018 Mar/Apr;79(2). doi: 10.4088/JCP.15m10330. PMID: 29474007.
96. Hirschtritt ME, Pagano ME, Christian KM, et al. Moderators of fluoxetine treatment response for children and adolescents with comorbid depression and substance use disorders. *J Subst Abuse Treat*. 2012 Jun;42(4):366-72. doi: 10.1016/j.jsat.2011.09.010. PMID: 22116008.
97. Curry J, Rohde P, Simons A, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1427-39. doi: 10.1097/01.chi.0000240838.78984.e2. PMID: 17135988.
98. Kratochvil CJ, May DE, Silva SG, et al. Treatment response in depressed adolescents with and without co-morbid attention-deficit/hyperactivity disorder in the Treatment for Adolescents with Depression Study. *J Child Adolesc Psychopharmacol*. 2009 Oct;19(5):519-27. doi: 10.1089/cap.2008.0143. PMID: 19877976.
99. Iftene F, Predescu E, Stefan S, et al. Rational-emotive and cognitive-behavior therapy (REBT/CBT) versus pharmacotherapy versus REBT/CBT plus pharmacotherapy in the treatment of major depressive disorder in youth; a randomized clinical trial. *Psychiatry Res*. 2015 Feb 28;225(3):687-94. doi: 10.1016/j.psychres.2014.11.021. PMID: 25500320.

100. Spirito A, Wolff JC, Seaboyer LM, et al. Concurrent treatment for adolescent and parent depressed mood and suicidality: feasibility, acceptability, and preliminary findings. *J Child Adolesc Psychopharmacol*. 2015 Mar;25(2):131-9. doi: 10.1089/cap.2013.0130. PMID: 24828247.
101. Melvin GA, Tonge BJ, King NJ, et al. A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *J Am Acad Child Adolesc Psychiatry*. 2006 Oct;45(10):1151-61. doi: 10.1097/01.chi.0000233157.21925.71. PMID: 17003660.
102. Heiligenstein JH, Hoog SL, Wagner KD, et al. Fluoxetine 40-60 mg versus fluoxetine 20 mg in the treatment of children and adolescents with a less-than-complete response to nine-week treatment with fluoxetine 10-20 mg: a pilot study. *J Child Adolesc Psychopharmacol*. 2006 Feb-Apr;16(1-2):207-17. doi: 10.1089/cap.2006.16.207. PMID: 16553541.
103. Clarke G, Debar L, Lynch F, et al. A randomized effectiveness trial of brief cognitive-behavioral therapy for depressed adolescents receiving antidepressant medication. *J Am Acad Child Adolesc Psychiatry*. 2005 Sep;44(9):888-98. PMID: 16113617.
104. Wilkinson PO, Goodyer IM. The effects of cognitive-behavioural therapy on mood-related ruminative response style in depressed adolescents. *Child Adolesc Psychiatry Ment Health*. 2008 Jan 29;2(1):3. doi: 10.1186/1753-2000-2-3. PMID: 18230146.
105. Kim SM, Han DH, Lee YS, et al. Combined cognitive behavioral therapy and bupropion for the treatment of problematic on-line game play in adolescents with major depressive disorder. *Comput Human Behav*. 2012;28(5):1954-9. PMID: CN-00853199.
106. Jelalian E, Jandasek B, Wolff JC, et al. Cognitive-behavioral therapy plus healthy lifestyle enhancement for depressed, overweight/obese adolescents: results of a pilot trial. *J Clin Child Adolesc Psychol*. 2016 Jun 16:1-10. doi: 10.1080/15374416.2016.1163705. PMID: 27310418.
107. Nelson EL. Cognitive behavioral therapy for childhood depression: a comparison of face-to-face and interactive televideo settings. *Diss Abstr Int*. 2004;65(3-b):1558. PMID: CN-00508148.
108. Gunlicks-Stoessel M, Mufson L. Innovations in practice: a pilot study of interpersonal psychotherapy for depressed adolescents and their parents. *Child & Adolescent Mental Health*. 2016;21(4):225-30. doi: 10.1111/camh.12167. PMID: 118833587.
109. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA*. 2008 Feb 27;299(8):901-13. doi: 10.1001/jama.299.8.901. PMID: 18314433.
110. Trowell J, Joffe I, Campbell J, et al. Childhood depression: a place for psychotherapy. An outcome study comparing individual psychodynamic psychotherapy and family therapy. *Eur Child Adolesc Psychiatry*. 2007 Apr;16(3):157-67. doi: 10.1007/s00787-006-0584-x. PMID: 17200793.
111. Bernstein GA, Borchardt CM, Perwien AR, et al. Imipramine plus cognitive-behavioral therapy in the treatment of school refusal. *J Am Acad Child Adolesc Psychiatry*. 2000 Mar;39(3):276-83. doi: 10.1097/00004583-200003000-00008. PMID: 10714046.
112. Wilkinson P, Kelvin R, Roberts C, et al. Clinical and psychosocial predictors of suicide attempts and nonsuicidal self-injury in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT). *Am J Psychiatry*. 2011 May;168(5):495-501. doi: 10.1176/appi.ajp.2010.10050718. PMID: 21285141.
113. Deas D, Randall CL, Roberts JS, et al. A double-blind, placebo-controlled trial of sertraline in depressed adolescent alcoholics: a pilot study. *Hum Psychopharmacol*. 2000 Aug;15(6):461-9. doi: 10.1002/1099-1077(200008)15:6<461::aid-hup209>3.0.co;2-j. PMID: 12404308.

114. Dietz LJ, Mufson L, Irvine H, et al. Family-based interpersonal psychotherapy for depressed preadolescents: an open-treatment trial. *Early Interv Psychiatry*. 2008 Aug;2(3):154-61. doi: 10.1111/j.1751-7893.2008.00077.x. PMID: 21352148.
115. Foster S, Mohler-Kuo M, Tay L, et al. Estimating patient-specific treatment advantages in the 'Treatment for Adolescents with Depression Study'. *J Psychiatr Res*. 2019 May;112:61-70. doi: 10.1016/j.jpsychires.2019.02.021. PMID: 30856378.
116. Brent DA, Emslie GJ, Clarke GN, et al. Predictors of spontaneous and systematically assessed suicidal adverse events in the treatment of SSRI-resistant depression in adolescents (TORDIA) study. *Am J Psychiatry*. 2009 Apr;166(4):418-26. doi: 10.1176/appi.ajp.2008.08070976. PMID: 19223438.
117. Storch EA, Wilhelm S, Sprich S, et al. Efficacy of augmentation of cognitive behavior therapy with weight-adjusted d-cycloserine vs placebo in pediatric obsessive-compulsive disorder: a randomized clinical trial. *JAMA Psychiatry*. 2016 Aug 1;73(8):779-88. doi: 10.1001/jamapsychiatry.2016.1128. PMID: 27367832.
118. Strasser F, Sweeney C, Willey J, et al. Impact of a half-day multidisciplinary symptom control and palliative care outpatient clinic in a comprehensive cancer center on recommendations, symptom intensity, and patient satisfaction: a retrospective descriptive study. *J Pain Symptom Manage*. 2004 Jun;27(6):481-91. doi: 10.1016/j.jpainsymman.2003.10.011. PMID: 15165646.
119. Emslie G, Kratochvil C, Vitiello B, et al. Treatment for Adolescents with Depression Study (TADS): safety results. *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1440-55. doi: 10.1097/01.chi.0000240840.63737.1d. PMID: 17135989.
120. Goodyer IM, Reynolds S, Barrett B, et al. Cognitive behavioural therapy and short-term psychoanalytical psychotherapy versus a brief psychosocial intervention in adolescents with unipolar major depressive disorder (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled superiority trial. *Lancet Psychiatry*. 2017 Feb;4(2):109-19. doi: 10.1016/S2215-0366(16)30378-9. PMID: 27914903.
121. O'Keeffe S, Martin P, Goodyer IM, et al. Prognostic implications for adolescents with depression who drop out of psychological treatment during a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2019 Apr 1. doi: 10.1016/j.jaac.2018.11.019. PMID: 30946974.
122. O'Keeffe S, Martin P, Goodyer IM, et al. Predicting dropout in adolescents receiving therapy for depression. *Psychother Res*. 2018 Sep;28(5):708-21. doi: 10.1080/10503307.2017.1393576. PMID: 29084488.
123. Emslie GJ, Kennard BD, Mayes TL, et al. Continued effectiveness of relapse prevention cognitive-behavioral therapy following fluoxetine treatment in youth with major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. 2015 Dec;54(12):991-8. doi: 10.1016/j.jaac.2015.09.014. PMID: 26598474.
124. Asarnow JR. Depression in childhood: one year outcomes of family versus individual treatment. *J Am Acad Child Adolesc Psychiatry*. 2018;57(10):S289-S90. doi: 10.1016/j.jaac.2018.07.692. PMID: CN-01653013.
125. Poole LA, Lewis AJ, Toumbourou JW, et al. A multi-family group intervention for adolescent depression: the BEST MOOD program. *Fam Process*. 2017;56(2):317-30. doi: 10.1111/famp.12218. PMID: 2017-25520-002.
126. Barbe RP, Bridge J, Birmaher B, et al. Suicidality and its relationship to treatment outcome in depressed adolescents. *Suicide Life Threat Behav*. 2004 Spring;34(1):44-55. PMID: 15106887.

127. Rohde P, Seeley JR, Kaufman NK, et al. Predicting time to recovery among depressed adolescents treated in two psychosocial group interventions. *J Consult Clin Psychol*. 2006 Feb;74(1):80-8. doi: 10.1037/0022-006X.74.1.80. PMID: 16551145.
128. Jureidini JN, McHenry LB, Mansfield PR. Clinical trials and drug promotion: selective reporting of study 329. *Int J Risk Saf Med*. 2008;20(1-2):73-81. doi: 10.3233/JRS-2008-0426.
129. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006 Mar;63(3):332-9. doi: 10.1001/archpsyc.63.3.332. PMID: 16520440.
130. Hearst ED. Review and evaluation of clinical data: citalopram hydrochloride. Silver Spring, MD: US Food and Drug Administration; 2002. <https://www.fda.gov/media/88584/download>. Accessed on February 26 2020.
131. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorders. *JAMA*. 2003;290(8):1033-41. PMID: CN-00463133.
132. von Knorring AL, Olsson GI, Thomsen PH, et al. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol*. 2006 Jun;26(3):311-5. doi: 10.1097/01.jcp.0000219051.40632.d5. PMID: 16702897.
133. Simeon JG, Dinicola VF, Ferguson HB, et al. Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. *Prog Neuropsychopharmacol Biol Psychiatry*. 1990;14(5):791-5. PMID: 2293257.
134. Geller B, Cooper TB, Graham DL, et al. Pharmacokinetically designed double-blind placebo-controlled study of nortriptyline in 6- to 12-year-olds with major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. 1992 Jan;31(1):34-44. doi: 10.1097/00004583-199201000-00007. PMID: 1537779.
135. Kratochvil C, Emslie G, Silva S, et al. Acute time to response in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1412-8. doi: 10.1097/01.chi.0000237710.73755.14. PMID: 17135986.
136. Dietz LJ, Marshal MP, Burton CM, et al. Social problem solving among depressed adolescents is enhanced by structured psychotherapies. *J Consult Clin Psychol*. 2014 Apr;82(2):202-11. doi: 10.1037/a0035718. PMID: 24491077.
137. Barbe RP, Bridge JA, Birmaher B, et al. Lifetime history of sexual abuse, clinical presentation, and outcome in a clinical trial for adolescent depression. *J Clin Psychiatry*. 2004 Jan;65(1):77-83. PMID: 14744173.
138. Brent DA, Kolko DJ, Birmaher B, et al. Predictors of treatment efficacy in a clinical trial of three psychosocial treatments for adolescent depression. *J Am Acad Child Adolesc Psychiatry*. 1998 Sep;37(9):906-14. doi: 10.1097/00004583-199809000-00010. PMID: 9735610.
139. Garoff FF, Heinonen K, Pesonen A-K, et al. Depressed youth: treatment outcome and changes in family functioning in individual and family therapy. *J Fam Ther*. 2012 Feb;34(1):4-23. doi: 10.1111/j.1467-6427.2011.00541.x. PMID: 104634633. Language: English. Entry Date: 20120227. Revision Date: 20150711. Publication Type: Journal Article.
140. Bernstein GA, Anderson LK, Hektner JM, et al. Imipramine compliance in adolescents. *J Am Acad Child Adolesc Psychiatry*. 2000 Mar;39(3):284-91. doi: 10.1097/00004583-200003000-00009. PMID: 10714047.
141. NCT00812812. Paxil Japanese Post Marketing Paediatric Study in Depression (Double-blind, Placebo Controlled Study). 2008.
142. Temple R. Anti-depressant drug use in pediatric populations. Silver Spring, MD: U.S. Food & Drug Administration; 2004. Accessed on September 29 2019.



143. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007 Apr 18;297(15):1683-96. doi: 10.1001/jama.297.15.1683. PMID: 17440145.
144. Hopkins K, Crosland P, Elliott N, et al. Diagnosis and management of depression in children and young people: summary of updated NICE guidance. *BMJ*. 2015 Mar 4;350:h824. doi: 10.1136/bmj.h824. PMID: 25739880.
145. Stone M, Laughren T, Jones M, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. In *BMJ* (online)
146. Substance Abuse and Mental Health Services Administration. Behavioral health barometer: United States, volume 5: indicators as measured through the 2017 National Survey on Drug Use and Health and the National Survey of Substance Abuse Treatment Services. HHS Publication No. SMA-19-Baro-17-US. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2019.
147. Costello EJ, Erkanli A, Angold A. Is there an epidemic of child or adolescent depression? *J Child Psychol Psychiatry*. 2006 Dec;47(12):1263-71. doi: 10.1111/j.1469-7610.2006.01682.x. PMID: 17176381.
148. Merikangas KR, He JP, Brody D, et al. Prevalence and treatment of mental disorders among US children in the 2001-2004 NHANES. *Pediatrics*. 2010 Jan;125(1):75-81. doi: 10.1542/peds.2008-2598. PMID: 20008426.
149. Richardson LP, Ludman E, McCauley E, et al. Collaborative care for adolescents with depression in primary care: a randomized clinical trial. *JAMA*. 2014;312(8):809-16. doi: 10.1001/jama.2014.9259. PMID: CN-01000139.
150. Rao U, Chen LA. Characteristics, correlates, and outcomes of childhood and adolescent depressive disorders. *Dialogues Clin Neurosci*. 2009;11(1):45-62. PMID: 19432387.
151. Katon W, Richardson L, Russo J, et al. Depressive symptoms in adolescence: the association with multiple health risk behaviors. *Gen Hosp Psychiatry*. 2010 May-Jun;32(3):233-9. doi: 10.1016/j.genhosppsych.2010.01.008. PMID: 20430225.
152. Thapar A, Collishaw S, Pine DS, et al. Depression in adolescence. *Lancet*. 2012 Mar 17;379(9820):1056-67. doi: 10.1016/S0140-6736(11)60871-4. PMID: 22305766.
153. Glied S, Pine DS. Consequences and correlates of adolescent depression. *Arch Pediatr Adolesc Med*. 2002 Oct;156(10):1009-14. PMID: 12361447.

## Appendix A. Search Strategy

### Childhood Depression Final Searches, Published Literature in PubMed/Medline, Cochrane Library, PsycINFO, and CINAHL, 5-29-19

#### PubMed 5-29-19

Search PubMed Query	Items Found
#1 Search ("Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR Depression[MeSH] OR depress*[Title/Abstract] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed[Title/Abstract] OR "Dysthymic Disorder"[Mesh] OR dysthymia OR dysthymic OR "Persistent Depressive Disorder"[ALL FIELDS])	472201
#2 Search ("Antidepressive Agents, Second-Generation"[MeSH] OR "Serotonin Uptake Inhibitors"[MeSH] OR "Antidepressive Agents"[MeSH] OR antidepressant*[Title/Abstract] OR antidepressives[Title/Abstract] OR ("antidepressive agent"[Title/Abstract] OR "antidepressive agents"[Title/Abstract] OR "antidepressive drug"[Title/Abstract] OR "antidepressive drugs"[Title/Abstract] OR "selective serotonin reuptake inhibitor"[Title/Abstract] OR "selective serotonin reuptake inhibitors"[Title/Abstract] OR ssri[Title/Abstract] OR ssris[Title/Abstract] OR Fluoxetine[MeSH] OR fluoxetine[Title/Abstract] OR "Vilazodone Hydrochloride"[Mesh] OR vilazodone[Title/Abstract] OR Prozac[Title/Abstract] OR Fluvoxamine[MeSH] OR Fluvoxamine[Title/Abstract] OR "mirtazapine" [Supplementary Concept] OR mirtazapine[Title/Abstract] OR "nefazodone"[Supplementary Concept] OR nefazodone[Title/Abstract] OR "Trazodone"[Mesh] OR trazodone[Title/Abstract] OR "vortioxetine"[Supplementary Concept] OR vortioxetine[Title/Abstract] OR luvox[Title/Abstract] OR Paroxetine[MeSH] OR paroxetine[Title/Abstract] OR paxil[Title/Abstract] OR Sertraline[MeSH] OR sertraline[Title/Abstract] OR Zoloft[Title/Abstract] OR Citalopram[MeSH] OR citalopram[Title/Abstract] OR celexa[Title/Abstract] OR escitalopram[Title/Abstract] OR Lexapro[Title/Abstract] OR "serotonin norepinephrine reuptake inhibitors"[All Fields] OR snri*[All Fields] OR "norepinephrine reuptake inhibitors"[all fields] OR venlafaxine[All Fields] OR duloxetine[All Fields] OR Bupropion[MeSH] OR Bupropion[All Fields] OR "Amitriptyline"[Mesh] OR Amitriptyline[tiab] OR "Desipramine"[Mesh] OR desipramine[tiab] OR "Imipramine"[Mesh] OR imipramine[tiab] OR "Nortriptyline"[Mesh] OR nortriptyline[tiab] OR "Doxepin"[Mesh] OR doxepin[tiab] OR "Clomipramine"[Mesh] OR clomipramine[tiab] OR Elavil[tiab] OR Enovil[tiab] OR Levate[tiab] OR Anafranil[tiab] OR Norpramin[tiab] OR Pertofrane[tiab] OR Adapin[tiab] OR Silenor[tiab] OR Sinequan[tiab] OR Tofranil[tiab] OR "Aventyl Hydrochloride"[tiab] OR Pamelor[tiab] OR "Selegiline"[Mesh] or selegiline[tiab] OR Eldepryl[tiab] OR Zelapar[tiab] OR "rasagiline" [Supplementary Concept] OR rasagiline[tiab] OR Azilect[tiab] OR "Isocarboxazid"[Mesh] OR Isocarboxazid[tiab] OR Marplan[tiab] OR "Phenelzine"[Mesh] OR Phenelzine[tiab] OR Nardil[tiab] OR "Tranylcypromine"[Mesh] OR Tranylcypromine[tiab] OR Parnate[tiab] OR Asagiline[tiab])	132335
#3 Search (#1 and #2)	60321

Search PubMed Query	Items Found
#4 Search (Psychotherapy[MeSH] OR Psychotherapy, Brief[MeSH] OR Psychotherapy, Group[MeSH] OR psychotherapy*[Title/Abstract] OR Cognitive Therapy[MeSH] OR (cognitive[Title/Abstract] AND (therap*[Title/Abstract] OR treatment*[Title/Abstract] OR intervention*[Title/Abstract])) OR "Behavior Therapy"[MeSH] OR (behavior*[Title/Abstract] AND (therap*[Title/Abstract] OR treatment*[Title/Abstract] OR intervention*[Title/Abstract])) OR CBT[Title/Abstract] OR (interpersonal[Title/Abstract] AND therap*[Title/Abstract]) OR (interpersonal[Title/Abstract] AND intervention*[Title/Abstract]) OR IPT[Title/Abstract] OR e-health[Title/Abstract] OR ehealth[Title/Abstract] OR (Internet[tiab] AND health[tiab]) OR "behavioral activation"[Title/Abstract] OR "Delivery of Health Care, Integrated"[Mesh] OR "integrated care"[Title/Abstract] OR "integrative care"[Title/Abstract] OR "Self-Help Groups"[MeSH] OR "self help"[Title/Abstract] OR Family Therapy[MeSH] OR ("family support"[Title/Abstract] OR (parent*[Title/Abstract] AND education[Title/Abstract]) OR Parents/education[MeSH] OR Counseling[MeSH] OR "Directive Counseling"[MeSH] OR counsel*[Title/Abstract] OR "Problem Solving"[MeSH] OR "problem solving"[Title/Abstract] OR "Adaptation, Psychological"[Mesh] OR "coping skills"[Title/Abstract] OR "Phototherapy"[Mesh] OR "light therapy"[Title/Abstract] OR phototherapy[Title/Abstract] OR "light therapies"[Title/Abstract] OR "Amitriptyline/adverse effects"[Mesh] OR "Amitriptyline/poisoning"[Mesh] OR "Amitriptyline/toxicity"[Mesh] OR "Desipramine/adverse effects"[Mesh] OR "Desipramine/poisoning"[Mesh] OR "Desipramine/toxicity"[Mesh] OR "Imipramine/adverse effects"[Mesh] OR "Imipramine/poisoning"[Mesh] OR "Imipramine/toxicity"[Mesh] OR "Nortriptyline/adverse effects"[Mesh] OR "Nortriptyline/poisoning"[Mesh] OR "Nortriptyline/toxicity"[Mesh] OR "Doxepin/adverse effects"[Mesh] OR "Doxepin/poisoning"[Mesh] OR "Doxepin/toxicity"[Mesh] OR "Clomipramine/adverse effects"[Mesh] OR "Clomipramine/poisoning"[Mesh] OR "Clomipramine/toxicity"[Mesh] OR "Selegiline/adverse effects"[Mesh] OR "Selegiline/poisoning"[Mesh] OR "Selegiline/toxicity"[Mesh] OR "Isocarboxazid/adverse effects"[Mesh] OR "Isocarboxazid/poisoning"[Mesh] OR "Isocarboxazid/toxicity"[Mesh] OR "Phenelzine/adverse effects"[Mesh] OR "Phenelzine/poisoning"[Mesh] OR "Phenelzine/toxicity"[Mesh] OR "Tranlycypromine/adverse effects"[Mesh] OR "Tranlycypromine/poisoning"[Mesh] OR "Tranlycypromine/toxicity"[Mesh])	839928
#5 Search (#1 and #4)	80795
#6 Search ("Deep Brain Stimulation"[Mesh] OR Neurofeedback[tw] OR "brain stimulation"[Title/Abstract] OR ((complement*[tw] OR CAM[tiab]) AND therap*[tw]) OR "collaborative care"[ALL FIELDS] OR "coordinated care"[tw] OR "co-located care"[ALL FIELDS] OR "co-managed care"[ALL FIELDS] OR "shared care"[tw] OR "stepped care"[ALL FIELDS] OR REBT[Title/Abstract] OR "Rational Emotive Behavior Therapy"[ALL FIELDS] OR "Mindfulness Based Stress Reduction"[ALL FIELDS] OR MBSR[Title/Abstract] OR "Mindfulness Meditation"[ALL FIELDS] OR Meditation[tw] OR "relaxation therapy"[All Fields] OR Hypnosis[Mesh] OR "Hypnosis, Anesthetic"[Mesh] OR autohypno*[tw] OR auto-hypno*[tw] or hypnosis[tw] OR hypnot*[tw] OR hypnotherap*[tw] OR hypno-therap*[tw] OR posthypnot*[tw] OR post-hypnot*[tw] OR selfhypno*[tw] OR self-hypno*[tw] OR (guided[tw] AND (imagery[tw] OR visualization[tw] OR visualization[tw])) OR (autogenic*[tw] AND train*[tw]) OR (imagery[tw] AND therap*[tw]) OR "integrative restoration"[tw] OR (irest[tw] NOT "international reading speed") or "Katathym-imaginative Psychotherapy"[tw] OR "mental practice"[tw] OR "mental rehearsal"[tw] OR "mind-body"[tw] OR "Biofeedback, Psychology"[Mesh] OR biofeedback*[tw] OR bio-feedback*[tw] or neuro-feedback*[tw] OR Neuro-therap*[tw] OR neurotherap*[tw] OR (autonomic*[tw] AND train*[tw]) OR "Combined Modality Therapy"[ALL FIELDS] OR Diet Therapy[Mesh] OR Exercise[Mesh] OR Exercise[tw] OR "Physical Activity"[ALL FIELDS] OR "Relaxation Therapy"[ALL FIELDS] OR Yoga[tw] OR Acupuncture[tw] OR "Tai Ji"[Mesh] OR "tai chi"[ALL FIELDS] OR "music therapy"[ALL FIELDS] OR "art therapy"[ALL FIELDS] OR "massage therapy"[ALL FIELDS] OR Spirituality[tw] OR "Dietary Supplements"[Mesh:NoExp] OR "St. John's Wort"[ALL FIELDS] OR Hypericum[tw] OR Inositol[tw] OR Melatonin[tw] OR SAME[tw] OR Selenium[tw] OR L-tryptophan[tw] OR "Folic Acid"[ALL FIELDS] OR Folate[tw] OR "Fish Oil"[ALL FIELDS] OR "Omega-3 Fatty Acids"[ALL FIELDS] OR 5-HTP[tw] OR "Vitamin E"[ALL FIELDS] OR Zinc[tw] OR Chromium[tw] OR "Ginkgo biloba"[ALL FIELDS])	2338638
#7 Search (#1 and #6)	64731
#8 Search (#3 or #5 or #7)	170240
#9 Search ((#8 AND Humans[Mesh:NOEXP]) OR (#8 NOT Animals[Mesh:NOEXP]))	150186
#10 Search ((#8 AND Humans[Mesh:NOEXP]) OR (#8 NOT Animals[Mesh:NOEXP])) Filters: Humans	135405

Search PubMed Query	Items Found
#11 Search ((#8 AND Humans[Mesh:NOEXP]) OR (#8 NOT Animals[Mesh:NOEXP])) Filters: Humans; Child: birth-18 years	26225
#12 Search (Children*[Title/Abstract] OR child[Title/Abstract] OR childhood[Title/Abstract] OR teen[Title/Abstract] OR teens[Title/Abstract] OR teenage*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract] OR adolescen*[Title/Abstract] OR boys[Title/Abstract] OR girls[Title/Abstract] OR youth[Title/Abstract] OR youths[Title/Abstract])	1666225
#13 Search (#10 and #12)	17321
#14 Search (#11 or #13)	31049
#15 Search (#11 or #13) Filters: Randomized Controlled Trial	4036
#16 Search (#11 or #13) Filters: Randomized Controlled Trial; Controlled Clinical Trial	4442
#17 Search (#11 or #13) Filters: Randomized Controlled Trial; Controlled Clinical Trial; Clinical Trial	5275
#18 Search ((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	747177
#19 Search (#14 and #18)	5235
#20 Search (#17 or #19)	5947
#21 Search ("Case Reports"[pt] OR Editorial[pt] OR Letter[pt] OR News[pt])	3530602
#22 Search (#20 not #21)	5892
#23 Search ("systematic review"[ti] OR "meta-analysis"[pt] OR "meta-analysis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR ("systematic review"[tiab] AND review[pt]) OR meta synthesis[ti] OR "cochrane database syst rev"[ta])	208812
#24 Search (#14 and #23)	789
#25 Search (#24 not #21)	784
#26 Search (Harm*[Title/Abstract] OR adverse effects[SH] OR chemically induced[SH] OR drug effects[SH] OR mortality[SH] OR poisoning[SH] OR toxicity[SH] OR adverse effect*[Title/Abstract] OR adverse event*[Title/Abstract] OR adverse reaction*[Title/Abstract] OR Adverse Drug Reaction Reporting Systems[MeSH] OR Accidents[Mesh] OR accident*[Title/Abstract] OR Drug Toxicity[MeSH] OR Drug Hypersensitivity[MeSH] OR Death[MeSH] OR death*[Title/Abstract] OR Suicide[MeSH] OR Suicide, Attempted[MeSH] OR suicide[Title/Abstract] OR suicidal*[Title/Abstract] OR mania[Title/Abstract] OR manic episode*[Title/Abstract] OR overdos*[TW] OR self damage*[Title/Abstract] OR self injur*[Title/Abstract] OR "Self Injurious Behavior"[MeSH] OR self inflict*[Title/Abstract])	6049585
#27 Search (#14 and #26)	8728
#28 Search ("Antidepressive Agents, Second-Generation/adverse effects"[Mesh] OR "Antidepressive Agents, Second-Generation/poisoning"[Mesh] OR "Antidepressive Agents, Second-Generation/toxicity"[Mesh] OR "Serotonin Uptake Inhibitors/adverse effects"[Mesh] OR "Serotonin Uptake Inhibitors/poisoning"[Mesh] OR "Serotonin Uptake Inhibitors/toxicity"[Mesh] OR "Fluoxetine/adverse effects"[Mesh] OR "Fluoxetine/poisoning"[Mesh] OR "Fluoxetine/toxicity"[Mesh] OR "Fluvoxamine /adverse effects"[Mesh] OR "Fluvoxamine /poisoning"[Mesh] OR "Fluvoxamine /toxicity"[Mesh] OR "Paroxetine /adverse effects"[Mesh] OR "Paroxetine /poisoning"[Mesh] OR "Paroxetine /toxicity"[Mesh] OR "Sertraline /adverse effects"[Mesh] OR "Sertraline /poisoning"[Mesh] OR "Sertraline /toxicity"[Mesh] OR "Citalopram /adverse effects"[Mesh] OR "Citalopram /poisoning"[Mesh] OR "Citalopram /toxicity"[Mesh] OR "Trazodone/adverse effects"[Mesh] OR "Trazodone/poisoning"[Mesh] OR "Trazodone/toxicity"[Mesh] OR "Vilazodone Hydrochloride/adverse effects"[Mesh] OR "Vilazodone Hydrochloride/poisoning"[Mesh])	9411
#29 Search ((#28 AND Humans[Mesh:NOEXP]) OR (#28 NOT Animals[Mesh:NOEXP]))	8980
#30 Search ((#28 AND Humans[Mesh:NOEXP]) OR (#28 NOT Animals[Mesh:NOEXP])) Filters: English	8185
#31 Search ((#28 AND Humans[Mesh:NOEXP]) OR (#28 NOT Animals[Mesh:NOEXP])) Filters: English; Child: birth-18 years	1800
#32 Search (#30 and #12)	683
#33 Search (#31 or #32)	1882
#34 Search (#33 not #21)	1368
#35 Search (#34 not (#22 or #25))	955
#36 Search (#23 and #35)	17

<b>Search PubMed Query</b>		<b>Items Found</b>
#37	Search (#20 not #21) Filters: English	5892
#38	Search (#20 not #21) Filters: Publication date from 2018/01/01; English	<b>402</b>
#39	Search (#24 not #21) Filters: English	784
#40	Search (#24 not #21) Filters: Publication date from 2018/01/01; English	<b>138</b>
#41	Search (#34 not (#22 or #25)) Filters: Publication date from 2018/01/01	<b>22</b>
#42	Search (#23 and #35) Filters: Publication date from 2018/01/01	<b>1</b>
#43	Search (("retraction"[All Fields] OR "Retracted Publication"[pt]) AND (#22 or #25 or #35 or #36))	<b>3</b>

**Cochrane Library, 5-29-19**

ID	Cochrane Library Search	Hits
#1	[mh "Depressive Disorder"] or [mh "Depressive Disorder, Major"] or [mh Depression] or depress*:ti,ab or depression:ti,ab or depressive:ti,ab or depressed:ti,ab or [mh "Dysthymic Disorder"] or dysthymia:ti,ab,kw or dysthymic:ti,ab,kw or "Persistent Depressive Disorder":ti,ab,kw	69640
#2	[mh "Antidepressive Agents, Second-Generation"] or [mh "Serotonin Uptake Inhibitors"] or [mh "Antidepressive Agents"] or antidepressant*:ti,ab or antidepressives:ti,ab or "antidepressive agent":ti,ab or "antidepressive agents":ti,ab or "antidepressive drug":ti,ab or "antidepressive drugs":ti,ab or "selective serotonin reuptake inhibitor":ti,ab or "selective serotonin reuptake inhibitors":ti,ab or ssri:ti,ab or ssris:ti,ab or [mh Fluoxetine] or fluoxetine:ti,ab or [mh "Vilazodone Hydrochloride"] or vilazodone:ti,ab or Prozac:ti,ab or [mh Fluvoxamine] or Fluvoxamine:ti,ab or mirtazapine:ti,ab,kw or nefazodone:ti,ab,kw or [mh Trazodone] or trazodone:ti,ab or vortioxetine:ti,ab,kw or luvox:ti,ab or [mh Paroxetine] or paroxetine:ti,ab or paxil:ti,ab or [mh Sertraline] or sertraline:ti,ab or Zoloft:ti,ab or [mh Citalopram] or citalopram:ti,ab or celexa:ti,ab or escitalopram:ti,ab,kw or Lexapro:ti,ab or "serotonin norepinephrine reuptake inhibitors":ti,ab,kw or snri*:ti,ab,kw or "norepinephrine reuptake inhibitors":ti,ab,kw or venlafaxine:ti,ab,kw or duloxetine:ti,ab,kw or [mh Bupropion] or Bupropion:ti,ab,kw OR [mh Amitriptyline] or Amitriptyline:ti,ab or [mh Desipramine] or desipramine:ti,ab or [mh Imipramine] or imipramine:ti,ab or [mh Nortriptyline] or nortriptyline:ti,ab or [mh Doxepin] or doxepin:ti,ab or [mh Clomipramine] or clomipramine:ti,ab or Elavil:ti,ab or Enovil:ti,ab or Levate:ti,ab or Anafranil:ti,ab or Norpramin:ti,ab or Pertofrane:ti,ab or Adapin:ti,ab or Silenor:ti,ab or Sinequan:ti,ab or Tofranil:ti,ab or "Aventyl Hydrochloride":ti,ab or Pamelor:ti,ab or [mh Selegiline] or selegiline:ti,ab or Eldepryl:ti,ab or Zelapar:ti,ab or rasagiline:ti,ab,kw or Azilect:ti,ab or [mh Isocarboxazid] or Isocarboxazid:ti,ab or Marplan:ti,ab or [mh Phenelzine] or Phenelzine:ti,ab or Nardil:ti,ab or [mh Tranylcypromine] or Tranylcypromine:ti,ab or Parnate:ti,ab or [mh Asagiline]	27805
#3	#1 and #2	16554
#4	[mh Psychotherapy] or [mh "Psychotherapy, Brief"] or [mh "Psychotherapy, Group"] or psychotherapy*:ti,ab or [mh "Cognitive Therapy"] or (cognitive:ti,ab and (therap*:ti,ab or treatment*:ti,ab or intervention*:ti,ab)) or [mh "Behavior Therapy"] or (behavior*:ti,ab and (therap*:ti,ab or treatment*:ti,ab or intervention*:ti,ab)) or CBT:ti,ab or (interpersonal:ti,ab and therap*:ti,ab) or (interpersonal:ti,ab and intervention*:ti,ab) or IPT:ti,ab or e-health:ti,ab or ehealth:ti,ab or (Internet:ti,ab and health*:ti,ab) or "behavioral activation":ti,ab or [mh "Delivery of Health Care, Integrated"] or "integrated care":ti,ab or "integrative care":ti,ab or [mh "Self-Help Groups"] or "self help":ti,ab or [mh "Family Therapy"] or "family support":ti,ab or (parent*:ti,ab and education:ti,ab) or [mh Parents/ED] or [mh Counseling] or [mh "Directive Counseling"] or counsel*:ti,ab or [mh "Problem Solving"] or "problem solving":ti,ab or [mh "Adaptation, Psychological"] or "coping skills":ti,ab or [mh Phototherapy] or "light therapy":ti,ab or phototherapy:ti,ab or "light therapies":ti,ab	117217
#5	#1 and #4	22453
#6	[mh "Deep Brain Stimulation"] or Neurofeedback:ti,ab,kw or "brain stimulation":ti,ab,kw or ((complement*:ti,ab or CAM:ti,ab) and therap*:ti,ab,kw) or "collaborative care":ti,ab,kw or "coordinated care":ti,ab,kw or "co-located care":ti,ab,kw or "co-managed care":ti,ab,kw or "shared care":ti,ab,kw or "stepped care":ti,ab,kw or REBT:ti,ab or "Rational Emotive Behavior Therapy":ti,ab,kw or "Mindfulness Based Stress Reduction":ti,ab,kw or MBSR:ti,ab or "Mindfulness Meditation":ti,ab,kw or Meditation:ti,ab,kw or "relaxation therapy":ti,ab,kw or [mh Hypnosis] or [mh "Hypnosis, Anesthetic"] or autohypno*:ti,ab,kw or "auto-hypno*":ti,ab,kw or hypnosis:ti,ab,kw or hypnot*:ti,ab,kw or hypnotherap*:ti,ab,kw or "hypno-therap*":ti,ab,kw or posthypnot*:ti,ab,kw or "post-hypnot*":ti,ab,kw or selfhypno*:ti,ab,kw or "self-hypno*":ti,ab,kw or (guided:ti,ab,kw and (imagery:ti,ab,kw or visualization:ti,ab,kw or visualization:ti,ab,kw)) or (autogenic*:ti,ab,kw and train*:ti,ab,kw) or (imagery:ti,ab,kw and therap*:ti,ab,kw) or "integrative restoration":ti,ab,kw or (irest:ti,ab,kw not "international reading speed") or "Katathym-imaginative Psychotherapy":ti,ab,kw or "mental practice":ti,ab,kw or "mental rehearsal":ti,ab,kw or "mind-body":ti,ab,kw or [mh "Biofeedback, Psychology"] or biofeedback*:ti,ab,kw or "bio-feedback":ti,ab,kw or "neuro-feedback*":ti,ab,kw or "neuro-therap*":ti,ab,kw or neurotherap*:ti,ab,kw or (autonomic*:ti,ab,kw and train*:ti,ab,kw) or "Combined Modality Therapy":ti,ab,kw or [mh "Diet Therapy"] or [mh Exercise] or Exercise:ti,ab,kw or "Physical Activity":ti,ab,kw or "Relaxation Therapy":ti,ab,kw or Yoga:ti,ab,kw or Acupuncture:ti,ab,kw or [mh "Tai Ji"] or "tai chi":ti,ab,kw or "music therapy":ti,ab,kw or "art therapy":ti,ab,kw or "massage therapy":ti,ab,kw or Spirituality:ti,ab,kw or [mh ^"Dietary Supplements"] or "St. John's Wort":ti,ab,kw or Hypericum:ti,ab,kw or Inositol:ti,ab,kw or Melatonin:ti,ab,kw or SAME:ti,ab,kw or Selenium:ti,ab,kw or "L-tryptophan":ti,ab,kw or "Folic Acid":ti,ab,kw or Folate:ti,ab,kw or "Fish Oil":ti,ab,kw or "Omega-3 Fatty Acids":ti,ab,kw OR 5HTP or "5-HTP" or "Vitamin E":ti,ab,kw or Zinc:ti,ab,kw or Chromium:ti,ab,kw or "Ginkgo biloba":ti,ab,kw	256451
#7	#1 and #6	18040

<b>ID</b>	<b>Cochrane Library Search</b>	<b>Hits</b>
#8	#3 or #5 or #7	45038
#9	Children*:ti,ab,kw or child:ti,ab,kw or childhood:ti,ab,kw or teen:ti,ab,kw or teens:ti,ab,kw or teenage*:ti,ab,kw or pediatric*:ti,ab,kw or paediatric*:ti,ab,kw or adolescen*:ti,ab,kw or boys:ti,ab,kw or girls:ti,ab,kw or youth:ti,ab,kw or youths:ti,ab,kw	226677
#10	#8 and #9	7316
#11	(review and systematic) or "systematic review" or ("review literature as topic" and systematic) or "meta-analysis"	47194
#12	#10 and #11 with Cochrane Library publication date from Jan 2018 to Dec 2019, in Cochrane Reviews and Cochrane Protocols	22
#13	((controlled:ti or controlled:ab) and (trial:ti or trial:ab)) or "controlled clinical trial" or "randomized controlled trial":pt or "randomized controlled trial as topic":pt or "single-blind method":pt or "double-blind method":pt or "random allocation":pt	826083
#14	#10 and #13 in Trials	5616
#15	"Case Reports":pt or Editorial:pt or Letter:pt or News:pt	15310
#16	#14 not (#15 or #12) Cochrane Library publication date from Jan 2018 to Dec 2019	950
#17	Harm*:ti,ab,kw or [mh "Long Term Adverse Effects"] or [mh /AE,CI,DE,MO,PO,TO] or adverse effect*:ti,ab or adverse event*:ti,ab or adverse reaction*:ti,ab or "adverse outcome":ti,ab or "adverse outcomes":ti,ab or [mh "Adverse Drug Reaction Reporting Systems"] or [mh Accidents] or accident*:ti,ab or [mh "Drug Toxicity"] or [mh "Drug Hypersensitivity"] or [mh Death] or death*:ti,ab or [mh Suicide] or [mh "Suicide, Attempted"] or suicide:ti,ab or suicidal*:ti,ab or mania:ti,ab or "manic episode" *:ti,ab or overdos*:ti,ab or self damage*:ti,ab or self injur*:ti,ab or [mh "Self Injurious Behavior"] or self inflict*:ti,ab	402717
#18	#10 and #17	2413
#19	[mh "Antidepressive Agents, Second-Generation"/AE] or [mh "Antidepressive Agents, Second-Generation"/PO] or [mh "Antidepressive Agents, Second-Generation"/TO] or [mh "Serotonin Uptake Inhibitors"/AE] or [mh "Serotonin Uptake Inhibitors"/PO] or [mh "Serotonin Uptake Inhibitors"/TO] or [mh Fluoxetine/AE] or [mh Fluoxetine/PO] or [mh Fluoxetine/TO] or [mh Fluvoxamine/AE] or [mh Fluvoxamine/PO] or [mh Fluvoxamine/TO] or [mh Paroxetine/AE] or [mh Paroxetine/PO] or [mh Paroxetine/TO] or [mh Sertraline/AE] or [mh Sertraline/PO] or [mh Sertraline/TO] or [mh Citalopram/AE] or [mh Citalopram/PO] or [mh Citalopram/TO] or [mh Trazodone/AE] or [mh Trazodone/PO] or [mh Trazodone/TO] or [mh "Vilazodone Hydrochloride"/AE] or [mh "Vilazodone Hydrochloride"/PO] OR [mh Amitriptyline/AE] or [mh Amitriptyline/PO] or [mh Amitriptyline/TO] or [mh Desipramine/AE] or [mh Desipramine/PO] or [mh Desipramine/TO] or [mh Imipramine/AE] or [mh Imipramine/PO] or [mh Imipramine/TO] or [mh Nortriptyline/AE] or [mh Nortriptyline/PO] or [mh Nortriptyline/TO] or [mh Doxepin/AE] or [mh Doxepin/PO] or [mh Doxepin/TO] or [mh Clomipramine/AE] or [mh Clomipramine/PO] or [mh Clomipramine/TO] or [mh Selegiline/AE] or [mh Selegiline/PO] or [mh Selegiline/TO] or [mh Isocarboxazid/AE] or [mh Isocarboxazid/PO] or [mh Isocarboxazid/TO] or [mh Phenelzine/AE] or [mh Phenelzine/PO] or [mh Phenelzine/TO] or [mh Tranylcypromine/AE] or [mh Tranylcypromine/PO] or [mh Tranylcypromine/TO]	2315
#20	#19 and #9	635
#21	#18 or #20	2625
#22	#21 not #15	2613
#23	#22 not (#12 or #16) Cochrane Library publication date from Jan 2018 to Dec 2019	3

**PsycINFO, 5/29/19**

#	PsycINFO Query	Limiters/Expanders	Last Run Via	Results
S1	DE "Depression (Emotion)" OR (DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR depressive OR depression OR depressed OR dysthymic OR dysthymia	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	344,151
S2	TX "antidepress*" OR TX Bupropion OR TX Celexa OR TX Citalopram OR TX Duloxetine OR TX Escitalopram OR TX Fluoxetine OR TX Fluvoxamine OR TX Lexapro OR TX Luvox OR TX Mirtazapine OR TX Nefazodone OR TX Paroxetine OR TX Paxil OR TX Prozac OR TX Sertraline OR TX Trazodone OR TX Venlafaxine OR TX Vilazodone OR TX Vortioxetine OR TX Zoloft OR TX "norepinephrine reuptake inhibitor" OR TX "norepinephrine reuptake inhibitors" TX "selective serotonin reuptake inhibitor" OR TX "selective serotonin reuptake inhibitors" OR TX "serotonin uptake inhibitor" OR TX "serotonin uptake inhibitors" OR TX SSRI OR TX SSRIs OR TX "serotonin norepinephrine reuptake inhibitor" TX "serotonin norepinephrine reuptake inhibitors" OR TX SNRI OR TX SNRIs OR TX Amitriptyline or TX Desipramine or TX Imipramine or TX Nortriptyline or TX Doxepin or TX Clomipramine or TX Elavil or TX Enovil or TX Levate or TX Anafranil or TX Norpramin or TX Pertofrane or TX Adapin or TX Silenor or TX Sinequan or TX Tofranil or TX "Aventyl Hydrochloride" or TX Pamelor or TX Selegiline or TX Eldepryl or TX Zelapar or TX rasagiline or TX Azilect or TX Isocarboxazid or TX Marplan or TX Phenelzine or TX Nardil or TX Tranylcypromine or TX Parnate or TX Asagiline	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1928
S3	S1 AND S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	919



#	PsycINFO Query	Limiters/Expanders	Last Run Via	Results
S4	DE "Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Affirmative Therapy" OR DE "Analytical Psychotherapy" OR DE "Autogenic Training" OR DE "Behavior Therapy" OR DE "Brief Psychotherapy" OR DE "Brief Relational Therapy" OR DE "Child Psychotherapy" OR DE "Client Centered Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Conversion Therapy" OR DE "Eclectic Psychotherapy" OR DE "Emotion Focused Therapy" OR DE "Existential Therapy" OR DE "Experiential Psychotherapy" OR DE "Expressive Psychotherapy" OR DE "Eye Movement Desensitization Therapy" OR DE "Feminist Therapy" OR DE "Gestalt Therapy" OR DE "Group Psychotherapy" OR DE "Guided Imagery" OR DE "Humanistic Psychotherapy" OR DE "Hypnotherapy" OR DE "Individual Psychotherapy" OR DE "Insight Therapy" OR DE "Integrative Psychotherapy" OR DE "Interpersonal Psychotherapy" OR DE "Logotherapy" OR DE "Narrative Therapy" OR DE "Network Therapy" OR DE "Persuasion Therapy" OR DE "Primal Therapy" OR DE "Psychoanalysis" OR DE "Psychodrama" OR DE "Psychodynamic Psychotherapy" OR DE "Psychotherapeutic Counseling" OR DE "Rational Emotive Behavior Therapy" OR DE "Reality Therapy" OR DE "Relationship Therapy" OR DE "Solution Focused Therapy" OR DE "Supportive Psychotherapy" OR DE "Transactional Analysis"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	205,552
S5	DE "Behavioral Activation System" OR DE "Integrated Services" OR DE "Family Therapy" OR DE "Conjoint Therapy" OR DE "Strategic Family Therapy" OR DE "Structural Family Therapy" OR DE "Self-Help Techniques" OR DE "Self-Management" OR DE "Counseling" OR DE "Community Counseling" OR DE "Cross Cultural Counseling" OR DE "Educational Counseling" OR DE "Group Counseling" OR DE "Microcounseling" OR DE "Multicultural Counseling" OR DE "Occupational Guidance" OR DE "Pastoral Counseling" OR DE "Peer Counseling" OR DE "Premarital Counseling" OR DE "Psychotherapeutic Counseling" OR DE "Rehabilitation Counseling" OR DE "School Counseling"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	91,801
S6	TX "cognitive behavior therapy" OR TX CBT OR TX "cognitive therapy" OR TX psychotherapy AND (cognitive OR (therap* OR treatment* OR intervention*)) OR (behavior* AND (therap* OR treatment* OR intervention*)) OR (interpersonal AND (therap* OR psychotherapy*)) OR TX IPT OR TX e-health OR TX ehealth OR (Internet* AND Health*) OR TX "behavioral activation" OR TX "delivery of health care" OR (integrat* AND (service* OR care*)) OR TX "family support" OR (Parent* and education*) OR TX counsel* OR TX "Problem Solving"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,010,070

#	PsycINFO Query	Limiters/Expanders	Last Run Via	Results
S7	DE "Emotional Adjustment" OR DE "Emotional Control" OR DE "Identity Crisis" OR TX "psychological adaptation" OR DE "Coping Behavior" OR TX "coping skills" OR TX Phototherapy OR TX "light therapy" OR TX "Deep Brain Stimulation"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	73,892
S8	TX "Alternative Medicine" OR TX Acupuncture OR TX Aromatherapy OR TX Folk Medicine OR TX Faith Healing OR TX CAM OR (complement* AND therap*) OR TX "collaborative care" OR TX "coordinated care" OR TX "co-located care" OR TX "co-managed care" OR TX "shared care" OR TX "stepped care" OR TX "Rational Emotive Behavior Therapy" OR TX "Mindfulness Based Stress Reduction" OR TX MBSR OR TX "Mindfulness Meditation" OR TX Meditation OR TX "relaxation therapy" OR TX Hypnosis OR TX autohypno* OR TX auto-hypno* OR TX hypnosis OR TX hypnot* OR TX hypnotherap* OR TX hypno-therap* OR TX posthypnot* OR TX post-hypnot* OR TX selfhypno* OR TX self-hypno* OR (TX guided AND (TX imagery OR TX visualization OR TX visualization)) OR (TX autogenic* AND train*) OR (TX imagery AND TX therap*) OR TX "integrative restoration" OR (TX irect NOT "international reading speed") OR TX "Katathym-imaginative Psychotherapy" OR TX "mental practice" OR TX "mental rehearsal" OR TX "mind-body" OR TX biofeedback* OR TX bio-feedback* OR TX Neurofeedback OR TX neuro-feedback* OR TX neuro-therap* OR TX neurotherap* OR (TX autonomic* AND TX train*) OR TX "Combined Modality Therapy" OR DE "Dietary Restraint" OR TX "diet therapy" OR TX "Dietary Supplements" OR DE "Exercise" OR DE "Aerobic Exercise" OR TX "Weightlifting" OR TX "Yoga" OR TX "Physical Activity" OR TX "Relaxation Therapy" OR TX "Progressive Relaxation Therapy" OR TX "tai ji" OR TX "tai chi" OR TX "Music Therapy" OR TX "Art Therapy" OR TX "Massage Therapy" OR TX Spirituality OR DE "Dietary Supplements" OR DE "Hypericum Perforatum" OR TX "St. John's Wort" OR TX Hypericum OR TX Inositol OR TX Melatonin OR TX SAMe OR TX Selenium OR TX "L-tryptophan" OR TX "Folic Acid" OR TX Folate OR TX "Fish Oil" OR TX Omega-3 Fatty Acids" OR TX 5-HTP OR TX "Vitamin E" OR TX Zinc OR TX Chromium OR TX "Gingko biloba"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	452,570
S9	S4 OR S5 OR S6 OR S7 OR S8	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,425,557

#	PsycINFO Query	Limiters/Expanders	Last Run Via	Results
S10	S1 AND S9	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	147,541
S11	S3 OR S10	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	148,195
S12	S11	Limiters - English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human; Methodology: CLINICAL TRIAL Published Date: 20180101- 20191231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	<b>110</b>
S13	S11	Limiters - English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human; Methodology: - Systematic Review, META ANALYSIS, METASYNTHESIS Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	292
S14	S13 NOT S12	Published Date: 20180101- 20191231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	<b>37</b>
S15	MM "Accidents" OR TX "Adverse Effects" OR TX "adverse effect" or TX "adverse event" OR TX "adverse events" OR TX "adverse outcome" OR TX "adverse outcomes" OR TX "adverse reaction" OR TX "adverse reactions" OR TX "chemically induced" OR MM "Death and Dying" OR DE "Drug Allergies" OR DE "Drug Dependency" OR TX "drug effects" OR DE "Drug Sensitivity" OR TX harm* OR TX "manic episode" OR TX mortality OR TX overdose OR DE "Patient Safety" OR TX "self damage" OR DE "Self-Injurious Behavior" OR DE "Side Effects (Drug)" OR MM "Suicide" OR MM "Toxicity" OR MM "Neurotoxicity"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	216,632

#	PsycINFO Query	Limiters/Expanders	Last Run Via	Results
S16	S11 and S15	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	14,045
S17	S16	Limiters - English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,279
S18	S17 and (S12 or S14)	Limiters - English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	21
S19	S17 not S18	Limiters - English; Language: English; Age Groups: Childhood (birth-12 yrs), Adolescence (13-17 yrs); Population Group: Human Published Date: 20180101- 20191231  Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	<b>109</b>
S20	S19	Limiters - Methodology: - Systematic Review, META ANALYSIS, METASYNTHESIS Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	0

**Cumulative Index to Nursing and Allied Health (CINAHL), 5/29/19**

#	CINAHL Query	Limiters/Expanders	Last Run Via	Results
S1	MH Depression+ OR TI depress* OR AB depress* OR TI depression OR AB depression OR TI depressive OR AB depressive OR TI depressed OR AB depressed OR dysthymia OR dysthymic	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	148,403
S2	MH "Antidepressive Agents+" OR MH "Serotonin Uptake Inhibitors+" OR TI antidepressant* OR AB antidepressant* OR TI antidepressives OR "antidepressive agent" OR "antidepressive agents" OR "antidepressive drug" OR "antidepressive drugs" OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR ssri OR ssris OR Fluoxetine OR vilazodone OR Prozac OR Fluvoxamine OR "mirtazapine" OR "nefazodone" OR trazodone OR "vortioxetine" OR luvox OR Paroxetine OR paroxetine OR paxil OR Sertraline OR Zoloft OR Citalopram OR celexa OR escitalopram OR Lexapro OR "serotonin norepinephrine reuptake inhibitors" OR snri* OR "norepinephrine reuptake inhibitors" OR venlafaxine OR duloxetine OR Bupropion OR Amitriptyline OR Desipramine OR Imipramine OR NORtriptyline OR Doxepin OR Clomipramine OR Elavil OR Enovil OR Levate OR Anafranil OR NORpramin OR Pertofrane OR Adapin OR Silenor OR Sinequan OR Tofranil OR "Aventyl Hydrochloride" OR Pamelor OR Selegiline OR Eldepryl OR Zelapar OR rasagiline OR Azilect OR Isocarboxazid OR Marplan OR Phenelzine OR Nardil OR Tranylcypromine OR Parnate OR Asagiline	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	31,813
S3	S1 AND S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	15,313
S4	Psychotherapy OR "Cognitive Therapy" OR (cognitive AND (therap* OR treatment* OR intervention*)) OR "Behavior Therapy" OR (behavior* AND (therap* OR treatment* OR intervention*)) OR CBT OR (interpersonal AND therap*) OR (interpersonal AND intervention*) OR IPT OR e-health OR ehealth OR (Internet AND health) OR "behavioral activation" OR "Integrated Delivery of Health Care" OR "integrated care" OR "integrative care" OR "self help" OR Family Therapy OR "family support" OR (parent* AND education) OR counsel* OR "Problem Solving" OR "Psychological adaptation" OR "coping skills" OR "light therapy" OR phototherapy OR "light therapies"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	323,502
S5	S1 AND S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	30,879

#	CINAHL Query	Limiters/Expanders	Last Run Via	Results
S6	"Deep Brain Stimulation" OR Neurofeedback OR "brain stimulation" OR ((complement* OR CAM) AND therap*) OR "collaborative care" OR "coordinated care" OR "co-located care" OR "co-managed care" OR "shared care" OR "stepped care" OR REBT OR "Rational Emotive Behavior Therapy" OR "Mindfulness Based Stress Reduction" OR MBSR OR Meditation OR "relaxation therapy" OR Hypnosis OR autohypno* OR auto-hypno* OR hypnot* OR hypnotherap* OR hypno-therap* OR posthypnot* OR post-hypnot* OR selfhypno* OR self-hypno* OR (guided AND (imagery OR visualization) OR (autogenic* AND train*) OR (imagery AND therap*) OR "integrative restoration" OR (irest NOT "international reading speed") OR "Katathym-imaginative Psychotherapy" OR "mental practice" OR "mental rehearsal" OR "mind-body" OR "Biofeedback, Psychology" OR biofeedback* OR bio-feedback* OR neuro-feedback* OR Neuro-therap* OR neurotherap* OR (autonomic* AND train*) OR "Combined Modality Therapy" OR "Diet Therapy" OR Exercise OR "Physical Activity" OR "Relaxation Therapy" OR Yoga OR Acupuncture OR "Tai Ji" OR "tai chi" OR "music therapy" OR "art therapy" OR "massage therapy" OR Spirituality OR "Dietary Supplements" OR "dietary supplement" OR "St. John's Wort" OR Hypericum OR Inositol OR Melatonin OR SAME OR Selenium OR L-tryptophan OR "Folic Acid" OR Folate OR "Fish Oil" OR "Omega-3 Fatty Acids" OR 5-HTP OR "Vitamin E" OR Zinc OR Chromium OR "Gingko biloba"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	488,957
S7	S1 and S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	20,598
S8	S3 or S5 or S7	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	55,610
S9	S8	Limiters - English Language; Human; Age Groups: Adolescent: 13-18 years, All Child Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	7,689

#	CINAHL Query	Limiters/Expanders	Last Run Via	Results
S10	(Children* OR child OR childhood OR teen OR teens OR teenage* OR pediatric* OR paediatric* OR adolescen* OR boys OR girls OR youth OR youths)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	969,061
S11	S8	Limiters - English Language; Human Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	32,066
S12	S10 AND S11	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	8,624
S13	S9 OR S12	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	8,777
S14	S13	Limiters - Publication Type: Clinical Trial, Randomized Controlled Trial Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	1,352
S15	((randomized AND controlled AND trial) OR (controlled AND trial) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method" OR "Double-Blind Method" OR "Random Allocation")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	165,747
S16	S13 and S15	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	1,332

#	CINAHL Query	Limiters/Expanders	Last Run Via	Results
S17	S14 OR S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	1,766
S18	S17	Limiters - Publication Type: Case Study, Editorial, Letter Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	19
S19	S17 NOT S18	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	1,747
S20	S19	Limiters - Exclude MEDLINE records Published Date: 20180101-20191231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	98
S21	S13	Limiters - Publication Type: Meta Analysis, Meta Synthesis, Systematic Review Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	376
S22	S21	Limiters - Exclude MEDLINE records Published Date: 20180101-20191231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	25
S23	Harm* OR MW "adverse effects" OR MW "chemically induced" OR MW "drug effects" OR MW mortality OR MW poisoning OR MW toxicity OR adverse effect* OR adverse event* OR adverse reaction* OR "Adverse Drug Reaction Reporting Systems" OR Accidents OR accident* OR "Drug Toxicity" OR "Drug Hypersensitivity" OR Death OR death* OR Suicide OR suicide OR suicidal* OR mania OR manic episode* OR overdos* OR self damage* OR self injur* OR "Self Injurious Behavior" OR self inflict*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	932,034



#	CINAHL Query	Limiters/Expanders	Last Run Via	Results
S24	S13 and S23	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	2,010
S25	S24 NOT S19	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	1,525
S26	S25 NOT S21	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	1,449
S27	(MH "Antidepressive Agents, Second-Generation" AND "adverse effects") OR (MH "Antidepressive Agents, Second-Generation" AND poisoning) OR (MH "Antidepressive Agents, Second-Generation" AND toxicity) OR (MH "Serotonin Uptake Inhibitors" AND "adverse effects") OR (MH "Serotonin Uptake Inhibitors" AND poisoning) OR (MH "Serotonin Uptake Inhibitors" AND toxicity) OR (MH Fluoxetine AND "adverse effects") OR (MH Fluoxetine AND poisoning) OR (MH Fluoxetine AND toxicity) OR (MH Fluvoxamine AND "adverse effects") OR (MH Fluvoxamine AND poisoning) OR (MH Fluvoxamine AND toxicity) OR (MH Paroxetine AND "adverse effects") OR (MH Paroxetine AND poisoning) OR (MH Paroxetine AND toxicity) OR (MH Sertraline AND "adverse effects") OR (MH Sertraline AND poisoning) OR (MH Sertraline AND toxicity) OR (MH Citalopram AND "adverse effects") OR (MH Citalopram AND poisoning) OR (MH Citalopram AND toxicity) OR (MH Trazodone AND "adverse effects") OR (MH Trazodone AND poisoning) OR (MH Trazodone AND toxicity) OR (MH "Vilazodone Hydrochloride" AND "adverse effects") OR (MH "Vilazodone Hydrochloride" AND poisoning)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	3,655
S28	S27	Limiters - English Language; Human; Age Groups: Adolescent: 13-18 years, All Child Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	282

#	CINAHL Query	Limiters/Expanders	Last Run Via	Results
S29	S26 OR S28	Limiters - English Language; Human; Age Groups: Adolescent: 13-18 years, All Child Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	345
S30	S29	Limiters - Exclude MEDLINE records Published Date: 20180101-20191231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	87
S31	S30	Limiters - Publication Type: Meta Analysis, Meta Synthesis, Systematic Review Published Date: 20180101-20191231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	0

## Appendix B. Inclusion/Exclusion Criteria

**Table B-1, Inclusion/Exclusion Criteria**

PICOTS	Inclusion	Exclusion
Population	<p>Children and adolescents (<math>\leq 18</math> years old) with a depressive disorder (MDD or PDD/dysthymic disorder) as indicated by a diagnosis made from an established taxonomy (e.g., DSM, ICD) via administration of a structured or semi-structured clinical interview (CIDI, DISC, SCID, PRIME-MD, Kinder-DIPS, K-SADS, DICA, CAS, SADS, DAWBA, SCAN), use of a cutpoint indicative of clinical MDD or PDD/dysthymic disorder as measured by a clinically validated depression scale (BDI, CDI, CESD, PHQ, MFQ, Child-S),<sup>a</sup> or via a clinician diagnosis</p> <p>Subgroups of interest (KQ s 1b, 2b, 3b, 4b, 5b) include those distinguished by patient characteristics (e.g., developmental age—child or adolescent, gender, race/ethnicity), parent/caregiver characteristics, disorder characteristics (e.g., type, severity), history of previous treatment, comorbid condition, and exposure to a traumatic life event</p>	<p>All other children and adolescents (<math>\leq 18</math> years old); all adults <math>&gt;18</math> years old.</p>
Intervention	<p>Nonpharmacological interventions:</p> <p>Psychological/psychosocial: Cognitive behavioral therapy, rational emotive behavior therapy, behavioral activation, other behavioral therapy, interpersonal therapy, directive counseling, Katathym-imaginative Psychotherapy, family therapy, parent education, self-help groups, problem-solving therapy, autonomic training, combined-modality therapy, psychological adaptation therapies</p> <p>Lifestyle: Exercise (physical activity), diet therapy, mindfulness (including mindfulness-based stress reduction), meditation (including mindfulness mediation), relaxation therapy, massage therapy, music therapy, art therapy, integrative restoration, visualization, tai-chi, yoga, spirituality, acupuncture</p> <p>Supplements: St. John's Wort, SAME, fish oil, melatonin, L-tryptophan, folic acid, 5-HTP, zinc, chromium, ginkgo biloba, vitamin E, omega-3 fatty acids, hypericum, inositol, selenium</p> <p>Other: Electroconvulsive therapy, transcranial magnetic stimulation, light therapy (phototherapy), hypnotherapy (including self-hypnotherapy), neurofeedback, deep brain stimulation, biofeedback</p> <p>Pharmacological interventions: Selective serotonin reuptake inhibitors (SSRIs): Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, vilazodone</p> <p>Serotonin and norepinephrine reuptake inhibitors (SNRIs): Duloxetine, venlafaxine</p> <p>Tricyclic antidepressants: <i>Amitriptyline</i>, desipramine, imipramine, nortriptyline, doxepin, <i>clomipramine</i></p> <p>Monoamine oxidase inhibitors: <i>Rasagiline</i>, <i>selegiline</i>, <i>isocarboxazid</i>, <i>phenelzine</i>, <i>tranylcypromine</i></p> <p>Atypical antidepressants: Bupropion, mirtazapine, nefazodone, trazodone, vortioxetine</p> <p>Combination interventions: Any combined treatment that includes two or more types of nonpharmacological, pharmacological, and/or collaborative care interventions, either started together or given as augments to initial treatment types</p> <p>Collaborative care interventions: Collaborative care, integrated care, integrative care, stepped care, coordinated care, co-managed care, co-located care</p>	<p>All other interventions</p>

PICOTS	Inclusion	Exclusion
Comparator	KQ 1: Treatment as usual, sham, attention control, wait list control KQ 2: Placebo, treatment as usual, attention control, wait list control KQ 3: Treatment as usual, placebo, sham, attention control, wait list control KQ 4: Treatment as usual, placebo, sham, attention control, wait list control KQ 5: Any nonpharmacologic, pharmacologic, or collaborative care intervention alone or in combination	All other comparators
Outcomes	Benefits: Remission Response Relapse Depressive symptoms Suicidality Mortality Functional impairment Harms: Any AEs of intervention (e.g., death, serious adverse events)	All other outcomes
Time frame	Any publication dates At least 6 weeks of treatment	Less than 6 weeks of treatment
Settings	Outpatient care in countries with at least part of the sample from a very high Human Development Index <sup>b</sup>	Inpatient care, studies conducted in countries without a very high Human Development Index
Study design	For benefits: Adolescents (sample age >12 and ≤18): randomized controlled trials (RCTs) Children (sample age ≤12): RCTs or controlled clinical trials (CCTs) For harms: RCTs, CCTs, and observational studies <sup>c</sup> Reference lists of relevant systematic reviews published in 2013 or later will be used to ensure our search strategies captured all relevant studies.	All other designs and studies using included designs that do not meet the sample size criterion <sup>d</sup>
Language	Studies published in English	Studies published in languages other than English

<sup>a</sup> In the absence of clear, clinically validated cutoffs of depression scales used to indicate a either MDD or PDD/dysthymic disorder, we consulted two recent systematic reviews<sup>1, 2</sup> on the topic and discussed required thresholds with our Technical Expert Panel (TEP) for each scale. In the absence of agreed-upon thresholds, we restricted the analysis to diagnosed disorders.

<sup>b</sup> <http://hdr.undp.org/en/content/human-development-index-hdi>

<sup>c</sup> We evaluated the yield for harms. When studies with sample sizes of 1,000 or more participants were available for a given intervention and comparator, we restricted the analysis to that group. If large samples were not available, we include studies with smaller sample sizes

<sup>d</sup> Excluded designs include editorials, systematic reviews, and pooled analysis.

AE = adverse event; BDI = Beck Depression Inventory; CAS: The Child Assessment Schedule; CBT = cognitive behavioral therapy; CCT = controlled clinical trial; CIDI = Composite International Diagnostic Interview; CDI = Children's Depression Inventory; CES-D = Center for Epidemiological Studies Depression Scale; Child-S: Children's Depression Screener; DAWBA = The Development and Wellbeing Assessment; DICA = Diagnostic Interview for Children and Adolescents; DISC = Diagnostic Interview Schedule for Children; DSM = *Diagnostic and Statistical Manual*; IPT = interpersonal therapy; Kinder-DIPS = The Diagnostic Interview for Psychiatric Disorders in Children and Adolescents; K-SADS = The Schedule for Affective Disorders and Schizophrenia for School-Age Children; KQ = Key Question; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; PDD = persistent depressive disorder; PHQ = Patient Health Questionnaire; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; PRIME-MD = The Primary Care Evaluation of Mental Disorders; RCT = randomized controlled trial; SADS = The Schedule for Affective Disorders and Schizophrenia; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; SCID = Structured Clinical Interview for DSM disorders.

## Appendix C. Excluded Studies

X1 – Ineligible Population  
 X2 – Ineligible Intervention  
 X3 – Ineligible Comparators  
 X4 – Ineligible Outcomes  
 X5 – Ineligible Timeframe  
 X6 – Ineligible by Publication Type  
 X7 – Ineligible Setting  
 X8 – Ineligible Country  
 X9 – Ineligible Study Design  
 X10 – Abstract Superseded by Publication  
 X11 – Non-English  
 X12 – Duplicate  
 X13 – Not Retrievable

- |  |  |
|--|--|
| <p>1. General practitioner clinical trials. Chlordiazepoxide with amitriptyline in neurotic depression. Practitioner. 1969;202(209):437-40. PMID: 4886196. Exclusion Code: X1.</p> <p>2. Nocturnal enuresis in children. Med Lett Drugs Ther. 1969 Mar 7;11(5):19-20. PMID: 5781646. Exclusion Code: X1.</p> <p>3. Antidepressant effects of tranquilizers. Practitioner. 1971 Jan;206(231):146-8. PMID: 4924637. Exclusion Code: X1.</p> <p>4. Zimelidine: a second generation antidepressant. A report from the general practitioner research group. Practitioner. 1982 Sep;226(1371):1625-8. PMID: 6216471. Exclusion Code: X1.</p> <p>5. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. N Engl J Med. 2001 Apr 26;344(17):1279-85. doi: 10.1056/nejm200104263441703. PMID: 11323729. Exclusion Code: X1.</p> | <p>6. Weighing the benefits of omega-3 fatty acids for childhood depression. Brown University Child &amp; Adolescent Psychopharmacology Update. 2006;8(8):1-4. PMID: 106209762. Language: English. Entry Date: 20070112. Revision Date: 20150711. Publication Type: Journal Article. Exclusion Code: X6.</p> <p>7. Cognitive behavioral therapy + alternative selective serotonin reuptake inhibitor better than alternative SSRI alone in adolescent depression. J Natl Med Assoc. 2008;100(6):762-3. PMID: CN-01759349. Exclusion Code: X6.</p> <p>8. Effectiveness of taking in the good based-bibliotherapy intervention program among depressed Filipino female adolescents. Asian J Psychiatr. 2016 Oct 1;23:99-107. doi: 10.1016/j.ajp.2016.07.011. PMID: CN-01196570. Exclusion Code: X8.</p> <p>9. Evaluation of the effectiveness of the friends for life program on children's anxiety and depression. Iranian journal of psychiatry. 2017;12(4):269-77. PMID: CN-01471636. Exclusion Code: X8.</p> |
|--|--|

10. Corrections: (The Lancet Psychiatry (2017) 4 (2)(109-119) (S2215036616303789) (10.1016/S2215-0366(16)30378-9)). Lancet Psychiatry. 2017;4(8):582. doi: 10.1016/S2215-0366%2817%2930283-3. PMID: CN-01475235. Exclusion Code: X12.
11. Cost-effectiveness of cognitive behavioral therapy for depressed youth declining antidepressants. Pediatrics. 2018;141(2). doi: 10.1542/peds.2017-1969. PMID: CN-01603216. Exclusion Code: X4.
12. Ackerson J, Scogin F, McKendree-Smith N, et al. Cognitive bibliotherapy for mild and moderate adolescent depressive symptomatology. J Consult Clin Psychol. 1998 Aug;66(4):685-90. PMID: 9735587. Exclusion Code: X9.
13. Ahlen J, Hursti T, Tanner L, et al. Prevention of anxiety and depression in Swedish school children: a cluster-randomized effectiveness study. Prev Sci. 2018;19(2):147-58. doi: 10.1007/s11121-017-0821-1. PMID: 2017-32052-001. Exclusion Code: X1.
14. Ahn JH, Patkar AA. Escitalopram for the treatment of major depressive disorder in youth. Expert Opin Pharmacother. 2011 Oct;12(14):2235-44. doi: 10.1517/14656566.2011.604632. PMID: 21895554. Exclusion Code: X6.
15. Ajac IK, Giroux LJ, Hill JA. Bupropion: study of treatment in depressed patients. J Fla Med Assoc. 1983 May;70(5):356-60. PMID: 6409980. Exclusion Code: X1.
16. Alacqua M, Trifiro G, Arcoraci V, et al. Use and tolerability of newer antipsychotics and antidepressants: a chart review in a paediatric setting. Pharm World Sci. 2008 Jan;30(1):44-50. doi: 10.1007/s11096-007-9139-6. PMID: 17588130. Exclusion Code: X1.
17. Alavi A, Sharifi B, Ghanizadeh A, et al. Effectiveness of cognitive-behavioral therapy in decreasing suicidal ideation and hopelessness of the adolescents with previous suicidal attempts. Iranian journal of pediatrics. 2013;23(4):467-72. PMID: CN-00918908. Exclusion Code: X8.
18. Alderman J, Wolkow R, Chung M, et al. Sertraline treatment of children and adolescents with obsessive-compulsive disorder or depression: pharmacokinetics, tolerability, and efficacy. J Am Acad Child Adolesc Psychiatry. 1998 Apr;37(4):386-94. doi: 10.1097/00004583-199804000-00016. PMID: 9549959. Exclusion Code: X1.
19. Alderman J, Wolkow R, Fogel IM. Drug concentration monitoring with tolerability and efficacy assessments during open-label, long-term sertraline treatment of children and adolescents. J Child Adolesc Psychopharmacol. 2006 Feb-Apr;16(1-2):117-29. doi: 10.1089/cap.2006.16.117. PMID: 16553533. Exclusion Code: X9.
20. Alfonso M, Ferrer R, Such P. Safety and tolerability of fluvoxamine in adolescent depression. 8th European College of Neuropsychopharmacology Congress; 1995 Sep 30-Oct 4; Venice, Italy. Exclusion Code: X3.
21. Almeida-Montes LG, Friederichsen A. Treatment of major depressive disorder with fluoxetine in children and adolescents. A double-blind, placebo-controlled study. Psiquiatria biologica. 2005;12(5):198-205. PMID: CN-00557743. Exclusion Code: X11.
22. Amaya MM, Reinecke MA, Silva SG, et al. Parental marital discord and treatment response in depressed adolescents. J Abnorm Child Psychol. 2011 Apr;39(3):401-11. doi: 10.1007/s10802-010-9466-2. PMID: 20957515. Exclusion Code: X3.
23. Ambrosini PJ, Wagner KD, Biederman J, et al. Multicenter open-label sertraline study in adolescent outpatients with major depression. J Am Acad Child Adolesc Psychiatry. 1999 May;38(5):566-72. doi: 10.1097/00004583-199905000-00018. PMID: 10230188. Exclusion Code: X1.
24. Amr M, El-Mogy A, Shams T, et al. Efficacy of vitamin C as an adjunct to fluoxetine therapy in pediatric major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. Nutr J. 2013 Mar 9;12:31. doi: 10.1186/1475-2891-12-31. PMID: 23510529. Exclusion Code: X2.

25. Anderson R, Ukoumunne OC, Sayal K, et al. Cost-effectiveness of classroom-based cognitive behaviour therapy in reducing symptoms of depression in adolescents: a trial-based analysis. *J Child Psychol Psychiatry*. 2014 Dec;55(12):1390-7. doi: 10.1111/jcpp.12248. PMID: 24813670. Exclusion Code: X1.
26. Annesi J. Relationship between self-efficacy and changes in rated tension and depression for 9 to 12-yr-old children enrolled in a 12-wk after-school physical activity program. *Percept Mot Skills*. 2004;99(1):191-4. PMID: CN-00710751. Exclusion Code: X1.
27. Apter A, Kronenberg S, Brent D. Turning darkness into light: a new landmark study on the treatment of adolescent depression. Comments on the TADS study. *Eur Child Adolesc Psychiatry*. 2005;14(3):113-6. doi: 10.1007/s00787-005-0474-7. PMID: 2005-07206-001. Exclusion Code: X6.
28. Apter A, Lipschitz A, Fong R, et al. Evaluation of suicidal thoughts and behaviors in children and adolescents taking paroxetine. *J Child Adolesc Psychopharmacol*. 2006 Feb-Apr;16(1-2):77-90. doi: 10.1089/cap.2006.16.77. PMID: 16553530. Exclusion Code: X6.
29. Archer J. Randomised controlled trial: collaborative care improves clinical outcomes for adolescents with depression treated in primary care. *Evid Based Med*. 2015;20(1):20. doi: 10.1136/ebmed-2014-110108. PMID: CN-01072499. Exclusion Code: X6.
30. Arnold LE, Young AS, Belury MA, et al. Omega-3 fatty acid plasma levels before and after supplementation: correlations with mood and clinical outcomes in the Omega-3 and therapy studies. *J Child Adolesc Psychopharmacol*. 2017 Apr;27(3):223-33. doi: 10.1089/cap.2016.0123. PMID: 28157380. Exclusion Code: X1.
31. Asarnow JR, Jaycox LH, Duan N, et al. Effectiveness of a quality improvement intervention for adolescent depression in primary care clinics: a randomized controlled trial. *JAMA*. 2005 Jan 19;293(3):311-9. doi: 10.1001/jama.293.3.311. PMID: 15657324. Exclusion Code: X9.
32. Asarnow JR, Jaycox LH, Tang L, et al. Long-term benefits of short-term quality improvement interventions for depressed youths in primary care. *Am J Psychiatry*. 2009 Sep;166(9):1002-10. doi: 10.1176/appi.ajp.2009.08121909. PMID: 19651711. Exclusion Code: X1.
33. Asarnow JR, Porta G, Spirito A, et al. Suicide attempts and nonsuicidal self-injury in the treatment of resistant depression in adolescents: findings from the TORDIA study. *J Am Acad Child Adolesc Psychiatry*. 2011 Aug;50(8):772-81. doi: 10.1016/j.jaac.2011.04.003. PMID: 21784297. Exclusion Code: X3.
34. Asarnow JR, Porta G, Spirito A, et al. TORDIA: nonsuicidal self-injury and attempted suicide. *Brown University Child & Adolescent Behavior Letter*. 2011 Aug;27(9):3-. doi: 10.1016/j.jaac.2011.04.003. PMID: 104688880. Language: English. Entry Date: 20111004. Revision Date: 20150711. Publication Type: Journal Article. Exclusion Code: X12.
35. Atkinson S, Thurman L, Ramaker S, et al. Safety, tolerability, and efficacy of desvenlafaxine in children and adolescents with major depressive disorder: results from two open-label extension trials. *CNS Spectr*. 2018 Nov 13;1-11. doi: 10.1017/s1092852918001128. PMID: 30419989. Exclusion Code: X3.
36. Attari A, Moghaddam FY, Soltani M, et al. Comparison of fluoxetine and nortriptyline effects on treatment of children and adolescents involved in major depressive disorder. XIII World Congress of Psychiatry; 2005 September 10-15; Cairo, Egypt. 12016. Exclusion Code: X10.
37. Attari A, Moghaddam Y, Hasanzadeh A, et al. Comparison of efficacy of fluoxetine with nortriptyline in treatment of major depression in children and adolescents: a double-blind study. *J Res Med Sci*. 2006;11(1):24-30. PMID: CN-00613152. Exclusion Code: X8.
38. Avci A, Diler RS, Kibar M, et al. Comparison of moclobemide and placebo in young adolescents with major depressive disorder. *Annals of medical sciences*. 1999;8(1):31-40. PMID: CN-00214555. Exclusion Code: X5.

39. Azevedo da Silva R, de Azevedo Cardoso T, Campos Mondin T, et al. Is narrative cognitive therapy as effective as cognitive behavior therapy in the treatment for depression in young adults? . *J Nerv Ment Dis.* 2017 Dec;205(12):918-24. doi: 10.1097/nmd.0000000000000758. PMID: 29099406. Exclusion Code: X8.
40. Baardewijk M, Vis PM, Einarson TR. Cost effectiveness of duloxetine compared with venlafaxine-XR in the treatment of major depressive disorder (Structured abstract). *Curr Med Res Opin.* 2005;21(8):1271-9. PMID: NHSEED-22005001387. Exclusion Code: X1.
41. Bai S, Zeledon LR, D'Amico EJ, et al. Reducing health risk behaviors and improving depression in adolescents: a randomized controlled trial in primary care clinics. *J Pediatr Psychol.* 2018 Oct 1;43(9):1004-16. doi: 10.1093/jpepsy/psy048. PMID: 30016473. Exclusion Code: X1.
42. Bakken RJ, Paczkowski M, Kramer HP, et al. Effects of atomoxetine on attention-deficit/hyperactivity disorder in clinical pediatric treatment settings: a naturalistic study. *Curr Med Res Opin.* 2008;24(2):449-60. doi: 10.1185/030079908X253627. PMID: 2010-10311-002. Exclusion Code: X9.
43. Bangs ME, Emslie GJ, Spencer TJ, et al. Efficacy and safety of atomoxetine in adolescents with attention-deficit/hyperactivity disorder and major depression. *J Child Adolesc Psychopharmacol.* 2007 Aug;17(4):407-20. doi: 10.1089/cap.2007.0066. PMID: 17822337. Exclusion Code: X2.
44. Barak Y, Swartz M, Levy D, et al. Age-related differences in the side effect profile of citalopram. *Prog Neuropsychopharmacol Biol Psychiatry.* 2003 May;27(3):545-8. doi: 10.1016/s0278-5846(03)00041-1. PMID: 12691792. Exclusion Code: X1.
45. Barbui C, Patten SB. Antidepressant dose and the risk of deliberate self-harm. *Epidemiology and Psychiatric Sciences.* 2014;23(4):329-31. doi: 10.1017/S2045796014000456. PMID: 2014-49909-005. Exclusion Code: X6.
46. Barranco SF, Thrash ML, Hackett E, et al. Early onset of response to doxepin treatment. *J Clin Psychiatry.* 1979 Jun;40(6):265-9. PMID: 376498. Exclusion Code: X1.
47. Barzilay S, Feldman D, Snir A, et al. The interpersonal theory of suicide and adolescent suicidal behavior. *J Affect Disord.* 2015;183:68-74. doi: 10.1016/j.jad.2015.04.047. PMID: 2015-29290-011. Exclusion Code: X2.
48. Baumgartner JL, Emslie GJ, Crismon ML. Citalopram in children and adolescents with depression or anxiety. *Ann Pharmacother.* 2002 Nov;36(11):1692-7. doi: 10.1345/aph.1C078. PMID: 12398561. Exclusion Code: X9.
49. Baune B, Hay P. Suicide rates and antidepressant prescribing: a casual or causal relationship? *PLoS Med.* 2006 Jun;3(6):e220. doi: 10.1371/journal.pmed.0030220. PMID: 16752953. Exclusion Code: X9.
50. Baving L, Schmidt MH. Evaluated treatment approaches in child and adolescent psychiatry II. *Z Kinder Jugendpsychiatr Psychother.* 2001;29(3):206-20. doi: 10.1024//1422-4917.29.3.206. PMID: CN-01741031. Exclusion Code: X11.
51. Becker-Weidman EG, Jacobs RH, Reinecke MA, et al. Social problem-solving among adolescents treated for depression. *Behav Res Ther.* 2010 Jan;48(1):11-8. doi: 10.1016/j.brat.2009.08.006. PMID: 19775677. Exclusion Code: X3.
52. Becker-Weidman EG, Reinecke MA, Jacobs RH, et al. Predictors of hopelessness among clinically depressed youth. *Behav Cogn Psychother.* 2009 May;37(3):267-91. doi: 10.1017/s1352465809005207. PMID: 19368751. Exclusion Code: X3.
53. Bee P, Pedley R, Rithalia A, et al. Health services and delivery research. Self-care support for children and adolescents with long-term conditions: the REFOCUS evidence synthesis. Southampton, UK: NIHR Journals Library; 2018. Exclusion Code: X9.



54. Beffert JW. Aerobic exercise as treatment of depressive symptoms in early adolescents. Dissertation abstracts international. 1994;54(9-a):3374. PMID: CN-00711792. Exclusion Code: X7.
55. Bennett SD, Cuijpers P, Ebert DD, et al. Practitioner review: unguided and guided self-help interventions for common mental health disorders in children and adolescents: a systematic review and meta-analysis. *J Child Psychol Psychiatry*. 2019 Feb 18. doi: 10.1111/jcpp.13010. PMID: 30775782. Exclusion Code: X9.
56. Berard RMF. Clinical trials and tribulations in the pharmacological treatment of adolescent depression. *Xxist Collegium Internationale Neuro Psychopharmacologicum*; 1998 Jul 12-16; Glasgow, Scotland. 10976. Exclusion Code: X8.
57. Bergman H, Kornor H, Nikolakopoulou A, et al. Client feedback in psychological therapy for children and adolescents with mental health problems. *Cochrane Database Syst Rev*. 2018 Aug 20;8:Cd011729. doi: 10.1002/14651858.CD011729.pub2. PMID: 30124233. Exclusion Code: X1.
58. Bernstein GA, Hektner JM, Borchardt CM, et al. Treatment of school refusal: one-year follow-up. *J Am Acad Child Adolesc Psychiatry*. 2001 Feb;40(2):206-13. doi: 10.1097/00004583-200102000-00015. PMID: 11211369. Exclusion Code: X9.
59. Bevan Jones R, Thapar A, Stone Z, et al. Psychoeducational interventions in adolescent depression: a systematic review. *Patient Educ Couns*. 2018 May;101(5):804-16. doi: 10.1016/j.pec.2017.10.015. PMID: 29103882. Exclusion Code: X9.
60. Biederman J. Sudden death in children treated with a tricyclic antidepressant. *J Am Acad Child Adolesc Psychiatry*. 1991;30(3):495-8. doi: 10.1097/00004583-199105000-00023. PMID: 1991-31177-001. Exclusion Code: X6.
61. Biegel GM, Brown KW, Shapiro SL, et al. Mindfulness-based stress reduction for the treatment of adolescent psychiatric outpatients: a randomized clinical trial. *J Consult Clin Psychol*. 2009 Oct;77(5):855-66. doi: 10.1037/a0016241. PMID: 19803566. Exclusion Code: X1.
62. Bienert SE. Use of SSRIs in children. *J Fam Pract*. 1998 Feb;46(2):118. PMID: 9487315. Exclusion Code: X6.
63. Biernacki C, Martin P, Goldberg PH, et al. Treatments for pediatric depression. In: Nathan PE, Gorman JM, Nathan PE, Gorman JM, eds. *A guide to treatments that work*. New York, NY, US: Oxford University Press; 2015:355-79. Exclusion Code: X6.
64. Bilek EL, Ehrenreich-May J. An open trial investigation of a transdiagnostic group treatment for children with anxiety and depressive symptoms. *Behav Ther*. 2012 Dec;43(4):887-97. doi: 10.1016/j.beth.2012.04.007. PMID: 23046789. Exclusion Code: X9.
65. Birmaher B, Brent DA, Kolko D, et al. Clinical outcome after short-term psychotherapy for adolescents with major depressive disorder. *Arch Gen Psychiatry*. 2000 Jan;57(1):29-36. PMID: 10632230. Exclusion Code: X9.
66. Birmaher B, Waterman GS, Ryan ND, et al. Randomized, controlled trial of amitriptyline versus placebo for adolescents with "treatment-resistant" major depression. *J Am Acad Child Adolesc Psychiatry*. 1998 May;37(5):527-35. doi: 10.1097/00004583-199805000-00015. PMID: 9585655. Exclusion Code: X7.
67. Blazquez A, Mas S, Plana MT, et al. Plasma fluoxetine concentrations and clinical improvement in an adolescent sample diagnosed with major depressive disorder, obsessive-compulsive disorder, or generalized anxiety disorder. *J Clin Psychopharmacol*. 2014 Jun;34(3):318-26. doi: 10.1097/jcp.0000000000000121. PMID: 24743718. Exclusion Code: X3.
68. Blockman M. Selective serotonin reuptake inhibitors in children with major depression. *S Afr Med J*. 2006;96(6):476-7. PMID: CN-00709634. Exclusion Code: X6.

69. Bogen S, Legenbauer T, Gest S, et al. Morning bright light therapy: a helpful tool for reducing comorbid symptoms of affective and behavioral dysregulation in juvenile depressed inpatients? A pilot trial. *Z Kinder Jugendpsychiatr Psychother*. 2017 Jan;45(1):34-41. doi: 10.1024/1422-4917/a000442. PMID: 27299514. Exclusion Code: X7.
70. Bolton P, Bass J, Betancourt T, et al. Interventions for depression symptoms among adolescent survivors of war and displacement in northern Uganda: a randomized controlled trial. *JAMA*. 2007 Aug 1;298(5):519-27. doi: 10.1001/jama.298.5.519. PMID: 17666672. Exclusion Code: X8.
71. Bostic JQ, Prince J, Brown K, et al. A retrospective study of citalopram in adolescents with depression. *J Child Adolesc Psychopharmacol*. 2001 Summer;11(2):159-66. doi: 10.1089/104454601750284063. PMID: 11436955. Exclusion Code: X9.
72. Bottelier MA, Schouw ML, Klomp A, et al. The effects of Psychotropic drugs On Developing brain (ePOD) study: methods and design. *BMC Psychiatry*. 2014 Feb 19;14:48. doi: 10.1186/1471-244x-14-48. PMID: 24552282. Exclusion Code: X6.
73. Bottelier MA, Schrantz AGM, Wingen GA, et al. Treatment with fluoxetine in adolescents may aggravate emotional dysregulation: a power analysis for future studies. *Eur Neuropsychopharmacol*. 2015;25:S461-s2. PMID: CN-01163210. Exclusion Code: X6.
74. Boulos C, Kutcher S, Marton P, et al. Response to desipramine treatment in adolescent major depression. *Psychopharmacol Bull*. 1991;27(1):59-65. PMID: CN-00077189. Exclusion Code: X1.
75. Bounoua N, Abbott C, Zisk A, et al. Emotion regulation and spillover of interpersonal stressors to postsession insight among depressed and suicidal adolescents. *J Consult Clin Psychol*. 2018;86(7):593-603. doi: 10.1037/ccp0000316. PMID: 2018-30216-003. Exclusion Code: X4.
76. Boylan K, MacPherson HA, Fristad MA. Examination of disruptive behavior outcomes and moderation in a randomized psychotherapy trial for mood disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(7):699-708. doi: 10.1016/j.jaac.2013.04.014. PMID: CN-00905241. Exclusion Code: X1.
77. Braconnier A, Le Coent R, Cohen D. Paroxetine versus clomipramine in adolescents with severe major depression: a double-blind, randomized, multicenter trial. *J Am Acad Child Adolesc Psychiatry*. 2003 Jan;42(1):22-9. PMID: 12500073. Exclusion Code: X1.
78. Brenner SL, Burns BJ, Curry JF, et al. Mental health service use among adolescents following participation in a randomized clinical trial for depression. *J Clin Child Adolesc Psychol*. 2015;44(4):551-8. doi: 10.1080/15374416.2014.881291. PMID: 24661263. Exclusion Code: X3.
79. Brent D. A clinical trial comparing three psychotherapies for adolescent depression: differential efficacy and predictors of outcome. *WPA Thematic Conference*; 1997 November; Jerusalem. 9876: p. 9. Exclusion Code: X10.
80. Brent DA. Antidepressants and pediatric depression--the risk of doing nothing. *N Engl J Med*. 2004 Oct 14;351(16):1598-601. doi: 10.1056/NEJMp048228. PMID: 15483276. Exclusion Code: X6.
81. Brent DA. The treatment of SSRI-resistant depression in adolescents (TORDIA): in search of the best next step. *Depress Anxiety*. 2009;26(10):871-4. doi: 10.1002/da.20617. PMID: 19798756. Exclusion Code: X6.
82. Brent DA, Birmaher B, Kolko D, et al. Subsyndromal depression in adolescents after a brief psychotherapy trial: course and outcome. *J Affect Disord*. 2001 Mar;63(1-3):51-8. PMID: 11246080. Exclusion Code: X3.

83. Brent DA, Brunwasser SM, Hollon SD, et al. Effect of a cognitive-behavioral prevention program on depression 6 years after implementation among at-risk adolescents: a randomized clinical trial. *JAMA Psychiatry*. 2015 Nov;72(11):1110-8. doi: 10.1001/jamapsychiatry.2015.1559. PMID: 26421861. Exclusion Code: X1.
84. Brent DA, Gibbons R. Initial dose of antidepressant and suicidal behavior in youth: start low, go slow. *JAMA Intern Med*. 2014 Jun;174(6):909-11. doi: 10.1001/jamainternmed.2013.14016. PMID: 24781493. Exclusion Code: X6.
85. Brent DA, Greenhill LL, Compton S, et al. The Treatment of Adolescent Suicide Attempters study (TASA): predictors of suicidal events in an open treatment trial. *J Am Acad Child Adolesc Psychiatry*. 2009 Oct;48(10):987-96. doi: 10.1097/CHI.0b013e3181b5db4. PMID: 19730274. Exclusion Code: X9.
86. Brent DA, Kolko DJ, Birmaher B, et al. A clinical trial for adolescent depression: predictors of additional treatment in the acute and follow-up phases of the trial. *J Am Acad Child Adolesc Psychiatry*. 1999 Mar;38(3):263-70; discussion 70-1. doi: 10.1097/00004583-199903000-00012. PMID: 10087687. Exclusion Code: X3.
87. Brent R. Efficacy of cognitive therapy for adolescent depression and the relationship of empathy to outcome. Dissertation abstracts international. 1987;47(12-A Pt 1):4322-3. PMID: CN-00711156. Exclusion Code: X9.
88. Bridge JA, Barbe RP, Birmaher B, et al. Emergent suicidality in a clinical psychotherapy trial for adolescent depression. *Am J Psychiatry*. 2005 Nov;162(11):2173-5. doi: 10.1176/appi.ajp.162.11.2173. PMID: 16263860. Exclusion Code: X3.
89. Bridge JA, Birmaher B, Iyengar S, et al. Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. *Am J Psychiatry*. 2009 Jan;166(1):42-9. doi: 10.1176/appi.ajp.2008.08020247. PMID: 19047322. Exclusion Code: X9.
90. Briere FN, Rohde P, Stice E, et al. Group-based symptom trajectories in indicated prevention of adolescent depression. *Depress Anxiety*. 2016 May;33(5):444-51. doi: 10.1002/da.22440. PMID: 26457813. Exclusion Code: X1.
91. Brown JSL, Blackshaw E, Stahl D, et al. School-based early intervention for anxiety and depression in older adolescents: a feasibility randomised controlled trial of a self-referral stress management workshop programme ("DISCOVER"). *J Adolesc*. 2019 Feb;71:150-61. doi: 10.1016/j.adolescence.2018.11.009. PMID: 30738219. Exclusion Code: X1.
92. Brown LK, Kennard BD, Emslie GJ, et al. Effective treatment of depressive disorders in medical clinics for adolescents and young adults living with HIV: a controlled trial. *J Acquir Immune Defic Syndr*. 2016 Jan 1;71(1):38-46. doi: 10.1097/qai.0000000000000803. PMID: 26761270. Exclusion Code: X1.
93. Brown RA, Lewinsohn PM. A psychoeducational approach to the treatment of depression: comparison of group, individual, and minimal contact procedures. *J Consult Clin Psychol*. 1984 Oct;52(5):774-83. PMID: 6501663. Exclusion Code: X1.
94. Bru L, Solholm R, Idsoe T. Participants' experiences of an early cognitive behavioral intervention for adolescents with symptoms of depression. *Emotional and behavioural difficulties*. 2013;18(1):24-43. PMID: CN-00861854. Exclusion Code: X9.
95. Burcu M, Zito JM, Safer DJ, et al. Association of antidepressant medications with incident type 2 diabetes among Medicaid-insured youths. *JAMA Pediatr*. 2017 Dec 1;171(12):1200-7. doi: 10.1001/jamapediatrics.2017.2896. PMID: 29049533. Exclusion Code: X1.
96. Burdick KE, Goldman R, Tocco M, et al. Effect of lurasidone on neurocognitive performance in children and adolescents with bipolar depression: results from a placebocontrolled short-term study and an open-label extension study. *J Am Acad Child Adolesc Psychiatry*. 2017;56(10):S266. doi: 10.1016/j.jaac.2017.09.320. PMID: CN-01452267. Exclusion Code: X1.

97. Burdick KE, Goldman R, Tocco M, et al. Effect of lurasidone on neurocognitive performance in children and adolescents with bipolar depression: interim analysis at week 52 of a 2-year open-label extension study. *Bipolar disorders*. 2018;20(Supplement 1):68-9. doi: 10.1111/bdi.12619. PMID: CN-01466419. Exclusion Code: X1.
98. Byford S, Barrett B, Roberts C, et al. Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. *Br J Psychiatry*. 2007 Dec;191:521-7. doi: 10.1192/bjp.bp.107.038984. PMID: 18055956. Exclusion Code: X1.
99. Caballero J, Nahata MC. Selective serotonin-reuptake inhibitors and suicidal ideation and behavior in children. *Am J Health Syst Pharm*. 2005 Apr 15;62(8):864-7. PMID: 15821279. Exclusion Code: X6.
100. Caelear AL, Christensen H, Mackinnon A, et al. The YouthMood Project: a cluster randomized controlled trial of an online cognitive behavioral program with adolescents. *J Consult Clin Psychol*. 2009 Dec;77(6):1021-32. doi: 10.1037/a0017391. PMID: 19968379. Exclusion Code: X1.
101. Callister R, Giles A, Nasstasia Y, et al. 12-weeks supervised exercise training is a feasible and efficacious treatment for reducing depression in youth with major depressive disorder. *J Sci Med Sport*. 2013;16:e16. doi: 10.1016/j.jsams.2013.10.040. PMID: CN-01011862. Exclusion Code: X1.
102. Camacho A, Gonzalez P, Castaneda SF, et al. Improvement in Depressive Symptoms Among Hispanic/Latinos Receiving a Culturally Tailored IMPACT and Problem-Solving Intervention in a Community Health Center. *Community Ment Health J*. 2015 May;51(4):385-92. doi: 10.1007/s10597-014-9750-7. PMID: 25107309. Exclusion Code: X1.
103. Caporino N. Child/adolescent anxiety multimodal extended long-term study: depression and suicide outcomes. *J Am Acad Child Adolesc Psychiatry*. 2017;56(10):S318. doi: 10.1016/j.jaac.2017.07.639. PMID: CN-01452306. Exclusion Code: X1.
104. Carandang C, Jabbal R, MacBride A, et al. A review of escitalopram and citalopram in child and adolescent depression. *J Can Acad Child Adolesc Psychiatry*. 2011;20(4):315-24. PMID: CN-01754288. Exclusion Code: X9.
105. Carlson G, Rapport M, Kelly K, et al. Methylphenidate and desipramine in hospitalized children with comorbid behavior and mood disorders: separate and combined effects on behavior and mood. *J Child Adolesc Psychopharmacol*. 1995;5(3):191-204. PMID: CN-00184672. Exclusion Code: X1.
106. Carter T, Callaghan P, Khalil E, et al. The effectiveness of a preferred intensity exercise programme on the mental health outcomes of young people with depression: a sequential mixed methods evaluation. *BMC Public Health*. 2012 Mar 13;12:187. doi: 10.1186/1471-2458-12-187. PMID: 22414319. Exclusion Code: X6.
107. Carter T, Guo B, Turner D, et al. Preferred intensity exercise for adolescents receiving treatment for depression: a pragmatic randomised controlled trial. *BMC Psychiatry*. 2015 Oct 14;15:247. doi: 10.1186/s12888-015-0638-z. PMID: 26467764. Exclusion Code: X1.
108. Castro A, Lopez-Del-Hoyo Y, Peake C, et al. Adherence predictors in an Internet-based intervention program for depression. *Cogn Behav Ther*. 2018 May;47(3):246-61. doi: 10.1080/16506073.2017.1366546. PMID: 28871896. Exclusion Code: X9.
109. Cavaiola AA, Lavender N. Suicidal behavior in chemically dependent adolescents. *Adolescence*. 1999 Win 1999;34(136):735-44. PMID: 2000-07190-009. Exclusion Code: X1.
110. Chabrol H, Peresson G. Pulse clomipramine for depressed adolescents. *Am J Psychiatry*. 1998;155(7):995. PMID: CN-00342831. Exclusion Code: X6.

111. Chadi N, Kaufman M, Weisbaum E, et al. Comparison of an in-person vs. ehealth mind-fulness meditation-based intervention for adolescents with chronic medical conditions: a mixed methods study. *Journal of adolescent health*. Conference: society for adolescent health and medicine annual meeting 2018. United states. 2018;62(2 Supplement 1):S12. PMID: CN-01463205. Exclusion Code: X6.
112. Charkhandeh M, Talib MA, Hunt CJ. The clinical effectiveness of cognitive behavior therapy and an alternative medicine approach in reducing symptoms of depression in adolescents. *Psychiatry Res*. 2016 May 30;239:325-30. doi: 10.1016/j.psychres.2016.03.044. PMID: 27058159. Exclusion Code: X1.
113. Cheng M, Rooney RM, Kane RT, et al. Do parent mental illness and family living arrangement moderate the effects of the aussie optimism program on depression and anxiety in children? *Front Psychiatry*. 2018;9:183. doi: 10.3389/fpsy.2018.00183. PMID: 29946269. Exclusion Code: X1.
114. Cheung A, Kusumakar V, Kutcher S, et al. Maintenance study for adolescent depression. *J Child Adolesc Psychopharmacol*. 2008 Aug;18(4):389-94. doi: 10.1089/cap.2008.0001. PMID: 18759650. Exclusion Code: X1.
115. Cheung A, Mayes T, Levitt A, et al. Anxiety as a predictor of treatment outcome in children and adolescents with depression. *J Child Adolesc Psychopharmacol*. 2010;20(3):211-6. PMID: CN-00763696. Exclusion Code: X9.
116. Cheung K, Aarts N, Noordam R, et al. Antidepressant use and the risk of suicide: a population-based cohort study. *J Affect Disord*. 2015;174:479-84. doi: 10.1016/j.jad.2014.12.032. PMID: 2015-08840-066. Exclusion Code: X1.
117. Chi X, Bo A, Liu T, et al. Effects of mindfulness-based stress reduction on depression in adolescents and young adults: a systematic review and meta-analysis. *Front Psychol*. 2018;9:1034. doi: 10.3389/fpsyg.2018.01034. PMID: 29977221. Exclusion Code: X1.
118. Chorpita BF, Daleiden EL, Park AL, et al. Child STEPs in California: a cluster randomized effectiveness trial comparing modular treatment with community implemented treatment for youth with anxiety, depression, conduct problems, or traumatic stress. *J Consult Clin Psychol*. 2017 Jan;85(1):13-25. doi: 10.1037/ccp0000133. PMID: 27548030. Exclusion Code: X1.
119. Chorpita BF, Weisz JR, Daleiden EL, et al. Long-term outcomes for the Child STEPs randomized effectiveness trial: a comparison of modular and standard treatment designs with usual care. *J Consult Clin Psychol*. 2013 Dec;81(6):999-1009. doi: 10.1037/a0034200. PMID: 23978169. Exclusion Code: X1.
120. Christiansen E, Agerbo E, Bilenberg N, et al. SSRIs and risk of suicide attempts in young people - A Danish observational register-based historical cohort study, using propensity score. *Nord J Psychiatry*. 2016;70(3):167-75. doi: 10.3109/08039488.2015.1065291. PMID: 26251067. Exclusion Code: X1.
121. Chu BC, Crocco ST, Arnold CC, et al. Sustained implementation of cognitive-behavioral therapy for youth anxiety and depression: long-term effects of structured training and consultation on therapist practice in the field. *Prof Psychol Res Pr*. 2015 Feb;46(1):70-9. doi: 10.1037/a0038000. PMID: 26366037. Exclusion Code: X1.
122. Chu BC, Crocco ST, Esseling P, et al. Transdiagnostic group behavioral activation and exposure therapy for youth anxiety and depression: initial randomized controlled trial. *Behav Res Ther*. 2016 Jan;76:65-75. doi: 10.1016/j.brat.2015.11.005. PMID: 26655958. Exclusion Code: X1.
123. Churchill R, Gill D. Drug treatment of childhood depression. *Bandolier*. 1996;87-. PMID: 108228593. Language: English. Entry Date: 20110624. Revision Date: 20150712. Publication Type: Journal Article. Exclusion Code: X9.
124. Clarizio H. Cognitive-behavioral treatment of childhood depression. *Psychol Sch*. 1985;22(3):308-22. PMID: CN-00709423. Exclusion Code: X6.

125. Clark DC, Goebel AE. Siblings of youth suicide victims. In: Pfeffer CR, Pfeffer CR, eds. *Severe stress and mental disturbance in children*. Arlington, VA, US: American Psychiatric Association; 1996:361-89. Exclusion Code: X6.
126. Clarke G. Cognitive-behavioral treatment and prevention of adolescent depression. 155th Annual Meeting of the American Psychiatric Association; 2002 May 18-23rd; Philadelphia, PA. 11839. Exclusion Code: X13.
127. Clarke G, Harvey AG. The complex role of sleep in adolescent depression. *Child Adolesc Psychiatr Clin N Am*. 2012 Apr;21(2):385-400. doi: 10.1016/j.chc.2012.01.006. PMID: 22537732. Exclusion Code: X6.
128. Clarke G, Hops H, Lewinsohn PM, et al. Cognitive-behavioral group treatment of adolescent depression: prediction of outcome. *Behav Ther*. 1992;23(3):341-54. PMID: CN-00180508. Exclusion Code: X3.
129. Clarke G, McGlinchey EL, Hein K, et al. Cognitive-behavioral treatment of insomnia and depression in adolescents: a pilot randomized trial. *Behav Res Ther*. 2015 Jun;69:111-8. doi: 10.1016/j.brat.2015.04.009. PMID: 25917009. Exclusion Code: X1.
130. Clarke J, Proudfoot J, Birch MR, et al. Effects of mental health self-efficacy on outcomes of a mobile phone and web intervention for mild-to-moderate depression, anxiety and stress: secondary analysis of a randomised controlled trial. *BMC Psychiatry*. 2014 Sep 26;14:272. doi: 10.1186/s12888-014-0272-1. PMID: 25252853. Exclusion Code: X1.
131. Clarkin JF, Glick ID, Haas GL, et al. A randomized clinical trial of inpatient family intervention. V. Results for affective disorders. *J Affect Disord*. 1990 Jan;18(1):17-28. PMID: 2136866. Exclusion Code: X7.
132. Cohen JR. Predictors and effects of support person involvement in the Youth-Nominated Support Team-Version I intervention for suicidal youth. US: ProQuest Information & Learning; 2005. Exclusion Code: X1.
133. Connor DF. Paroxetine and the FDA. *J Am Acad Child Adolesc Psychiatry*. 2004;43(2):127-. doi: 10.1097/00004583-200402000-00001. PMID: 2004-10559-001. Exclusion Code: X6.
134. Cooper WO, Callahan ST, Shintani A, et al. Antidepressants and suicide attempts in children. *Pediatrics*. 2014 Feb;133(2):204-10. doi: 10.1542/peds.2013-0923. PMID: 24394688. Exclusion Code: X1.
135. Cornelius J, Chung T, Douaihy A, et al. Mirtazapine pilot trial in youthful MDD/AUD subjects. *Am J Addict*. 2017;26(3):250-1. doi: 10.1111/ajad.12545. PMID: CN-01364499. Exclusion Code: X1.
136. Cornelius JR, Bukstein OG, Birmaher B, et al. Fluoxetine in adolescents with major depression and an alcohol use disorder: an open-label trial. *Addict Behav*. 2001 Sep-Oct;26(5):735-9. PMID: 11676382. Exclusion Code: X1.
137. Cornelius JR, Bukstein OG, Douaihy AB, et al. Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults. *Drug Alcohol Depend*. 2010 Nov 1;112(1-2):39-45. doi: 10.1016/j.drugalcdep.2010.05.010. PMID: 20576364. Exclusion Code: X1.
138. Cornelius JR, Bukstein OG, Salloum IM, et al. Fluoxetine in depressed AUD adolescents: a 1-year follow-up evaluation. *J Child Adolesc Psychopharmacol*. 2004 Spring;14(1):33-8. doi: 10.1089/104454604773840463. PMID: 15142389. Exclusion Code: X1.
139. Cornelius JR, Bukstein OG, Wood DS, et al. Double-blind placebo-controlled trial of fluoxetine in adolescents with comorbid major depression and an alcohol use disorder. *Addict Behav*. 2009 Oct;34(10):905-9. doi: 10.1016/j.addbeh.2009.03.008. PMID: 19321268. Exclusion Code: X1.
140. Cornelius JR, Chung TA, Douaihy A, et al. Double-blind mirtazapine pilot trial in AUD/MDD. *Alcoholism: Clinical and Experimental Research*. 2016;40:16A-247A. doi: 10.1111/acer.13084. PMID: CN-01267390. Exclusion Code: X1.

141. Cornelius JR, Clark DB, Bukstein OG, et al. Fluoxetine in adolescents with comorbid major depression and an alcohol use disorder: a five-year follow-up study. *J Dual Diagn.* 2005;2(1):11-25. PMID: 106223356. Language: English. Entry Date: 20070126. Revision Date: 20150711. Publication Type: Journal Article. Exclusion Code: X1.
142. Cornelius JR, Clark DB, Bukstein OG, et al. Acute phase and five-year follow-up study of fluoxetine in adolescents with major depression and a comorbid substance use disorder: a review. *Addict Behav.* 2005 Oct;30(9):1824-33. doi: 10.1016/j.addbeh.2005.07.007. PMID: 16102905. Exclusion Code: X1.
143. Cornelius JR, Douaihy A, Bukstein OG, et al. Evaluation of cognitive behavioral therapy/motivational enhancement therapy (CBT/MET) in a treatment trial of comorbid MDD/AUD adolescents. *Addict Behav.* 2011 Aug;36(8):843-8. doi: 10.1016/j.addbeh.2011.03.016. PMID: 21530092. Exclusion Code: X1.
144. Cornelius JR, Salloum IM, Ferrell R, et al. Treatment trial and long-term follow-up evaluation among co-morbid youth with major depression and a cannabis use disorder. In: Columbus AM, Columbus AM, eds. *Advances in psychology research.* Hauppauge, NY, US: Nova Science Publishers; 2012:109-21. Exclusion Code: X1.
145. Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 2006 Jul;45(7):771-91. doi: 10.1097/01.chi.0000220851.94392.30. PMID: 16832314. Exclusion Code: X6.
146. Correll CU, Pleak RR. Paroxetine in the treatment of adolescent major depression. *J Am Acad Child Adolesc Psychiatry.* 2002 Nov;41(11):1269; author reply 70. doi: 10.1097/00004583-200211000-00001. PMID: 12410065. Exclusion Code: X6.
147. Cortese S, Tomlinson A, Cipriani A. Meta-review: network meta-analyses in child and adolescent psychiatry. *J Am Acad Child Adolesc Psychiatry.* 2019 Feb;58(2):167-79. doi: 10.1016/j.jaac.2018.07.891. PMID: 30738544. Exclusion Code: X9.
148. Coughtrey A, Millington A, Bennett S, et al. The effectiveness of psychosocial interventions for psychological outcomes in pediatric oncology: a systematic review. *J Pain Symptom Manage.* 2018 Mar;55(3):1004-17. doi: 10.1016/j.jpainsymman.2017.09.022. PMID: 28962919. Exclusion Code: X1.
149. Courtney DB. Selective serotonin reuptake inhibitor and venlafaxine use in children and adolescents with major depressive disorder: a systematic review of published randomized controlled trials. *Canadian journal of psychiatry.* 2004;49(8):557-63. PMID: CN-01773098. Exclusion Code: X12.
150. Croarkin P. Recent developments in non-invasive brain stimulation for adolescents with major depressive disorder. *Brain Stimul.* 2019;12(2):411-. doi: 10.1016/j.brs.2018.12.329. PMID: CN-01787164. Exclusion Code: X6.
151. Cubero-Millan I, Molina-Carballo A, Machado-Casas I, et al. Methylphenidate ameliorates depressive comorbidity in ADHD children without any modification on differences in serum melatonin concentration between ADHD subtypes. *Int J Mol Sci.* 2014 Sep 25;15(9):17115-29. doi: 10.3390/ijms150917115. PMID: 25257531. Exclusion Code: X1.
152. Cummings CM, Fristad MA. Medications prescribed for children with mood disorders: effects of a family-based psychoeducation program. *Exp Clin Psychopharmacol.* 2007 Dec;15(6):555-62. doi: 10.1037/1064-1297.15.6.555. PMID: 18179308. Exclusion Code: X1.
153. Curry J, Silva S, Rohde P, et al. Recovery and recurrence following treatment for adolescent major depression. *Arch Gen Psychiatry.* 2011 Mar;68(3):263-9. doi: 10.1001/archgenpsychiatry.2010.150. PMID: 21041606. Exclusion Code: X9.
154. Curry JF, Wells KC. Striving for effectiveness in the treatment of adolescent depression: cognitive behavior therapy for multisite community intervention. *Cogn Behav Pract.* 2005;12(2):177-85. PMID: CN-00596564. Exclusion Code: X6.

155. Curtis SE. Cognitive-behavioral treatment of adolescent depression: effects on multiple parameters. *Dissertation abstracts international*. 1993;53(9-b):4948. PMID: CN-00709729. Exclusion Code: X1.
156. Czaja AS, Valuck RJ, Anderson HD. Comparative safety of selective serotonin reuptake inhibitors among pediatric users with respect to adverse cardiac events. *Pharmacoepidemiol Drug Saf*. 2013 Jun;22(6):607-14. doi: 10.1002/pds.3420. PMID: 23456956. Exclusion Code: X1.
157. David-Ferdon C, Kaslow NJ. Evidence-based psychosocial treatments for child and adolescent depression (Structured abstract). *J Clin Child Adolesc Psychol*. 2008;37(1):62-104. PMID: DARE-12008103483. Exclusion Code: X9.
158. Daviss WB, Bentivoglio P, Racusin R, et al. Bupropion sustained release in adolescents with comorbid attention-deficit/hyperactivity disorder and depression. *J Am Acad Child Adolesc Psychiatry*. 2001 Mar;40(3):307-14. doi: 10.1097/00004583-200103000-00010. PMID: 11288772. Exclusion Code: X9.
159. De Cuyper S, Timbremont B, Braet C, et al. Treating depressive symptoms in schoolchildren: a pilot study. *Eur Child Adolesc Psychiatry*. 2004 Apr;13(2):105-14. doi: 10.1007/s00787-004-0366-2. PMID: 15103536. Exclusion Code: X1.
160. de Voogd EL, de Hullu E, Burnett Heyes S, et al. Imagine the bright side of life: a randomized controlled trial of two types of interpretation bias modification procedure targeting adolescent anxiety and depression. *PLoS One*. 2017;12(7):e0181147. doi: 10.1371/journal.pone.0181147. PMID: 28715495. Exclusion Code: X1.
161. de Voogd EL, Wiers RW, Prins PJM, et al. Online attentional bias modification training targeting anxiety and depression in unselected adolescents: short- and long-term effects of a randomized controlled trial. *Behav Res Ther*. 2016 Dec;87:11-22. doi: 10.1016/j.brat.2016.08.018. PMID: 27585484. Exclusion Code: X1.
162. De Voogd EL, Wiers RW, Salemink E. Online visual search attentional bias modification for adolescents with heightened anxiety and depressive symptoms: A randomized controlled trial. *Behav Res Ther*. 2017 May;92:57-67. doi: 10.1016/j.brat.2017.02.006. PMID: 28257982. Exclusion Code: X1.
163. de Voogd L, Wiers RW, de Jong PJ, et al. A randomized controlled trial of multi-session online interpretation bias modification training: Short- and long-term effects on anxiety and depression in unselected adolescents. *PLoS One*. 2018;13(3):e0194274. doi: 10.1371/journal.pone.0194274. PMID: 29543838. Exclusion Code: X1.
164. DelBello M, Detke HC, Landry J, et al. Safety and efficacy of olanzapine/fluoxetine combination versus placebo in patients aged 10 to 17 in the acute treatment of major depressive episodes associated with bipolar disorder. *Neuropsychopharmacology*. 2012;38:S99-s100. doi: 10.1038/npp.2012.220. PMID: CN-01058079. Exclusion Code: X1.
165. DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disorders*. 2009;11(5):483-93. doi: 10.1111/j.1399-5618.2009.00728.x. PMID: 2009-10679-003. Exclusion Code: X1.
166. DelBello MP, Hochadel TJ, Portland KB, et al. A double-blind, placebo-controlled study of Selegiline Transdermal System (STS) in depressed adolescents. *Neuropsychopharmacology*. 2011;36:S348-s9. doi: 10.1038/npp.2011.293. PMID: CN-01020469. Exclusion Code: X10.
167. Delini-Stula A, Baier D, Kohnen R, et al. Undesirable blood pressure changes under naturalistic treatment with moclobemide, a reversible MAO-A inhibitor—results of the drug utilization observation studies. *Pharmacopsychiatry*. 1999;32(2):61-7. doi: 10.1055/s-2007-979193. PMID: 1999-05356-003. Exclusion Code: X1.



168. Detke HC, DelBello MP, Landry J, et al. Olanzapine/Fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2015 Mar;54(3):217-24. doi: 10.1016/j.jaac.2014.12.012. PMID: 25721187. Exclusion Code: X1.
169. Diamond G, Siqueland L, Diamond GM. Attachment-based family therapy for depressed adolescents: programmatic treatment development. *Clin Child Fam Psychol Rev*. 2003;6(2):107-27. doi: 10.1023/A:1023782510786. PMID: 2003-06174-003. Exclusion Code: X4.
170. Diamond GS, Wintersteen MB, Brown GK, et al. Attachment-based family therapy for adolescents with suicidal ideation: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2010 Feb;49(2):122-31. PMID: 20215934. Exclusion Code: X1.
171. Diaz-Gonzalez MC, Perez Duenas C, Sanchez-Raya A, et al. Mindfulness-based stress reduction in adolescents with mental disorders: a randomised clinical trial. *Psicothema*. 2018 May;30(2):165-70. doi: 10.7334/psicothema2017.259. PMID: 29694316. Exclusion Code: X1.
172. Dickerson JF, Lynch FL, Bar L, et al. Cost-effectiveness of a brief primary care cognitive behavioral therapy intervention for depressed adolescents who decline pharmacotherapy. *Journal of mental health policy and economics*. 2015;18:S9-s10. PMID: CN-01142724. Exclusion Code: X10.
173. Dickerson JF, Lynch FL, Clarke G, et al. Potential benefit: a new methodological framework for economic evaluation of adherence promotion in existing medical technologies. *Journal of mental health policy and economics*. 2015;18:S9. PMID: CN-01142725. Exclusion Code: X1.
174. Dinan TG. A double-blind, placebo-controlled trial of sertraline in depressed adolescent alcoholics: a pilot study. *Hum Psychopharmacol*. 2000;15(6):461-9. doi: 10.1002/1099-1077%28200008%2915:6%3C461::AID-HUP209%3E3.0.CO. PMID: CN-00315734. Exclusion Code: X12.
175. Doggrell SA. Fluoxetine--do the benefits outweigh the risks in adolescent major depression? *Expert Opin Pharmacother*. 2005 Jan;6(1):147-50. doi: 10.1517/14656566.6.1.147. PMID: 15709892. Exclusion Code: X6.
176. Domino ME, Burns BJ, Silva SG, et al. Cost-effectiveness of treatments for adolescent depression: results from TADS. *Am J Psychiatry*. 2008 May;165(5):588-96. doi: 10.1176/appi.ajp.2008.07101610. PMID: 18413703. Exclusion Code: X4.
177. Domino ME, Foster EM, Vitiello B, et al. Relative cost-effectiveness of treatments for adolescent depression: 36-week results from the TADS randomized trial. *J Am Acad Child Adolesc Psychiatry*. 2009 Jul;48(7):711-20. doi: 10.1097/CHI.0b013e3181a2b319. PMID: 19465880. Exclusion Code: X4.
178. Donnelly CL, Wagner KD, Rynn M, et al. Sertraline in children and adolescents with major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. 2006 Oct;45(10):1162-70. doi: 10.1097/01.chi.0000233204.51050.f0. PMID: 17003661. Exclusion Code: X9.
179. Dornseif BE, Dunlop SR, Potvin JH, et al. Effect of dose escalation after low-dose fluoxetine therapy. *Psychopharmacol Bull*. 1989;25(1):71-9. PMID: 2672072. Exclusion Code: X1.
180. Doshi P. Putting GlaxoSmithKline to the test over paroxetine. *BMJ*. 2013 Nov 12;347:f6754. doi: 10.1136/bmj.f6754. PMID: 24222673. Exclusion Code: X6.
181. Duberg A, Hagberg L, Sunvisson H, et al. Influencing self-rated health among adolescent girls with dance intervention: a randomized controlled trial. *JAMA Pediatr*. 2013 Jan;167(1):27-31. doi: 10.1001/jamapediatrics.2013.421. PMID: 23403597. Exclusion Code: X1.
182. Dujovne VF. Comparison of cognitive-behavioral to pharmacological treatment of depression in prepubertal children. *Dissertation abstracts international*. 1994;54(10-b):5384. PMID: CN-00711354. Exclusion Code: X6.

183. Dunning DL, Griffiths K, Kuyken W, et al. Research review: the effects of mindfulness-based interventions on cognition and mental health in children and adolescents - a meta-analysis of randomized controlled trials. *J Child Psychol Psychiatry*. 2019 Mar;60(3):244-58. doi: 10.1111/jcpp.12980. PMID: 30345511. Exclusion Code: X1.
184. Duong MT, Cruz RA, King KM, et al. Twelve-month outcomes of a randomized trial of the positive thoughts and action program for depression among early adolescents. *Prev Sci*. 2016 Apr;17(3):295-305. doi: 10.1007/s11121-015-0615-2. PMID: 26486632. Exclusion Code: X1.
185. Eckshtain D, Gaynor ST. Combining individual cognitive behaviour therapy and caregiver-child sessions for childhood depression: an open trial. *Clin Child Psychol Psychiatry*. 2012 Apr;17(2):266-83. doi: 10.1177/1359104511404316. PMID: 21733933. Exclusion Code: X1.
186. Eckshtain D, Gaynor ST. Combined individual cognitive behavior therapy and parent training for childhood depression: 2- to 3-year follow-up. *Child Fam Behav Ther*. 2013;35(2):132-43. doi: 10.1080/07317107.2013.789362. PMID: 104172065. Language: English. Entry Date: 20130606. Revision Date: 20150711. Publication Type: Journal Article. Exclusion Code: X9.
187. Eckshtain D, Kuppens S, Ugueto A, et al. Meta-analysis: 13-year follow-up of psychotherapy effects on youth depression. *J Am Acad Child Adolesc Psychiatry*. 2019 Apr 17. doi: 10.1016/j.jaac.2019.04.002. PMID: 31004739. Exclusion Code: X9.
188. Eckshtain D, Marchette LK, Schleider J, et al. Parental depressive symptoms as a predictor of outcome in the treatment of child depression. *J Abnorm Child Psychol*. 2018 May;46(4):825-37. doi: 10.1007/s10802-017-0323-4. PMID: 28643207. Exclusion Code: X1.
189. Edraki M, Rambod M, Molazem Z. The effect of coping skills training on depression, anxiety, stress, and self-efficacy in adolescents with diabetes: a randomized controlled trial. *Int J Community Based Nurs Midwifery*. 2018 Oct;6(4):324-33. PMID: 30465005. Exclusion Code: X1.
190. Edwards JG, Inman WH, Wilton L, et al. Prescription-event monitoring of 10,401 patients treated with fluvoxamine. *Br J Psychiatry*. 1994 Mar;164(3):387-95. PMID: 7993416. Exclusion Code: X1.
191. Eggert LL, Thompson EA, Herting JR, et al. Reducing suicide potential among high-risk youth: tests of a school-based prevention program. *Suicide Life Threat Behav*. 1995 Summer;25(2):276-96. PMID: 7570788. Exclusion Code: X9.
192. Eikelenboom M, Beekman ATF, Penninx BWJH, et al. A 6-year longitudinal study of predictors for suicide attempts in major depressive disorder. *Psychol Med*. 2019;49(6):911-21. doi: 10.1017/S0033291718001423. PMID: 135430207. Language: English. Entry Date: 20190322. Revision Date: 20190330. Publication Type: Article. Journal Subset: Biomedical. Exclusion Code: X2.
193. Emslie G. Predictors and moderators of relapse in depressed youth. *Neuropsychiatrie de l'enfance ET de l'adolescence*. 2012;60(5 suppl. 1):S168. doi: 10.1016/j.neurenf.2012.04.242. PMID: CN-01089339. Exclusion Code: X10.
194. Emslie G. Pediatric MDD: sequential treatment with fluoxetine and relapse prevention CBT. *Eur Child Adolesc Psychiatry*. 2013;22(2 suppl. 1):S112-s3. doi: 10.1007/s00787-013-0423-9. PMID: CN-01024193. Exclusion Code: X1.
195. Emslie G, Clarke G, Wagner K, et al. The treatment of SSRI-resistant depression in adolescents (tordia). *World psychiatry*. 2009;8(Suppl 1):37. PMID: CN-00718478. Exclusion Code: X6.
196. Emslie GJ. Depression in children and adolescents. 9th Congress of the Association of European Psychiatrists 1998 Copenhagen, Denmark. 10426: pp. No. Lilly-SAT3-4. Exclusion Code: X10.
197. Emslie GJ, Heiligenstein JH, Hoog SL, et al. Fluoxetine for maintenance of recovery from depression in children and adolescents: a placebo-controlled, randomized clinical trial. 154th Annual Meeting of the American Psychiatric Association; 2001 May 5-10; New Orleans, LA. 12051: p. Nr736. Exclusion Code: X10.

198. Emslie GJ, Hughes CW, Crismon ML, et al. A feasibility study of the childhood depression medication algorithm: the Texas Children's Medication Algorithm Project (CMAP). *J Am Acad Child Adolesc Psychiatry*. 2004 May;43(5):519-27. PMID: 15100558. Exclusion Code: X9.
199. Emslie GJ, Kennard BD, Mayes TL, et al. Insomnia moderates outcome of serotonin-selective reuptake inhibitor treatment in depressed youth. *J Child Adolesc Psychopharmacol*. 2012 Feb;22(1):21-8. doi: 10.1089/cap.2011.0096. PMID: 22257126. Exclusion Code: X9.
200. Emslie GJ, Mayes T, Porta G, et al. Treatment of Resistant Depression in Adolescents (TORDIA): week 24 outcomes. *Am J Psychiatry*. 2010 Jul;167(7):782-91. doi: 10.1176/appi.ajp.2010.09040552. PMID: 20478877. Exclusion Code: X3.
201. Emslie GJ, Rush AJ, Weinberg WA, et al. Fluoxetine in child and adolescent depression: acute and maintenance treatment. *Depress Anxiety*. 1998;7(1):32-9. PMID: 9592630. Exclusion Code: X3.
202. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind placebo controlled trial of fluoxetine in depressed children and adolescents. *Sixth World Congress of Biological Psychiatry*; 1997 Jun 22-27; Nice, France. 10715. Exclusion Code: X10.
203. Emslie GJ, Weinberg WA, Mayes TL. Treatment of children with antidepressants: focus on selective serotonin reuptake inhibitors. *Depress Anxiety*. 1998;8 Suppl 1:13-7. PMID: 9809209. Exclusion Code: X6.
204. Emslie GJ, Yeung PP, Kunz NR. Long-term, open-label venlafaxine extended-release treatment in children and adolescents with major depressive disorder. *CNS Spectr*. 2007 Mar;12(3):223-33. PMID: 17329983. Exclusion Code: X9.
205. Eskin M, Ertekin K, Demir H. Efficacy of a problem-solving therapy for depression and suicide potential in adolescents and young adults. *Cognit Ther Res*. 2008;32(2):227-45. doi: 10.1007/s10608-007-9172-8. PMID: CN-00707177. Exclusion Code: X1.
206. Ewais T, Begun J, Kenny M, et al. Protocol for a pilot randomised controlled trial of mindfulness-based cognitive therapy in youth with inflammatory bowel disease and depression. *BMJ Open*. 2019 Apr 20;9(4):e025568. doi: 10.1136/bmjopen-2018-025568. PMID: 31005923. Exclusion Code: X1.
207. Falola MI, Limdi N, Shelton RC. Clinical and genetic predictors of delayed remission after multiple levels of antidepressant treatment: toward early identification of depressed individuals for advanced care options. *J Clin Psychiatry*. 2017;78(9):e1291-e8. doi: 10.4088/JCP.17m11448. PMID: CN-01451430. Exclusion Code: X1.
208. Feehan CJ, Vostanis P. Cognitive-behavioural therapy for depressed children: children's and therapists' impressions. *Behav Cogn Psychother*. 1996;24(2):171-83. doi: 10.1017/S1352465800017422. PMID: 1998-04652-007. Exclusion Code: X10.
209. Feeny NC, Silva SG, Reinecke MA, et al. An exploratory analysis of the impact of family functioning on treatment for depression in adolescents. *J Clin Child Adolesc Psychol*. 2009 Nov;38(6):814-25. doi: 10.1080/15374410903297148. PMID: 20183665. Exclusion Code: X3.
210. Feltner C, Weber RP, Stuebe A, et al. AHRQ comparative effectiveness reviews. Breastfeeding programs and policies, breastfeeding uptake, and maternal health outcomes in developed countries. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018. Exclusion Code: X1.
211. Fernandes ST, D'Silva F. Effectiveness of music therapy on depression, anxiety and stress among haemodialysis patients. *International Journal of Nursing Education*. 2019;11(1):124-9. doi: 10.5958/0974-9357.2019.00024.2. PMID: 134633669. Language: English. Entry Date: 20190213. Revision Date: 20190213. Publication Type: Article. Journal Subset: Continental Europe. Exclusion Code: X1.
212. Findling RL, Feeny NC, Stansbrey RJ, et al. Somatic treatment for depressive illnesses in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 2002;11(3):555-78. doi: 10.1016/S1056-4993(02)00010-X. PMID: CN-01769337. Exclusion Code: X9.

213. Findling RL, Groark J, Chiles D, et al. Safety and tolerability of desvenlafaxine in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014 May;24(4):201-9. doi: 10.1089/cap.2012.0126. PMID: 24611442. Exclusion Code: X9.
214. Findling RL, Groark J, Tourian KA, et al. Pharmacokinetics and tolerability of single-ascending doses of desvenlafaxine administered to children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2016 Dec;26(10):909-21. doi: 10.1089/cap.2016.0009. PMID: 27428303. Exclusion Code: X7.
215. Findling RL, McNamara NK, O'Riordan MA, et al. An open-label pilot study of St. John's wort in juvenile depression. *J Am Acad Child Adolesc Psychiatry*. 2003 Aug;42(8):908-14. doi: 10.1097/01.chi.0000046900.27264.2a. PMID: 12874492. Exclusion Code: X9.
216. Findling RL, Myers C, O'Riordan MA, et al. An open-label dosing study of paroxetine in depressed children and adolescents. *Current Therapeutic Research*. 2002;63(9):588-601. PMID: 106814059. Language: English. Entry Date: 20030314. Revision Date: 20150711. Publication Type: Journal Article. Exclusion Code: X3.
217. Findling RL, Nucci G, Piergies AA, et al. Multiple dose pharmacokinetics of paroxetine in children and adolescents with major depressive disorder or obsessive-compulsive disorder. *Neuropsychopharmacology*. 2006 Jun;31(6):1274-85. doi: 10.1038/sj.npp.1300960. PMID: 16319918. Exclusion Code: X1.
218. Findling RL, Preskorn SH, Marcus RN, et al. Nefazodone pharmacokinetics in depressed children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2000 Aug;39(8):1008-16. doi: 10.1097/00004583-200008000-00016. PMID: 10939229. Exclusion Code: X3.
219. Findling RL, Robb AS, DelBello M, et al. Pharmacokinetics and safety of vortioxetine in pediatric patients. *J Child Adolesc Psychopharmacol*. 2017 Aug;27(6):526-34. doi: 10.1089/cap.2016.0155. PMID: 28333546. Exclusion Code: X5.
220. Findling RL, Robb AS, DelBello MP, et al. A 6-month open-label extension study of vortioxetine in pediatric patients with depressive or anxiety disorders. *J Child Adolesc Psychopharmacol*. 2018;28(1):47-54. doi: 10.1089/cap.2017.0047. PMID: 2018-03285-006. Exclusion Code: X1.
221. Fine S, Forth A, Gilbert M, et al. Group therapy for adolescent depressive disorder: a comparison of social skills and therapeutic support. *J Am Acad Child Adolesc Psychiatry*. 1991;30(1):79-85. PMID: CN-00216224. Exclusion Code: X9.
222. Fleischhaker C, Böhme R, Sixt B, et al. Dialectical Behavioral Therapy for Adolescents (DBT-A): a clinical trial for patients with suicidal and self-injurious behavior and borderline symptoms with a one-year follow-up. *Child and Adolescent Psychiatry and Mental Health*. 2011;5. doi: 10.1186/1753-2000-5-3. PMID: 2011-04497-001. Exclusion Code: X1.
223. Flynn D, Kells M, Joyce M, et al. Innovations in practice: dialectical behaviour therapy for adolescents: multisite implementation and evaluation of a 16-week programme in a public community mental health setting. *Child & Adolescent Mental Health*. 2019;24(1):76-83. doi: 10.1111/camh.12298. PMID: 134324827. Language: English. Entry Date: 20190131. Revision Date: 20190208. Publication Type: Article. Journal Subset: Biomedical. Exclusion Code: X3.
224. Forest Laboratories. A double-blind study comparing citalopram (LU 10-171, 10-40mg per day) and placebo in the treatment of major depression in adolescents. <http://www.forestclinicaltrials.com/>. 2005. PMID: CN-00633972. Exclusion Code: X7.
225. Fornaro M, Martino M, Mattei C, et al. Duloxetine-bupropion combination for treatment-resistant atypical depression: a double-blind, randomized, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2014 Aug;24(8):1269-78. doi: 10.1016/j.euroneuro.2014.04.004. PMID: 24842649. Exclusion Code: X1.

226. Fristad M, Nader E, Healy KZ, et al. Impact of individual-family psychoeducational psychotherapy (IF-PEP) on improved health habits for children with mood disorders. *Journal of alternative and complementary medicine*. 2014;20(5):A88. doi: 10.1089/acm.2014.5233. PMID: CN-01063893. Exclusion Code: X4.
227. Fristad MA, Black SR, Arnold LE. Long-term naturalistic follow-up of youth with mood disorders following omega-3 treatment and psychotherapy. *J Am Acad Child Adolesc Psychiatry*. 2016;55(10 Supplement 1):S335. doi: 10.1016/j.jaac.2016.07.404. PMID: CN-01304705. Exclusion Code: X3.
228. Fristad MA, Verducci JS, Walters K, et al. Impact of multifamily psychoeducational psychotherapy in treating children aged 8 to 12 years with mood disorders. *Arch Gen Psychiatry*. 2009 Sep;66(9):1013-21. doi: 10.1001/archgenpsychiatry.2009.112. PMID: 19736358. Exclusion Code: X1.
229. Gabbay V, Freed RD, Alonso CM, et al. A double-blind placebo-controlled trial of Omega-3 fatty acids as a monotherapy for adolescent depression. *J Clin Psychiatry*. 2018 Jun 26;79(4). doi: 10.4088/JCP.17ml1596. PMID: 29985566. Exclusion Code: X1.
230. Gagiano C. Paroxetine in adolescent depression. *XI World Congress of Psychiatry*; 1999 August 6-11; Hamburg. 12266: Abstracts Voume II. p. 111. Exclusion Code: X10.
231. Garcia-Carrion R, Villarejo-Carballido B, Villardon-Gallego L. Children and adolescents mental health: a systematic review of interaction-based interventions in schools and communities. *Front Psychol*. 2019;10:918. doi: 10.3389/fpsyg.2019.00918. PMID: 31068881. Exclusion Code: X9.
232. Garcia-Delgar B, Morer A, Varela E, et al. Activation in children and adolescents treated with selective serotonin reuptake inhibitors: a weighty reason? *J Clin Psychopharmacol*. 2018 Oct;38(5):475-80. doi: 10.1097/jcp.0000000000000923. PMID: 30063503. Exclusion Code: X7.
233. Garland EJ. Facing the evidence: antidepressant treatment in children and adolescents. *CMAJ*. 2004 Feb 17;170(4):489-91. PMID: 14970097. Exclusion Code: X6.
234. Gau JM, Stice E, Rohde P, et al. Negative life events and substance use moderate cognitive behavioral adolescent depression prevention intervention. *Cogn Behav Ther*. 2012;41(3):241-50. doi: 10.1080/16506073.2011.649781. PMID: 22414236. Exclusion Code: X1.
235. Gaynor ST, Weersing VR, Kolko DJ, et al. The prevalence and impact of large sudden improvements during adolescent therapy for depression: a comparison across cognitive-behavioral, family, and supportive therapy. *J Consult Clin Psychol*. 2003;71(2):386-93. doi: 10.1037/0022-006X.71.2.386. PMID: CN-01719330. Exclusion Code: X2.
236. Geller B, Cooper TB, Graham DL, et al. Pharmacokinetically designed double-blind placebo-controlled study of nortriptyline in 6- to 12-year-olds with major depressive disorder. *Annual Progress in Child Psychiatry & Child Development*. 1993:477-502. PMID: 1994-34474-001. Exclusion Code: X10.
237. Geller B, Cooper TB, Graham DL, et al. Double-blind placebo-controlled study of nortriptyline in depressed adolescents using a "fixed plasma level" design. *Psychopharmacol Bull*. 1990;26(1):85-90. PMID: CN-00068981. Exclusion Code: X12.
238. Geller B, Cooper TB, Zimmerman B, et al. Lithium for prepubertal depressed children with family history predictors of future bipolarity: a double-blind, placebo-controlled study. *J Affect Disord*. 1998 Nov;51(2):165-75. PMID: 10743849. Exclusion Code: X2.
239. Geller B, Fox LW, Cooper TB, et al. Baseline and 2- to 3-year follow-up characteristics of placebo-washout responders from the nortriptyline study of depressed 6- to 12-year-olds. *J Am Acad Child Adolesc Psychiatry*. 1992;31(4):622-8. doi: 10.1097/00004583-199207000-00008. PMID: CN-00086122. Exclusion Code: X3.

240. Geller B, Fox LW, Fletcher M. Effect of tricyclic antidepressants on switching to mania and on the onset of bipolarity in depressed 6- to 12-year-olds. *J Am Acad Child Adolesc Psychiatry*. 1993;32(1):43-50. PMID: CN-00213911. Exclusion Code: X9.
241. Gentil V, Kerr-Correa F, Moreno R, et al. Double-blind comparison of venlafaxine and amitriptyline in outpatients with major depression with or without melancholia. *J Psychopharmacol*. 2000 Mar;14(1):61-6. doi: 10.1177/026988110001400108. PMID: 10757255. Exclusion Code: X8.
242. Gest S, Holtmann M, Bogen S, et al. Chronotherapeutic treatments for depression in youth. *Eur Child Adolesc Psychiatry*. 2016 Feb;25(2):151-61. doi: 10.1007/s00787-015-0720-6. PMID: 25982568. Exclusion Code: X7.
243. Ghaziuddin N, Merchant C, Dopp R, et al. A naturalistic study of suicidal adolescents treated with an SSRI: suicidal ideation and behavior during 3-month post-hospitalization period. *Asian J Psychiatr*. 2014;11:13-9. doi: 10.1016/j.ajp.2014.03.014. PMID: 2014-49506-005. Exclusion Code: X9.
244. Gibbons RD, Hur K, Bhaumik DK, et al. The relationship between antidepressant medication use and rate of suicide. *Arch Gen Psychiatry*. 2005 Feb;62(2):165-72. doi: 10.1001/archpsyc.62.2.165. PMID: 15699293. Exclusion Code: X9.
245. Gibbons RD, Hur K, Bhaumik DK, et al. The relationship between antidepressant prescription rates and rate of early adolescent suicide. *Am J Psychiatry*. 2006 Nov;163(11):1898-904. doi: 10.1176/ajp.2006.163.11.1898. PMID: 17074941. Exclusion Code: X9.
246. Gijzen MWM, Creemers DHM, Rasing SPA, et al. Evaluation of a multimodal school-based depression and suicide prevention program among Dutch adolescents: design of a cluster-randomized controlled trial. *BMC Psychiatry*. 2018;18. PMID: 2018-22853-001. Exclusion Code: X1.
247. Ginsburg GS, Albano AM, Findling RL, et al. Integrating cognitive behavioral therapy and pharmacotherapy in the treatment of adolescent depression. *Cogn Behav Pract*. 2005;12(2):252-62. PMID: CN-00595045. Exclusion Code: X6.
248. Glass RM. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *J Pediatr*. 2005;146(1):145. PMID: CN-00594070. Exclusion Code: X10.
249. Glod CA, Lynch A, Berkowitz C, et al. Bupropion versus citalopram versus placebo in adolescents with major depression. 157th Annual Meeting of the American Psychiatric Association; 2004 May 1-6; New York, NY. 12039. Exclusion Code: X9.
250. Glod CA, Lynch A, Flynn E, et al. Open trial of bupropion SR in adolescent major depression. *J Child Adolesc Psychiatr Nurs*. 2003 Jul-Sep;16(3):123-30. PMID: 14603988. Exclusion Code: X9.
251. Goldstein BI, Shamseddeen W, Spirito A, et al. Substance use and the treatment of resistant depression in adolescents. *J Am Acad Child Adolesc Psychiatry*. 2009 Dec;48(12):1182-92. doi: 10.1097/CHI.0b013e3181bef6e8. PMID: 19858762. Exclusion Code: X4.
252. Gomez L. The relationship between depressive withdrawal and aggressive behavior among adolescents receiving treatment for depression. US: ProQuest Information & Learning; 2018. Exclusion Code: X2.
253. Goodman SH, Cullum KA, Dimidjian S, et al. Opening windows of opportunities: evidence for interventions to prevent or treat depression in pregnant women being associated with changes in offspring's developmental trajectories of psychopathology risk. *Dev Psychopathol*. 2018 Aug;30(3):1179-96. doi: 10.1017/s0954579418000536. PMID: 30068424. Exclusion Code: X1.

254. Goodyer I, Dubicka B, Wilkinson P, et al. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial. *BMJ*. 2007 Jul 21;335(7611):142. doi: 10.1136/bmj.39224.494340.55. PMID: 17556431. Exclusion Code: X1.
255. Goodyer I, on behalf of ADAPTTT. Adolescent depression antidepressant and psychotherapy trial (adapt). *World psychiatry*. 2009;8(Suppl 1):36. PMID: CN-00718526. Exclusion Code: X10.
256. Goodyer IM, Dubicka B, Wilkinson P, et al. A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. *Health Technol Assess*. 2008 May;12(14):iii-iv, ix-60. PMID: 18462573. Exclusion Code: X3.
257. Goodyer IM, Wilkinson PO. Practitioner review: therapeutics of unipolar major depressions in adolescents. *Journal of Child Psychology & Psychiatry*. 2019;60(3):232-43. doi: 10.1111/jcpp.12940. PMID: 134826514. Language: English. Entry Date: 20190223. Revision Date: 20190228. Publication Type: Article. Journal Subset: Biomedical. Exclusion Code: X9.
258. Gopinath S, Katon WJ, Russo JE, et al. Clinical factors associated with relapse in primary care patients with chronic or recurrent depression. *J Affect Disord*. 2007 Aug;101(1-3):57-63. doi: 10.1016/j.jad.2006.10.023. PMID: 17156852. Exclusion Code: X1.
259. Gothelf D, Rubinstein M, Shemesh E, et al. Pilot study: fluvoxamine treatment for depression and anxiety disorders in children and adolescents with cancer. *J Am Acad Child Adolesc Psychiatry*. 2005 Dec;44(12):1258-62. doi: 10.1097/01.chi.0000181042.29208.eb. PMID: 16292117. Exclusion Code: X1.
260. Gottlieb L, Martinovich Z, Meyers KM, et al. Treatment for depression enhances protection: findings from the Treatment for Adolescents With Depression Study (TADS). *Int J Cogn Ther*. 2016;9(1):38-56. doi: 10.1521/ijct\_2016\_09\_02. PMID: 2016-22581-003. Exclusion Code: X4.
261. Grist R, Croker A, Denne M, et al. Technology delivered interventions for depression and anxiety in children and adolescents: a systematic review and meta-analysis. *Clin Child Fam Psychol Rev*. 2019 Jun;22(2):147-71. doi: 10.1007/s10567-018-0271-8. PMID: 30229343. Exclusion Code: X9.
262. Groves S, Backer HS, van den Bosch W, et al. Dialectical behaviour therapy with adolescents. *Child & Adolescent Mental Health*. 2012 May;17(2):65-75. doi: 10.1111/j.1475-3588.2011.00611.x. PMID: 104352403. Language: English. Entry Date: 20130120. Revision Date: 20150711. Publication Type: Journal Article. Exclusion Code: X6.
263. Grunebaum MF, Ellis SP, Duan N, et al. Pilot randomized clinical trial of an SSRI vs bupropion: effects on suicidal behavior, ideation, and mood in major depression. *Neuropsychopharmacology*. 2012 Feb;37(3):697-706. doi: 10.1038/npp.2011.247. PMID: 21993207. Exclusion Code: X1.
264. Gualtieri CT, Golden RN, Fahs JJ. New developments in pediatric psychopharmacology. *J Dev Behav Pediatr*. 1983 Sep;4(3):202-9. PMID: 6355189. Exclusion Code: X6.
265. Gualtieri CT, Johnson LG. Antidepressant side effects in children and adolescents. *J Child Adolesc Psychopharmacol*. 2006;16(1-2):147-57. doi: 10.1089/cap.2006.16.147. PMID: 2006-04415-015. Exclusion Code: X1.
266. Guan K, Boustani MM, Chorpita BF. "Teaching moments" in psychotherapy: addressing emergent life events using strategies from a modular evidence-based treatment. *Behav Ther*. 2019 Jan;50(1):101-14. doi: 10.1016/j.beth.2018.03.014. PMID: 30661551. Exclusion Code: X1.
267. Gunlicks-Stoessel M, Mufson L. Early patterns of symptom change signal remission with interpersonal psychotherapy for depressed adolescents. *Depress Anxiety*. 2011 Jul;28(7):525-31. doi: 10.1002/da.20849. PMID: 21721071. Exclusion Code: X3.

268. Gunlicks-Stoessel M, Mufson L, Bernstein G, et al. Critical decision points for augmenting interpersonal psychotherapy for depressed adolescents: a pilot sequential multiple assignment randomized trial. *J Am Acad Child Adolesc Psychiatry*. 2019;58(1):80-91. doi: 10.1016/j.jaac.2018.06.032. PMID: 2018-65865-013. Exclusion Code: X9.
269. Gunlicks-Stoessel M, Mufson L, Jekal A, et al. The impact of perceived interpersonal functioning on treatment for adolescent depression: IPT-A versus treatment as usual in school-based health clinics. *J Consult Clin Psychol*. 2010 Apr;78(2):260-7. doi: 10.1037/a0018935. PMID: 20350036. Exclusion Code: X1.
270. Gunlicks-Stoessel M, Mufson L, Westervelt A, et al. A pilot SMART for developing an adaptive treatment strategy for adolescent depression. *J Clin Child Adolesc Psychol*. 2016 Jul-Aug;45(4):480-94. doi: 10.1080/15374416.2015.1015133. PMID: 25785788. Exclusion Code: X9.
271. Gunlicks-Stoessel M, Mufson L, Westervelt A, et al. An adaptive treatment strategy for adolescent depression: beginning with NBSP; interpersonal psychotherapy for depressed adolescents. *J Am Acad Child Adolesc Psychiatry*. 2016;55(10 Supplement 1):S39. doi: 10.1016/j.jaac.2016.07.586. PMID: CN-01304629. Exclusion Code: X3.
272. Gunlicks-Stoessel M, Westervelt A, Reigstad K, et al. The role of attachment style in interpersonal psychotherapy for depressed adolescents. *Psychother Res*. 2019 Jan;29(1):78-85. doi: 10.1080/10503307.2017.1315465. PMID: 28436756. Exclusion Code: X3.
273. Guy W, Wilson WH, Ban TA, et al. A double-blind clinical trial of fluvoxamine and imipramine in patients with primary depression. *Psychopharmacol Bull*. 1984 Winter;20(1):73-8. PMID: 6425916. Exclusion Code: X1.
274. Haapasalo-Pesu KM, Vuola T, Lahelma L, et al. Mirtazapine in the treatment of adolescents with major depression: an open-label, multicenter pilot study. *J Child Adolesc Psychopharmacol*. 2004 Summer;14(2):175-84. doi: 10.1089/1044546041649110. PMID: 15319015. Exclusion Code: X9.
275. Haby MM, Tonge B, Littlefield L, et al. Cost-effectiveness of cognitive behavioural therapy and selective serotonin reuptake inhibitors for major depression in children and adolescents. *Aust N Z J Psychiatry*. 2004 Aug;38(8):579-91. doi: 10.1080/j.1440-1614.2004.01421.x. PMID: 15298580. Exclusion Code: X9.
276. Hall WD. How have the SSRI antidepressants affected suicide risk? *Lancet*. 2006 Jun 17;367(9527):1959-62. doi: 10.1016/s0140-6736(06)68860-0. PMID: 16782468. Exclusion Code: X6.
277. Hall WD, Lucke J. How have the selective serotonin reuptake inhibitor antidepressants affected suicide mortality? *Aust N Z J Psychiatry*. 2006 Nov-Dec;40(11-12):941-50. doi: 10.1080/j.1440-1614.2006.01917.x. PMID: 17054562. Exclusion Code: X6.
278. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006 Mar;63(3):332-9. doi: 10.1001/archpsyc.63.3.332. PMID: 16520440. Exclusion Code: X9.
279. Han DH, Renshaw PF. Bupropion in the treatment of problematic online game play in patients with major depressive disorder. *J Psychopharmacol*. 2012 May;26(5):689-96. doi: 10.1177/0269881111400647. PMID: 21447539. Exclusion Code: X1.
280. Hargreaves MA, Maxwell C. The speed of action of desipramine: a controlled trial. *Int J Neuropsychiatry*. 1967 Apr;3(2):140-1. PMID: 5339863. Exclusion Code: X1.
281. Harrington R. Controlled trial of a brief cognitive-behavioural intervention in adolescents parents with depressive disorders. *Eur Psychiatry*. 1996;11(Suppl 4):158s. PMID: CN-00239208. Exclusion Code: X1.
282. Harrington R. A randomised control trial of fluoxetine and cognitive behaviour therapy versus fluoxetine alone in adolescents with major depression. *National research register*. 2003(3). PMID: CN-00418230. Exclusion Code: X13.



283. Harrington R, Dubicka B, Leech A, et al. Randomised controlled trial of fluoxetine and cognitive-behaviour therapy versus fluoxetine alone in adolescents with major depression (Adapt Trial). 30th Annual Conference of the British Association for Behavioural and Cognitive Psychotherapies; 2002 July 17 - 20; Warwick. 11692. Exclusion Code: X10.
284. Harrington R, Kerfoot M, Dyer E, et al. Randomized trial of a home-based family intervention for children who have deliberately poisoned themselves. *J Am Acad Child Adolesc Psychiatry*. 1998 May;37(5):512-8. PMID: 9585653. Exclusion Code: X4.
285. Harrington R, Whittaker J, Shoebridge P. Psychological treatment of depression in children and adolescents. A review of treatment research. *Br J Psychiatry*. 1998;173(OCT.):291-8. PMID: CN-01755513. Exclusion Code: X5.
286. Hasan KZ, Akhtar MI. Double blind clinical study comparing doxepin and imipramine in depression. *Curr Ther Res Clin Exp*. 1971 Jun;13(6):327-36. PMID: 4996218. Exclusion Code: X1.
287. Hashemian P, Sadjadi SA. Evaluation of neurofeedback therapy in adolescents with major depressive disorder who take fluoxetine. *African Journal of Psychiatry (South Africa)*. 2015;18(1) (no pagination). doi: 10.4172/Psychiatry.1000180. PMID: CN-01161590. Exclusion Code: X8.
288. Haskell DS, McNair DM, Fisher S, et al. A controlled outpatient trial of perphenazine--amitriptyline and chlorpromazine. *J Clin Pharmacol*. 1974 Oct;14(10):536-42. PMID: 4610016. Exclusion Code: X1.
289. Hassiotis A, Serfaty M, Azam K, et al. Manualised Individual Cognitive Behavioural Therapy for mood disorders in people with mild to moderate intellectual disability: a feasibility randomised controlled trial. *J Affect Disord*. 2013 Oct;151(1):186-95. doi: 10.1016/j.jad.2013.05.076. PMID: 23827533. Exclusion Code: X1.
290. Hawley CJ, Pattinson HA, Quick SJ, et al. A protocol for the pharmacologic treatment of major depression. A field test of a potential prototype. *J Affect Disord*. 1998 Jan;47(1-3):87-96. PMID: 9476748. Exclusion Code: X1.
291. Hayes AM, Strauss JL. Dynamic systems theory as a paradigm for the study of change in psychotherapy: an application to cognitive therapy for depression. *J Consult Clin Psychol*. 1998 Dec;66(6):939-47. PMID: 9874907. Exclusion Code: X1.
292. Hayes BD, Klein-Schwartz W, Clark RF, et al. Comparison of toxicity of acute overdoses with citalopram and escitalopram. *J Emerg Med*. 2010 Jul;39(1):44-8. doi: 10.1016/j.jemermed.2008.06.030. PMID: 19081700. Exclusion Code: X1.
293. Hayes TA, Panitch ML, Barker E. Imipramine dosage in children: a comment on "imipramine and electrocardiographic abnormalities in hyperactive children". *Am J Psychiatry*. 1975 May;132(5):546-7. doi: 10.1176/ajp.132.5.546. PMID: 1119617. Exclusion Code: X6.
294. Hayward C, Varady S, Albano AM, et al. Cognitive-behavioral group therapy for social phobia in female adolescents: results of a pilot study. *J Am Acad Child Adolesc Psychiatry*. 2000 Jun;39(6):721-6. doi: 10.1097/00004583-200006000-00010. PMID: 10846306. Exclusion Code: X1.
295. Healy D. Are selective serotonin reuptake inhibitors a risk factor for adolescent suicide? *Can J Psychiatry*. 2009 Feb;54(2):69-71; discussion 6-7. doi: 10.1177/070674370905400201. PMID: 19254434. Exclusion Code: X6.
296. Hektner JM, August GJ, Bloomquist ML, et al. A 10-year randomized controlled trial of the Early Risers conduct problems preventive intervention: effects on externalizing and internalizing in late high school. *J Consult Clin Psychol*. 2014 Apr;82(2):355-60. doi: 10.1037/a0035678. PMID: 24447007. Exclusion Code: X1.

297. Helgadóttir B, Hallgren M, Kullberg CLE, et al. Sticking with it? Factors associated with exercise adherence in people with mild to moderate depression. *Psychol Sport Exerc.* 2018;35:104-10. doi: 10.1016/j.psychsport.2017.11.011. PMID: 127984788. Language: English. Entry Date: 20180306. Revision Date: 20180306. Publication Type: Article. Exclusion Code: X1.
298. Hendricks CB. A study of the use of music therapy techniques in a group for the treatment of adolescent depression. *Dissertation abstracts international.* 2001;62(2-a):0472. PMID: CN-00710269. Exclusion Code: X1.
299. Herxheimer A, Mintzes B. Antidepressants and adverse effects in young patients: uncovering the evidence. *CMAJ.* 2004 Feb 17;170(4):487-9. PMID: 14970096. Exclusion Code: X6.
300. Hetrick S, McKenzie J, Merry S. The use of SSRIs in children and adolescents (Structured abstract). *Curr. Opin. Psychiatry.* 2010;23(1):53-7. PMID: DARE-12010005839. Exclusion Code: X12.
301. Hetrick SE, Cox GR, Merry SN. Treatment-resistant depression in adolescents: is the addition of cognitive behavioral therapy of benefit? (Structured abstract). *Psychol Res Behav Manag.* 2011;4(2):97-112. PMID: DARE-12013008192. Exclusion Code: X9.
302. Hetrick SE, McKenzie JE, Merry SN. The use of SSRIs in children and adolescents. *Curr. Opin. Psychiatry.* 2010 Jan;23(1):53-7. doi: 10.1097/YCO.0b013e328334bc92. PMID: 19934760. Exclusion Code: X9.
303. Hetrick SE, Yuen HP, Bailey E, et al. Internet-based cognitive behavioural therapy for young people with suicide-related behaviour (Reframe-IT): a randomised controlled trial. *Evidence Based Mental Health.* 2017;20(3):76-82. doi: 10.1136/eb-2017-102719. PMID: 124401710. Language: English. Entry Date: 20170904. Revision Date: 20170904. Publication Type: Article. Exclusion Code: X1.
304. Heyne D, Sauter FM, Van Widenfelt BM, et al. School refusal and anxiety in adolescence: non-randomized trial of a developmentally sensitive cognitive behavioral therapy. *J Anxiety Disord.* 2011 Oct;25(7):870-8. doi: 10.1016/j.janxdis.2011.04.006. PMID: 21602027. Exclusion Code: X1.
305. Hickman C. The acceptability, feasibility, and preliminary effects of a cognitive behavioral skills building intervention in adolescents with chronic daily headaches. *US: ProQuest Information & Learning;* 2013. Exclusion Code: X1.
306. Hickman C, Jacobson D, Melnyk BM. Randomized controlled trial of the acceptability, feasibility, and preliminary effects of a cognitive behavioral skills building intervention in adolescents with chronic daily headaches: a pilot study. *J Pediatr Health Care.* 2015 Jan-Feb;29(1):5-16. doi: 10.1016/j.pedhc.2014.05.001. PMID: 25017938. Exclusion Code: X1.
307. Hides LM, Elkins KS, Scaffidi A, et al. Does the addition of integrated cognitive behaviour therapy and motivational interviewing improve the outcomes of standard care for young people with comorbid depression and substance misuse? *Med J Aust.* 2011 Aug 1;195(3):S31-7. PMID: 21806516. Exclusion Code: X1.
308. Hill RM. Open trial and pilot randomized controlled trial of a novel program to reduce perceived burdensomeness. *US: ProQuest Information & Learning;* 2016. Exclusion Code: X1.
309. Hilton RC, Rengasamy M, Mansoor B, et al. Impact of treatments for depression on comorbid anxiety, attentional, and behavioral symptoms in adolescents with selective serotonin reuptake inhibitor-resistant depression. *J Am Acad Child Adolesc Psychiatry.* 2013 May;52(5):482-92. doi: 10.1016/j.jaac.2013.02.013. PMID: 23622849. Exclusion Code: X4.
310. Hoek W, Schuurmans J, Koot HM, et al. Effects of Internet-based guided self-help problem-solving therapy for adolescents with depression and anxiety: a randomized controlled trial. *PLoS One.* 2012;7(8):e43485. doi: 10.1371/journal.pone.0043485. PMID: 22952691. Exclusion Code: X1.

311. Hogberg G, Antonuccio DO, Healy D. Suicidal risk from TADS study was higher than it first appeared. *Int J Risk Saf Med*. 2015;27(2):85-91. doi: 10.3233/jrs-150645. PMID: 26410011. Exclusion Code: X6.
312. Hogberg G, Hallstrom T. Mood regulation focused CBT based on memory reconsolidation, reduced suicidal ideation and depression in youth in a randomised controlled study. *Int J Environ Res Public Health*. 2018;15(5 (no pagination)). doi: 10.3390/ijerph15050921. PMID: CN-01606583. Exclusion Code: X9.
313. Holt T, Jensen TK, Wentzel-Larsen T. The change and the mediating role of parental emotional reactions and depression in the treatment of traumatized youth: results from a randomized controlled study. *Child and adolescent psychiatry and mental health*. 2014;8(1). doi: 10.1186/1753-2000-8-11. PMID: CN-00988268. Exclusion Code: X1.
314. Horigian VE, Weems CF, Robbins MS, et al. Reductions in anxiety and depression symptoms in youth receiving substance use treatment. *Am J Addict*. 2013 Jul-Aug;22(4):329-37. doi: 10.1111/j.1521-0391.2013.12031.x. PMID: 23795871. Exclusion Code: X1.
315. Horn H, Geiser-Elze A, Reck C, et al. [Efficacy of psychodynamic short-term psychotherapy for children and adolescents with depression]. *Prax Kinderpsychol Kinderpsychiatr*. 2005 Sep;54(7):578-97. PMID: 16180527. Exclusion Code: X11.
316. Howard KA, Griffiths KM, McKetin R, et al. Can a brief biologically-based psychoeducational intervention reduce stigma and increase help-seeking intentions for depression in young people? A randomised controlled trial. *Journal of Child & Adolescent Mental Health*. 2018;30(1):27-39. doi: 10.2989/17280583.2018.1467323. PMID: 130244029. Language: English. Entry Date: 20180622. Revision Date: 20180622. Publication Type: Article. Exclusion Code: X1.
317. Hoying J, Melnyk BM. COPE. *J Sch Nurs*. 2016;32(5):347-56. doi: 10.1177/1059840516635713. PMID: 117886087. Language: English. Entry Date: 20170922. Revision Date: 20180524. Publication Type: Article. Exclusion Code: X1.
318. Huang ML, Luo BY, Hu JB, et al. Repetitive transcranial magnetic stimulation in combination with citalopram in young patients with first-episode major depressive disorder: a double-blind, randomized, sham-controlled trial. *Aust N Z J Psychiatry*. 2012 Mar;46(3):257-64. doi: 10.1177/0004867411433216. PMID: 22391283. Exclusion Code: X1.
319. Huey SJ, Jr., Henggeler SW, Rowland MD, et al. Multisystemic therapy effects on attempted suicide by youths presenting psychiatric emergencies. *J Am Acad Child Adolesc Psychiatry*. 2004 Feb;43(2):183-90. doi: 10.1097/00004583-200402000-00014. PMID: 14726725. Exclusion Code: X7.
320. Hughes CW, Preskorn SH, Weller E, et al. Imipramine vs. placebo studies of childhood depression: baseline predictors of response to treatment and factor analysis of presenting symptoms. *Psychopharmacol Bull*. 1988;24(2):275-9. PMID: 3062660. Exclusion Code: X7.
321. Hysinger EB, Callahan ST, Caples TL, et al. Suicidal behavior differs among early and late adolescents treated with antidepressant agents. *Pediatrics*. 2011;128(3):447-54. PMID: 2011-20946-009. Exclusion Code: X1.
322. Hyun MS, Chung HI, Lee YJ. The effect of cognitive-behavioral group therapy on the self-esteem, depression, and self-efficacy of runaway adolescents in a shelter in South Korea. *Appl Nurs Res*. 2005 Aug;18(3):160-6. doi: 10.1016/j.apnr.2004.07.006. PMID: 16106334. Exclusion Code: X8.
323. Hyun MS, Nam KA, Kim MA. Randomized controlled trial of a cognitive-behavioral therapy for at-risk Korean male adolescents. *Arch Psychiatr Nurs*. 2010 Jun;24(3):202-11. doi: 10.1016/j.apnu.2009.07.005. PMID: 20488346. Exclusion Code: X8.

324. Idsoe T, Keles S, Olseth AR, et al. Cognitive behavioral treatment for depressed adolescents: results from a cluster randomized controlled trial of a group course. *BMC Psychiatry*. 2019 May 22;19(1):155. doi: 10.1186/s12888-019-2134-3. PMID: 31117989. Exclusion Code: X1.
325. Ignaszewski MJ, Waslick B. Update on randomized placebo-controlled trials in the past decade for treatment of major depressive disorder in child and adolescent patients: a systematic review. *J Child Adolesc Psychopharmacol*. 2018 Jul 31. doi: 10.1089/cap.2017.0174. PMID: 30063169. Exclusion Code: X9.
326. Isa A, Bernstein I, Trivedi M, et al. Understanding the impact of treatment on the dimensions of childhood depression. *J Child Adolesc Psychopharmacol*. 2017 Mar;27(2):160-6. doi: 10.1089/cap.2015.0023. PMID: 26862813. Exclusion Code: X9.
327. Isacson G, Holmgren P, Ahlner J. Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. *Acta Psychiatr Scand*. 2005 Apr;111(4):286-90. doi: 10.1111/j.1600-0447.2004.00504.x. PMID: 15740464. Exclusion Code: X1.
328. Jacobs RH, Becker-Weidman EG, Reinecke MA, et al. Treating depression and oppositional behavior in adolescents. *J Clin Child Adolesc Psychol*. 2010;39(4):559-67. doi: 10.1080/15374416.2010.486318. PMID: 20589566. Exclusion Code: X4.
329. Jacobs RH, Silva SG, Reinecke MA, et al. Dysfunctional attitudes scale perfectionism: a predictor and partial mediator of acute treatment outcome among clinically depressed adolescents. *J Clin Child Adolesc Psychol*. 2009 Nov;38(6):803-13. doi: 10.1080/15374410903259031. PMID: 20183664. Exclusion Code: X3.
330. Jacobs RH, Watkins ER, Peters AT, et al. Targeting ruminative thinking in adolescents at risk for depressive relapse: rumination-focused cognitive behavior therapy in a pilot randomized controlled trial with resting state fMRI. *PLoS One*. 2016;11(11):e0163952. doi: 10.1371/journal.pone.0163952. PMID: 27880789. Exclusion Code: X1.
331. Jain S, Carmody TJ, Trivedi MH, et al. A psychometric evaluation of the CDRS and MADRS in assessing depressive symptoms in children. *J Am Acad Child Adolesc Psychiatry*. 2007 Sep;46(9):1204-12. doi: 10.1097/chi.0b013e3180cc2575. PMID: 17712244. Exclusion Code: X3.
332. Januel D, Dumortier G, Verdon CM, et al. A double-blind sham controlled study of right prefrontal repetitive transcranial magnetic stimulation (rTMS): therapeutic and cognitive effect in medication free unipolar depression during 4 weeks. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006 Jan;30(1):126-30. doi: 10.1016/j.pnpbp.2005.08.016. PMID: 16242826. Exclusion Code: X1.
333. Jeffreys MC. Treatment adherence and engagement in a transdiagnostic behavioral treatment for pediatric anxiety and depression. *Treatment Adherence & Engagement in a Transdiagnostic Behavioral Treatment for Pediatric Anxiety & Depression*. 2017:1-. PMID: 129490532. Exclusion Code: X4.
334. Jelalian E, Jandasek B, Wolff JC, et al. Cognitive-behavioral therapy plus healthy lifestyle enhancement for depressed, overweight/obese adolescents: results of a pilot trial. *J Clin Child Adolesc Psychol*. 2019;48(sup1):S24-s33. doi: 10.1080/15374416.2016.1163705. PMID: 27310418. Exclusion Code: X12.
335. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA*. 2004 Jul 21;292(3):338-43. doi: 10.1001/jama.292.3.338. PMID: 15265848. Exclusion Code: X1.
336. Jick H, Ulicickas M, Dean A. Comparison of frequencies of suicidal tendencies among patients receiving fluoxetine, lofepramine, mianserin, or trazodone. *Pharmacotherapy*. 1992;12(6):451-4. PMID: 1492009. Exclusion Code: X1.
337. Johansen AN, Stenzhorn AA, Rosenzweig M, et al. Prescribing patterns and safety monitoring of duloxetine using the Danish Register of Medicinal Product Statistics as a source. *Scand J Public Health*. 2013 Dec;41(8):866-73. doi: 10.1177/1403494813496599. PMID: 23885111. Exclusion Code: X9.

338. Johnson A, Giuffre RM, O'Malley K. ECG changes in pediatric patients on tricyclic antidepressants, desipramine, and imipramine. *Can J Psychiatry*. 1996 Mar;41(2):102-6. doi: 10.1177/070674379604100207. PMID: 8705955. Exclusion Code: X3.
339. Jon DI, Kim DH, Seo HJ, et al. Augmentation of aripiprazole for depressed patients with an inadequate response to antidepressant treatment: a 6-week prospective, open-label, multicenter study. *Clin Neuropharmacol*. 2013 Sep-Oct;36(5):157-61. doi: 10.1097/WNF.0b013e3182a31f3d. PMID: 24045606. Exclusion Code: X1.
340. Jordan J, Carter JD, McIntosh VV, et al. Metacognitive therapy versus cognitive behavioural therapy for depression: a randomized pilot study. *Aust N Z J Psychiatry*. 2014 Oct;48(10):932-43. doi: 10.1177/0004867414533015. PMID: 24810871. Exclusion Code: X1.
341. Joyce NR, Schuler MS, Hadland SE, et al. Variation in the 12-month treatment trajectories of children and adolescents after a diagnosis of depression. *JAMA Pediatr*. 2018;172(1):49-56. doi: 10.1001/jamapediatrics.2017.3808. PMID: 127221344. Language: English. Entry Date: 20180117. Revision Date: 20180517. Publication Type: Article. Exclusion Code: X2.
342. Joyce PR, Mulder RT, Luty SE, et al. A differential response to nortriptyline and fluoxetine in melancholic depression: the importance of age and gender. *Acta Psychiatr Scand*. 2003 Jul;108(1):20-3. PMID: 12807373. Exclusion Code: X1.
343. Julious SA. Efficacy and suicidal risk for antidepressants in paediatric and adolescent patients. *Stat Methods Med Res*. 2013 Apr;22(2):190-218. doi: 10.1177/0962280211432210. PMID: 22267546. Exclusion Code: X9.
344. Kanarek KS, Thomson PD, Levin SE. The management of imipramine (Tofranil) intoxication in children. *S Afr Med J*. 1973 May 19;47(19):835-8. PMID: 4707915. Exclusion Code: X6.
345. Kanchanatawan B, Tangwongchai S, Sughondhabhirom A, et al. Add-on treatment with curcumin has antidepressive effects in Thai patients with major depression: results of a randomized double-blind placebo-controlled study. *Neurotox Res*. 2018 Apr;33(3):621-33. doi: 10.1007/s12640-017-9860-4. PMID: 29327213. Exclusion Code: X8.
346. Kanner KD. High versus low-intensity exercise as part of an inpatient treatment program for childhood and adolescent depression. *Dissertation abstracts international*. 1991;51(8-b):4053. PMID: CN-00711560. Exclusion Code: X7.
347. Karami S, Ghasemzadeh A, Saadat M, et al. Effects of group counseling with cognitive-behavioral approach on reducing divorce children's depression. *Procedia, social and behavioral sciences*. 2012;46:77-81. PMID: CN-01039186. Exclusion Code: X8.
348. Kashani JH, Shekim WO, Reid JC. Amitriptyline in children with major depressive disorder: a double-blind crossover pilot study. *J Am Acad Child Psychiatry*. 1984 May;23(3):348-51. PMID: 6736501. Exclusion Code: X7.
349. Kasper S, Angelescu IG, Szegedi A, et al. Superior efficacy of St John's wort extract WS 5570 compared to placebo in patients with major depression: a randomized, double-blind, placebo-controlled, multicenter trial. *BMC Med*. 2006;4:14. doi: 10.1186/1741-7015-4-14. PMID: CN-00566059. Exclusion Code: X1.
350. Kasper S, Angelescu IG, Szegedi A, et al. Placebo controlled continuation treatment with Hypericum extract WS 5570 after recovery from a mild or moderate depressive episode. *Wien Med Wochenschr*. 2007;157(13-14):362-6. doi: 10.1007/s10354-007-0441-7. PMID: 17704988. Exclusion Code: X1.
351. Kaufman NK, Rohde P, Seeley JR, et al. Potential mediators of cognitive-behavioral therapy for adolescents with comorbid major depression and conduct disorder. *J Consult Clin Psychol*. 2005 Feb;73(1):38-46. doi: 10.1037/0022-006x.73.1.38. PMID: 15709830. Exclusion Code: X3.

352. Kay M, Guernsey de Zapien J, Wilson CA, et al. Evaluating treatment efficacy by triangulation. *Soc Sci Med*. 1993 Jun;36(12):1545-54. PMID: 8327918. Exclusion Code: X1.
353. Kay-Lambkin FJ, Baker AL, Palazzi K, et al. Therapeutic alliance, client need for approval, and perfectionism as differential moderators of response to ehealth and traditionally delivered treatments for comorbid depression and substance use problems. *Int J Behav Med*. 2017 Oct;24(5):728-39. doi: 10.1007/s12529-017-9676-x. PMID: 28819922. Exclusion Code: X11.
354. Kazdin AE. In high-risk adolescents, cognitive-behavioural therapy reduced depression at 6 months more than assessment alone but did not differ from bibliotherapy or supportive-expressive therapy. *Evid Based Med*. 2009;14(2):51-. doi: 10.1136/ebm.14.2.51. PMID: CN-01717538. Exclusion Code: X1.
355. Kaz'mina O, Oleichik IV, Zeziulia TN, et al. [Cognitive behavioral therapy of residual symptoms in patients with juvenile depression]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2002;102(9):22-5. PMID: 12378877. Exclusion Code: X11.
356. Keegan D, Bowen RC, Blackshaw S, et al. A comparison of fluoxetine and amitriptyline in the treatment of major depression. *Int Clin Psychopharmacol*. 1991 Summer;6(2):117-24. PMID: 1960381. Exclusion Code: X1.
357. Keerthy D, Youk A, Srinath AI, et al. Effect of psychotherapy on health care utilization in children with inflammatory bowel disease and depression. *J Pediatr Gastroenterol Nutr*. 2016 Dec;63(6):658-64. doi: 10.1097/mpg.0000000000001207. PMID: 27035372. Exclusion Code: X3.
358. Keles S, Idsoe T. A meta-analysis of group Cognitive Behavioral Therapy (CBT) interventions for adolescents with depression. *J Adolesc*. 2018 Aug;67:129-39. doi: 10.1016/j.adolescence.2018.05.011. PMID: 29957492. Exclusion Code: X9.
359. Keller MB, Ryan ND, Birmaher B, et al. Paroxetine and imipramine in the treatment of adolescent depression. 151st Annual Meeting of the American Psychiatric Association; 1998 May 30 - Jun 4; Toronto. 10716: p. No. 206. Exclusion Code: X1.
360. Keller MB, Trivedi MH, Thase ME, et al. The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study: outcomes from the acute and continuation phases. *Biol Psychiatry*. 2007 Dec 15;62(12):1371-9. doi: 10.1016/j.biopsych.2007.04.040. PMID: 17825800. Exclusion Code: X1.
361. Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry*. 2006 Dec;63(12):1337-44. doi: 10.1001/archpsyc.63.12.1337. PMID: 17146008. Exclusion Code: X1.
362. Kendrick T, Chatwin J, Dowrick C, et al. Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREShold for AntiDepressant response) study. *Health Technol Assess*. 2009 Apr;13(22):iii-iv, ix-xi, 1-159. doi: 10.3310/hta13220. PMID: 19401066. Exclusion Code: X1.
363. Kendrick T, Simons L, Mynors-Wallis L, et al. A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study. *Health Technol Assess*. 2005 Sep;9(37):1-104, iii. PMID: 16153354. Exclusion Code: X1.
364. Kennard BD, Clarke GN, Weersing VR, et al. Effective components of TORDIA cognitive-behavioral therapy for adolescent depression: preliminary findings. *J Consult Clin Psychol*. 2009 Dec;77(6):1033-41. doi: 10.1037/a0017411. PMID: 19968380. Exclusion Code: X3.

365. Kennard BD, Silva SG, Mayes TL, et al. Assessment of safety and long-term outcomes of initial treatment with placebo in TADS. *Am J Psychiatry*. 2009 Mar;166(3):337-44. doi: 10.1176/appi.ajp.2008.08040487. PMID: 19147693. Exclusion Code: X9.
366. Kennard BD, Silva SG, Tonev S, et al. Remission and recovery in the Treatment for Adolescents with Depression Study (TADS): acute and long-term outcomes. *J Am Acad Child Adolesc Psychiatry*. 2009 Feb;48(2):186-95. doi: 10.1097/CHI.0b013e31819176f9. PMID: 19127172. Exclusion Code: X9.
367. Kennard BD, Stewart SM, Hughes JL, et al. Developing cognitive behavioral therapy to prevent depressive relapse in youth. *Cogn Behav Pract*. 2008;15(4):387-99. doi: 10.1016/j.cbpra.2008.02.006. PMID: CN-00707780. Exclusion Code: X6.
368. Kerfoot M, Harrington R, Harrington V, et al. A step too far? Randomized trial of cognitive-behaviour therapy delivered by social workers to depressed adolescents. *Eur Child Adolesc Psychiatry*. 2004 Apr;13(2):92-9. doi: 10.1007/s00787-004-0362-6. PMID: 15103534. Exclusion Code: X9.
369. Khan A, Faucett J, Emslie GJ, et al. Efficacy and safety of anti-manic agents in children and adults. *Isr J Psychiatry Relat Sci*. 2012;49(2):122-7. PMID: 22801291. Exclusion Code: X9.
370. Khan A, Leventhal RM, Khan SR, et al. Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database. *J Clin Psychopharmacol*. 2002 Feb;22(1):40-5. PMID: 11799341. Exclusion Code: X1.
371. Kim SW, Stewart R, Kim JM, et al. Relationship between a history of a suicide attempt and treatment outcomes in patients with depression. *J Clin Psychopharmacol*. 2011 Aug;31(4):449-56. doi: 10.1097/JCP.0b013e3182217d51. PMID: 21694625. Exclusion Code: X9.
372. Kim YS. The effect of a group counseling program on depression and suicidal prevention in high school students. *J Korean Acad Community Health Nurs*. 2009;20(3):343-50. PMID: CN-01305983. Exclusion Code: X10.
373. King CA, Gipson PY, Horwitz AG, et al. Teen options for change: an intervention for young emergency patients who screen positive for suicide risk. *Psychiatr Serv*. 2015 Jan 1;66(1):97-100. doi: 10.1176/appi.ps.201300347. PMID: 25321886. Exclusion Code: X1.
374. King CA, Hill RM, Wynne HA, et al. Adolescent suicide risk screening: the effect of communication about type of follow-up on adolescents' screening responses. *J Clin Child Adolesc Psychol*. 2012;41(4):508-15. doi: 10.1080/15374416.2012.680188. PMID: 22540534. Exclusion Code: X1.
375. King CA, Klaus N, Kramer A, et al. The Youth-Nominated Support Team-Version II for suicidal adolescents: a randomized controlled intervention trial. *J Consult Clin Psychol*. 2009;77(5):880-93. doi: 10.1037/a0016552. PMID: 2009-17643-009. Exclusion Code: X1.
376. Kircanski K, Williams LM, Gotlib IH. Heart rate variability as a biomarker of anxious depression response to antidepressant medication. *Depress Anxiety*. 2019 Jan;36(1):63-71. doi: 10.1002/da.22843. PMID: 30311742. Exclusion Code: X1.
377. Kirschbaum-Lesch I, Gest S, Legenbauer T, et al. Feasibility and efficacy of bright light therapy in depressed adolescent inpatients. *Z Kinder Jugendpsychiatr Psychother*. 2018 Sep;46(5):423-9. doi: 10.1024/1422-4917/a000603. PMID: 30015544. Exclusion Code: X1.
378. Klein RG. Pharmacotherapy of adolescent depression. *Clin Neuropharmacol*. 1992;15(Suppl 1 Pt A):227a-8a. PMID: 1498821. Exclusion Code: X6.
379. Klieger-Grossmann C, Weitzner B, Panchaud A, et al. Pregnancy outcomes following use of escitalopram: a prospective comparative cohort study. *J Clin Pharmacol*. 2012 May;52(5):766-70. doi: 10.1177/0091270011405524. PMID: 22075232. Exclusion Code: X1.

380. Knox M, Lentini J, Cummings T, et al. Game-based biofeedback for paediatric anxiety and depression. *Mental health in family medicine*. 2011;8(3):195-203. PMID: CN-00851806. Exclusion Code: X1.
381. Knutsen ML, Czajkowski NO, Ormhaug SM. Changes in posttraumatic stress symptoms, cognitions, and depression during treatment of traumatized youth. *Behav Res Ther*. 2018;111:119-26. doi: 10.1016/j.brat.2018.10.010. PMID: 2018-60668-017. Exclusion Code: X1.
382. Kobak KA, Mundt JC, Kennard B. Integrating technology into cognitive behavior therapy for adolescent depression: a pilot study. *Ann Gen Psychiatry*. 2015;14(1 (no pagination)):37. doi: 10.1186/s12991-015-0077-8. PMID: 26535048. Exclusion Code: X1.
383. Kodet JD. Effectiveness of psychotherapy for youth in poverty: a benchmarking study of a public behavioral health agency using a client feedback system. US: ProQuest Information & Learning; 2017. Exclusion Code: X9.
384. Kolevzon A, Bird LM, Burdine RD, et al. Topline results from a phase 2 adult and adolescent Angelman Syndrome clinical trial: a randomized, double-blind, safety and efficacy study of gaboxadol (Ov101). *J Am Acad Child Adolesc Psychiatry*. 2018;57(10):S182-. doi: 10.1016/j.jaac.2018.09.159. PMID: CN-01653001. Exclusion Code: X1.
385. Kolko DJ, Brent DA, Baugher M, et al. Cognitive and family therapies for adolescent depression: treatment specificity, mediation, and moderation. *J Consult Clin Psychol*. 2000 Aug;68(4):603-14. PMID: 10965636. Exclusion Code: X4.
386. Konradt CE, Cardoso TA, Mondin TC, et al. Impact of resilience on the improvement of depressive symptoms after cognitive therapies for depression in a sample of young adults. *Trends Psychiatry Psychother*. 2018 Jul-Sep;40(3):226-31. doi: 10.1590/2237-6089-2017-0047. PMID: 30304118. Exclusion Code: X1.
387. Kornstein S, Chang CT, Gommoll CP, et al. Vilazodone efficacy in subgroups of patients with major depressive disorder: a post-hoc analysis of four randomized, double-blind, placebo-controlled trials. *Int Clin Psychopharmacol*. 2018 Jul;33(4):217-23. doi: 10.1097/yic.0000000000000217. PMID: 29608461. Exclusion Code: X1.
388. Kovacs M. Psychotherapy for young dysthymic children. *Cochrane Library*. 2005(3). PMID: CN-00508103. Exclusion Code: X6.
389. Kovacs M, Sherrill J, George CJ, et al. Contextual emotion-regulation therapy for childhood depression: description and pilot testing of a new intervention. *J Am Acad Child Adolesc Psychiatry*. 2006 Aug;45(8):892-903. doi: 10.1097/01.chi.0000222878.74162.5a. PMID: 16865031. Exclusion Code: X9.
390. Kowalenko N, Rapee RM, Simmons J, et al. Short-term effectiveness of a school-based early intervention program for adolescent depression. *Clin Child Psychol Psychiatry*. 2005;10(4):493-507. doi: 10.1177/1359104505056311. PMID: CN-00575337. Exclusion Code: X9.
391. Kowatch RA, Carmody TJ, Emslie GJ, et al. Prediction of response to fluoxetine and placebo in children and adolescents with major depression: a hypothesis generating study. *J Affect Disord*. 1999 Aug;54(3):269-76. PMID: 10467970. Exclusion Code: X3.
392. Kragh-Sorensen P, Hansen CE, Larsen NE, et al. Long-term treatment of endogenous depression with nortriptyline with control of plasma levels. *Psychol Med*. 1974;4(2):174-80. PMID: CN-00010282. Exclusion Code: X1.
393. Kramer AD, Feiguine RJ. Clinical effects of amitriptyline in adolescent depression. A pilot study. *J am acad child psychiatr*. 1981;20(3):636-44. PMID: CN-00192921. Exclusion Code: X7.
394. Kramer J, Conijn B, Oijevaar P, et al. Effectiveness of a web-based solution-focused brief chat treatment for depressed adolescents and young adults: randomized controlled trial. *J Med Internet Res*. 2014 May 29;16(5):e141. doi: 10.2196/jmir.3261. PMID: 24874006. Exclusion Code: X1.



395. Kratochvil CJ, Newcorn JH, Arnold LE, et al. Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. *J Am Acad Child Adolesc Psychiatry*. 2005 Sep;44(9):915-24. doi: 10.1097/01.chi.0000169012.81536.38. PMID: 16113620. Exclusion Code: X1.
396. Kratochvil CJ, Simons A, Vitiello B, et al. A multisite psychotherapy and medication trial for depressed adolescents: background and benefits. *Cogn Behav Pract*. 2005;12(2):159-65. PMID: CN-00596547. Exclusion Code: X6.
397. Kreuze LJ, Pijnenborg GHM, de Jonge YB, et al. Cognitive-behavior therapy for children and adolescents with anxiety disorders: a meta-analysis of secondary outcomes. *J Anxiety Disord*. 2018 Dec;60:43-57. doi: 10.1016/j.janxdis.2018.10.005. PMID: 30447493. Exclusion Code: X9.
398. Krieger FV, Pheula GF, Coelho R, et al. An open-label trial of risperidone in children and adolescents with severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2011 Jun;21(3):237-43. doi: 10.1089/cap.2010.0123. PMID: 21663426. Exclusion Code: X1.
399. Kroll L, Harrington R, Jayson D, et al. Pilot study of continuation cognitive-behavioral therapy for major depression in adolescent psychiatric patients. *J Am Acad Child Adolesc Psychiatry*. 1996 Sep;35(9):1156-61. doi: 10.1097/00004583-199609000-00013. PMID: 8824059. Exclusion Code: X9.
400. Kronenberg S, Apter A, Brent D, et al. Serotonin transporter polymorphism (5-HTTLPR) and citalopram effectiveness and side effects in children with depression and/or anxiety disorders. *J Child Adolesc Psychopharmacol*. 2007 Dec;17(6):741-50. doi: 10.1089/cap.2006.0144. PMID: 18315446. Exclusion Code: X1.
401. Kurki M, Anttila M, Koivunen M, et al. Depressed adolescents' adherence to an Internet-based self-help programme to assess depression: preliminary findings. Abstracts from the 14th International Congress of ESCAP European Society for Child and Adolescent Psychiatry 2011 Jun 11-15; Helsinki, Finland. 11982: European child and adolescent psychiatry. Exclusion Code: X4.
402. Kutcher S, Boulos C, Ward B, et al. Response to desipramine treatment in adolescent depression: a fixed-dose, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 1994 Jun;33(5):686-94. PMID: 8056732. Exclusion Code: X1.
403. Kwok SYCL, Gu M, Kit KTK. Positive psychology intervention to alleviate child depression and increase life satisfaction. *Res Soc Work Pract*. 2016;26(4):350-61. doi: 10.1177/1049731516629799. PMID: 115739626. Language: English. Entry Date: 20180326. Revision Date: 20180326. Publication Type: Article. Exclusion Code: X1.
404. Langer AI, Schmidt C, Aguilar-Parra JM, et al. [Effects of a mindfulness intervention in Chilean high schoolers]. *Rev Med Chil*. 2017 Apr;145(4):476-82. doi: 10.4067/s0034-98872017000400008. PMID: 28748995. Exclusion Code: X11.
405. Larsson B. Cognitive outcome of childhood depression using cognitive behavior therapy. *Lakartidningen*. 2002;99(16):1810-2, 5-9. PMID: CN-01756056. Exclusion Code: X9.
406. Law W, 3rd, Petti TA, Kazdin AE. Withdrawal symptoms after graduated cessation of imipramine in children. *Am J Psychiatry*. 1981 May;138(5):647-50. doi: 10.1176/ajp.138.5.647. PMID: 7235061. Exclusion Code: X7.
407. Lee CS, Williamson LR, Martin SE, et al. Adverse events in very young children prescribed psychotropic medications: preliminary findings from an acute clinical sample. *J Child Adolesc Psychopharmacol*. 2015 Aug;25(6):509-13. doi: 10.1089/cap.2015.0034. PMID: 26262905. Exclusion Code: X1.

408. Lee H, Zerr A, Dickerson JF, et al. Brief behavioral therapy for anxiety and depression in pediatric primary care: uptake of intervention and community services by ethnic minority families. *Journal of the american academy of child and adolescent psychiatry*. 55 (4) (pp 295-300), 2016. Date of publication: 01 apr 2016. 2016;55(10 Supplement 1):S181. doi: 10.1016/j.jaac.2016.09.252. PMID: CN-01304638. Exclusion Code: X1.
409. LeMoult J, Colich N, Joormann J, et al. Interpretation bias training in depressed adolescents: near- and far-transfer effects. *J Abnorm Child Psychol*. 2018 Jan;46(1):159-67. doi: 10.1007/s10802-017-0285-6. PMID: 28299526. Exclusion Code: X9.
410. Lenze SN, Pautsch J, Luby J. Parent-child interaction therapy emotion development: a novel treatment for depression in preschool children. *Depress Anxiety*. 2011 Feb;28(2):153-9. doi: 10.1002/da.20770. PMID: 21284068. Exclusion Code: X9.
411. Leonard HL, Meyer MC, Swedo SE, et al. Electrocardiographic changes during desipramine and clomipramine treatment in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1995 Nov;34(11):1460-8. doi: 10.1097/00004583-199511000-00012. PMID: 8543513. Exclusion Code: X1.
412. Leong C, Alessi-Severini S, Enns MW, et al. Cerebrovascular, cardiovascular, and mortality events in new users of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors: a propensity score-matched population-based study. *J Clin Psychopharmacol*. 2017 Jun;37(3):332-40. doi: 10.1097/jcp.0000000000000701. PMID: 28383363. Exclusion Code: X9.
413. Levkovitz Y, Harel EV, Roth Y, et al. Deep transcranial magnetic stimulation over the prefrontal cortex: evaluation of antidepressant and cognitive effects in depressive patients. *Brain Stimul*. 2009 Oct;2(4):188-200. doi: 10.1016/j.brs.2009.08.002. PMID: 20633419. Exclusion Code: X1.
414. Lewinsohn PM, Clarke GN, Hops H, et al. Cognitive-behavioral treatment for depressed adolescents. *Behav Ther*. 1990;21(4):385-401. PMID: CN-00179805. Exclusion Code: X1.
415. Lewinsohn PM, Rohde P, Clarke GN, et al. Cognitive-behavioral treatment for depressed adolescents: treatment outcome and the role of parental involvement. In preparation. 1994. PMID: CN-00712788. Exclusion Code: X10.
416. Lewis CC, Simons AD, Nguyen LJ, et al. Impact of childhood trauma on treatment outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2010 Feb;49(2):132-40. PMID: 20215935. Exclusion Code: X4.
417. Lewis CC, Simons AD, Silva SG, et al. The role of readiness to change in response to treatment of adolescent depression. *J Consult Clin Psychol*. 2009 Jun;77(3):422-8. doi: 10.1037/a0014154. PMID: 19485584. Exclusion Code: X3.
418. Liddle B, Spence SH. Cognitive-behaviour therapy with depressed primary school children: a cautionary note. *Behav Psychother*. 1990;18(2):85-102. PMID: CN-00180545. Exclusion Code: X1.
419. Liehr P, Diaz N. A pilot study examining the effect of mindfulness on depression and anxiety for minority children. *Arch Psychiatr Nurs*. 2010 Feb;24(1):69-71. doi: 10.1016/j.apnu.2009.10.001. PMID: 20117691. Exclusion Code: X1.
420. Lipsedge MS, Rees WL. A double-blind comparison of dothiepin and amitriptyline for the treatment of depression with anxiety. *Psychopharmacologia*. 1971;19(2):153-62. PMID: 5565736. Exclusion Code: X1.
421. Lobo ED, Quinlan T, Prakash A. Pharmacokinetics of orally administered duloxetine in children and adolescents with major depressive disorder. *Clin Pharmacokinet*. 2014;53(8):731-40. doi: 10.1007/s40262-014-0149-y. PMID: CN-00998765. Exclusion Code: X9.

422. Logsdon MC, Foltz MP, Stein B, et al. Adapting and testing telephone-based depression care management intervention for adolescent mothers. *Arch Womens Ment Health*. 2010 Aug;13(4):307-17. doi: 10.1007/s00737-009-0125-y. PMID: 20020164. Exclusion Code: X9.
423. Lopresti AL, Drummond PD, Inarejos-Garcia AM, et al. Affron((R)), a standardised extract from saffron (*Crocus sativus* L.) for the treatment of youth anxiety and depressive symptoms: a randomised, double-blind, placebo-controlled study. *J Affect Disord*. 2018 May;232:349-57. doi: 10.1016/j.jad.2018.02.070. PMID: 29510352. Exclusion Code: X1.
424. Luby J. A randomized controlled trial of parent-child psychotherapy in early childhood depression. *J Am Acad Child Adolesc Psychiatry*. 2018;57(10):S289-. doi: 10.1016/j.jaac.2018.07.691. PMID: CN-01653014. Exclusion Code: X1.
425. Luby JL, Barch DM, Whalen D, et al. A randomized controlled trial of parent-child psychotherapy targeting emotion development for early childhood depression. *Am J Psychiatry*. 2018 Nov 1;175(11):1102-10. doi: 10.1176/appi.ajp.2018.18030321. PMID: 29921144. Exclusion Code: X12.
426. Lucas A, Lockett H, Grimm F. Amitriptyline in childhood depressions. *Dis Nerv Syst*. 1965;26(2):105-10. PMID: CN-00712028. Exclusion Code: X1.
427. Lukin K. Predictors and moderators of treatment adherence in depressed youths. US: ProQuest Information & Learning; 2012. Exclusion Code: X3.
428. Lynch FL, Dickerson JF, Clarke G, et al. Incremental cost-effectiveness of combined therapy vs medication only for youth with selective serotonin reuptake inhibitor-resistant depression: treatment of SSRI-resistant depression in adolescents trial findings. *Arch Gen Psychiatry*. 2011 Mar;68(3):253-62. doi: 10.1001/archgenpsychiatry.2011.9. PMID: 21383263. Exclusion Code: X9.
429. Maalouf FT, Porta G, Vitiello B, et al. Do sub-syndromal manic symptoms influence outcome in treatment resistant depression in adolescents? A latent class analysis from the TORDIA study. *J Affect Disord*. 2012 Apr;138(1-2):86-95. doi: 10.1016/j.jad.2011.12.021. PMID: 22284022. Exclusion Code: X3.
430. Malhotra S, Santosh PJ. Loading dose imipramine--new approach to pharmacotherapy of melancholic depression. *J Psychiatr Res*. 1996 Jan-Feb;30(1):51-8. PMID: 8736467. Exclusion Code: X1.
431. Malinina EV, Zabozaeva IV. Use of Torin (sertraline) in the treatment of depressive and obsessive-compulsive disorders in children. *Neurosci Behav Physiol*. 2011;41(8):849-51. doi: 10.1007/s11055-011-9497-3. PMID: 2011-25100-013. Exclusion Code: X1.
432. Maneeton N, Srisurapanont M. Tricyclic antidepressants for depressive disorders in children and adolescents: a meta-analysis of randomized-controlled trials. *Chotmaihet thangphaet [Journal of the Medical Association of Thailand]*. 2000;83(11):1367-74. PMID: CN-01725320. Exclusion Code: X12.
433. Manglick M, Rajaratnam SM, Taffe J, et al. Persistent sleep disturbance is associated with treatment response in adolescents with depression. *Aust N Z J Psychiatry*. 2013 Jun;47(6):556-63. doi: 10.1177/0004867413481630. PMID: 23508680. Exclusion Code: X3.
434. Manicavasagar V, Horswood D, Burckhardt R, et al. Feasibility and effectiveness of a web-based positive psychology program for youth mental health: randomized controlled trial. *J Med Internet Res*. 2014 Jun 4;16(6):e140. doi: 10.2196/jmir.3176. PMID: 24901900. Exclusion Code: X1.
435. Mansoor B, Rengasamy M, Hilton R, et al. The bidirectional relationship between body mass index and treatment outcome in adolescents with treatment-resistant depression. *J Child Adolesc Psychopharmacol*. 2013 Sep;23(7):458-67. doi: 10.1089/cap.2012.0095. PMID: 24024532. Exclusion Code: X9.

436. March J, Silva S, Curry J, et al. The Treatment for Adolescents with Depression Study (TADS): outcomes over 1 year of naturalistic follow-up. *Am J Psychiatry*. 2009 Oct;166(10):1141-9. doi: 10.1176/appi.ajp.2009.08111620. PMID: 19723787. Exclusion Code: X9.
437. March J, Silva S, Vitiello B. The Treatment for Adolescents with Depression Study (TADS): methods and message at 12 weeks. *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1393-403. doi: 10.1097/01.chi.0000237709.35637.c0. PMID: 17135984. Exclusion Code: X6.
438. March JS. Treatment for adolescents with depression study (TADS). 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta, GA. 10143. Exclusion Code: X10.
439. March JS, Moon RL, Johnston H. Fluoxetine-TCA interaction. *J Am Acad Child Adolesc Psychiatry*. 1990 Nov;29(6):985-6. doi: 10.1097/00004583-199011000-00033. PMID: 2273036. Exclusion Code: X6.
440. March JS, Silva S, Petrycki S, et al. The Treatment for Adolescents with Depression Study (TADS): long-term effectiveness and safety outcomes. *Arch Gen Psychiatry*. 2007 Oct;64(10):1132-43. doi: 10.1001/archpsyc.64.10.1132. PMID: 17909125. Exclusion Code: X9.
441. March JS, Silva S, Petrycki S, et al. Fluoxetine plus cognitive behavioural therapy was most effective for adolescents with major depressive disorder. *Evid Based Med*. 2005;10:46. PMID: CN-00875747. Exclusion Code: X6.
442. March JS, Vitiello B. Clinical messages from the Treatment for Adolescents With Depression Study (TADS). *Am J Psychiatry*. 2009 Oct;166(10):1118-23. doi: 10.1176/appi.ajp.2009.08101606. PMID: 19723786. Exclusion Code: X6.
443. March JS, Vitiello B. Benefits exceed risks of newer antidepressant medications in youth--maybe. *Clin Pharmacol Ther*. 2009 Oct;86(4):355-7. doi: 10.1038/clpt.2009.172. PMID: 19763113. Exclusion Code: X6.
444. Markowitz JC, Klerman GL, Clougherty KF, et al. Treatment of depressed HIV-positive patients - Conference abstract. 150th Annual Meeting of the American Psychiatric Association; 1997 May 17-22; San Diego, CA. 9383. Exclusion Code: X1.
445. Marks IM. The maturing of therapy. Some brief psychotherapies help anxiety/depressive disorders but mechanisms of action are unclear. *Br J Psychiatry*. 2002;180:200-4. PMID: CN-01743976. Exclusion Code: X1.
446. Martin F, Oliver T. Behavioral activation for children and adolescents: a systematic review of progress and promise. *Eur Child Adolesc Psychiatry*. 2019 Apr;28(4):427-41. doi: 10.1007/s00787-018-1126-z. PMID: 29476253. Exclusion Code: X9.
447. Martinez V, Rojas G, Martinez P, et al. Remote collaborative depression care program for adolescents in Araucania Region, Chile: randomized controlled trial. *J Med Internet Res*. 2018 Jan 31;20(1):e38. doi: 10.2196/jmir.8021. PMID: 29386172. Exclusion Code: X1.
448. Martsenkovsky I, Martsenkovska I, Martsenkovskiy D. Risperidon and atomoxetine in the treatment of several and challending behaviors in children with PDD. *Eur Psychiatry*. 2015;30:195. PMID: CN-01100971. Exclusion Code: X8.
449. Martsenkovskiy D. Efficacy and safety of fluoxetine in the treatment of posttraumatic stress disorder in children and adolescents. *European neuropsychopharmacology*. 2015;25:S643-s4. PMID: CN-01163180. Exclusion Code: X8.
450. Mathews CA. Integrating pharmacogenetic testing into a child psychiatry clinic. *J Am Acad Child Adolesc Psychiatry*. 2018;57(10):S301-. doi: 10.1016/j.jaac.2018.07.735. PMID: CN-01653015. Exclusion Code: X1.
451. Mathie RT, Ulbrich-Zurni S, Viksveen P, et al. Systematic review and meta-analysis of randomised, other-than-placebo controlled, trials of individualised homeopathic treatment. *Homeopathy*. 2018 Nov;107(4):229-43. doi: 10.1055/s-0038-1667129. PMID: 30121049. Exclusion Code: X9.

452. Mathie RT, Ulbrich-Zürni S, Viksveen P, et al. Systematic review and meta-analysis of andomised, other-than-placebo controlled, trials of individualised homeopathic treatment. *Homeopathy*. 2018;107(4):229-43. doi: 10.1055/s-0038-1667129. PMID: 132995349. Language: English. Entry Date: 20181116. Revision Date: 20181116. Publication Type: Article. Journal Subset: Alternative/Complementary Therapies. Exclusion Code: X12.
453. May DE, Kratochvil CJ, Puumala SE, et al. A manual-based intervention to address clinical crises and retain patients in the Treatment of Adolescents With Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2007 May;46(5):573-81. doi: 10.1097/chi.0b013e3180323342. PMID: 17450048. Exclusion Code: X4.
454. Mayes TL, Tao R, Rintelmann JW, et al. Do children and adolescents have differential response rates in placebo-controlled trials of fluoxetine? *CNS Spectr*. 2007 Feb;12(2):147-54. PMID: 17277715. Exclusion Code: X9.
455. Mayes TL, Tao R, Rintelmann JW, et al. Do children and adolescents have differential responsive rates in placebo-controlled trials of fluoxetine? *CNS Spectr*. 2007;12(2):147-54. PMID: CN-01719497. Exclusion Code: X4.
456. McCabe R, Garside R, Backhouse A, et al. Effectiveness of brief psychological interventions for suicidal presentations: a systematic review. *BMC Psychiatry*. 2018 May 3;18(1):120. doi: 10.1186/s12888-018-1663-5. PMID: 29724203. Exclusion Code: X9.
457. McCarty CA, Violette HD, Duong MT, et al. A randomized trial of the positive thoughts and action program for depression among early adolescents. *J Clin Child Adolesc Psychol*. 2013;42(4):554-63. doi: 10.1080/15374416.2013.782817. PMID: 23560384. Exclusion Code: X1.
458. McCauley E, Gudmundsen G, Schloredt K, et al. The adolescent behavioral activation program: adapting behavioral activation as a treatment for depression in adolescence. *J Clin Child Adolesc Psychol*. 2016;45(3):291-304. doi: 10.1080/15374416.2014.979933. PMID: 25602170. Exclusion Code: X1.
459. McCulliss D, Chamberlain D. Bibliotherapy for youth and adolescents—School-based application and research. *Journal of Poetry Therapy*. 2013;26(1):13-40. doi: 10.1080/08893675.2013.764052. PMID: 104314498. Exclusion Code: X6.
460. McGlinchey EL, Reyes-Portillo JA, Turner JB, et al. Innovations in practice: the relationship between sleep disturbances, depression, and interpersonal functioning in treatment for adolescent depression. *Child Adolesc Ment Health*. 2017;22(2):96-9. doi: 10.1111/camh.12176. PMID: CN-01371129. Exclusion Code: X1.
461. McGrath BJ, Stoukides CA. Fluoxetine and suicidal ideation. *DICP*. 1991 Jun;25(6):607-9. PMID: 1877271. Exclusion Code: X6.
462. McKee LG, Parent J, Forehand R, et al. Reducing youth internalizing symptoms: effects of a family-based preventive intervention on parental guilt induction and youth cognitive style. *Dev Psychopathol*. 2014 May;26(2):319-32. doi: 10.1017/s0954579413001016. PMID: 24438999. Exclusion Code: X1.
463. McMakin DL, Olinio TM, Porta G, et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. *J Am Acad Child Adolesc Psychiatry*. 2012;51(4):404-11. doi: 10.1016/j.jaac.2012.01.011. PMID: 2012-08100-015. Exclusion Code: X3.
464. McNamara R, Strawn J, Stahl L, et al. Effects of fish oil monotherapy on emotion-generated cortical activity in depressed bipolar offspring: a double-blind placebo-controlled fMRI study. *Neuropsychopharmacology*. 2014;39:S228. doi: 10.1038/npp.2014.280. PMID: CN-01066376. Exclusion Code: X1.
465. McNamara RK, Jandacek R, Rider T, et al. Effects of fish oil supplementation on prefrontal metabolite concentrations in adolescents with major depressive disorder: a preliminary 1H MRS study. *Nutr Neurosci*. 2016 May;19(4):145-55. doi: 10.1179/1476830514y.0000000135. PMID: 24915543. Exclusion Code: X3.

466. McNamara RK, Strawn SR, Stahl L, et al. Effects of long-chain omega-3 fatty acid monotherapy on cortical biochemistry in depressed bipolar offspring: a double-blind placebo-controlled 1H MRS study. *Biol Psychiatry*. 2014;75(9 suppl. 1):121s. doi: 10.1016/j.biopsych.2014.03.014. PMID: CN-01060475. Exclusion Code: X1.
467. Mehlum L, Ramberg M, Tormoen AJ, et al. Dialectical behavior therapy compared with enhanced usual care for adolescents with repeated suicidal and self-harming behavior: outcomes over a one-year follow-up. *J Am Acad Child Adolesc Psychiatry*. 2016 Apr;55(4):295-300. doi: 10.1016/j.jaac.2016.01.005. PMID: 27015720. Exclusion Code: X9.
468. Mehlum L, Tormoen AJ, Ramberg M, et al. Dialectical behavior therapy for adolescents with repeated suicidal and self-harming behavior: a randomized trial. *J Am Acad Child Adolesc Psychiatry*. 2014 Oct;53(10):1082-91. doi: 10.1016/j.jaac.2014.07.003. PMID: 25245352. Exclusion Code: X1.
469. Meister R, Abbas M, Antel J, et al. Placebo response rates and potential modifiers in double-blind randomized controlled trials of second and newer generation antidepressants for major depressive disorder in children and adolescents: a systematic review and meta-regression analysis. *Eur Child Adolesc Psychiatry*. 2018 Dec 8. doi: 10.1007/s00787-018-1244-7. PMID: 30535589. Exclusion Code: X9.
470. Melnyk BM, Jacobson D, Kelly S, et al. Improving the mental health, healthy lifestyle choices, and physical health of Hispanic adolescents: a randomized controlled pilot study. *J Sch Health*. 2009 Dec;79(12):575-84. doi: 10.1111/j.1746-1561.2009.00451.x. PMID: 19909421. Exclusion Code: X1.
471. Melnyk BM, Jacobson D, Kelly SA, et al. Twelve-month effects of the COPE Healthy Lifestyles TEEN Program on overweight and depressive symptoms in high school adolescents. *J Sch Health*. 2015 Dec;85(12):861-70. doi: 10.1111/josh.12342. PMID: 26522175. Exclusion Code: X1.
472. Melnyk BM, Kelly S, Jacobson D, et al. The COPE healthy lifestyles TEEN randomized controlled trial with culturally diverse high school adolescents: baseline characteristics and methods. *Contemp Clin Trials*. 2013 Sep;36(1):41-53. doi: 10.1016/j.cct.2013.05.013. PMID: 23748156. Exclusion Code: X1.
473. Melton ST, Kirkwood CK, Farrar TW, et al. Economic evaluation of paroxetine and imipramine in depressed outpatients. *Psychopharmacol Bull*. 1997;33(1):93-100. PMID: 9133757. Exclusion Code: X1.
474. Melvin GA, Dudley AL, Gordon MS, et al. Augmenting cognitive behavior therapy for school refusal with fluoxetine: a randomized controlled trial. *Child Psychiatry Hum Dev*. 2017 Jun;48(3):485-97. doi: 10.1007/s10578-016-0675-y. PMID: 27485100. Exclusion Code: X1.
475. Mendels J, Johnston R, Mattes J, et al. Efficacy and safety of b.i.d. doses of venlafaxine in a dose-response study. *Psychopharmacol Bull*. 1993;29(2):169-74. PMID: 8290661. Exclusion Code: X1.
476. Mendels J, Reimherr F, Marcus RN, et al. A double-blind, placebo-controlled trial of two dose ranges of nefazodone in the treatment of depressed outpatients. *J Clin Psychiatry*. 1995;56 Suppl 6:30-6. PMID: 7649971. Exclusion Code: X1.
477. Mendels J, Schless AP. Antidepressant effects of desipramine administered in two dosage schedules. *Dis Nerv Syst*. 1977 Apr;38(4):249-51. PMID: 321197. Exclusion Code: X1.
478. Mendels J, Schless AP. Comparative efficacy of alprazolam, imipramine, and placebo administered once a day in treating depressed patients. *J Clin Psychiatry*. 1986;47(7):357-61. PMID: CN-00043402. Exclusion Code: X1.
479. Mendelson T, Greenberg MT, Dariotis JK, et al. Feasibility and preliminary outcomes of a school-based mindfulness intervention for urban youth. *J Abnorm Child Psychol*. 2010 Oct;38(7):985-94. doi: 10.1007/s10802-010-9418-x. PMID: 20440550. Exclusion Code: X1.

480. Mendenhall AN. Predictors of service utilization among youth diagnosed with mood disorders. *J Child Fam Stud*. 2012;21(4):603-11. doi: 10.1007/s10826-011-9512-x. PMID: 2012-19355-006. Exclusion Code: X4.
481. Mendenhall AN, Fristad MA, Early TJ. Factors influencing service utilization and mood symptom severity in children with mood disorders: effects of multifamily psychoeducation groups (MFPGs). *J Consult Clin Psychol*. 2009;77(3):463-73. doi: 10.1037/a0014527. PMID: 2009-08093-009. Exclusion Code: X1.
482. Merlob P, Birk E, Sirota L, et al. Are selective serotonin reuptake inhibitors cardiac teratogens? Echocardiographic screening of newborns with persistent heart murmur. *Birth Defects Res A Clin Mol Teratol*. 2009 Oct;85(10):837-41. doi: 10.1002/bdra.20615. PMID: 19691085. Exclusion Code: X1.
483. Merry S, McDowell H, Wild CJ, et al. A randomized placebo-controlled trial of a school-based depression prevention program. *J Am Acad Child Adolesc Psychiatry*. 2004 May;43(5):538-47. doi: 10.1097/00004583-200405000-00007. PMID: 15100560. Exclusion Code: X1.
484. Merry SN, Stasiak K, Shepherd M, et al. The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression: randomised controlled non-inferiority trial. *Br Med J*. 2012;344(7857):1-16. PMID: 2012-14158-001. Exclusion Code: X1.
485. Meyer EC, Coll CT, Lester BM, et al. Family-based intervention improves maternal psychological well-being and feeding interaction of preterm infants. *Pediatrics*. 1994 Feb;93(2):241-6. PMID: 8121735. Exclusion Code: X1.
486. Meyer JM, McNamara JP, Reid AM, et al. Prospective relationship between obsessive-compulsive and depressive symptoms during multimodal treatment in pediatric obsessive-compulsive disorder. *Child Psychiatry Hum Dev*. 2014;45(2):163-72. doi: 10.1007/s10578-013-0388-4. PMID: 23756717. Exclusion Code: X9.
487. Micco JA, Henin A, Hirshfeld-Becker DR. Efficacy of interpretation bias modification in depressed adolescents and young adults. *Cognit Ther Res*. 2014;38(2):89-102. doi: 10.1007/s10608-013-9578-4. PMID: CN-00985202. Exclusion Code: X1.
488. Midgley N, Parkinson S, Holmes J, et al. 'Did I bring it on myself?' an exploratory study of the beliefs that adolescents referred to mental health services have about the causes of their depression. *Eur Child Adolesc Psychiatry*. 2017;26(1):25-34. doi: 10.1007/s00787-016-0868-8. PMID: 2016-25613-001. Exclusion Code: X4.
489. Miklowitz DJ, Schneck CD, Singh MK, et al. Early intervention for symptomatic youth at risk for bipolar disorder: a randomized trial of family-focused therapy. *J Am Acad Child Adolesc Psychiatry*. 2013 Feb;52(2):121-31. doi: 10.1016/j.jaac.2012.10.007. PMID: 23357439. Exclusion Code: X1.
490. Milgrom J, Holt C, Holt CJ, et al. Feasibility study and pilot randomised trial of an antenatal depression treatment with infant follow-up. *Arch Womens Ment Health*. 2015 Oct;18(5):717-30. doi: 10.1007/s00737-015-0512-5. PMID: 25709044. Exclusion Code: X1.
491. Milgrom J, Holt C, Schembri C, et al. Pilot results on child outcomes of antenatal depression treatment. *Arch Womens Ment Health*. 2015;18(2):372. doi: 10.1007/s00737-014-0488-6. PMID: CN-01100610. Exclusion Code: X1.
492. Milgrom J, Holt CJ, Gemmill AW, et al. Treating postnatal depressive symptoms in primary care: a randomised controlled trial of GP management, with and without adjunctive counselling. *BMC Psychiatry*. 2011 May 27;11:95. doi: 10.1186/1471-244x-11-95. PMID: 21615968. Exclusion Code: X1.
493. Miller DK, Chibnall JT, Videen SD, et al. Supportive-affective group experience for persons with life-threatening illness: reducing spiritual, psychological, and death-related distress in dying patients. *J Palliat Med*. 2005;8(2):333-43. doi: 10.1089/jpm.2005.8.333. PMID: CN-00511874. Exclusion Code: X1.

494. Miller L, Hlastala SA, Mufson L, et al. Interpersonal psychotherapy for mood and behavior dysregulation: pilot randomized trial. *Depress Anxiety*. 2018 Jun;35(6):574-82. doi: 10.1002/da.22761. PMID: 29719093. Exclusion Code: X1.
495. Miller M, Pate V, Swanson SA, et al. Antidepressant class, age, and the risk of deliberate self-harm: a propensity score matched cohort study of SSRI and SNRI users in the USA. *CNS Drugs*. 2014 Jan;28(1):79-88. doi: 10.1007/s40263-013-0120-8. PMID: 24146116. Exclusion Code: X1.
496. Miller M, Swanson SA, Azrael D, et al. Antidepressant dose, age, and the risk of deliberate self-harm. *JAMA Intern Med*. 2014 Jun;174(6):899-909. doi: 10.1001/jamainternmed.2014.1053. PMID: 24782035. Exclusion Code: X1.
497. Miller PR, Champelli JW, Dinello FA. Imipramine in the treatment of enuretic schoolchildren. A double-blind study. *Am J Dis Child*. 1968 Jan;115(1):17-20. PMID: 5635054. Exclusion Code: X1.
498. Miller WC, Marcotte DB, McCurdy L. A controlled study of single-dose administration of imipramine pamoate in endogenous depression. *Curr Ther Res Clin Exp*. 1973;15(10):700-6. PMID: CN-00009188. Exclusion Code: X1.
499. Moldenhauer Z. Adolescent depression: a primary care pilot intervention study: University of Rochester School of Nursing; 2004. Exclusion Code: X1.
500. Mosholder A, Bates C. Desipramine side-effect. *J Am Acad Child Adolesc Psychiatry*. 1991 Nov;30(6):1026. doi: 10.1097/00004583-199111000-00030. PMID: 1757433. Exclusion Code: X6.
501. Mubarak AR, Zeitz J, Slee P. Effectiveness of an intervention programme for teenage girls with self-harm in Adelaide, South Australia. In: Slee PT, Skrzypiec G, Cefai C, Slee PT, Skrzypiec G, Cefai C, eds. *Child and adolescent wellbeing and violence prevention in schools*. New York, NY, US: Routledge/Taylor & Francis Group; 2018:209-16. Exclusion Code: X1.
502. Mufson L, Dorta KP, Wickramaratne P, et al. A randomized effectiveness trial of interpersonal psychotherapy for depressed adolescents. *Arch Gen Psychiatry*. 2004 Jun;61(6):577-84. doi: 10.1001/archpsyc.61.6.577. PMID: 15184237. Exclusion Code: X1.
503. Mulder R, Rucklidge JJ, Toop L. Restoring Study 329: paroxetine neither effective nor safe for adolescents. *Aust N Z J Psychiatry*. 2016 Sep;50(9):922-3. doi: 10.1177/0004867416657412. PMID: 27389067. Exclusion Code: X6.
504. Muller S, Rohde P, Gau JM, et al. Moderators of the effects of indicated group and bibliotherapy cognitive behavioral depression prevention programs on adolescents' depressive symptoms and depressive disorder onset. *Behav Res Ther*. 2015 Dec;75:1-10. doi: 10.1016/j.brat.2015.10.002. PMID: 26480199. Exclusion Code: X1.
505. Muratori F, Picchi L, Bruni G, et al. A two-year follow-up of psychodynamic psychotherapy for internalizing disorders in children. *J Am Acad Child Adolesc Psychiatry*. 2003;42(3):331-9. PMID: CN-00596463. Exclusion Code: X10.
506. Murphy JE, Ankier SI. An evaluation of trazodone in the treatment of depression. *Neuropharmacology*. 1980 Dec;19(12):1217-8. PMID: 7003428. Exclusion Code: X1.
507. Nakonezny PA, Hughes CW, Mayes TL, et al. A comparison of various methods of measuring antidepressant medication adherence among children and adolescents with major depressive disorder in a 12-week open trial of fluoxetine. *J Child Adolesc Psychopharmacol*. 2010 Oct;20(5):431-9. doi: 10.1089/cap.2009.0108. PMID: 20973714. Exclusion Code: X3.
508. Nakonezny PA, Mayes TL, Byerly MJ, et al. Predicting placebo response in adolescents with major depressive disorder: the Adolescent Placebo Impact Composite Score (APICS). *J Psychiatr Res*. 2015 Sep;68:346-53. doi: 10.1016/j.jpsychires.2015.05.003. PMID: 26028546. Exclusion Code: X3.



509. Nelson E, Barnard M, Cain S. Feasibility of telemedicine intervention for childhood depression. *CPR*. 2006 Sep;6(3):191-5. PMID: CN-00712018. Exclusion Code: X9.
510. Neumann CL, Reichenberg JL, Graves HR, et al. The differential effects of alcohol and cannabis on mood states in a sample of youth with co-occurring mental health and substance use disorders. *J Am Acad Child Adolesc Psychiatry*. 2016;55(10 Supplement 1):S146-s7. doi: 10.1016/j.jaac.2016.09.147. PMID: CN-01304647. Exclusion Code: X9.
511. Newcorn JH. Selective serotonin reuptake inhibitor treatment of major depressive disorder in children and adolescents. *Curr Psychiatry Rep*. 2004 Apr;6(2):85-7. PMID: 15038909. Exclusion Code: X9.
512. Newman TB. A black-box warning for antidepressants in children? *N Engl J Med*. 2004 Oct 14;351(16):1595-8. doi: 10.1056/NEJMp048279. PMID: 15483275. Exclusion Code: X6.
513. Neznanov NG, Bortsov AV. [A new quality of the therapy of anxiety and depression--escitalopram]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2005;105(2):79-84. PMID: 15792148. Exclusion Code: X11.
514. Niederhofer H, von Klitzing K. Bright light treatment as add-on therapy for depression in 28 adolescents: a randomized trial. *Primary Care Companion for CNS Disorders*. 2011;13(6):9p-p. PMID: 108174096. Language: English. Entry Date: 20120518. Revision Date: 20150712. Publication Type: Journal Article. Exclusion Code: X5.
515. Niederhofer H, von Klitzing K. Bright light treatment as mono-therapy of non-seasonal depression for 28 adolescents. *Int J Psychiatry Clin Pract*. 2012 Sep;16(3):233-7. doi: 10.3109/13651501.2011.625123. PMID: 22809107. Exclusion Code: X1.
516. Nilsson M, Joliat M, Miner C, et al. Safety of subchronic treatment with fluoxetine for major depressive disorder in children and adolescents. *J Child Adolesc Psychopharmacol*. 2004;14(3):412-7. doi: 10.1089/cap.2004.14.412. PMID: CN-00503097. Exclusion Code: X9.
517. Nissen G. [Psychotropic drugs for children]. *MMW Munch Med Wochenschr*. 1981 Feb 13;123(7):245-6. PMID: 6780896. Exclusion Code: X11.
518. Nixon MK, Milin R, Simeon JG, et al. Sertraline effects in adolescent major depression and dysthymia: a six-month open trial. *J Child Adolesc Psychopharmacol*. 2001 Summer;11(2):131-42. doi: 10.1089/104454601750284036. PMID: 11436952. Exclusion Code: X9.
519. Nobile M, Bellotti B, Marino C, et al. An open trial of paroxetine in the treatment of children and adolescents diagnosed with dysthymia. *J Child Adolesc Psychopharmacol*. 2000 Summer;10(2):103-9. doi: 10.1089/cap.2000.10.103. PMID: 10933120. Exclusion Code: X9.
520. Nobile M, Cataldo GM, Marino C, et al. Diagnosis and treatment of dysthymia in children and adolescents. *CNS Drugs*. 2003;17(13):927-46. doi: 10.2165/00023210-200317130-00001. PMID: 2003-10756-001. Exclusion Code: X6.
521. Normann N, Morina N. The efficacy of metacognitive therapy: a systematic review and meta-analysis. *Front Psychol*. 2018;9:2211. doi: 10.3389/fpsyg.2018.02211. PMID: 30487770. Exclusion Code: X9.
522. Oberste M, Grossheinrich N, Wunram HL, et al. Effects of a 6-week, whole-body vibration strength-training on depression symptoms, endocrinological and neurobiological parameters in adolescent inpatients experiencing a major depressive episode (the "Balancing Vibrations Study"): study protocol for a randomized placebo-controlled trial. *Trials*. 2018 Jul 3;19(1):347. doi: 10.1186/s13063-018-2747-8. PMID: 29970142. Exclusion Code: X7.
523. O'Brien F, Olden N, Migone M, et al. Group cognitive behavioural therapy for children with anxiety disorder - An evaluation of the 'Friends for Youth' programme. *Ir J Psychol Med*. 2007;24(1):5-12. PMID: CN-00642156. Exclusion Code: X1.

524. Offidani E, Fava GA, Tomba E, et al. Excessive mood elevation and behavioral activation with antidepressant treatment of juvenile depressive and anxiety disorders: a systematic review. *Psychother Psychosom*. 2013;82(3):132-41. doi: 10.1159/000345316. PMID: 23548764. Exclusion Code: X9.
525. O'Kearney R, Gibson M, Christensen H, et al. Effects of a cognitive-behavioural internet program on depression, vulnerability to depression and stigma in adolescent males: a school-based controlled trial. *Cogn Behav Ther*. 2006;35(1):43-54. doi: 10.1080/16506070500303456. PMID: 16500776. Exclusion Code: X1.
526. O'Kearney R, Kang K, Christensen H, et al. A controlled trial of a school-based Internet program for reducing depressive symptoms in adolescent girls. *Depress Anxiety*. 2009;26(1):65-72. doi: 10.1002/da.20507. PMID: 18828141. Exclusion Code: X9.
527. O'Kearney R, Kang K, Gibson M, et al. A CBT internet program for depression in adolescents (MoodGYM): effects on depressive symptoms, attributional style, self-esteem and beliefs about depression. In: Einstein DA, Einstein DA, eds. *Innovations and advances in cognitive behaviour therapy*. Bowen Hills, QLD, Australia: Australian Academic Press; 2007:197-204. Exclusion Code: X6.
528. O'Leary-Barrett M, Topper L, Al-Khudhairy N, et al. Two-year impact of personality-targeted, teacher-delivered interventions on youth internalizing and externalizing problems: a cluster-randomized trial. *J Am Acad Child Adolesc Psychiatry*. 2013 Sep;52(9):911-20. doi: 10.1016/j.jaac.2013.05.020. PMID: 23972693. Exclusion Code: X1.
529. Oleichik IV, Artiouch VV. The treatment of cognitive symptoms of adolescent endogenous depressive disorders. 11th European College of Neuropsychopharmacology Congress; 1998 Paris, France. 10538: p. P1.085. Exclusion Code: X1.
530. O'Shea G, Spence SH, Donovan CL. Group versus individual interpersonal psychotherapy for depressed adolescents. *Behav Cogn Psychother*. 2015 Jan;43(1):1-19. doi: 10.1017/s1352465814000216. PMID: 25600515. Exclusion Code: X1.
531. O'Toole MS, Arendt MB, Pedersen CM. Testing an app-assisted treatment for suicide prevention in a randomized controlled trial: effects on suicide risk and depression. *Behav Ther*. 2019 Mar;50(2):421-9. doi: 10.1016/j.beth.2018.07.007. PMID: 30824256. Exclusion Code: X1.
532. Oud M, de Winter L, Vermeulen-Smit E, et al. Effectiveness of CBT for children and adolescents with depression: a systematic review and meta-regression analysis. *Eur Psychiatry*. 2019 Apr;57:33-45. doi: 10.1016/j.eurpsy.2018.12.008. PMID: 30658278. Exclusion Code: X9.
533. Palermo TM, Law EF, Fales J, et al. Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: a randomized controlled multicenter trial. *Pain*. 2016 Jan;157(1):174-85. doi: 10.1097/j.pain.0000000000000348. PMID: 26335910. Exclusion Code: X1.
534. Palermo TM, Wilson AC, Peters M, et al. Randomized controlled trial of an Internet-delivered family cognitive-behavioral therapy intervention for children and adolescents with chronic pain. *Pain*. 2009 Nov;146(1-2):205-13. doi: 10.1016/j.pain.2009.07.034. PMID: 19695776. Exclusion Code: X1.
535. Park EJ, Shin MS, Jung KM, et al. The efficacy of a short-term group program for treating depressive disorder in female adolescents: a comparison of the cognitive-behavioral and psychoeducation programs: a preliminary study. *J Korean Acad Child Adolesc Psychiatr*. 2009;20(1):29-38. PMID: CN-01046210. Exclusion Code: X11.
536. Parker AG, Hetrick SE, Jorm AF, et al. The effectiveness of simple psychological and physical activity interventions for high prevalence mental health problems in young people: a factorial randomised controlled trial. *J Affect Disord*. 2016 May 15;196:200-9. doi: 10.1016/j.jad.2016.02.043. PMID: 26926659. Exclusion Code: X1.

537. Parraga J. Psychological treatments in childhood depression: cognitive therapy, skinner therapy and mixed therapy. A comparative study. *Revista de neuropsiquiatria infantil*. 1984;2(3):107-35. PMID: CN-00711162. Exclusion Code: X11.
538. Pataki CS, Carlson GA, Kelly KL, et al. Side effects of methylphenidate and desipramine alone and in combination in children. *J Am Acad Child Adolesc Psychiatry*. 1993;32(5):1065-72. doi: 10.1097/00004583-199309000-00028. PMID: CN-00096215. Exclusion Code: X7.
539. Pathak S, Kratochvil CJ, Rogers GM, et al. Comparative efficacy of cognitive behavioral therapy, fluoxetine, and their combination in depressed adolescents: initial lessons from the Treatment for Adolescents with Depression Study. *Curr Psychiatry Rep*. 2005;7(6):429-34. PMID: CN-00595893. Exclusion Code: X6.
540. Patton GC, Bond L, Carlin JB, et al. Promoting social inclusion in schools: a group-randomized trial of effects on student health risk behavior and well-being. *Am J Public Health*. 2006 Sep;96(9):1582-7. doi: 10.2105/ajph.2004.047399. PMID: 16873760. Exclusion Code: X1.
541. Pearlstein TB, Stone AB, Lund SA, et al. Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. *J Clin Psychopharmacol*. 1997 Aug;17(4):261-6. PMID: 9241004. Exclusion Code: X1.
542. Peters AT, Jacobs RH, Feldhaus C, et al. Trajectories of functioning into emerging adulthood following treatment for adolescent depression. *J Adolesc Health*. 2016 Mar;58(3):253-9. doi: 10.1016/j.jadohealth.2015.09.022. PMID: 26576820. Exclusion Code: X9.
543. Petti TA, Conners CK. Changes in behavioral ratings of depressed children treated with imipramine. *J Am Acad Child Psychiatry*. 1983 Jul;22(4):355-60. PMID: 6348130. Exclusion Code: X7.
544. Petti TA, Law W. Imipramine treatment of depressed children: a double-blind pilot study. *J Clin Psychopharmacol*. 1982;2(2):107-10. PMID: 7042769. Exclusion Code: X7.
545. Phillips G, Renton A, Moore DG, et al. The Well London program--a cluster randomized trial of community engagement for improving health behaviors and mental wellbeing: baseline survey results. *Trials*. 2012 Jul 6;13:105. doi: 10.1186/1745-6215-13-105. PMID: 22769971. Exclusion Code: X1.
546. Phipps MG, Zlotnick C, Raker CA, et al. Prenatal intervention to prevent postpartum depression in adolescent mothers. *Reproductive sciences (Thousand Oaks, Calif.)*. 2011;18(3):282A-. doi: 10.1177/193371912011183s067. PMID: CN-01716887. Exclusion Code: X1.
547. Pierson K, Addington D, Addington J, et al. Serum monitoring of antipsychotic drug levels during concomitant administration of sertraline and antipsychotic medication. *Can J Psychiatry*. 2006 Oct;51(11):715-8. doi: 10.1177/070674370605101109. PMID: 17121171. Exclusion Code: X1.
548. Porter S, McConnell T, McLaughlin K, et al. Music therapy for children and adolescents with behavioural and emotional problems: a randomised controlled trial. *J Child Psychol Psychiatry*. 2017 May;58(5):586-94. doi: 10.1111/jcpp.12656. PMID: 27786359. Exclusion Code: X1.
549. Possel P, Horn AB, Groen G, et al. School-based prevention of depressive symptoms in adolescents: a 6-month follow-up. *J Am Acad Child Adolesc Psychiatry*. 2004 Aug;43(8):1003-10. doi: 10.1097/01.chi.0000126975.56955.98. PMID: 15266195. Exclusion Code: X1.
550. Preskorn SH, Weller E, Hughes C, et al. Plasma monitoring of tricyclic antidepressants: defining the therapeutic range for imipramine in depressed children. *Clin Neuropharmacol*. 1986;9(Suppl 4):265-7. PMID: 3552217. Exclusion Code: X7.
551. Preskorn SH, Weller EB, Hughes CW, et al. Relationship of plasma imipramine levels to CNS toxicity in children. *Am J Psychiatry*. 1988 Jul;145(7):897. doi: 10.1176/ajp.145.7.897. PMID: 3381941. Exclusion Code: X6.

552. Preskorn SH, Weller EB, Weller RA, et al. Plasma levels of imipramine and adverse effects in children. *Am J Psychiatry*. 1983 Oct;140(10):1332-5. doi: 10.1176/ajp.140.10.1332. PMID: 6624965. Exclusion Code: X3.
553. Puig-Antich J, Perel JM, Lupatkin W, et al. Imipramine in prepubertal major depressive disorders. *Arch Gen Psychiatry*. 1987 Jan;44(1):81-9. PMID: 3541830. Exclusion Code: X9.
554. Rabe-Jablonska J. Therapeutic effects and tolerability of fluvoxamine treatment in adolescents with dysthymia. *J Child Adolesc Psychopharmacol*. 2000 Spring;10(1):9-18. doi: 10.1089/cap.2000.10.9. PMID: 10755577. Exclusion Code: X1.
555. Randell BP, Eggert LL, Pike KC. Immediate post intervention effects of two brief youth suicide prevention interventions. *Suicide Life Threat Behav*. 2001 Spring;31(1):41-61. PMID: 11326768. Exclusion Code: X1.
556. Ranney ML, Goldstick J, Eisman A, et al. Effects of a brief ED-based alcohol and violence intervention on depressive symptoms. *Gen Hosp Psychiatry*. 2017 May;46:44-8. doi: 10.1016/j.genhosppsych.2017.01.008. PMID: 28622815. Exclusion Code: X1.
557. Reed MK. Social skills training to reduce depression in adolescents. *Adolescence*. 1994 Summer;29(114):293-302. PMID: 8085482. Exclusion Code: X1.
558. Regan J, Hamer G, Wright A, et al. SSRI and suicide in adolescents. *Tenn Med*. 2004 Mar;97(3):121-2. PMID: 15054945. Exclusion Code: X6.
559. Reid SC, Kauer SD, Hearps SJ, et al. A mobile phone application for the assessment and management of youth mental health problems in primary care: a randomised controlled trial. *BMC Fam Pract*. 2011 Nov 29;12:131. doi: 10.1186/1471-2296-12-131. PMID: 22123031. Exclusion Code: X1.
560. Reinblatt SP, DosReis S, Walkup JT, et al. Activation adverse events induced by the selective serotonin reuptake inhibitor fluvoxamine in children and adolescents. *J Child Adolesc Psychopharmacol*. 2009 Apr;19(2):119-26. doi: 10.1089/cap.2008.040. PMID: 19364290. Exclusion Code: X1.
561. Renaud J, Brent DA, Baugher M, et al. Rapid response to psychosocial treatment for adolescent depression: a two-year follow-up. *J Am Acad Child Adolesc Psychiatry*. 1998 Nov;37(11):1184-90. doi: 10.1097/00004583-199811000-00019. PMID: 9808930. Exclusion Code: X9.
562. Rengasamy M, Mansoor BM, Hilton R, et al. The bi-directional relationship between parent-child conflict and treatment outcome in treatment-resistant adolescent depression. *J Am Acad Child Adolesc Psychiatry*. 2013 Apr;52(4):370-7. doi: 10.1016/j.jaac.2013.01.012. PMID: 23582868. Exclusion Code: X9.
563. Reynolds WM, Coats KI. A comparison of cognitive-behavioral therapy and relaxation training for the treatment of depression in adolescents. *J Consult Clin Psychol*. 1986 Oct;54(5):653-60. PMID: 3534032. Exclusion Code: X1.
564. Rey-Sanchez F, Gutierrez-Casares JR. Paroxetine in children with major depressive disorder: an open trial. *J Am Acad Child Adolesc Psychiatry*. 1997 Oct;36(10):1443-7. PMID: 9334558. Exclusion Code: X9.
565. Richardson L, McCauley E, Katon W. Collaborative care for adolescent depression: a pilot study. *Gen Hosp Psychiatry*. 2009 Jan-Feb;31(1):36-45. doi: 10.1016/j.genhosppsych.2008.09.019. PMID: 19134509. Exclusion Code: X1.
566. Richardson LP, Ludman E, McCauley E, et al. Collaborative care for adolescents with depression in primary care: a randomized clinical trial. *JAMA*. 2014;312(8):809-16. doi: 10.1001/jama.2014.9259. PMID: CN-01000139. Exclusion Code: X1.
567. Riggs PD, Lohman M, Davies R, et al. Randomized controlled trial of fluoxetine/placebo and cognitive behavioral treatments in depressed adolescents with substance use disorders. *Proceedings of the 67th Annual Scientific Meeting of the College on Problems of Drug Dependence*; 2005 June 19-23; Orlando, FL. 11504. Exclusion Code: X10.

568. Riggs PD, Mikulich-Gilbertson SK, Davies RD, et al. A randomized controlled trial of fluoxetine and cognitive behavioral therapy in adolescents with major depression, behavior problems, and substance use disorders. *Arch Pediatr Adolesc Med.* 2007 Nov;161(11):1026-34. doi: 10.1001/archpedi.161.11.1026. PMID: 17984403. Exclusion Code: X1.
569. Rintelmann JW, Emslie GJ, Rush AJ, et al. The effects of extended evaluation on depressive symptoms in children and adolescents. *J Affect Disord.* 1996 Nov 25;41(2):149-56. PMID: 8961043. Exclusion Code: X9.
570. Rith-Najarian LR, Mesri B, Park AL, et al. Durability of cognitive behavioral therapy effects for youth and adolescents with anxiety, depression, or traumatic stress: a meta-analysis on long-term follow-ups. *Behav Ther.* 2019 Jan;50(1):225-40. doi: 10.1016/j.beth.2018.05.006. PMID: 30661562. Exclusion Code: X9.
571. Ritschel LA, Ramirez CL, Cooley JL, et al. Behavioral activation for major depression in adolescents: results from a pilot study. *Clinical Psychology: Science and Practice.* 2016;23(1):39-57. Exclusion Code: X3.
572. Roberson K. Dose may matter: higher risk of suicide for young people at certain doses of SSRIs. *Evidence-Based Practice.* 2015;18(1):5-. PMID: 103750268. Language: English. Entry Date: 20150204. Revision Date: 20150710. Publication Type: Journal Article. Exclusion Code: X6.
573. Robinson J, Yuen HP, Gook S, et al. Can receipt of a regular postcard reduce suicide-related behaviour in young help seekers? A randomized controlled trial. *Early Intervention in Psychiatry.* 2012;6(2):145-52. doi: 10.1111/j.1751-7893.2011.00334.x. PMID: 2012-10424-005. Exclusion Code: X1.
574. Rodriguez RP, Mardomingo SM, San SCJ, et al. Paroxetine for treating depression in adolescents. 8th European College of Neuropsychopharmacology Congress; 1995 Sep 30-Oct 4; Venice, Italy. 10324. Exclusion Code: X9.
575. Rohde P, Clarke GN, Lewinsohn PM, et al. Impact of comorbidity on a cognitive-behavioral group treatment for adolescent depression. *J Am Acad Child Adolesc Psychiatry.* 2001 Jul;40(7):795-802. doi: 10.1097/00004583-200107000-00014. PMID: 11437018. Exclusion Code: X9.
576. Rohde P, Jorgensen JS, Seeley JR, et al. Pilot evaluation of the coping course: a cognitive-behavioral intervention to enhance coping skills in incarcerated youth. *J Am Acad Child Adolesc Psychiatry.* 2004 Jun;43(6):669-76. doi: 10.1097/01.chi.0000121068.29744.a5. PMID: 15167083. Exclusion Code: X1.
577. Rohde P, Silva SG, Tonev ST, et al. Achievement and maintenance of sustained response during the Treatment for Adolescents With Depression Study continuation and maintenance therapy. *Arch Gen Psychiatry.* 2008 Apr;65(4):447-55. doi: 10.1001/archpsyc.65.4.447. PMID: 18391133. Exclusion Code: X9.
578. Rohde P, Stice E, Gau JM, et al. Reduced substance use as a secondary benefit of an indicated cognitive-behavioral adolescent depression prevention program. *Psychol Addict Behav.* 2012;26(3):599-608. doi: 10.1037/a0028269. PMID: 2012-11650-001. Exclusion Code: X1.
579. Rohde P, Stice E, Shaw H, et al. Indicated cognitive behavioral group depression prevention compared to bibliotherapy and brochure control: acute effects of an effectiveness trial with adolescents. *J Consult Clin Psychol.* 2014 Feb;82(1):65-74. doi: 10.1037/a0034640. PMID: 24099432. Exclusion Code: X1.
580. Rohde P, Stice E, Shaw H, et al. Effectiveness trial of an indicated cognitive-behavioral group adolescent depression prevention program versus bibliotherapy and brochure control at 1- and 2-year follow-up. *J Consult Clin Psychol.* 2015 Aug;83(4):736-47. doi: 10.1037/ccp0000022. PMID: 25894666. Exclusion Code: X1.

581. Rohde P, Waldron HB, Turner CW, et al. Sequenced versus coordinated treatment for adolescents with comorbid depressive and substance use disorders. *J Consult Clin Psychol*. 2014 Apr;82(2):342-8. doi: 10.1037/a0035808. PMID: 24491069. Exclusion Code: X1.
582. Rootes-Murdy K, Carlucci M, Tibbs M, et al. Non-suicidal self-injury and electroconvulsive therapy: outcomes in adolescent and young adult populations. *J Affect Disord*. 2019;250:94-8. doi: 10.1016/j.jad.2019.02.057. PMID: 2019-20567-015. Exclusion Code: X3.
583. Rossello J, Bernal G, Rivera-Medina C. Individual and group CBT and IPT for Puerto Rican adolescents with depressive symptoms. *Cultur Divers Ethnic Minor Psychol*. 2008 Jul;14(3):234-45. doi: 10.1037/1099-9809.14.3.234. PMID: 18624588. Exclusion Code: X1.
584. Rossello J, Bernal G, Rivera-Medina C. Individual and group CBT and IPT for Puerto Rican adolescents with depressive symptoms. *Journal of Latina/o Psychology*. 2012;1(S):36-51. PMID: CN-00856277. Exclusion Code: X1.
585. Rossouw TI, Fonagy P. Mentalization-based treatment for self-harm in adolescents: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2012 Dec;51(12):1304-13.e3. doi: 10.1016/j.jaac.2012.09.018. PMID: 23200287. Exclusion Code: X4.
586. Rossow T. Self harm in adolescence, is MBT the answer?: an RCT. *Adolesc Psychiatry*. 2012;2(1):102. PMID: CN-01033258. Exclusion Code: X1.
587. Rounsaville BJ, Klerman GL, Weissman MM. Do psychotherapy and pharmacotherapy for depression conflict? Empirical evidence from a clinical trial. *Arch Gen Psychiatry*. 1981 Jan;38(1):24-9. PMID: 7006556. Exclusion Code: X1.
588. Russell JL, Spiller HA, Chounthirath T, et al. Pediatric ingestion of vilazodone compared to other selective serotonin reuptake inhibitor medications. *Clin Toxicol (Phila)*. 2017 Jun;55(5):352-6. doi: 10.1080/15563650.2017.1287375. PMID: 28421837. Exclusion Code: X1.
589. Rutherford BR, Sneed JR, Tandler JM, et al. Deconstructing pediatric depression trials: an analysis of the effects of expectancy and therapeutic contact. *J Am Acad Child Adolesc Psychiatry*. 2011 Aug;50(8):782-95. doi: 10.1016/j.jaac.2011.04.004. PMID: 21784298. Exclusion Code: X9.
590. Ryan N. SSRI's in child and adolescent depression. 39th Annual Meeting of the American College of Neuropsychopharmacology; 2000 Dec 10-14; San Juan, Puerto Rico. 12112. Exclusion Code: X13.
591. Ryan ND, Puig-Antich J, Cooper T, et al. Imipramine in adolescent major depression: plasma level and clinical response. *Acta Psychiatr Scand*. 1986 Mar;73(3):275-88. PMID: 3716845. Exclusion Code: X1.
592. Ryan ND, Puig-Antich J, Cooper TB, et al. Relative safety of single versus divided dose imipramine in adolescent major depression. *J Am Acad Child Adolesc Psychiatry*. 1987 May;26(3):400-6. doi: 10.1097/00004583-198705000-00021. PMID: 3597296. Exclusion Code: X4.
593. Rynn MA, Siqueland L, Rickels K. Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *Am J Psychiatry*. 2001 Dec;158(12):2008-14. doi: 10.1176/appi.ajp.158.12.2008. PMID: 11729017. Exclusion Code: X1.
594. Sakolsky DJ, Perel JM, Emslie GJ, et al. Antidepressant exposure as a predictor of clinical outcomes in the Treatment of Resistant Depression in Adolescents (TORDIA) study. *J Clin Psychopharmacol*. 2011 Feb;31(1):92-7. doi: 10.1097/JCP.0b013e318204b117. PMID: 21192150. Exclusion Code: X3.
595. Salari E, Shahrivar Z, Mahmoudi-Gharaei J, et al. Parent-only group cognitive behavioral intervention for children with anxiety disorders: a control group study. *J Can Acad Child Adolesc Psychiatry*. 2018;27(2):130-6. PMID: CN-01607527. Exclusion Code: X1.

596. Sallee FR, Vrindavanam NS, Deas-Nesmith D, et al. Pulse intravenous clomipramine for depressed adolescents: double-blind, controlled trial. *Am J Psychiatry*. 1997 May;154(5):668-73. doi: 10.1176/ajp.154.5.668. PMID: 9137123. Exclusion Code: X2.
597. Sallee FR, Vrindavanam NS, Deas-Nesmith D, et al. Parenteral clomipramine challenge in depressed adolescents: mood and neuroendocrine response. *Biol Psychiatry*. 1998 Oct 1;44(7):562-7. PMID: 9787880. Exclusion Code: X9.
598. Sanford M, Boyle M, McCleary L, et al. A pilot study of adjunctive family psychoeducation in adolescent major depression: feasibility and treatment effect. *J Am Acad Child Adolesc Psychiatry*. 2006 Apr;45(4):386-495. doi: 10.1097/01.chi.0000198595.68820.10. PMID: 16601642. Exclusion Code: X1.
599. Santisteban DA, Mena MP, Muir J, et al. The efficacy of two adolescent substance abuse treatments and the impact of comorbid depression: results of a small randomized controlled trial. *Psychiatr Rehabil J*. 2015 Mar;38(1):55-64. doi: 10.1037/prj0000106. PMID: 25799306. Exclusion Code: X1.
600. Santomauro D, Sheffield J, Sofronoff K. Depression in adolescents with ASD: a pilot RCT of a group intervention. *J Autism Dev Disord*. 2016 Feb;46(2):572-88. doi: 10.1007/s10803-015-2605-4. PMID: 26404701. Exclusion Code: X1.
601. Santor DA, Kusumakar V. Open trial of interpersonal therapy in adolescents with moderate to severe major depression: effectiveness of novice IPT therapists. *J Am Acad Child Adolesc Psychiatry*. 2001 Feb;40(2):236-40. doi: 10.1097/00004583-200102000-00019. PMID: 11211373. Exclusion Code: X1.
602. Saraf KR, Klein DF, Gittelman-Klein R, et al. Imipramine side effects in children. *Psychopharmacologia*. 1974 Jul 11;37(3):265-74. PMID: 4852352. Exclusion Code: X1.
603. Saranya W, Darawan T, Hunsä S, et al. Randomized controlled trial of computerized cognitive behavioral therapy program for adolescent offenders with depression. *Pacific Rim International Journal of Nursing Research*. 2017;21(1):32-43. PMID: 121819021. Language: English. Entry Date: 20170330. Revision Date: 20170330. Publication Type: Article. Exclusion Code: X8.
604. Saulsberry A, Marko-Holguin M, Blomeke K, et al. Randomized clinical trial of a primary care internet-based intervention to prevent adolescent depression: one-year outcomes. *J Can Acad Child Adolesc Psychiatry*. 2013;22(2):106-17. PMID: CN-00907030. Exclusion Code: X11.
605. Schaik AM. No added value of cognitive behavior therapy in adolescents with depression. *Ned Tijdschr Geneesk*. 2008;152(1):56. PMID: CN-00711634. Exclusion Code: X11.
606. Schleider J, Weisz J. A single-session growth mindset intervention for adolescent anxiety and depression: 9-month outcomes of a randomized trial. *J Child Psychol Psychiatry*. 2018;59(2):160-70. doi: 10.1111/jcpp.12811. PMID: 2017-41876-001. Exclusion Code: X1.
607. Schneeweiss S, Patrick AR, Solomon DH, et al. Comparative safety of antidepressant agents for children and adolescents regarding suicidal acts. *Pediatrics*. 2010 May;125(5):876-88. doi: 10.1542/peds.2009-2317. PMID: 20385637. Exclusion Code: X1.
608. Schroder C, Dorks M, Kollhorst B, et al. Extent and risks of antidepressant off-label use in children and adolescents in Germany between 2004 and 2011. *Pharmacoepidemiol Drug Saf*. 2017 Nov;26(11):1395-402. doi: 10.1002/pds.4289. PMID: 28840629. Exclusion Code: X9.
609. Scott K, Lewis CC, Marti CN. Trajectories of symptom change in the treatment for adolescents with depression study. *J Am Acad Child Adolesc Psychiatry*. 2019 Mar;58(3):319-28. doi: 10.1016/j.jaac.2018.07.908. PMID: 30768414. Exclusion Code: X4.

610. Sethi S. Treating youth depression and anxiety: a randomised controlled trial examining the efficacy of computerised versus face-to-face cognitive behaviour therapy. *Aust Psychol.* 2013;48(4):249-57. doi: 10.1111/ap.12006. PMID: CN-01038553. Exclusion Code: X1.
611. Shain BN, Naylor M, Shipley JE, et al. Imipramine effects on sleep in depressed adolescents: a preliminary report. *Biol Psychiatry.* 1990 Sep 1;28(5):459-62. PMID: 2207223. Exclusion Code: X7.
612. Shamseddeen W, Clarke G, Keller MB, et al. Adjunctive sleep medications and depression outcome in the treatment of serotonin-selective reuptake inhibitor resistant depression in adolescents study. *J Child Adolesc Psychopharmacol.* 2012 Feb;22(1):29-36. doi: 10.1089/cap.2011.0027. PMID: 22251024. Exclusion Code: X3.
613. Shamseddeen W, Clarke G, Wagner KD, et al. Treatment-resistant depressed youth show a higher response rate if treatment ends during summer school break. *J Am Acad Child Adolesc Psychiatry.* 2011 Nov;50(11):1140-8. doi: 10.1016/j.jaac.2011.07.022. PMID: 22024002. Exclusion Code: X3.
614. Shamsie SJ, Barriga C. The hazards of use of monoamine oxidase inhibitors in disturbed adolescents. *Can Med Assoc J.* 1971 Apr 17;104(8):715. PMID: 5550381. Exclusion Code: X6.
615. Silveira R, Jainer AK, Singh R. Paroxetine in the treatment of adolescent major depression. *J Am Acad Child Adolesc Psychiatry.* 2002 Nov;41(11):1270; author reply 1. doi: 10.1097/00004583-200211000-00003. PMID: 12410066. Exclusion Code: X6.
616. Silverstone PH, Bercov M, Suen VY, et al. Initial findings from a novel school-based program, EMPATHY, which may help reduce depression and suicidality in youth. *PLoS One.* 2015;10(5):e0125527. doi: 10.1371/journal.pone.0125527. PMID: 25974146. Exclusion Code: X4.
617. Simeon JG, Dinicola VF, Ferguson HB, et al. Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. *Prog Neuropsychopharmacol Biol Psychiatry.* 1990;14(5):791-5. PMID: 2293257. Exclusion Code: X1.
618. Sims AC. Trial of a sustained release form of amitriptyline in the treatment of depressive illness. *Br J Psychiatry.* 1972 Jan;120(554):65-7. PMID: 4557436. Exclusion Code: X1.
619. Slawson D. Can depression in children and adolescents be treated with fluoxetine? Evidence-Based Practice. 1998;1(2):6-insert 2p. PMID: 106934724. Language: English. Entry Date: 20020628. Revision Date: 20150711. Publication Type: Journal Article. Exclusion Code: X13.
620. Slee N, Garnefski N, van der Leeden R, et al. Cognitive-behavioural intervention for self-harm: randomised controlled trial. *Br J Psychiatry.* 2008 Mar;192(3):202-11. doi: 10.1192/bjp.bp.107.037564. PMID: 18310581. Exclusion Code: X1.
621. Smith P, Scott R, Eshkevari E, et al. Computerised CBT for depressed adolescents: randomised controlled trial. *Behav Res Ther.* 2015 Oct;73:104-10. doi: 10.1016/j.brat.2015.07.009. PMID: 26301756. Exclusion Code: X1.
622. Song L, Yu X, Guo P. Comparative study of mirtazapine and paroxetine in the treatment of depression in childhood. *Chin J Health Psychol.* 2005;13(5):347-8. PMID: CN-00709628. Exclusion Code: X11.
623. Sorensen MJ, Thomsen H. What evidence is there for treating depression in children and adolescents with cognitive therapy? *Ugeskr Laeger.* 2007;169(14-15):1294-9. PMID: CN-01751523. Exclusion Code: X11.
624. Spence SH, Sheffield JK, Donovan CL. Long-term outcome of a school-based, universal approach to prevention of depression in adolescents. *J Consult Clin Psychol.* 2005 Feb;73(1):160-7. doi: 10.1037/0022-006x.73.1.160. PMID: 15709843. Exclusion Code: X1.



625. Spinhoven P, Klein N, Kennis M, et al. The effects of cognitive-behavior therapy for depression on repetitive negative thinking: a meta-analysis. *Behav Res Ther.* 2018 Jul;106:71-85. doi: 10.1016/j.brat.2018.04.002. PMID: 29699700. Exclusion Code: X9.
626. Srivastava P, Mehta M, Sagar R, et al. Computer assisted cognitive behavior therapy for adolescents with depression-a pilot study. *Eur Psychiatry.* 2015;30:427. PMID: CN-01100965. Exclusion Code: X8.
627. Stadterman J, Freed RD, Ostrover R, et al. Randomized control trial of omega-3 fatty acids in adolescents with major depressive disorder. *J Am Acad Child Adolesc Psychiatry.* 2016;55(10 Supplement 1):S168-s9. doi: 10.1016/j.jaac.2016.09.213. PMID: CN-01304606. Exclusion Code: X6.
628. Stallard P, Richardson T, Velleman S, et al. Computerized CBT (Think, Feel, Do) for depression and anxiety in children and adolescents: outcomes and feedback from a pilot randomized controlled trial. *Behav Cogn Psychother.* 2011 May;39(3):273-84. doi: 10.1017/s135246581000086x. PMID: 21272393. Exclusion Code: X1.
629. Stark KD. A comparison of the relative efficacy of self-control therapy and behavior therapy for the reduction of depression in children. *Dissertation abstracts international.* 1985;46(4-b):1348. PMID: CN-00711900. Exclusion Code: X10.
630. Stark KD, Reynolds WM, Kaslow NJ. A comparison of the relative efficacy of self-control therapy and a behavioral problem-solving therapy for depression in children. *J Abnorm Child Psychol.* 1987 Mar;15(1):91-113. PMID: 3571741. Exclusion Code: X5.
631. Stasiak K, Hatcher S, Frampton C, et al. A pilot double blind randomized placebo controlled trial of a prototype computer-based cognitive behavioural therapy program for adolescents with symptoms of depression. *Behav Cogn Psychother.* 2014 Jul;42(4):385-401. doi: 10.1017/s1352465812001087. PMID: 23253641. Exclusion Code: X1.
632. Staton RD, Wilson H, Brumback RA. Cognitive improvement associated with tricyclic antidepressant treatment of childhood major depressive illness. *Percept Mot Skills.* 1981 Aug;53(1):219-34. doi: 10.2466/pms.1981.53.1.219. PMID: 7290870. Exclusion Code: X9.
633. Steel CM, O'Duffy J, Brown SS. Clinical effects and treatment of imipramine and amitriptyline poisoning in children. *Br Med J.* 1967 Sep 9;3(5566):663-7. PMID: 6038346. Exclusion Code: X9.
634. Stein LA, Clair M, Lebeau R, et al. Motivational interviewing to reduce substance-related consequences: effects for incarcerated adolescents with depressed mood. *Drug Alcohol Depend.* 2011 Nov 1;118(2-3):475-8. doi: 10.1016/j.drugalcdep.2011.03.023. PMID: 21531089. Exclusion Code: X1.
635. Stein REK, Zitner LE, Jensen PS. Interventions for adolescent depression in primary care. *Pediatrics.* 2006;118(2):669-82. doi: 10.1542/peds.2005-2086. PMID: CN-01764086. Exclusion Code: X12.
636. Steinberg EB, Sayger TV, Szykula SA. The effects of strategic and behavioral family therapies on child behavior and depression. *Contemporary family therapy: an international journal.* 1997;19(4):537-51. PMID: CN-00712705. Exclusion Code: X1.
637. Stice E, Rohde P, Gau J, et al. Relation of depression to perceived social support: results from a randomized adolescent depression prevention trial. *Behav Res Ther.* 2011 May;49(5):361-6. doi: 10.1016/j.brat.2011.02.009. PMID: 21439551. Exclusion Code: X1.
638. Stice E, Rohde P, Gau JM, et al. Efficacy trial of a brief cognitive-behavioral depression prevention program for high-risk adolescents: effects at 1- and 2-year follow-up. *J Consult Clin Psychol.* 2010 Dec;78(6):856-67. doi: 10.1037/a0020544. PMID: 20873893. Exclusion Code: X1.

639. Stice E, Rohde P, Seeley JR, et al. Brief cognitive-behavioral depression prevention program for high-risk adolescents outperforms two alternative interventions: a randomized efficacy trial. *J Consult Clin Psychol*. 2008 Aug;76(4):595-606. doi: 10.1037/a0012645. PMID: 18665688. Exclusion Code: X1.
640. Stikkelbroek Y, Bodden D. Effectiveness of cognitive behaviours therapy (CBT), in clinically depressed adolescents versus Treatment As Usual (TAU). *European child and adolescent psychiatry*. 2015;24(1 suppl. 1):S119. doi: 10.1007/s00787-015-0714-4. PMID: CN-01098690. Exclusion Code: X6.
641. Straub J, Koelch M, Fegert J, et al. Innovations in practice: MICHI, a brief cognitive-behavioural group therapy for adolescents with depression - a pilot study of feasibility in an inpatient setting...manualised group therapy programme. *Child & Adolescent Mental Health*. 2013;18(4):247-50. doi: 10.1111/j.1475-3588.2012.00678.x. PMID: 104143292. Language: English. Entry Date: 20131022. Revision Date: 20150711. Publication Type: Journal Article. Exclusion Code: X1.
642. Straub J, Sproeber N, Plener PI, et al. A brief cognitive-behavioural group therapy programme for the treatment of depression in adolescent outpatients: a pilot study. *Child and adolescent psychiatry and mental health*. 2014;8(1):9. doi: 10.1186/1753-2000-8-9. PMID: CN-01038822. Exclusion Code: X9.
643. Strawn JR, Adler CM, McNamara RK, et al. Antidepressant tolerability in anxious and depressed youth at high risk for bipolar disorder: a prospective naturalistic treatment study. *Bipolar Disorders*. 2014;16(5):523-30. doi: 10.1111/bdi.12113. PMID: 2014-32258-005. Exclusion Code: X1.
644. Strober M, Rao U, DeAntonio M, et al. Effects of electroconvulsive therapy in adolescents with severe endogenous depression resistant to pharmacotherapy. *Biol Psychiatry*. 1998 Mar 1;43(5):335-8. PMID: 9513748. Exclusion Code: X1.
645. Sun M, Rith-Najarian LR, Williamson TJ, et al. Treatment features associated with youth cognitive behavioral therapy follow-up effects for internalizing disorders: a meta-analysis. *J Clin Child Adolesc Psychol*. 2019;48(sup1):S269-s83. doi: 10.1080/15374416.2018.1443459. PMID: 29677451. Exclusion Code: X9.
646. Swart J, Apsche J. A comparative treatment efficacy study of conventional therapy and mode deactivation therapy (MDT) for adolescents with conduct disorders, mixed personality disorders, and experiences of childhood trauma. *International Journal of Behavioral Consultation & Therapy*. 2014;9(1):23-9. PMID: 103933846. Language: English. Entry Date: 20140423. Revision Date: 20180305. Publication Type: Journal Article. Exclusion Code: X7.
647. Swart J, Apsche J. A comparative study of mode deactivation therapy (MDT) as an effective treatment of adolescents with suicidal and non-suicidal self-injury behaviors. *International Journal of Behavioral Consultation & Therapy*. 2014;9(3):47-52. PMID: 103750891. Exclusion Code: X1.
648. Szigethy E, Kenney E, Carpenter J, et al. Cognitive-behavioral therapy for adolescents with inflammatory bowel disease and subsyndromal depression. *J Am Acad Child Adolesc Psychiatry*. 2007 Oct;46(10):1290-8. doi: 10.1097/chi.0b013e3180f6341f. PMID: 17885570. Exclusion Code: X1.
649. Szigethy E, Youk AO, Gonzalez-Heydrich J, et al. Effect of 2 psychotherapies on depression and disease activity in pediatric Crohn's disease. *Inflamm Bowel Dis*. 2015 Jun;21(6):1321-8. doi: 10.1097/mib.0000000000000358. PMID: 25822010. Exclusion Code: X1.
650. Takagaki K, Okamoto Y, Jinnin R, et al. Enduring effects of a 5-week behavioral activation program for subthreshold depression among late adolescents: an exploratory randomized controlled trial. *Neuropsychiatr Dis Treat*. 2018;14:2633-41. doi: 10.2147/NDT.S172385. PMID: CN-01725843. Exclusion Code: X1.

651. Takagaki K, Okamoto Y, Jinnin R, et al. Behavioral activation for late adolescents with subthreshold depression: a randomized controlled trial. *Eur Child Adolesc Psychiatry*. 2016 Nov;25(11):1171-82. doi: 10.1007/s00787-016-0842-5. PMID: 27003390. Exclusion Code: X1.
652. Tang TC, Jou SH, Ko CH, et al. Randomized study of school-based intensive interpersonal psychotherapy for depressed adolescents with suicidal risk and parasuicide behaviors. *Psychiatry Clin Neurosci*. 2009 Aug;63(4):463-70. doi: 10.1111/j.1440-1819.2009.01991.x. PMID: 19531111. Exclusion Code: X8.
653. Thomas JR, Petry RA, Goldman JR. Comparison of cognitive and behavioral self-control treatments of depression. *Psychol Rep*. 1987;60(3 Pt 1):975-82. PMID: CN-00595027. Exclusion Code: X1.
654. Thompson EA, Eggert LL, Herting JR. Mediating effects of an indicated prevention program for reducing youth depression and suicide risk behaviors. *Suicide Life Threat Behav*. 2000 Fall;30(3):252-71. PMID: 11079638. Exclusion Code: X9.
655. Thompson RD, Craig A, Crawford EA, et al. Longitudinal results of cognitive behavioral treatment for youths with inflammatory bowel disease and depressive symptoms. *J Clin Psychol Med Settings*. 2012 Sep;19(3):329-37. doi: 10.1007/s10880-012-9301-8. PMID: 22699797. Exclusion Code: X1.
656. Thomsen H, Sorensen MJ. Evidence for psychopharmacological treatment of depression in children and adolescents? *Ugeskr Laeger*. 2007;169(14-15):1289-94. PMID: CN-01751522. Exclusion Code: X9.
657. Tolahunase MR, Sagar R, Dada R. 5-HTTLPR and MTHFR 677C>T polymorphisms and response to yoga-based lifestyle intervention in major depressive disorder: a randomized active-controlled trial. *Indian J Psychiatry*. 2018 Oct-Dec;60(4):410-26. doi: 10.4103/psychiatry.IndianJPsychiatry\_398\_17. PMID: 30581206. Exclusion Code: X1.
658. Tompson MC, Sugar CA, Asarnow JR. Family-focused treatment for childhood depressive disorders versus individual supportive treatment: results of a randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2016;55(10 Supplement 1):S335. doi: 10.1016/j.jaac.2016.07.403. PMID: CN-01304707. Exclusion Code: X10.
659. Topooco N, Berg M, Johansson S, et al. Chat- and internet-based cognitive-behavioural therapy in treatment of adolescent depression: randomised controlled trial. *BJPsych Open*. 2018 Jul;4(4):199-207. doi: 10.1192/bjo.2018.18. PMID: 29988969. Exclusion Code: X1.
660. Topooco NW, Andersson G. Digital cognitive-behavioral therapy in the treatment of adolescent depression: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2017;56(10):S299-s300. doi: 10.1016/j.jaac.2017.09.411. PMID: CN-01452302. Exclusion Code: X1.
661. Townsend E, Hawton K, Altman DG, et al. The efficacy of problem-solving treatments after deliberate self-harm: meta-analysis of randomized controlled trials with respect to depression, hopelessness and improvement in problems. *Psychol Med*. 2001;31(6):979-88. doi: 10.1017/S0033291701004238. PMID: CN-01715969. Exclusion Code: X9.
662. Trebatická J, Hradečná Z, Böhmer F, et al. Emulsified omega-3 fatty-acids modulate the symptoms of depressive disorder in children and adolescents: a pilot study. *Child and Adolescent Psychiatry and Mental Health*. 2017;11. doi: 10.1186/s13034-017-0167-2. PMID: 2017-29603-001. Exclusion Code: X1.
663. Tulbure BT, Andersson G, Salagean N, et al. Religious versus conventional internet-based cognitive behavioral therapy for depression. *J Relig Health*. 2018 Oct;57(5):1634-48. doi: 10.1007/s10943-017-0503-0. PMID: 29067598. Exclusion Code: X1.

664. Turner D, Carter T, Sach T, et al. Cost-effectiveness of a preferred intensity exercise programme for young people with depression compared with treatment as usual: an economic evaluation alongside a clinical trial in the UK. *BMJ Open*. 2017 Nov 26;7(11):e016211. doi: 10.1136/bmjopen-2017-016211. PMID: 29180592. Exclusion Code: X1.
665. Turrini G, Purgato M, Acarturk C, et al. Efficacy and acceptability of psychosocial interventions in asylum seekers and refugees: systematic review and meta-analysis. *Epidemiol Psychiatr Sci*. 2019 Feb 11;1-13. doi: 10.1017/s2045796019000027. PMID: 30739625. Exclusion Code: X9.
666. Tutus D, Keller F, Sachser C, et al. Change in parental depressive symptoms in trauma-focused cognitive-behavioral therapy: results from a randomized controlled trial. *J Child Adolesc Psychopharmacol*. 2017 Mar;27(2):200-5. doi: 10.1089/cap.2016.0136. PMID: 28051337. Exclusion Code: X1.
667. Tze-Chun T, Shih-Yin H. Efficacy of school-based interpersonal psychotherapy to adolescents of early detected depressive and suicide ideations: randomized control study. Early intervention in psychiatry (abstracts of the 7th international conference on early psychosis - early psychoses: a lifetime perspective); 2010 29 Nov - 1 Dec; Amsterdam, Netherlands. 12082. Exclusion Code: X1.
668. Uchida M, Spencer AE, Kenworthy T, et al. A pilot study: cardiac parameters in children receiving new-generation antidepressants. *J Clin Psychopharmacol*. 2017 Jun;37(3):359-62. doi: 10.1097/jcp.0000000000000683. PMID: 28301398. Exclusion Code: X1.
669. Umetsu R, Abe J, Ueda N, et al. Association between selective serotonin reuptake inhibitor therapy and suicidality: analysis of U.S. Food and Drug Administration adverse event reporting system data. *Biol Pharm Bull*. 2015;38(11):1689-99. doi: 10.1248/bpb.b15-00243. PMID: 26521821. Exclusion Code: X1.
670. Valuck RJ, Orton HD, Libby AM. Antidepressant discontinuation and risk of suicide attempt: a retrospective, nested case-control study. *J Clin Psychiatry*. 2009;70(8):1069-77. doi: 10.4088/JCP.08m04943. PMID: 2012-02478-001. Exclusion Code: X3.
671. van der Zanden R, Galindo-Garre F, Curie K, et al. Online cognitive-based intervention for depression: exploring possible circularity in mechanisms of change. *Psychol Med*. 2014 Apr;44(6):1159-70. doi: 10.1017/s003329171300175x. PMID: 23866103. Exclusion Code: X1.
672. van der Zanden R, Kramer J, Gerrits R, et al. Effectiveness of an online group course for depression in adolescents and young adults: a randomized trial. *J Med Internet Res*. 2012 Jun 7;14(3):e86. doi: 10.2196/jmir.2033. PMID: 22677437. Exclusion Code: X1.
673. van Harmelen A-L, Gibson JL, St Clair MC, et al. Friendships and family support reduce subsequent depressive symptoms in at-risk adolescents. *PLoS One*. 2016;11(5). PMID: 2016-55993-001. Exclusion Code: X9.
674. Van Voorhees BW. A randomized controlled trial of a primary care internet based depression prevention intervention for adolescents (CATCH-IT): 12-month outcomes. *J Investig Med*. 2010;58(4):654-. doi: 10.231/JIM.0b013e3181d85541. PMID: CN-01760682. Exclusion Code: X1.
675. Van Voorhees BW, Fogel J, Reinecke MA, et al. Randomized clinical trial of an Internet-based depression prevention program for adolescents (Project CATCH-IT) in primary care: 12-week outcomes. *J Dev Behav Pediatr*. 2009 Feb;30(1):23-37. doi: 10.1097/DBP.0b013e3181966c2a. PMID: 19194326. Exclusion Code: X1.
676. Varley CK. Treating depression in children and adolescents: what options now? *CNS Drugs*. 2006;20(1):1-13. doi: 10.2165/00023210-200620010-00001. PMID: 2006-02632-001. Exclusion Code: X6.
677. Venturini F, Sung JC, Nichol MB, et al. Utilization patterns of antidepressant medications in a patient population served by a primary care medical group. *J Manag Care Pharm*. 1999;5(3):243-9. Exclusion Code: X1.

678. Vigerland S, Serlachius E, Thulin U, et al. Long-term outcomes and predictors of internet-delivered cognitive behavioral therapy for childhood anxiety disorders. *Behav Res Ther*. 2017;90:67-75. doi: 10.1016/j.brat.2016.12.008. PMID: 2017-03717-010. Exclusion Code: X1.
679. Vitiello B. Combined fluoxetine with cognitive-behavioral therapy vs. monotherapy in the treatment of adolescents with major depressive disorder. *Directions in psychiatry*. 2007;27(2):73-82. PMID: CN-00711448. Exclusion Code: X6.
680. Vitiello B. Combined cognitive-behavioural therapy and pharmacotherapy for adolescent depression: does it improve outcomes compared with monotherapy? *CNS Drugs*. 2009;23(4):271-80. PMID: 19374457. Exclusion Code: X6.
681. Vitiello B, Brent DA, Greenhill LL, et al. Depressive symptoms and clinical status during the Treatment of Adolescent Suicide Attempters (TASA) Study. *J Am Acad Child Adolesc Psychiatry*. 2009 Oct;48(10):997-1004. doi: 10.1097/CHI.0b013e3181b5db66. PMID: 20854770. Exclusion Code: X9.
682. Vitiello B, Emslie G, Clarke G, et al. Long-term outcome of adolescent depression initially resistant to selective serotonin reuptake inhibitor treatment: a follow-up study of the TORDIA sample. *J Clin Psychiatry*. 2011 Mar;72(3):388-96. doi: 10.4088/JCP.09m05885blu. PMID: 21208583. Exclusion Code: X9.
683. Vitiello B, Ordonez AE. Pharmacological treatment of children and adolescents with depression. *Expert Opin Pharmacother*. 2016 Dec;17(17):2273-9. doi: 10.1080/14656566.2016.1244530. PMID: 27690663. Exclusion Code: X9.
684. Vitiello B, Silva SG, Rohde P, et al. Suicidal events in the Treatment for Adolescents With Depression Study (TADS). *J Clin Psychiatry*. 2009 Apr 21;70(5):741-7. PMID: 19552869. Exclusion Code: X9.
685. Vitiello B, Swedo S. Antidepressant medications in children. *N Engl J Med*. 2004 Apr 8;350(15):1489-91. doi: 10.1056/NEJMp038248. PMID: 15071123. Exclusion Code: X6.
686. von Knorring AL, Olsson GI, Thomsen PH, et al. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol*. 2006 Jun;26(3):311-5. doi: 10.1097/01.jcp.0000219051.40632.d5. PMID: 16702897. Exclusion Code: X1.
687. Vostanis P, Feehan C, Grattan E. Two-year outcome of children treated for depression. *Eur Child Adolesc Psychiatry*. 1998 Mar;7(1):12-8. PMID: 9563808. Exclusion Code: X1.
688. Vostanis P, Feehan C, Grattan E, et al. Treatment for children and adolescents with depression: lessons from a controlled trial. *Clin Child Psychol Psychiatry*. 1996;1(2):199-212. doi: 10.1177/1359104596012003. PMID: 1999-01551-002. Exclusion Code: X1.
689. Vostanis P, Feehan C, Grattan E, et al. A randomised controlled out-patient trial of cognitive-behavioural treatment for children and adolescents with depression: 9-month follow-up. *J Affect Disord*. 1996 Sep 9;40(1-2):105-16. PMID: 8882920. Exclusion Code: X1.
690. Votta E, Manion I. Suicide, high-risk behaviors, and coping style in homeless adolescent males' adjustment. *J Adolesc Health*. 2004;34(3):237-43. doi: 10.1016/j.jadohealth.2003.06.002. PMID: 2004-11342-014. Exclusion Code: X1.
691. Wagner KD. Major depression in children and adolescents. *Psychiatric Annals*. 2003;33(4):266-70. doi: 10.3928/0048-5713-20030401-07. PMID: 2003-00542-004. Exclusion Code: X6.
692. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *JAMA*. 2003 Aug 27;290(8):1033-41. doi: 10.1001/jama.290.8.1033. PMID: 12941675. Exclusion Code: X9.
693. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorders. *JAMA*. 2003;290(8):1033-41. PMID: CN-00463133. Exclusion Code: X12.

694. Wagner KD, Asarnow JR, Vitiello B, et al. Out of the black box: treatment of resistant depression in adolescents and the antidepressant controversy. *J Child Adolesc Psychopharmacol*. 2012 Feb;22(1):5-10. doi: 10.1089/cap.2011.0045. PMID: 22251022. Exclusion Code: X6.
695. Wagner KD, Berard R, Stein MB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. *Arch Gen Psychiatry*. 2004 Nov;61(11):1153-62. doi: 10.1001/archpsyc.61.11.1153. PMID: 15520363. Exclusion Code: X1.
696. Wagner KD, Birmaher B, Carlson G, et al. Safety of paroxetine and imipramine in the treatment of adolescent depression. Annual meeting of new clinical drug evaluation program (NCDEU); 1998 Jun 11; Boca Raton, FL. 12253: p. Abstract No. 69. Exclusion Code: X1.
697. Wagner KD, Fershtman M. Potential mechanism of desipramine-related sudden death in children. *Psychosomatics*. 1993 Jan-Feb;34(1):80-3. doi: 10.1016/s0033-3182(93)71930-1. PMID: 8426895. Exclusion Code: X9.
698. Wagner KD, Robb AS, Findling R, et al. Citalopram is effective in the treatment of major depressive disorder in children and adolescents: results of a placebo-controlled trial. *Int J Neuropsychopharmacol*. 2002;5(Suppl 1):S161. PMID: CN-00394851. Exclusion Code: X10.
699. Wagner KD, Wohlberg C. Efficacy and safety of sertraline for treatment of pediatric major depressive disorder. 155th Annual Meeting of the American Psychiatric Association; 2002 May 18-23; Philadelphia, PA. 12123: p. Nr327. Exclusion Code: X10.
700. Wagner KD, Wohlberg CJ, Yang R. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder. *JAMA*. 2004;291(1):42. PMID: CN-00593222. Exclusion Code: X6.
701. Walkup J. The child/adolescent anxiety multimodal trial. *Eur Child Adolesc Psychiatry*. 2013;22(2 suppl. 1):S165. doi: 10.1007/s00787-013-0423-9. PMID: CN-01006225. Exclusion Code: X1.
702. Walkup J, Labellarte M. Complications of SSRI treatment. *J Child Adolesc Psychopharmacol*. 2001 Spring;11(1):1-4. doi: 10.1089/104454601750143320. PMID: 11322738. Exclusion Code: X6.
703. Wall CA, Croarkin PE, Sim LA, et al. Adjunctive use of repetitive transcranial magnetic stimulation in depressed adolescents: a prospective, open pilot study. *J Clin Psychiatry*. 2011 Sep;72(9):1263-9. doi: 10.4088/JCP.11m07003. PMID: 21951987. Exclusion Code: X9.
704. Walsh E, Harvey K, White I, et al. Prevalence and predictors of parasuicide in chronic psychosis. *Acta Psychiatr Scand*. 1999;100(5):375-82. doi: 10.1111/j.1600-0447.1999.tb10881.x. PMID: 1999-01571-008. Exclusion Code: X1.
705. Warden D, Riggs PD, Min SJ, et al. Major depression and treatment response in adolescents with ADHD and substance use disorder. *Drug Alcohol Depend*. 2012 Jan 1;120(1-3):214-9. doi: 10.1016/j.drugalcdep.2011.08.001. PMID: 21885210. Exclusion Code: X2.
706. Waxmonsky JG, Waschbusch DA, Belin P, et al. A randomized clinical trial of an integrative group therapy for children with severe mood dysregulation. *J Am Acad Child Adolesc Psychiatry*. 2016;55(3):196-207. doi: 10.1016/j.jaac.2015.12.011. PMID: 2016-10213-012. Exclusion Code: X1.
707. Waxmonsky JG, Wymbs FA, Pariseau ME, et al. A novel group therapy for children with ADHD and severe mood dysregulation. *J Atten Disord*. 2013 Aug;17(6):527-41. doi: 10.1177/1087054711433423. PMID: 22373865. Exclusion Code: X1.
708. Webb CA, Stanton CH, Bondy E, et al. Cognitive versus behavioral skills in CBT for depressed adolescents: disaggregating within-patient versus between-patient effects on symptom change. *J Consult Clin Psychol*. 2019;87(5):484-90. doi: 10.1037/ccp0000393  
10.1037/ccp0000393.supp (Supplemental). PMID: 2019-20571-004. Exclusion Code: X9.

709. Webb M, Burns J, Collin P. Providing online support for young people with mental health difficulties: challenges and opportunities explored. *Early Intervention in Psychiatry*. 2008;2(2):108-13. doi: 10.1111/j.1751-7893.2008.00066.x. PMID: 2008-05551-008. Exclusion Code: X6.
710. Wedin GP, Oderda GM, Klein-Schwartz W, et al. Relative toxicity of cyclic antidepressants. *Ann Emerg Med*. 1986 Jul;15(7):797-804. PMID: 3729101. Exclusion Code: X1.
711. Weersing VR, Brent DA, Rozenman MS, et al. Brief behavioral therapy for pediatric anxiety and depression in primary care: a randomized clinical trial. *JAMA Psychiatry*. 2017 Jun 1;74(6):571-8. doi: 10.1001/jamapsychiatry.2017.0429. PMID: 28423145. Exclusion Code: X1.
712. Weersing VR, Weisz JR. Community clinic treatment of depressed youth: benchmarking usual care against CBT clinical trials. *J Consult Clin Psychol*. 2002;70(2):299-310. doi: 10.1037//0022-006X.70.2.299. PMID: CN-00891529. Exclusion Code: X9.
713. Weisz J, Bearman SK, Santucci LC, et al. Initial test of a principle-guided approach to transdiagnostic psychotherapy with children and adolescents. *J Clin Child Adolesc Psychol*. 2017 Jan-Feb;46(1):44-58. doi: 10.1080/15374416.2016.1163708. PMID: 27442352. Exclusion Code: X9.
714. Weisz JR, Chorpita BF, Palinkas LA, et al. Testing standard and modular designs for psychotherapy treating depression, anxiety, and conduct problems in youth: a randomized effectiveness trial. *Arch Gen Psychiatry*. 2012 Mar;69(3):274-82. doi: 10.1001/archgenpsychiatry.2011.147. PMID: 22065252. Exclusion Code: X1.
715. Weisz JR, Kuppens S, Ng MY, et al. Are psychotherapies for young people growing stronger? Tracking trends over time for youth anxiety, depression, attention-deficit/hyperactivity disorder, and conduct problems. *Perspect Psychol Sci*. 2019 Mar;14(2):216-37. doi: 10.1177/1745691618805436. PMID: 30571478. Exclusion Code: X9.
716. Weisz JR, Southam-Gerow MA, Gordis EB, et al. Cognitive-behavioral therapy versus usual clinical care for youth depression: an initial test of transportability to community clinics and clinicians. *J Consult Clin Psychol*. 2009 Jun;77(3):383-96. doi: 10.1037/a0013877. PMID: 19485581. Exclusion Code: X1.
717. Weisz JR, Thurber CA, Sweeney L, et al. Brief treatment of mild-to-moderate child depression using primary and secondary control enhancement training. *J Consult Clin Psychol*. 1997 Aug;65(4):703-7. PMID: 9256573. Exclusion Code: X1.
718. Weisz JR, Ugueto AM, Herren J, et al. When the torch is passed, does the flame still burn? Testing a "train the supervisor" model for the Child STEPs treatment program. *J Consult Clin Psychol*. 2018;86(9):726-37. doi: 10.1037/ccp0000331. PMID: CN-01646454. Exclusion Code: X1.
719. Weitkamp K, Daniels JK, Hofmann H, et al. Psychoanalytic psychotherapy for children and adolescents with severe depressive psychopathology: preliminary results of an effectiveness trial. *Psychotherapy (Chic)*. 2014 Mar;51(1):138-47. doi: 10.1037/a0034178. PMID: 24377409. Exclusion Code: X9.
720. Wells KB, Tang L, Carlson GA, et al. Treatment of youth depression in primary care under usual practice conditions: observational findings from Youth Partners in Care. *J Child Adolesc Psychopharmacol*. 2012 Feb;22(1):80-90. doi: 10.1089/cap.2011.0074. PMID: 22251025. Exclusion Code: X1.
721. Wells KC, Albano AM. Parent involvement in CBT treatment of adolescent depression: experiences in the Treatment for Adolescents with Depression Study (TADS). *Cogn Behav Pract*. 2005;12(2):209-20. PMID: CN-00596200. Exclusion Code: X6.
722. Weniger J, Distelberg B, Vaswani D. Depression and anger as risk factors for suicide with inpatient adolescents. *Suicidology Online*. 2017;8(2):1-10. PMID: 129505018. Language: English. Entry Date: 20180517. Revision Date: 20180517. Publication Type: Article. Exclusion Code: X1.

723. Werry JS. The safety of desipramine. *J Am Acad Child Adolesc Psychiatry*. 1994 May;33(4):588-91. doi: 10.1097/00004583-199405000-00018. PMID: 8005913. Exclusion Code: X6.
724. Wheeler BW, Gunnell D, Metcalfe C, et al. The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study. *Br Med J*. 2008;336(7643):542-. doi: 10.1136/bmj.39462.375613.BE. PMID: 2008-03268-002. Exclusion Code: X9.
725. White CR, English D, Thompson R, et al. Youth self-report of emotional maltreatment: concordance with official reports and relation to outcomes. *Child Youth Serv Rev*. 2016;62:111-21. doi: 10.1016/j.chilgyouth.2016.02.004. PMID: 2016-10146-016. Exclusion Code: X1.
726. White N, Litovitz T, Clancy C. Suicidal antidepressant overdoses: a comparative analysis by antidepressant type. *J Med Toxicol*. 2008 Dec;4(4):238-50. PMID: 19031375. Exclusion Code: X1.
727. Whittaker R, Merry SN, Stasiak K, et al. Depression prevention by mobile phone: texting for the future? *Neuropsychiatrie de l'enfance ET de l'adolescence*. 2012;60(5 suppl. 1):S61. doi: 10.1016/j.neurenf.2012.05.553. PMID: CN-01076368. Exclusion Code: X1.
728. Whittaker R, Merry SN, Stasiak K, et al. MEMO: a multimedia mobile phone programme to prevent depression. *Neuropsychiatr Enfance Adolesc*. 2012;60(5 suppl. 1):S85-s6. doi: 10.1016/j.neurenf.2012.05.349. PMID: CN-01089349. Exclusion Code: X1.
729. Whittington CJ, Kendall T, Fonagy P, et al. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet*. 2004 Apr 24;363(9418):1341-5. doi: 10.1016/s0140-6736(04)16043-1. PMID: 15110490. Exclusion Code: X6.
730. Wijlaars LP, Nazareth I, Petersen I. Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in The Health Improvement Network (THIN). *PLoS One*. 2012;7(3):e33181. doi: 10.1371/journal.pone.0033181. PMID: 22427983. Exclusion Code: X2.
731. Wilansky-Traynor P, Manassis K, Monga S, et al. Cognitive behavioural therapy for depressed youth: predictors of attendance in a pilot study. *Journal de l'academie Canadienne de Psychiatrie de l'enfant ET de l'adolescent [Journal of the Canadian Academy of Child and Adolescent Psychiatry]*. 2010;19(2):81-7. PMID: CN-00850632. Exclusion Code: X4.
732. Wilens TE, Biederman J, Baldessarini RJ, et al. Electrocardiographic effects of desipramine and 2-hydroxydesipramine in children, adolescents, and adults treated with desipramine. *J Am Acad Child Adolesc Psychiatry*. 1993 Jul;32(4):798-804. doi: 10.1097/00004583-199307000-00014. PMID: 8340301. Exclusion Code: X1.
733. Wilens TE, Biederman J, Kwon A, et al. A systematic chart review of the nature of psychiatric adverse events in children and adolescents treated with selective serotonin reuptake inhibitors. *J Child Adolesc Psychopharmacol*. 2003 Summer;13(2):143-52. doi: 10.1089/104454603322163862. PMID: 12886909. Exclusion Code: X9.
734. Wilens TE, Biederman J, March JS, et al. Absence of cardiovascular adverse effects of sertraline in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1999 May;38(5):573-7. doi: 10.1097/00004583-199905000-00019. PMID: 10230189. Exclusion Code: X1.
735. Wilens TE, Biederman J, Spencer T, et al. A retrospective study of serum levels and electrocardiographic effects of nortriptyline in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1993 Mar;32(2):270-7. doi: 10.1097/00004583-199303000-00006. PMID: 8444754. Exclusion Code: X1.
736. Wilkinson P, Dubicka B, Kelvin R, et al. Treated depression in adolescents: predictors of outcome at 28 weeks. *Br J Psychiatry*. 2009 Apr;194(4):334-41. doi: 10.1192/bjp.bp.108.052381. PMID: 19336785. Exclusion Code: X1.



737. Winterrowd E. Friendship problems and suicidality in Mexican-American and European-American adolescents: a longitudinal analysis. US: ProQuest Information & Learning; 2011. Exclusion Code: X1.
738. Winters NC. Are antidepressants safe for adolescents? *Postgrad Med.* 2005 Sep;118(3):33-4. doi: 10.3810/pgm.2005.09.1784. PMID: 16201306. Exclusion Code: X9.
739. Woggon B, Angst J, Bleuler M, et al. Comparison of a new antidepressive, lofepramine, with imipramine in a double-blind multicentre trial. *Arch Psychiatr Nervenkr* (1970). 1975 Dec 31;221(2):157-65. PMID: 779718. Exclusion Code: X1.
740. Wohlfarth TD, van Zwieten BJ, Lekkerkerker FJ, et al. Antidepressants use in children and adolescents and the risk of suicide. *Eur Neuropsychopharmacol.* 2006 Feb;16(2):79-83. doi: 10.1016/j.euroneuro.2005.10.004. PMID: 16298514. Exclusion Code: X9.
741. Woldu H, Porta G, Goldstein T, et al. Pharmacokinetically and clinician-determined adherence to an antidepressant regimen and clinical outcome in the TORDIA trial. *J Am Acad Child Adolesc Psychiatry.* 2011 May;50(5):490-8. doi: 10.1016/j.jaac.2011.01.018. PMID: 21515198. Exclusion Code: X2.
742. Wong IC, Besag FM, Santosh PJ, et al. Use of selective serotonin reuptake inhibitors in children and adolescents. *Drug Saf.* 2004;27(13):991-1000. PMID: 15471506. Exclusion Code: X6.
743. Wong MM, Brower KJ, Zucker RA. Sleep problems, suicidal ideation, and self-harm behaviors in adolescence. *J Psychiatr Res.* 2011;45(4):505-11. doi: 10.1016/j.jpsychires.2010.09.005. PMID: 2010-20959-001. Exclusion Code: X1.
744. Wood A, Harrington R, Moore A. Controlled trial of a brief cognitive-behavioural intervention in adolescent patients with depressive disorders. *J Child Psychol Psychiatry.* 1996 Sep;37(6):737-46. PMID: 8894955. Exclusion Code: X1.
745. Wood A, Trainor G, Rothwell J, et al. Randomized trial of group therapy for repeated deliberate self-harm in adolescents. *J Am Acad Child Adolesc Psychiatry.* 2001 Nov;40(11):1246-53. doi: 10.1097/00004583-200111000-00003. PMID: 11699797. Exclusion Code: X1.
746. Woodberry KA, Popenoe EJ. Implementing dialectical behavior therapy with adolescents and their families in a community outpatient clinic. *Cogn Behav Pract.* 2008;15(3):277-86. doi: 10.1016/j.cbpra.2007.08.004. PMID: 2009-02886-005. Exclusion Code: X1.
747. Woodruff PWR, Higgins EM, du Vivier AWP, et al. Psychiatric illness in patients referred to a dermatology-psychiatry clinic. *Gen Hosp Psychiatry.* 1997;19(1):29-35. doi: 10.1016/S0163-8343(97)00155-2. PMID: 1997-02791-006. Exclusion Code: X1.
748. Wooltorton E. Paroxetine (Paxil, Seroxat): increased risk of suicide in pediatric patients. *CMAJ.* 2003 Sep 2;169(5):446. PMID: 12952810. Exclusion Code: X6.
749. Wooltorton E. Suicidal ideation among children taking atomoxetine (Strattera). *Can Med Assoc J.* 2005;173(12):1447-. doi: 10.1503/cmaj.051224. PMID: 2005-16108-003. Exclusion Code: X6.
750. Wren FJ, Foy JM, Ibeziako PI. Primary care management of child and adolescent depressive disorders. *Child Adolesc Psychiatr Clin N Am.* 2012;21(2):401-19. doi: 10.1016/j.chc.2012.01.008. PMID: 2012-11600-015. Exclusion Code: X6.
751. Wright B, Tindall L, Littlewood E, et al. Computerised cognitive-behavioural therapy for depression in adolescents: feasibility results and 4-month outcomes of a UK randomised controlled trial. *BMJ Open.* 2017 Jan 27;7(1):e012834. doi: 10.1136/bmjopen-2016-012834. PMID: 28132000. Exclusion Code: X1.
752. Wright D, Haaland W, Ludman E, et al. The costs and cost-effectiveness of collaborative care for adolescents with depression in primary care settings: a randomized clinical trial. *JAMA Pediatr.* 2016;170(11):1048-54. doi: 10.1001/jamapediatrics.2016.1721. PMID: CN-01244291. Exclusion Code: X4.

753. Wu CS, Wang SC, Cheng YC, et al. Association of cerebrovascular events with antidepressant use: a case-crossover study. *Am J Psychiatry*. 2011 May;168(5):511-21. doi: 10.1176/appi.ajp.2010.10071064. PMID: 21406464. Exclusion Code: X1.
754. Wu X, Liu F, Cai H, et al. Cognitive behaviour therapy combined fluoxetine treatment superior to cognitive behaviour therapy alone for school refusal. *International journal of pharmacology*. 2013;9(3):197-203. doi: 10.3923/ijp.2013.197.203. PMID: CN-00918969. Exclusion Code: X8.
755. Wunram HL, Hamacher S, Hellmich M, et al. Whole body vibration added to treatment as usual is effective in adolescents with depression: a partly randomized, three-armed clinical trial in inpatients. *Eur Child Adolesc Psychiatry*. 2017;1-18. doi: 10.1007/s00787-017-1071-2. PMID: CN-01430117. Exclusion Code: X7.
756. Wunram HL, Hamacher S, Hellmich M, et al. Whole body vibration added to treatment as usual is effective in adolescents with depression: a partly randomized, three-armed clinical trial in inpatients. *Eur Child Adolesc Psychiatry*. 2018 May;27(5):645-62. doi: 10.1007/s00787-017-1071-2. PMID: 29119301. Exclusion Code: X7.
757. Xu J, Chahal Z, Kennard BD, et al. Effects of insomnia on remission and relapse in depressed youth. *J Am Acad Child Adolesc Psychiatry*. 2016;55(10 Supplement 1):S239-s40. doi: 10.1016/j.jaac.2016.09.426. PMID: CN-01304694. Exclusion Code: X6.
758. Xu Y, Bai SJ, Lan XH, et al. Randomized controlled trials of serotonin-norepinephrine reuptake inhibitor in treating major depressive disorder in children and adolescents: a meta-analysis of efficacy and acceptability. *Braz J Med Biol Res*. 2016 May 24;49(6). doi: 10.1590/1414-431x20164806. PMID: 27240293. Exclusion Code: X9.
759. Yang L, Zhou X, Zhou C, et al. Efficacy and acceptability of cognitive behavioral therapy for depression in children: a systematic review and meta-analysis. *Acad Pediatr*. 2017 Jan - Feb;17(1):9-16. doi: 10.1016/j.acap.2016.08.002. PMID: 27989281. Exclusion Code: X9.
760. Yang LP, Scott LJ. Escitalopram in the treatment of major depressive disorder in adolescent patients. Profile report. *CNS Drugs*. 2010 Jul;24(7):621-3. doi: 10.2165/11204690-000000000-00000. PMID: 20527998. Exclusion Code: X6.
761. Yang LP, Scott LJ. Escitalopram: in the treatment of major depressive disorder in adolescent patients. *Paediatr Drugs*. 2010 Jun;12(3):155-63. doi: 10.2165/11204340-000000000-00000. PMID: 20481645. Exclusion Code: X6.
762. Yang W, Zhang JX, Ding Z, et al. Attention bias modification treatment for adolescents with major depression: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2016 Mar;55(3):208-18.e2. doi: 10.1016/j.jaac.2015.12.005. PMID: 26903254. Exclusion Code: X8.
763. Ye X, Bapuji SB, Winters SE, et al. Effectiveness of internet-based interventions for children, youth, and young adults with anxiety and/or depression: a systematic review and meta-analysis. *BMC Health Serv Res*. 2014 Jul 18;14:313. doi: 10.1186/1472-6963-14-313. PMID: 25037951. Exclusion Code: X9.
764. Yen C-F, Liu T-L, Ko C-H, et al. Mediating effects of bullying involvement on the relationship of body mass index with social phobia, depression, suicidality, and self-esteem and sex differences in adolescents in Taiwan. *Child Abuse Negl*. 2014;38(3):517-26. doi: 10.1016/j.chiabu.2013.07.015. PMID: 2013-31980-001. Exclusion Code: X2.
765. Young AS, Arnold LE, Wolfson HL, et al. Psychoeducational psychotherapy and Omega-3 supplementation improve co-occurring behavioral problems in youth with depression: results from a pilot RCT. *J Abnorm Child Psychol*. 2017 Jul;45(5):1025-37. doi: 10.1007/s10802-016-0203-3. PMID: 27604240. Exclusion Code: X4.
766. Young JF, Jones JD, Sbrilli MD, et al. Long-term effects from a school-based trial comparing interpersonal psychotherapy-adolescent skills training to group counseling. *J Clin Child Adolesc Psychol*. 2019;48(sup1):S362-s70. doi: 10.1080/15374416.2018.1479965. PMID: 29979882. Exclusion Code: X1.

767. Young JF, Mufson L, Davies M. Impact of comorbid anxiety in an effectiveness study of interpersonal psychotherapy for depressed adolescents. *J Am Acad Child Adolesc Psychiatry*. 2006 Aug;45(8):904-12. doi: 10.1097/01.chi.0000222791.23927.5f. PMID: 16865032. Exclusion Code: X4.
768. Zalsman G, Shoval G, Rotstein L. Pharmacotherapy for adolescent depression. In: Nolen-Hoeksema S, Hilt LM, Nolen-Hoeksema S, Hilt LM, eds. *Handbook of depression in adolescents*. New York, NY, US: Routledge/Taylor & Francis Group; 2009:571-88. Exclusion Code: X6.
769. Zappitelli MC, Bordin IA, Hatch JP, et al. Temperament and character traits in children and adolescents with major depressive disorder: a case-control study. *Compr Psychiatry*. 2013;54(4):346-53. doi: 10.1016/j.comppsy.2012.10.009. PMID: 2014-13519-007. Exclusion Code: X9.
770. Zatzick DF, Grossman DC. Association between traumatic injury and psychiatric disorders and medication prescription to youths aged 10-19. *Psychiatric services (Washington, D.C.)*. 2011;62(3):264-71. doi: 10.1176/appi.ps.62.3.264. PMID: CN-00891801. Exclusion Code: X2.
771. Zemestani M, Davoodi I, Honarmand MM, et al. Comparative effects of group metacognitive therapy versus behavioural activation in moderately depressed students. *Journal of Mental Health*. 2016;25(6):479-85. doi: 10.3109/09638237.2015.1057326. PMID: 120129935. Language: English. Entry Date: 20161218. Revision Date: 20180525. Publication Type: Article. Exclusion Code: X1.
772. Zhabenko O, Austic E, Conroy DA, et al. Substance use as a risk factor for sleep problems among adolescents presenting to the emergency department. *J Addict Med*. 2016;10(5):331-8. doi: 10.1097/ADM.0000000000000243. PMID: 118546692. Language: English. Entry Date: 20161027. Revision Date: 20161027. Publication Type: Article. Exclusion Code: X1.
773. Zhang J, Qin S, Zhou Y, et al. A randomized controlled trial of mindfulness-based Tai Chi Chuan for subthreshold depression adolescents. *Neuropsychiatr Dis Treat*. 2018;14:2313-21. doi: 10.2147/ndt.s173255. PMID: 30237716. Exclusion Code: X1.
774. Zhang Y, Zhou X, Pu J, et al. Antidepressants for depressive disorder in children and adolescents: a database of randomised controlled trials. *BMC Psychiatry*. 2018 May 31;18(1):162. doi: 10.1186/s12888-018-1749-0. PMID: 29855280. Exclusion Code: X9.
775. Zhang Y, Zhou X, Yang L, et al. Comparative efficacy and acceptability of psychotherapies for post-traumatic stress disorder in children and adolescents: study protocol for a systematic review and network meta-analysis. *BMJ Open*. 2018 Mar 12;8(3):e020198. doi: 10.1136/bmjopen-2017-020198. PMID: 29530911. Exclusion Code: X9.
776. Zhou X, Cipriani A, Furukawa TA, et al. Comparative efficacy and tolerability of new-generation antidepressants for major depressive disorder in children and adolescents: protocol of an individual patient data meta-analysis. *BMJ Open*. 2018 Jan 5;8(1):e018357. doi: 10.1136/bmjopen-2017-018357. PMID: 29306886. Exclusion Code: X9.
777. Zhou X, Qin B, Whittington C, et al. Comparative efficacy and tolerability of first-generation and newer-generation antidepressant medications for depressive disorders in children and adolescents: study protocol for a systematic review and network meta-analysis. *BMJ Open*. 2015 Sep 9;5(9):e007768. doi: 10.1136/bmjopen-2015-007768. PMID: 26353868. Exclusion Code: X6.
778. Ziervogel CF. Selective serotonin re-uptake inhibitors for children and adolescents. *Eur Child Adolesc Psychiatry*. 2000;9 Suppl 1:I20-6. PMID: 11140777. Exclusion Code: X6.

779. Zubrick SR, Hafekost J, Johnson SE, et al. The continuity and duration of depression and its relationship to non-suicidal self-harm and suicidal ideation and behavior in adolescents 12–17. *J Affect Disord.* 2017;220:49-56. doi: 10.1016/j.jad.2017.05.050. PMID: 28625-009. Exclusion Code: X9.
780. Zuckerman ML, Vaughan BL, Whitney J, et al. Tolerability of selective serotonin reuptake inhibitors in thirty-nine children under age seven: a retrospective chart review. In: Luby JL, Riddle MA, Luby JL, Riddle MA, eds. *Advances in preschool psychopharmacology*. New York, NY, US: Mary Ann Liebert Publishers; 2009:7-16. Exclusion Code: X9.

## Appendix D. Study Characteristics

Table D-1. KQ 1a: CBT versus pill placebo.....	D-4
Table D-2. KQ 1a: CBT versus wait-list control .....	D-10
Table D-3. KQ 1a: CBT (delivered to adolescent and parent) versus wait-list control.....	D-12
Table D-4. KQ 1a: CBT+TAU versus TAU/UC .....	D-13
Table D-5. KQ 1a: CBT (modified) versus UC .....	D-16
Table D-6. KQ 1a: CBT versus active control.....	D-17
Table D-7. KQ 1a: Relapse prevention CBT+continued antidepressant medication management versus continued medication management.....	D-23
Table D-8. KQ 1a: IPT versus wait-list control.....	D-26
Table D-9. KQ 1a: IPT versus active control (clinical monitoring) .....	D-27
Table D-10. KQ 1a: Family-based IPT versus active control.....	D-28
Table D-11. KQ 1a: Attachment-based family therapy versus wait-list control .....	D-30
Table D-12. KQ 1a: Attachment-based family therapy versus treatment as usual.....	D-31
Table D-13. KQ 1a: Family therapy versus placebo.....	D-33
Table D-14. KQ 1a: Family therapy versus. active control .....	D-34
Table D-15. KQ 1a: PCIT versus active control.....	D-37
Table D-16. KQ 1a: Psychoanalytic therapy versus active control .....	D-38
Table D-17. KQ 1a: Exercise versus active control.....	D-40
Table D-18. KQ 1a: Spirituality versus wait-list .....	D-41
Table D-19. KQ 1a: Omega-3 versus pill placebo.....	D-42
Table D-20. KQ 1b: Subpopulation analysis of CBT versus pill placebo .....	D-45
Table D-21. KQ 1b: Subpopulation analysis of CBT versus active control.....	D-49
Table D-22. KQ 1b: Family therapy versus placebo .....	D-53
Table D-23. KQ 1b: Family therapy versus. active control.....	D-54

Table D-24. KQ 1b: Omega-3 versus pill placebo .....	D-55
Table D-25. KQ 2a: Family therapy versus pill placebo .....	D-56
Table D-26. KQ 2a: SSRIs versus placebo .....	D-57
Table D-27. KQ 2a: Fluoxetine for relapse prevention versus placebo.....	D-79
Table D-28. KQ 2a: SNRIs versus placebo .....	D-82
Table D-29. KQ 2a: TCAs versus placebo .....	D-87
Table D-30. KQ 2a: Benefits of MAOIs versus placebo .....	D-96
Table D-31. KQ 2a: Venlafaxine plus active control versus placebo plus active control .....	D-97
Table D-32. KQ 2b Subpopulation analysis of SSRIs versus placebo .....	D-98
Table D-33. KQ 2b. Subpopulation analysis of fluoxetine for relapse prevention versus placebo .....	D-107
Table D-34. KQ 2b. Subpopulation analysis of TCAs versus placebo.....	D-109
Table D-35. KQ 3a and b. Fluoxetine plus CBT versus placebo.....	D-111
Table D-36. KQ 3a and b: Omega-3 versus other therapies .....	D-119
Table D-37. KQ 5a. CBT versus other psychotherapy .....	D-120
Table D-38. KQ 5a: Omega-3 versus other therapies.....	D-130
Table D-39. KQ 5a. Psychotherapy within-type comparisons of delivery methods or approaches .....	D-131
Table D-40. KQ 5a. Psychotherapy versus pharmacotherapy .....	D-140
Table D-41. KQ 5a. Psychotherapy plus pharmacotherapy versus psychotherapy .....	D-150
Table D-42. KQ 5a. Psychotherapy plus pharmacotherapy versus pharmacotherapy.....	D-163
Table D-43. KQ 5a: Omega-3 versus other therapies .....	D-176
Table D-44. KQ 5a. SSRIs versus SNRIs.....	D-177
Table D-45. KQ 5a. SSRIs versus TCAs.....	D-180
Table D-46. KQ 5a. Pharmacotherapy dose comparisons .....	D-185
Table D-47. KQ 5a. Treatment-resistant depression interventions.....	D-189
Table D-48. KQ 5b. Subpopulation analysis of psychotherapy within-type comparisons of delivery methods or approaches.....	D-195

Table D-49. KQ 5b. Subpopulation analysis of psychotherapy versus pharmacotherapy.....	D-198
Table D-50. KQ 5b. Subpopulation analysis of psychotherapy plus pharmacotherapy versus psychotherapy.....	D-203
Table D-51. KQ 5b. Subpopulation analysis of psychotherapy plus pharmacotherapy versus pharmacotherapy .....	D-207
Table D-52. KQ 5b. Subpopulation analysis of SSRIs versus TCAs .....	D-212
Table D-53. KQ 5b. Subpopulation analysis of pharmacotherapy dose comparisons.....	D-218
Table D-54. KQ 5b. Subpopulation analysis of TRD interventions .....	D-220

**Table D-1. KQ 1a: CBT versus pill placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Index	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Curry, 2006 <sup>4</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Emslie, 2006 <sup>5</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: March, 2004 <sup>3</sup> Companion: Kennard, 2006 <sup>6</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2009 <sup>8</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADs total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31  Oppositional defiant disorder ADHD: 29.03 No ADHD: 10.61	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Vitiello, 2006 <sup>7</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; KQ = Key Question; MDD = major depressive disorder; N = number; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-2. KQ 1a: CBT versus wait-list control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Clarke, 1999 <sup>9</sup>	United States RCT NR	Mix	Current DSM-III- R diagnosis of major psychiatric disorder or dysthymia	IG1: Child CBT (n=45) IG2: Child CBT with separate parent sessions (n=42) CG: Wait-list control (n=36) 8 weeks	Mean age: 16.2 (A) Age range: 14 to 18  Female: 71%  White: NR  Baseline depression HAM-D: Mean (SD) Overall: 14.2 (5.7) IG1: 13.0 (5.3) IG2: 15.1 (6.0) CG: 14.5 (5.9)  BDI: Mean (SD) Overall: 25.8 (9.5) IG1: 26.5 (9.4) IG2: 26.4 (8.7) CG: 24.2 (10.8)  CBCL depression: Mean (SD) IG1: 14.5 (4.0) IG2: 16.1 (5.5) CG: 14.9 (4.9)  Comorbid diagnosis Current anxiety disorder: 23.6% History of nonaffective disorder: 23.6%	Some concerns	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Rosello, 1999 <sup>10</sup>	United States (Puerto Rico) RCT University clinic	Mix	Diagnosis for MDD, dysthymia, or both	IG1: Interpersonal psychotherapy (n=23) IG2: CBT (n=25) CG: Wait list control (n=23) 12 weeks	Mean age: 14.7 (A) Age range: 13 to 18  Female: 54  White: NR  Baseline depression CDI score pretreatment, Mean (SD): IG1: 21.21 (7.53) IG2: 20.12 (6.95) CG: 20.13 (5.99)  Comorbid condition "Double depression" (N) IG1: 21 IG2: 16 CG: 17	High	Not applicable

BDI = Beck Depression Inventory; CBCL-Depression = child behavior checklist - depression; CBT = cognitive behavioral therapy; CG = Control Group; DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; N = number; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias.

**Table D-3. KQ 1a: CBT (delivered to adolescent and parent) versus wait-list control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Clarke, 1999 <sup>9</sup>	United States RCT NR	Mix	Current DSM-III- R diagnosis of major psychiatric disorder or dysthymia	IG1: Child CBT (n=45) IG2: Child CBT with separate parent sessions (n=42) CG: Wait-list control (n=36) 8 weeks	Mean age: 16.2 (A) Age range: 14 to 18  Female: 71%  White: NR  Baseline depression HAM-D: Mean (SD) Overall: 14.2 (5.7) IG1: 13.0 (5.3) IG2: 15.1 (6.0) CG: 14.5 (5.9)  BDI: Mean (SD) Overall: 25.8 (9.5) IG1: 26.5 (9.4) IG2: 26.4 (8.7) CG: 24.2 (10.8)  CBCL depression: Mean (SD) IG1: 14.5 (4.0) IG2: 16.1 (5.5) CG: 14.9 (4.9)  Comorbid diagnosis Current anxiety disorder: 23.6% History of nonaffective disorder: 23.6%	Some concerns	Not applicable

A= adolescent; BDI = Beck Depression Inventory; CBCL-Depression = child behavior checklist - depression; CBT = cognitive behavioral therapy; CG = Control Group; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; n = number; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.



**Table D-4. KQ 1a: CBT+TAU versus TAU/UC**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Companion: Brent, 1998 <sup>13</sup>	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD	IG1: Individual CBT (n=37) IG2: Systemic behavior family therapy (n=35) CG: Nondirective supportive therapy (n=35) 12 to 16 weeks	Mean age: IG: 15.7 IG2: 15.4 CG: 15.7 (A) Age range: 13 to 18  Female: IG1: 76% IG2: 77% CG: 74%  White: IG1: 76% IG2: 87% CG: 86%  Baseline depression BDI, mean (SD) IG1: 24.3 (8.1) IG2: 22.6 (8.2) CG: 25.7 (7.8)  Comorbid diagnosis Dysthymic disorder (%) IG1: 16.2 IG2: 25.7 CG: 25.7  Anxiety disorder (%) IG1: 37.8 IG2: 28.6 CG: 28.6	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
Brent, 1997 <sup>12</sup> Companion: Brent, 1998 <sup>13</sup> (continued)					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
					Disruptive disorder (%)				
					IG1: 16.2				
					IG2: 22.9				
					CG: 22.9				
Clarke, 2002 <sup>11</sup>	United States RCT Clinic	Mix	Current DSM-III diagnoses of MDD and/or dysthymia	IG: Group CBT (Adolescent Coping with Depression Course+usual care) (n=41) CG: Usual care (n=47) 8 weeks	Mean age: IG: 15.2 CG: 15.3 (A) Age range: 13 to 18			Some concerns	Some concerns
					Female: IG: 63% CG: 75%				
					White: IG: 90% CG: 92%				
					Baseline depression CDRS, mean (SD) IG: 49.8 (4.4) CG: TBD				
					HAM-D, mean (SD) IG: 12.0 (5.4) CG: 11.4 (5.0)				
					Comorbid conditions Anxiety without phobia or PTSD IG: 17.1 CG: 27.7				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
Clarke, 2002 <sup>11</sup> (continued)						Oppositional defiant disorder		
						IG: 17.1		
						CG: 19.1		
						ADHD		
						IG: 9.8		
						CG: 19.1		

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS = Children's Depression Rating Scale; CG = control group; DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; TBD = to be determined.

**Table D-5. KQ 1a: CBT (modified) versus UC**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Shirk, 2014 <sup>14</sup>	United States RCT Clinic	Mix	Met diagnostic criteria for a depressive disorder (e.g., MDD, dysthymic disorder, DDNOS)	IG: Modified CBT (n=20) CG: Usual care (n=23) 12 weeks	Mean age: 15.5 (A) Age range: 13 to 17  Female: 84% (calculated)  White: 49%  Baseline depression BDI-II: Mean (SD) IG: 29.85 (10.56) CG: 32.21 (12.99)  Prior traumatic event exposure Physical abuse: 49% Witnessed family violence: 58% Sexual abuse: 67% Verbal/emotional abuse: 47%  Comorbid conditions PTSD: 46.5%	Some concerns	Some concerns

BDI-II = Beck Depression Inventory-II; CBT = cognitive behavioral therapy; DD = depressive disorder; KQ = Key Question; MDD = major depressive disorder; NOS = not otherwise specified; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-6. KQ 1a: CBT versus active control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Brent, 1997 <sup>12</sup> Index	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD	IG1: Individual CBT (n=37) IG2: Systemic behavior family therapy (n=35) CG: Nondirective supportive therapy (n=35) 12 to 16 weeks	Mean age: IG1: 15.7 IG2: 15.4 CG: 15.7 (A) Age range: 13 to 18			High	High
					Female: IG1: 76% IG2: 77% CG: 74%				
					White: IG1: 76%; IG2: 89% CG: 86%				
					Baseline depression BDI, mean (SD) IG1: 24.3 (8.1) IG2: 22.6 (8.2) CG: 25.7 (7.8)				
					Comorbid diagnosis Dysthymic disorder (%) IG1: 16.2 IG2: 25.7 CG: 25.7				
					Anxiety disorder (%) IG1: 37.8 IG2: 28.6 CG: 28.6				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Brent, 1997 <sup>12</sup> Index (continued)					Disruptive disorder (%) IG1: 16.2 IG2: 22.9 CG: 22.9				
Goodyer, 2017 <sup>16</sup> Index	England RCT Clinic	MDD	DSM IV unipolar major depressive disorder	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Mean age: 15.6 (A) Age range: 11 to 17  Female: 75% White: 85%			Some concerns	Some concerns
					Baseline depression SSRI prescribed before trial entry, n/N (%) IG1: 32/125 (21) IG2: 28/155 (18) CG: 29/153 (19)				
					PTSD diagnosis IG1: 12 (7.8%) IG2: 14 (9%) CG: 6 (3.9%)				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Goodyer, 2017 <sup>16</sup> Companion: Goodyer, 2017 <sup>17</sup>	England RCT Clinic	MDD	DSM-IV unipolar MDD	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Mean age: 15.6 (A) Age range: 11 to 17  Female: 75% White: 85%  Baseline depression SSRI prescribed before trial entry, n/N (%) IG1: 32/125 (21) IG2: 28/155 (18) CG: 29/153 (19)  Prior traumatic event exposure MFQ, mean (SD) IG1: 46.2 (10.3) IG2: 45.4 (10.8) CG: 46.2 (10.6)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Goodyer, 2017 <sup>16</sup> Companion: O'Keeffe 2018 <sup>18</sup>	England RCT Clinic	MDD	DSM IV unipolar MDD	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Mean age: 15.6 (A) Age range: 11 to 17			Some concerns	Some concerns
					Female: 75%				
					White: 85%				
					Baseline depression SSRI prescribed before trial entry, n/N (%)				
					IG1: 32/125 (21)				
					IG2: 28/155 (18)				
					CG: 29/153 (19)				
					PTSD diagnosis				
					IG1: 12 (7.8%)				
					IG2: 14 (9%)				
					CG: 6 (3.9%)				



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
Goodyer, 2017 <sup>16</sup> Companion: O'Keeffe, 2019 <sup>19</sup>	England RCT Clinic	MDD	DSM IV unipolar MDD	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases				
					Mean age: 15.6 (A) Age range: 11 to 17			Some concerns	Some concerns
					Female: 75%				
					White: 85%				
					Baseline depression SSRI prescribed before trial entry, n/N (%)				
					IG1: 32/125 (21)				
					IG2: 28/155 (18)				
					CG: 29/153 (19)				
					PTSD diagnosis				
					IG1: 12 (7.8%)				
					IG2: 14 (9%)				
					CG: 6 (3.9%)				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Rohde, 2004 <sup>15</sup> Index	United States RCT Community	MDD	Current MDD	IG: Adolescent Coping with Depression Course (n=45) CG: Life skills/tutoring condition (n=48) 8 weeks	Mean age: IG: 15.1 CG: 15.1 (A) Age range: 13 to 17			Some concerns	Not applicable
					Female: IG: 60% CG: 37.5%				
					White: IG: 80% CG: 81%				
					Baseline depression BDI-II assessment at baseline: mean (SD) IG: 16.6 (12.8) CG: 15.4 (10.6)				
					Comorbid conditions Current dysthymia: 12.9% Current ADHD: 25.8% Current substance abuse or dependence disorder: 72.0% Current anxiety disorder: 33.3%				

ADHD = attention-deficit/hyperactivity disorder; BDI-II = Beck Depression Inventory-II; CBT = cognitive behavioral therapy; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; KQ = Key Question; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n/N = number; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; SSRI = selective serotonin reuptake inhibitors.

**Table D-7. KQ 1a: Relapse prevention CBT+continued antidepressant medication management versus continued medication management**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Kennard, 2008 <sup>20</sup>	Unites States RCT Clinic	MDD	Primary diagnosis of MDD for ≥4 weeks	IG: Relapse prevention CBT+continued antidepressant medication management (n=22) CG: Continued antidepressant medication management (n=24) 6 weeks	Mean age: 14.3 (A) Age range: 11 to 18  Female: 48%  White: 74%  Baseline depression CDRS-R at screening (acute phase): 58.0 (9.1) CDRS-R at 12 weeks (randomization baseline and start of continuation phase): 26.6 (5.2)  Comorbid diagnosis Two-thirds of the sample had a comorbid psychiatric disorder. Mean N (SD) of comorbidities: 0.95 (0.86)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Kennard, 2014 <sup>21</sup> Index	United States RCT Clinic	MDD	Primary diagnosis of MDD for at least ≥4 weeks	IG: Relapse prevention CBT plus continued antidepressant medication management (n=75) CG: Continued antidepressant medication management (n=69) 30 weeks	Mean age: 13.8 (A, C) Age range: 8 to 17  Female: 54%  White: 82%  Baseline depression CDRS-R at screening (acute phase): 58.0 (7.2) CDRS-R at 6 weeks (randomization baseline and start of continuation phase): 30.9 (5.7) CGI-S at screening (acute phase): 5.2 (0.7) CGI-S at 6 weeks (randomization baseline and start of continuation phase): 2.8 (0.7)  Comorbid conditions Behavior disorder: 33.7 Anxiety disorder: 22.2 Dysthymia: 16.7	Some concerns	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Kennard, 2014 <sup>21</sup> Companion: Emslie, 2015 <sup>22</sup>	United States RCT Clinic	MDD	Primary diagnosis of MDD for at least ≥4 weeks	IG: Relapse prevention CBT plus continued antidepressant medication management (n=42) CG: Continued antidepressant medication management (n=38) 78 weeks	Mean age: 13.8 (A,C) Age range: 8 to 17  Female: 54%  White: 82%  Baseline depression CDRS-R at screening (acute phase): 58.0 (7.2) CDRS-R at 6 weeks (randomization baseline and start of continuation phase): 30.9 (5.7) CGI-S at screening (acute phase): 5.2 (0.7) CGI-S at 6 weeks (randomization baseline and start of continuation phase): 2.8 (0.7)  Comorbid conditions Behavior disorder: 33.7 Anxiety disorder: 22.2 Dysthymia: 16.7	Some concerns	Not applicable

CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CGI-S = Clinical Global Impression Scale-Severity Scale; KQ = Key Question; MDD = major depressive disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-8. KQ 1a: IPT versus wait-list control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Rosello, 1999 <sup>10</sup>	United States (Puerto Rico) RCT University clinic	Mix	Diagnosis for MDD, dysthymia, or both	IG1: Interpersonal psychotherapy (n=23) IG2: CBT (n=25) CG: Wait list control (n=23) 12 weeks	Mean age: 14.7 (A) Age range: 13 to 18  Female: 54  White: NR  Baseline depression CDI score pretreatment, Mean (SD): IG1: 21.21 (7.53) IG2: 20.12 (6.95) CG: 20.13 (5.99)  Comorbid condition “Double depression” (N) IG1: 21 IG2: 16 CG: 17	High	Not applicable

CBT = cognitive behavioral therapy; KQ = Key Question; MDD = major depressive disorder; N = number; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-9. KQ 1a: IPT versus active control (clinical monitoring)**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Mufson, 1999 <sup>23</sup>	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD and HRSD score >15	IG: Interpersonal psychotherapy for depressed adolescents (n=24) CG: Clinical monitoring (n=24) 12 weeks	Mean age: 16.2 (A) Age range: 12 to 18  Female: 71%  White: NR  Baseline depression HAM-D: Mean (SD) Overall: 14.2 (5.7) IG1: 13.0 (5.3) IG2: 15.1 (6.0) CG: 14.5 (5.9)  BDI: Mean (SD) Overall: 25.8 (9.5) IG1: 26.5 (9.4) IG2: 26.4 (8.7) CG: 24.2 (10.8)  CBCL depression: Mean (SD) IG1: 14.5 (4.0) IG2: 16.1 (5.5) CG: 14.9 (4.9)  Comorbid diagnosis Current anxiety disorder: 23.6% History of nonaffective disorder: 23.6%	High	High

CBT = cognitive behavioral therapy; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; KQ = Key Question; MDD = major depressive disorder; N = number; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-10. KQ 1a: Family-based IPT versus active control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Dietz, 2015 <sup>24</sup>	United States RCT Clinic	Mix	Diagnosed with a current depressive disorder (MDD, dysthymia, DDNOS)	IG: Family-based Interpersonal psychotherapy (n=29) CG: Child-centered therapy (n=13) 14 sessions	Mean age IG: 10.6 CG: 11.1 (C) Age range: 7 to 12  Female IG: 62% CG: 77%  White IG: 79% CG: 40%  Baseline depression CDRS-R IG: 44.3 (1.4)  Comorbid conditions MDD IG: 19 (65.5) CG: 9 (69.2)  Depressive disorder IG: 10 (34.5%) CG: 4 (30.8%)  Suicidal ideation IG: 21 (72.4%) CG: 11 (84.6)  Nonsuicidal self-Injury IG: 6 (20.7%) CG: 4 (30.8%)	Some concerns	Not applicable



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
Dietz, 2015 <sup>24</sup> (continued)					Baseline Depression Severity			
					Prior Traumatic Event Exposure			
					Diagnosed Comorbid Conditions or Diseases			
					Comorbid ADHD			
					IG: 9 (31.0%)			
					CG:3 (23.1%)			
					Comorbid anxiety disorder			
					15(51.7%)			
					7(53.8%)			

ADHD = attention-deficit/hyperactivity disorder; CG = control group; DDNOS = depressive disorder not otherwise specified; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; N = number; RCT = randomized controlled trial; RoB = risk of bias.

**Table D-11. KQ 1a: Attachment-based family therapy versus wait-list control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Diamond, 2002 <sup>25</sup> Index	United States RCT Clinic	MDD	Primary DSM-III-R diagnosis of MDD	IG: Attachment-based family therapy (n=16) CG: Wait-list control (n=16) 12 weeks	Mean age: 14.9 (A) Age range: 13 to 17  Female: 78%  White: 31%  Baseline depression BDI score, mean (SD) IG: 23.8 (7.4) CG: 28.0 (7.1)  HAM-D at baseline, mean (SD): IG: 20.1 (5.6) CG: 17.1 (7.0)  Prior traumatic experience Unwanted sexual experiences: 19%	High	High

BDI = Beck Depression Inventory; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; N = number; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-12. KQ 1a: Attachment-based family therapy versus treatment as usual**

Patient Characteristics:					RoB Study Quality— Benefits	RoB Study Quality— Harms	
Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention			
					Mean Age		
					% Female		
					% White		
					Baseline Depression Severity		
					Prior Traumatic Event Exposure		
					Diagnosed Comorbid Conditions or Diseases		
Israel, 2013 <sup>26</sup>	Norway RCT University hospital	MDD	Met diagnostic criteria for major depression based on K- SADS-PL	IG: Attachment-based family therapy (n=11) CG: TAU (n=9) 12 weeks	Mean age: 15.6 (A) Age range: 13 to 17  Female: 55%  White: NR  Childhood depression BDI score, mean (SD) IG: 31.9 (9.1) CG: 29.7 (11.2)  CG subgroups: CG-tx: 34.2 (14.2) CG-WL: 26 (7.8)  HAM-D score, mean (SD) IG: 20.6 (4.6) CG: 19.7 (5.5)  CG subgroup: CG-tx: 22.7 (6.3) CG-WL: 17.2 (3.6)  Comorbid conditions Youth self-report scores, M (SD), % in clinical range  Attention problems IG: 68.18 (10.47), 54.5 CG: 66.22 (10.14), 22  Internalizing problems IG: 69.64 (11.38), 81.8 CG: 66.22 (18.48), 88.9	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
Israel, 2013 <sup>26</sup> (continued)						Externalizing problems IG: 64.55 (10.35), 54.5 CG: 62.89 (8.89) 56		

BDI = Beck Depression Inventory; HAM-D = Hamilton Depression Rating Scale; KQ = Key Question; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia; MDD = major depressive disorder; N = number; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; TAU = treatment as usual; tx = treatment; WL = wait-list.

**Table D-13. KQ 1a: Family therapy versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Fristad, 2009 <sup>27</sup>	United States RCT Clinic	Mix	Diagnosis of current MDD, dysthymic disorder, or DD NOS	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	Mean age: 11.6 (A,C) Age range: 7 to 14  Female: 43%  White: 57%  Baseline depression CDRS-R, mean (SD) IG1: 38 (9) IG2: 42 (9) IG3: 44 (12) CG: 44 (13)  PTSD, n (%) 7 (9.7%)  Anxiety disorders, n (%) 54 (75.0)  ADHD, n (%) 41 (56.9)  Disruptive behavior disorder, n (%) 22 (30.6)	Some concerns	Not applicable

ADHD = attention-deficit hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; DD = depressive disorder; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; n/N = number; NOS = not otherwise specified; PEP = psychoeducational psychotherapy; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; risk of bias; SD = standard deviation.

**Table D-14. KQ 1a: Family therapy versus active control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Index	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD	IG1: Individual CBT (n=37) IG2: Systemic behavior family therapy (n=35) CG: Nondirective supportive therapy (n=35) 12 to 16 weeks	Mean age: IG1: 15.7 IG2: 15.4 CG: 15.7 (A) Age range: 13 to 18  Female: IG1: 76% IG2: 77% CG: 74%  White: IG1: 76% IG2: 87% CG: 86%  Baseline depression BDI, mean (SD) IG1: 24.3 (8.1) IG2: 22.6 (8.2) CG: 25.7 (7.8)  Comorbid diagnosis Dysthymic disorder (%) IG1: 16.2 IG2: 25.7 CG: 25.7  Anxiety disorder (%) IG1: 37.8 IG2: 28.6 CG: 28.6	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Index (continued)					Disruptive disorder (%) IG1: 16.2 IG2: 22.9 CG: 22.9		
Poole, 2018 <sup>28</sup> Companion: Poole, 2017 <sup>29</sup>	Australia RCT Clinic	Mix	Diagnosis of current MDD, minor depressive disorder, or dysthymic disorder	IG: BEST MOOD family systems therapy CG: PAST family group therapy	Mean age: 15.2 (A) Age range: 12 to 18  Female: 73%  White: NR  SMFQ depression, mean (SE) IG: 18.8 (1.38) CG: 17.5 (1.35)	Some concerns	Not applicable
Tompson, 2017 <sup>30</sup> Companion: Asarnow <sup>31</sup>	United States RCT Clinic	Mix	Diagnosis of current MDD, dysthymic disorder, or DD NOS	IG: Family-focused treatment for childhood depression (n =67) CG: Individual supportive psychotherapy (n =67) 22 weeks	Mean age: 10.8 (A, C) Age range: 7 to 14  Female: 56%  White: 51%  Baseline depression CDRS-R, mean (SD) IG: 53.07 (10.42) CG: 54.10 (12.31)  CDI-CR, mean (SD) IG: 15.57 (11.11) CG: 15.11 (10.44)  CDI-PR, mean (SD) IG: 26.33 (7.54) CG: 26.78 (7.42)	Some concerns	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Tompson, 2017 <sup>30</sup> Companion: Asarnow <sup>31</sup> (continued)					Anxiety disorders, n (%) IG: 21 (31) CG: 29 (43)  Disruptive behavior disorder, n (%) IG: 24 (36) CG: 32 (48)		

BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CDI-CR = Children's Depression Inventory-Child Report; CDI-PR = Children's Depression Inventory-Parent Report; CDRS-R = Children's Depression Rating Scale-Revised; DD = depressive disorder; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; KQ = Key Question; MDD = major depressive disorder; N = number; NOS = not otherwise specified; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.



**Table D-15. KQ 1a: PCIT versus active control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Luby, 2012 <sup>32</sup>	United States RCT Community pediatricians' offices	MDD	Met diagnostic criteria for MDD	IG: Parent child interaction therapy (n=27) CG: Psycho- education (n=27) 12 weeks	Mean age: IG: 8% 3 yrs 40% 4 yrs 40% 5 yrs 12% 6 yrs (C)  CG: 39% 3 yrs 28% 4 yrs 22% 5 yrs 11% 6 yrs (C)  Age range: 3 to 7  Female: IG: 42% CG: 28%  White: IG: 86% CG: 78%  Baseline depression PAPA Mean (SD) IG: 42.8 (5.8) CG: 39.8 (10.3)  MDD severity sum Mean (SD) Score IG: 11.3 (4.2) CG: 9.0 (4.7)			High	High

KQ = Key Question; MDD = major depressive disorder; N = number; PAPA = Preschool Age Psychiatric Assessment; RCT = randomized controlled trial; RoB = risk of bias; yrs = years.

**Table D-16. KQ 1a: Psychoanalytic therapy versus active control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Goodyer, 2017 <sup>16</sup> Index	England RCT Clinic	MDD	DSM-IV unipolar major depressive disorder	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Mean age: 15.6 (A) Age range: 11 to 17  Female: 75%  White: 85%  Baseline depression SSRI prescribed before trial entry, n/N (%) IG1: 32/125 (21) IG2: 28/155 (18) CG: 29/153 (19)  PTSD diagnosis IG1: 12 (7.8%) IG2: 14 (9%) CG: 6 (3.9%)	Some concerns	Some concerns
Goodyer, 2017 <sup>16</sup> Companion: Goodyer, 2017 <sup>17</sup>	England RCT Clinic	MDD	DSM-IV unipolar MDD	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Mean age: 15.6 (A) Age range: 11 to 17  Female: 75%  White: 85%  Baseline depression SSRI prescribed before trial entry, n/N (%) IG1: 32/125 (21) IG2: 28/155 (18) CG: 29/153 (19)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Goodyer, 2017 <sup>16</sup> Companion: Goodyer, 2017 <sup>17</sup> (continued)					Prior traumatic event exposure MFQ, mean (SD) IG1: 46.2 (10.3) IG2: 45.4 (10.8) CG: 46.2 (10.6)		
Goodyer, 2017 <sup>16</sup> Companion: O'Keeffe 2018 <sup>18</sup>	England RCT Clinic	MDD	DSM-IV unipolar MDD	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Mean age: 15.6 (A) Age range: 11 to 17  Female: 75%  White: 85%  Baseline depression SSRI prescribed before trial entry, n/N (%) IG1: 32/125 (21) IG2: 28/155 (18) CG: 29/153 (19)	Some concerns	Some concerns
Goodyer, 2017 <sup>16</sup> Companion: O'Keeffe 2019 <sup>19</sup>	England RCT Clinic	MDD	DSM-IV unipolar MDD	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Mean age: 15.6 (A) Age range: 11 to 17  Female: 75%  White: 85%  Baseline depression SSRI prescribed before trial entry, n/N (%) IG1: 32/125 (21) IG2: 28/155 (18) CG: 29/153 (19)	Some concerns	Some concerns

CBT = cognitive behavioral therapy; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; KQ = Key Question; MDD = major depressive disorder; n/N = number; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; SSRI = selective serotonin reuptake inhibitors.

**Table D-17. KQ 1a: Exercise versus active control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Hughes, 2013 <sup>33</sup>	United States RCT health research institute	Mix	MDD only: 54% MDD+dysthymia : 19% MDD+anxiety disorder: 4% MDD+ADHD: 27%	IG: Aerobic exercise (n=16) CG: Nonstrenuous exercise group (n=14) 12 weeks	Mean age: 17 (A) Age range: 12 to 17  Female: 42%  White: 58%  Baseline depression CDRS: Mean (95% CI) IG: 50.9 (47.5 to 54.2) CG: 53.6 (49.9 to 57.2) p=0.268  Comorbid conditions MDD+dysthymia: 19% MDD+anxiety disorder: 4% MDD+behavior ADHD: 27%	Some concerns	Some concerns

ADHD = attention-deficit/hyperactivity disorder; CDRS = Children's Depression Rating Scale; CG = control group; CI = confidence interval; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; RCT = randomized controlled trial; RoB = risk of bias.

**Table D-18. KQ 1a: Spirituality versus wait-list**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Rickhi, 2015 <sup>34</sup>	Canada RCT Online	MDD	Met DSM-IV-TR criteria for MDD (mild to moderate severity)	IG: LEAP online non- faith-based spirituality program (n=18) CG: Wait-list (n=13) 8 weeks	Mean age IG: 15.3 CG: 15.2 (A) Age range: 13 to 24  Female IG: 78% CG: 92%  White: NR  Baseline depression CDRS-R, mean (SE) IG: 57.18 (1.87) CG: 61.67 (22.21)	Some concerns	Some concerns

CDRS = Children's Depression Rating Scale; CG = control group; IG = intervention group; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, TR; KQ = Key Question; LEAP = Listen-Empathize-Agree-Partner; MDD = major depressive disorder; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias.

**Table D-19. KQ 1a: Omega-3 versus pill placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Fristad, 2009 <sup>27</sup>	RCT	Mix	Diagnosis of current MDD, dysthymic disorder, or DD NOS	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	Mean age: 11.6 (A,C) Age range: 7 to 14  Female: 43%  White: 57%  Baseline depression CDRS-R, mean (SD) IG1: 38 (9) IG2: 42 (9) IG3: 44 (12) CG: 44 (13)  PTSD, n (%) 7 (9.7%)  Anxiety disorders, n (%) 54 (75.0)  ADHD, n (%) 41 (56.9)  Disruptive behavior disorder, n (%) 22 (30.6)	Low	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Nemets, 2006 <sup>35</sup>	Israel RCT Clinic	MDD	MDD	IG1: Omega-3 fatty acids (n=10) IG2: Placebo (n=10) 16 weeks	<p>Mean age: IG: 10.0 CG: 10.3 (C) Age range: 6 to 12</p> <p>Female: IG: 20% CG: 30%</p> <p>White: NR</p> <p>Baseline depression NR</p> <p>Comorbid conditions ADHD: IG: 20% CG: 30%</p> <p>OCD: IG: 10% CG: 0%</p> <p>Separation anxiety: IG: 10% CG: 10%</p> <p>Dysthymia: IG: 10% CG: 20%</p>	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
Nemets, 2006 <sup>35</sup> (continued)					Chronic tics			
					IG: 10%			
					CG: 0%			
					Panic disorder			
					IG: 0%			
					CG: 10%			

ADHD = attention-deficit/hyperactivity disorder; CG = control group; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; NR = not reported; OCD = obsessive compulsive disorder; RCT = randomized controlled trial; RoB = risk of bias.



**Table D-20. KQ 1b: Subpopulation analysis of CBT versus pill placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Index	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Curry, 2006 <sup>4</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2009 <sup>8</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADS total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
March, 2004 <sup>3</sup>						Oppositional defiant disorder		
Companion:						ADHD: 29.03		
Kratochvil, 2009 <sup>8</sup>						No ADHD: 10.61		
(continued)								

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; KQ = Key Question; MDD = major depressive disorder; N = number; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-21. KQ 1b: Subpopulation analysis of CBT versus active control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Index	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD	IG1: Individual CBT (n=37) IG2: Systemic behavior family therapy (n=35) CG: Nondirective supportive therapy (n=35) 12 to 16 weeks	Mean age: IG1: 15.7 IG2: 15.4 CG: 15.7 (A) Age range: 13 to 18  Female: IG1: 76% IG2: 77% CG: 74%  White: IG1: 76% IG2: 87% CG: 86%  Baseline depression BDI, mean (SD) IG1: 24.3 (8.1) IG2: 22.6 (8.2) CG: 25.7 (7.8)  Comorbid diagnosis: Dysthymic disorder (%) IG1: 16.2 IG2: 25.7 CG: 25.7  Anxiety disorder (%) IG1: 37.8 IG2: 28.6 CG: 28.6	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Index (continued)					Disruptive disorder (%) IG1: 16.2 IG2: 22.9 CG: 22.9		
Brent, 1997 <sup>12</sup> Companion: Barbe, 2004 <sup>36</sup>	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD	IG1: Individual CBT (n=37) IG2: Systemic behavior family therapy (n=35) CG: Nondirective supportive therapy (n=35) 12 to 16 weeks	Mean age: IG1: 15.7 IG2: 15.4 CG: 15.7 (A) Age range: 13 to 18  Female: IG1: 76% IG2: 77% CG: 74%  White: IG1: 76% IG2: 89% CG: 86%  Baseline depression BDI, mean (SD) IG1: 24.3 (8.1) IG2: 22.6 (8.2) CG: 25.7 (7.8)  Comorbid conditions Dysthymic disorder (%) IG1: 16.2 IG2: 25.7 CG: 25.7	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics: Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Companion: Barbe, 2004 <sup>36</sup> (continued)					Anxiety disorder (%) IG1: 37.8 IG2: 28.6 CG: 28.6  Disruptive disorder (%) IG1: 16.2 IG2: 22.9 CG: 22.9		
Rohde, 2004 <sup>15</sup> Index	United States RCT Community	MDD	Current MDD	IG: Adolescent Coping with Depression Course (n=45) CG: Life skills/tutoring condition (n=48) 8 weeks	Mean age: IG: 15.1 CG: 15.1 (A) Age range: 13 to 17  Female: IG: 60% CG: 37.5%  White: IG: 80% CG: 81%  Baseline depression BDI-II assessment at baseline: mean (SD) IG: 16.6 (12.8) CG: 15.4 (10.6)  Comorbid conditions Current dysthymia: 12.9% Current ADHD: 25.8% Current substance abuse or dependence disorder: 72.0% Current anxiety disorder: 33.3%	Some concerns	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Rohde, 2004 <sup>15</sup> Companion: Rohde, 2006 <sup>37</sup>	United States RCT Community	MDD	Current MDD	IG1: Adolescent Coping with Depression course (n=56) CG: Life skills/tutoring condition (n=58) 8 weeks	Mean age: 15.2 (A) Age range: 13 to 17  Female: 48%  White: 71%  Baseline depression NR	Some concerns	Not applicable

ADHD = attention-deficit/hyperactivity disorder; BDI-II = Beck Depression Inventory-II; CG = control group; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.



**Table D-22. KQ 1b: Family therapy versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Fristad, 2009 <sup>27</sup>	United States RCT Clinic	Mix	Diagnosis of current MDD, dysthymic disorder, or DD NOS	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	Mean age: 11.6 (A,C) Age range: 7 to 14  Female: 43%  White: 57%  Baseline depression CDRS-R, mean (SD) IG1: 38 (9) IG2: 42 (9) IG3: 44 (12) CG: 44 (13)  PTSD, n (%) 7 (9.7%)  Anxiety disorders, n (%) 54 (75.0)  ADHD, n (%) 41 (56.9)  Disruptive behavior disorder, n (%) 22 (30.6)	Some concerns	Not applicable

ADHD = attention-deficit hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; DD = depressive disorder; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; n/N = number; NOS = not otherwise specified; PEP = psychoeducational psychotherapy; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; risk of bias; SD = standard deviation.

**Table D-23. KQ 1b: Family therapy versus active control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:	RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
Poole, 2018 <sup>28</sup> Companion: Poole, 2017 <sup>29</sup>	Australia RCT Clinic	Mix	Diagnosis of current MDD, minor depressive disorder, or dysthymic disorder	IG: BEST MOOD family systems therapy CG: PAST family group therapy	Mean age: 15.2 (A) Age range: 12 to 18  Female: 73%  White: NR  SMFQ depression, mean (SE) IG: 18.8 (1.38) CG: 17.5 (1.35)	Some concerns	Not applicable

**Table D-24. KQ 1b: Omega-3 versus pill placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Fristad, 2009 <sup>27</sup>	RCT	Mix	Diagnosis of current MDD, dysthymic disorder, or DD NOS	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	Mean age: 11.6 (A,C) Age range: 7 to 14  Female: 43%  White: 57%  Baseline depression CDRS-R, mean (SD) IG1: 38 (9) IG2: 42 (9) IG3: 44 (12) CG: 44 (13)  PTSD, n (%) 7 (9.7%)  Anxiety disorders, n (%) 54 (75.0)  ADHD, n (%) 41 (56.9)  Disruptive behavior disorder, n (%) 22 (30.6)	Some concerns	Not applicable

**Table D-25. KQ 2a: Family therapy versus pill placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Frsitad 2019 <sup>27</sup>	United States RCT Clinic	Mix	Diagnosis of current MDD, dysthymic disorder, or DD NOS	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	Mean age: 11.6 (A,C) Age range: 7 to 14			Low	Not applicable
						Female: 43%			
						White: 57%			
					Baseline depression CDRS-R, mean (SD)				
					IG1: 38 (9)				
					IG2: 42 (9)				
					IG3: 44 (12)				
					CG: 44 (13)				
					PTSD, n (%)				
					7 (9.7%)				
					Anxiety disorders, n (%)				
					54 (75.0)				
					ADHD, n (%)				
					41 (56.9)				
					Disruptive behavior disorder, n (%)				
					22 (30.6)				

KQ = Key Question; MDD = major depressive disorder; RoB = risk of bias;

**Table D-26. KQ 2a: SSRIs versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Atkinson, 2014 <sup>38</sup>	United States, Finland, France, Germany, Slovakia, Estonia, Russia, Ukraine, and South Africa RCT 65 psychiatric clinical sites	Mix	MDD or other depressive disorders	IG1: Duloxetine (n=117) IG2: Fluoxetine (n=117) CG: Placebo (n=103) 10 weeks	Mean age: IG1: 13.1 IG2: 13.1 CG: 13.3 (A, C) Age range: 11 to 17  Female: IG1: 55% IG2: 52% CG: 50%  White: IG1: 80% IG2: 83% CG: 81%  Baseline depression CDS-R mean (SE) IG1: 59.2 (10.5) IG2: 58.8 (10.6) CG: 50.2 (11.7)  CGI-S IG1: 4.5 (0.6) IG2: 4.5 (0.6) CG: 4.6 (0.7)  Comorbid conditions Dysmenorrhea (females only): 6.8% Seasonal allergy: 6.2% Asthma: 5.9% Anxiety: 2.4% ADD/ADHD: 2.4% Oppositional defiant disorder: 2.4%	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Berard, 2006 <sup>39</sup>	Belgium, Italy, Spain, United Kingdom, Netherlands, Canada, South Africa, United Arab Emirates, Argentina, Mexico RCT Study centers	MDD	MDD	IG: Paroxetine (n=187) CG: Placebo (n=99) 12 weeks	Mean age: IG: 15.5 CG: 15.8 (A) Age range: 13 to 18			High	High
					Female: IG: 67% CG: 66%				
					White: IG: 69% CG: 66%				
					Baseline depression MADRS mean (SE) IG: 25.9 (0.5) CG: 25.9 (0.6)				
					CGI-S mean (SE) IG: 4.2 (0.1) CG: 4.2 (0.1)				
					BDI mean (SE) IG: 23.0 (0.8) CG: 22.4 (1.2)				
					Comorbid conditions Continuing major depressive episode, n (%) IG: 152 (83.5%) CG: 77 (82.8%)				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Berard, 2006 <sup>39</sup> (continued)							Anxiety disorder n (%) IG: 30 (16.5%) CG: 14 (15.1%)  ADHD n (%) IG: 3 (1.6%) CG: 0 (0.0%)		
Durgam, 2018 <sup>40</sup>	United States RCT Study centers	MDD	Diagnosis of MDD for a minimum of 6 weeks (based on DSM-IV-TR criteria and confirmed by K- SADS-PL)	IG1: Vilazodone 15 mg/d (n=175) IG2: Vilazodone 30 mg/d (n=180) CG: Placebo (n=174) 10 weeks	Mean age: IG1: 14.9 IG2: 14.6 CG: 14.9 (A) Age range: 12 to 17  Female: IG1: 59% IG2: 60% CG: 60%  White: IG1: 66% IG2: 67% CG: 64%  Baseline depression CDRS-R total score, mean (SD) IG1: 57.8 (8.7) IG2: 56.8 (8.5) CG: 57.5 (8.6)  CGI-S score, mean (SD) IG1: 4.6 (0.6) IG2: 4.6 (0.6) CG: 4.5 (0.6)			Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Emslie, 1997 <sup>41</sup>	United States RCT Clinic	MDD	DSM-III-R criteria for nonpsychotic MDD, single and recurrent	IG: Fluoxetine 20 mg/d (n=48) CG: Placebo (n=48) 8 weeks	Mean age: IG: 12.2 CG: 12.5 (A, C) Age range: 7 to 17			High	High
					Female: IG: 46% CG: 46%				
					White: IG: 73% CG: 85%				
					Baseline depression CDI/BDI, mean (SD, range) IG: 15.8 (10.6, 0-41) CG: 15.3 (11.9, 0-54)				
					WSAS, mean (SD, range) IG: 20.6 (11.8, 1-45) CG: 20.6 (12.8, 0-47)				
					CDRS-R total score, mean (SD, range) IG: 58.5 (10.5, 42-90) CG: 57.6 (10.4, 42-82)				
					CGAS total score, mean (SD, range) IG: 47.9 (8.3, 25-65) CG: 48.4 (7.8, 35-80)				
					CDRS-R average initial weekly score IG: 54.2 CG: 53.8				



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Emslie, 1997 <sup>41</sup> (continued)							Comorbid conditions Lifetime comorbid diagnoses, N (%) Dysthymia IG: 20 (41.7) CG: 14 (29.2)  Anxiety disorders IG: 32 (66.7) CG: 22 (45.8)  ADHD IG: 16 (33.3) CG: 13 (27.1)		
Emslie, 2002 <sup>42</sup> Index	United States RCT Clinic	MDD	Primary diagnosis of nonpsychotic MDD (single or recurrent) as defined by DSM- IV criteria	IG: Fluoxetine 0-20 mg/day (n=109) CG: Placebo (n=110) 9 weeks	Mean age: IG: 12.7 CG: 12.7 (A, C) Age range: 8 to 17  Female: IG: 50% CG: 49%  White: IG: 88% CG: 76%  Baseline depression BDI score, mean (SD) IG: 23.8 (7.4) CG: 28.0 (7.1)  HAM-D at baseline, mean (SD): IG: 20.1 (5.6) CG: 17.1 (7.0)			High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Emslie, 2006 <sup>43</sup>	United States and Canada RCT Study centers	MDD	DSM-IV diagnostic criteria for MDD	IG: Paroxetine (n=104) CG: Placebo (n=102) 8 weeks	Mean age: 12.0 (A, C) Age range: 7 to 17			Some concerns	Some concerns
					Female: 47%				
					White: 79%				
					Baseline depression CDRS-R Mean (SD) Total IG: 60.7 (9.37) CG: 62.6 (8.96)				
					Comorbid conditions Psychiatric comorbidity: 22.7% Most common: ADHD 15.3%				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie, 2009 <sup>44</sup> Index	United States RCT Study sites	MDD	Met diagnostic criteria for MDD	IG: Escitalopram (n=157) CG: Placebo (n=154) 8 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 59%  White: 76%  Baseline depression Mean duration of depressive episode in months (SD) IG: 15.7 (17.4) CG: 16.5 (15.4)  Mean age at onset (SD) IG: 12.4 (2.6) CG: 12.6 ( 2.5)  Comorbid conditions Recurrent MDD: 28.85% Previous and/or ongoing secondary psychiatric disorders: 14.74%  Top 3 secondary psychiatric disorders: (1) ADD/ADHD, (2) enuresis, (3) generalized anxiety disorder	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie, 2009 <sup>44</sup> Companion: Findling, 2013 <sup>45</sup>	United States RCT Study sites	MDD	Met diagnostic criteria for MDD	IG: Escitalopram (n=83) CG: Placebo (n=82) 16 to 20 weeks followup	Mean age: IG: 14.7 CG: 14.5 (A) Age range: 12 to 17  Female: IG: 59% CG: 59%  White: IG: 78% CG: 73%  Baseline depression Mean duration of depressive episode in months (SD) IG: 15.7 (17.4) CG: 16.5 (15.4)  Mean age at onset (SD) IG: 12.4 (2.6) CG: 12.6 ( 2.5)  Comorbid conditions Recurrent MDD: 28.85% Previous and/or ongoing secondary psychiatric disorders: 14.74%  Top 3 secondary psychiatric disorders: (1) ADD/ADHD, (2) enuresis, (3) generalized anxiety disorder	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Emslie 2014 <sup>46</sup>	United States, Canada, Mexico, and Argentina RCT 60 psychiatric clinical sites	Mix	MDD or other depressive disorders	IG1: Duloxetine 60 mg QD (n=108) IG2: Duloxetine 30 mg QD (n=116) IG3: Fluoxetine 20 mg QD (n=117) CG: Placebo (n=122) 10 weeks	Mean age: IG1: 12.9 IG2: 12.9 IG3: 13.0 CG: 13.1 (A, C) Age range: 11 to 17			High	High
					Female: IG1: 56% IG2: 41% IG3: 52% CG: 57%				
					White: IG1: 53% IG2: 54% IG3: 59% CG: 52%				
					Baseline depression CDS-R mean (SE) IG1: 59.3 (10.9) IG2: 59.8(11.0) IG3: 57.9(10.1) CG: 58.2(9.4)				
					CGI-S IG1: 4.6 (0.7) IG2: 4.6 (0.7) IG3: 4.6 (0.6) CG: 4.5 (0.6)				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Emslie 2014 <sup>46</sup> (continued)									
Findling, 2009 <sup>47</sup> Index	United States RCT Clinic	MDD	MDD or other DDs	IG: Fluoxetine (n=18) CG: Placebo (n=16) 8 weeks	Mean age: 16.5 (A) Age range: 12 to 17 Female: 15%  White: 73%  Baseline depression CDRS-R Mean (SD) IG: 53.0 (2.32) CG: 53.94 (2.46)  Comorbid conditions All had SUD (38.2% alcohol, 88.2% cannabis and 2.9% polysubstance)  ADHD: 32.4% PTSD: 5.9% Conduct disorder: 5.9%			Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
GlaxoSmithKline, 1998 <sup>48</sup>	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18			High	Not applicable
					Female: IG1: 62% IG2: 59% CG: 66%				
					White: IG1: 83% IG2: 87% CG: 81%				
					Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)				
					Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%				
					Anxiety disorder IG1: 19% IG2: 26% CG: 28%				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
GlaxoSmithKline, 1998 <sup>48</sup> (continued)					Externalizing disorder IG1: 25% IG2: 26% CG: 20%				
Keller, 2001 <sup>50</sup> Companion: Le Noury, 2016 <sup>51</sup>	United States and MDD Canada RCT Study centers		Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 6 months	Mean age: IG1: 14.8 IG2: 14.8 CG: 15.0 (A) Age range: 12 to 18			High	Not applicable
					Female: IG1: 65% IG2: 46% CG: 68%				
					White: IG1: 84% IG2: 92% CG: 81% (calculated)				
					Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)				



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Keller, 2001 <sup>50</sup> Index	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18			High	Not applicable
					Female: IG1: 62% IG2: 59% CG: 66%				
					White: IG1: 83% IG2: 87% CG: 81%				
					Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)				
					Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%				
					Anxiety disorder IG1: 19% IG2: 26% CG: 28%				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female		
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
Keller, 2001 <sup>50</sup> Index (continued)						Externalizing disorder IG1: 25% IG2: 26% CG: 20%		
Le Noury, 2015 <sup>49</sup>	United States and Canada RCT Academic psychiatry centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18		High	Not applicable
					Female: IG1: 62% IG2: 59% CG: 66%			
					White: IG1: 83% IG2: 87% CG: 81%			
					Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)			
					Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%			

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Le Noury, 2015 <sup>49</sup> (continued)									
							Anxiety disorder IG1: 19% IG2: 26% CG: 28%		
							Externalizing disorder IG1: 25% IG2: 26% CG: 20%		
March, 2004 <sup>3</sup> Index	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17			Some concerns	Some concerns
						Female: 54%			
						Black: 13% Hispanic: 9%			
						Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)			
						Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7			

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Emslie, 2006 <sup>5</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:	RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
March, 2004 <sup>3</sup> Companion: Kennard, 2006 <sup>6</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Vitiello, 2006 <sup>7</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Wagner, 2004 <sup>52</sup> Index	United States RCT Clinic	MDD	Primary diagnosis of MDD for at least 4 weeks	IG: Citalopram (n=93) CG: Placebo (n=85) 8 weeks	Mean age: IG: 12.2 CG: 12.4 (A, C) Age range: 7 to 17			Some concerns	Some concerns
					Female: IG: 52% CG: 52%				
					White: IG: 71% CG: 71%				
					Baseline depression CDRS mean (SD) IG: 54.5 CG: 56.6				
					Comorbid conditions Secondary ongoing anxiety disorder IG: 6 CG: 10				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Wagner, 2004 <sup>52</sup> Companion: Forest, 2001 <sup>53</sup>	United States RCT Clinic	MDD	Met DSM-IV criteria for MDD	IG: Citalopram (n=93) CG: Placebo (n=85) 8 weeks	Mean age: IG: 12.1 CG: 12.1 (A, C) Age range: 7 to 17			Some concerns	Some concerns
					Female: IG: 53% CG: 54%				
					White: IG: 81% CG: 73%				
					Baseline depression CDRS-R IG: 58.8 (1.2) CG: 57.8 (1.2)				



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Wagner, 2006 <sup>54</sup>	United States RCT NR	MDD	Primary diagnosis of MDD for at least 4 weeks with a CDRS-R score ≥40	IG: Escitalopram (n=132) CG: Placebo (n=136) 8 weeks	Mean age IG: 12.2 CG: 12.4 (A, C) Age range: 6 to 17			Some concerns	Some concerns
					Female: IG: 52% CG: 52%				
					White: IG: 71% CG: 71%				
					Baseline depression CDRS-R IG: 54.5 CG: 56.6				
					Comorbid conditions Secondary ongoing anxiety disorder IG: 6 CG: 10				
Weihs, 2018 <sup>55</sup>	United States, Mexico RCT Hospitals, academic institutions, private clinics, and clinical trial research centers	MDD	Meeting DSM- IV-TR criteria for MDD	IG1: Desvenlafaxine (25, 35, or 50 mg/d) (n=115) IG2: Fluoxetine (20 mg/d) (n=113) CG: Placebo (n=112) 8 weeks	Mean age: Children: 9.4 Adolescent: 14.8 (A, C) Age range: 7 to 17				
					Female: 54% (calculated)				
					White: 65% (calculated)				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Weihs, 2018 <sup>55</sup> (continued)					Baseline depression CDRS-R total score: Mean (SD) 56.5 (8.9)	High	Uncertain
					CGI-S score: Mean (SD) 4.5 (0.6)		
					Comorbid diagnosis ADHD IG1: 12.2% IG2: 13.4% CG: 5.4		
					Nonsuicidal self-injurious behavior IG1: 7.0% IG2: 8.0% CG: 12.5%		
					Insomnia IG1: 7.0% IG2: 6.3% CG: 8.0%		

A, C = adolescent/child; ADD = attention-deficit disorder; ADHD = attention-deficit/hyperactivity disorder; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory-II; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CDS-R = Carroll Depression Scales - Revised; CG = control group; CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, TR; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime version; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NR = not reported; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; SE = standard error; SUD = substance use disorder; WSAS = Work and Social Adjustment Scale.

**Table D-27. KQ 2a: Fluoxetine for relapse prevention versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Emslie, 2009 <sup>44</sup> Companion: Emslie, 2004 <sup>56</sup>	Unites States RCT Clinic	MDD	Primary diagnosis of nonpsychotic MDD (single or recurrent) as defined by DSM- IV criteria	IG: Continued treatment with fluoxetine at current dose (20- 60 mg/day) (n=20) CG: Switch to placebo (n=20) 32 weeks	Mean age: IG: 13.5 CG: 11.7 (A, C) Age range: 8 to 17			High	High
					Female: IG: 45% CG: 55%				
					White: IG: 85% CG: 100%				
					Baseline depression CDRS-R: IG: 21.9 CG: 24.0				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie, 2008 <sup>57</sup> Index	United States RCT Clinic	MDD	Primary diagnosis of MDD for at least 4 weeks	IG1: Fluoxetine continuation (n=50) CG: Placebo (n=52) 12 weeks acute treatment, 6 months of continuation treatment	<p>Mean age: Acute treatment: 11.8 Continuation: 11.5 (A, C) Age range: 7 to 18</p> <p>Female: Acute treatment: 42% Continuation: 36%</p> <p>White: Acute treatment: 75% Continuation: 71%</p> <p>Baseline depression Entered acute treatment (n=168) CDRS-R, mean (SD): 57.6 (7.3) CGI-S moderate, %: 30.4 CGI-S marked, %: 56.5 CGI-S severe, %: 13.1</p> <p>Entered continuation (n=102), mean (SD): CDRS-R: 57.7 (7.6) CGI-S: 4.8 (0.6) CGAS: 51.8 (5.7)</p> <p>Comorbid conditions Entered continuation (n=102): Comorbid anxiety disorder, mean (SD): 26 (25.5) Comorbid behavior disorder, mean (SD): 45 (44.1) Comorbid dysthymia, mean (SD): 34 (33.3)</p>	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:	RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
Emslie, 2008 <sup>57</sup> Companion: Kennard, 2018 <sup>58</sup>	United States RCT Clinic	MDD	Primary diagnosis of MDD for at least 4 weeks	IG1: Fluoxetine continuation (n=50) CG: Placebo (n=52) 12 weeks of acute treatment, 6 months of continuation treatment	Mean age: Acute treatment: 11.8 Continuation: 11.5 (A, C) Age range: 7 to 18  Female: Acute treatment: 42% Continuation: 36%  White: Acute treatment: 75% Continuation: 71%  Baseline depression Entered acute treatment (n=168) CDRS-R, mean (SD): 57.6 (7.3) CGI-S moderate, %: 30.4 CGI-S marked, %: 56.5 CGI-S severe, %: 13.1  Entered continuation (n=102), mean (SD): CDRS-R: 57.7 (7.6) CGI-S: 4.8 (0.6) CGAS: 51.8 (5.7)  Comorbid conditions Entered continuation (n=102): Comorbid anxiety disorder, mean (SD): 26 (25.5) Comorbid behavior disorder, mean (SD): 45 (44.1) Comorbid dysthymia, mean (SD): 34 (33.3)	Some concerns	Some concerns

A, C = adolescent/child; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-28. KQ 2a: SNRIs versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Atkinson, 2018 <sup>59</sup>	United States and Chile RCT NR	MDD	Met DSM-IV-TR criteria for MDD as the primary diagnosis	IG1: Low-dose desvenlafaxine (n=122) IG2: High-dose desvenlafaxine (n=121) CG: Placebo (n=120) 8 weeks	Mean age: IG1: 13.1 IG2: 12.9 CG: 13.2 (A, C) Age range: 7 to 17  Female: 57%  White: IG1: 70% IG2: 64% CG: 71%  Baseline depression IG1: 86 (70.49) IG2: 78 (64.46) CG: 85 (70.83)  Comorbid conditions Psych. condition other than MDD, % IG1: 23.0 IG2: 27.3 CG: 24.2  ADHD, % IG1: 9.8 IG2: 9.9 CG: 7.5	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Atkinson, 2018 <sup>59</sup> (continued)					Self-injurious behavior, % IG1: 4.9 IG2: 9.1 CG: 6.7  Insomnia, % IG1: 7.4 IG2: 5.8 CG: 4.2		
Emslie, 2007 <sup>60</sup>  Study 1 and Study 2 reported in one publication	United States RCT Clinical sites	MDD	Met DSM-IV criteria for MDD, CDRS-R score > 40 with ≤30% decrease between pre- study and baseline, CGI-S score ≥ 4, depressive symptoms for at least 1-month pre-study	IG: venlafaxine ER (112.5 mg, 150 mg, or 22mg based on weight) CG: Placebo	Mean age (SD): IG: 12.2 (2.6) CG: 12.3 (2.6)  Baseline depression CDRS-R mean (SD) IG: 56.4 (9.2) CG: 55.8 (8.4)  CGI-s mean (SD) IG: 4.5 (0.6) CG: 4.5 (0.7)  Female: IG: 44% CG: 47%	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie 2014 <sup>46</sup>	United States, Canada, Mexico, and Argentina RCT 60 psychiatric clinical sites	Mix	MDD or other depressive disorders	IG1: Duloxetine 60 mg QD (n=108) IG2: Duloxetine 30 mg QD (n=116) IG3: Fluoxetine 20 mg QD (n=117) CG: Placebo (n=122) 10 weeks	Mean age: IG1: 12.9 IG2: 12.9 IG3: 13.0 CG: 13.1 (A, C) Age range: 11 to 17  Female: IG1: 56% IG2: 41% IG3: 52% CG: 57%  White: IG1: 53% IG2: 54% IG3: 59% CG: 52%	High	High



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms	
Emslie 2014 <sup>46</sup> (continued)					Baseline depression CDS-R mean (SE) IG1: 59.3 (10.9) IG2: 59.8(11.0) IG3: 57.9(10.1) CG: 58.2(9.4)  CGI-S IG1: 4.6 (0.7) IG2: 4.6 (0.7) IG3: 4.6 (0.6) CG: 4.5 (0.6)  Comorbid conditions Asthma: 8.2% Dysmenorrhea (females only): 5.1% Insomnia: 4.5% Oppositional defiant disorder: 4.1% Generalized anxiety disorder: 2.2%			

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Weihls, 2018 <sup>55</sup>	United States, Mexico RCT Hospitals, academic institutions, private clinics, and clinical trial research centers	MDD	Meeting DSM- IV-TR criteria for MDD	IG1: Desvenlafaxine (25, 35, or 50 mg/d) (n=115) IG2: Fluoxetine (20 mg/d) (n=113) CG: Placebo (n=112) 8 weeks	Mean age: Children: 9.4 Adolescent: 14.8 (A, C) Age range: 7 to 17  Female: 54% (calculated)  White: 65% (calculated)  Baseline depression CDRS-R total score: Mean (SD) 56.5 (8.9)  CGI-S score: Mean (SD) 4.5 (0.6)  Comorbid diagnosis ADHD IG1: 12.2% IG2: 13.4% CG: 5.4  Nonsuicidal self-injurious behavior IG1: 7.0% IG2: 8.0% CG: 12.5%  Insomnia IG1: 7.0% IG2: 6.3% CG: 8.0%	High	Uncertain

A, C = adolescent/child; ADHD = attention-deficit/hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised; CDS-R = Carroll Depression Scales - Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, TR; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; SE = standard error.

**Table D-29. KQ 2a: TCAs versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Geller, 1989 <sup>61</sup>	United States RCT Clinic	MDD	Met research diagnostic criteria and DSM-III criteria for nondelusional MDD	IG: Nortriptyline (n=26) CG: Placebo (n=24) 8 weeks	Mean age: 9.7 (C) Age range: 5 to 12			Some concerns	Not applicable
					Female: 30%				
					White: 90%				
					Baseline depression CDRS Mean (SD) IG: 49.8 (4.4) CG: 49.6 (4.6)				
					Comorbid conditions Separation anxiety: 84.0 Antisocial behavior: 18.0				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:	RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
Geller, 1992 <sup>62</sup>	United States RCT NR	MDD	Research diagnostic criteria for MDD	IG: Nortriptyline (n=26) CG: Placebo (n=24) 8 weeks	Mean age: 9.7 (C) Age range: 6 to 12  Female: 30%  White: 90%  Baseline depression CDRS Mean (SD) IG: 49.9 (4.2) CG: 49.6 (4.6)  KGAS Mean (SD) IG: 37.7 (3.5) CG: 38.2 (3.0)  9-item KSADS Mean (SD) IG: 3.98 (0.42) CG: 3.89 (0.50)  Comorbid conditions RCS endogenous: 96% DSM-III melancholia: 74% Separation anxiety: 84% Antisocial behavior: 18%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
GlaxoSmithKline, 1998 <sup>48</sup>	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18			High	Not applicable
					Female: IG1: 62% IG2: 59% CG: 66%				
					White: IG1: 83% IG2: 87% CG: 81%				
					Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)				
					Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
GlaxoSmithKline, 1998 <sup>48</sup> (continued)							Anxiety disorder IG1: 19% IG2: 26% CG: 28%  Externalizing disorder IG1: 25% IG2: 26% CG: 20%		
Keller, 2001 <sup>50</sup> Index	United States and MDD Canada RCT Study centers		Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18  Female: IG1: 62% IG2: 59% CG: 66%  White: IG1: 83% IG2: 87% CG: 81%  Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)			High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female		
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
Keller, 2001 <sup>50</sup> Index (continued)						Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%  Anxiety disorder IG1: 19% IG2: 26% CG: 28%  Externalizing disorder IG1: 25% IG2: 26% CG: 20%		
Keller, 2001 <sup>50</sup> Companion: Le Noury, 2016 <sup>51</sup>	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 6 months	Mean age: IG1: 14.8 IG2: 14.8 CG: 15.0 (A) Age range: 12 to 18  Female: IG1: 65% IG2: 46% CG: 68%  White: IG1: 84% IG2: 92% CG: 81% (calculated)  Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)		High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:	RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
Klein, 1998 <sup>63</sup>	United States RCT Research clinics	MDD	Diagnosis of DSM-III-R MDD by a child psychiatrist	IG: Desipramine (n=23) CG: Placebo (n=22) 6 weeks	Mean age: 15.7 (A) Age range: 13 to 18  Female: 67%  White: 58%  Baseline depression HAM-D: Mean (SD) IG: 21.44 (3.7) CG: 21.33 (5.2)  Comorbid diagnosis Current Panic: 2% Social phobia: 29% Separation anxiety: 7% Single phobia: 2% OCD: 0 Any anxiety disorder: 31% Conduct disorder: 0 Optional defiant disorder: 2% ADHD: 4% Any behavior disorder: 7%	Some concerns	Some concerns



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Kye, 1996 <sup>64</sup>	United States RCT Clinic	MDD	Research diagnostic criteria for MDD	IG: Amitriptyline (n=18) CG: Placebo (n=13) 8 weeks	Mean age: IG: 14.6 CG: 15.1 (A) Age range: 12 to 17  Female: IG: 28% CG: 31% calculated  White: IG: 78% CG: 69% calculated  Baseline depression HAM-D mean (SD) ITT IG: 12.0 (4.5) CG: 13.2 (4.1)  Completers IG: 12.3 (5.6) CG: 15.3 (6.0)	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Le Noury, 2015 <sup>49</sup>	United States and Canada RCT Academic psychiatry centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18			High	Not applicable
					Female: IG1: 62% IG2: 59% CG: 66%				
					White: IG1: 83% IG2: 87% CG: 81%				
					Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)				
					Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%				
					Anxiety disorder IG1: 19% IG2: 26% CG: 28%				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:				RoB Study Quality—Benefits	RoB Study Quality—Harms	
					Mean Age	% Female	% White				
					Baseline Depression Severity						
					Prior Traumatic Event Exposure						
					Diagnosed Comorbid Conditions or Diseases						
					Le Noury, 2015 <sup>49</sup> (continued)	Externalizing disorder					
						IG1: 25%					
						IG2: 26%					
						CG: 20%					

A = adolescent; ADHD = attention-deficit/hyperactivity disorder; CDRS = Children's Depression Rating Scale; CG = control group; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KGAS = Kiddie Global Assessment Scale; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; KQ = Key Question; MDD = major depressive disorder; OCD = obsessive compulsive disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-30. KQ 2a: Benefits of MAOIs versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
DeBello, 2014 <sup>65</sup>	United States RCT Clinical sites	MDD	Moderate to severe MDD, based on K- SADS, and a CDRS-R score of >45	IG: Selegiline transdermal system (n=152) CG: Placebo (n=156) 12 weeks	Mean age: 14.8 (A) Age range: 12 to 17  Female: 64%  White: 47%  Baseline depression CDRS-R Mean (SD) IG: 56.7 (12.34) CG: 57.9 (12.57)	Some concerns	Some concerns

CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; IG = intervention group; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; KQ = Key Question; MDD = major depressive disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-31. KQ 2a: Venlafaxine plus active control versus placebo plus active control**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:	RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
Mandoki, 1997 <sup>66</sup>	United States RCT Clinic	MDD	Diagnosis of major depression as determined by DSM-IV criteria	IG: Venlafaxine and therapy (n=20) CG: Placebo and therapy (n=20) 6 weeks	Mean age: 12.8 (A, C) Age range: 8 to 18  Female: 24%  White: NR  Baseline depression NR	Some concerns	Not applicable

A, C = adolescent, child; CG = control group; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias.

**Table D-32. KQ 2b: Subpopulation analysis of SSRIs versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie, 1997 <sup>41</sup>	United States RCT Clinic	MDD	DSM-III-R criteria for nonpsychotic MDD, single and recurrent	IG: Fluoxetine 20 mg/d (n=48) CG: Placebo (n=48) 8 weeks	<p>Mean age: IG: 12.2 CG: 12.5 (A, C) Age range: 7 to 17</p> <p>Female: IG: 46% CG: 46%</p> <p>White: IG: 73% CG: 85%</p> <p>Baseline depression CDI/BDI, mean (SD, range) IG: 15.8 (10.6, 0-41) CG: 15.3 (11.9, 0-54)</p> <p>WSAS, mean (SD, range) IG: 20.6 (11.8, 1-45) CG: 20.6 (12.8, 0-47)</p> <p>CDRS-R total score, mean (SD, range) IG: 58.5 (10.5, 42-90) CG: 57.6 (10.4, 42-82)</p> <p>CGAS total score, mean (SD, range) IG: 47.9 (8.3, 25-65) CG: 48.4 (7.8, 35-80)</p>	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie, 1997 <sup>41</sup> (continued)					Baseline Depression Severity			
					Prior Traumatic Event Exposure			
					Diagnosed Comorbid Conditions or Diseases			
					CDRS-R average initial weekly score			
					IG: 54.2 CG: 53.8			
					Comorbid conditions			
					Lifetime comorbid diagnoses, N (%)			
					Dysthymia			
					IG: 20 (41.7) CG: 14 (29.2)			
					Anxiety disorders			
					IG: 32 (66.7) CG: 22 (45.8)			
					ADHD			
					IG: 16 (33.3) CG: 13 (27.1)			

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie, 2002 <sup>42</sup>	United States RCT Clinic	MDD	Primary diagnosis of nonpsychotic MDD (single or recurrent) as defined by DSM- IV criteria	IG: Fluoxetine 0-20 mg/day (n=109) CG: Placebo (n=110) 9 weeks	Mean age: IG: 12.7 CG: 12.7 (A, C) Age range: 8 to 17  Female: IG: 50% CG: 49%  White: IG: 88% CG: 76%  Baseline depression BDI score, mean (SD) IG: 23.8 (7.4) CG: 28.0 (7.1)  HAM-D at baseline, mean (SD): IG: 20.1 (5.6) CG: 17.1 (7.0)	High	High



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie, 2006 <sup>43</sup>	United States and Canada RCT Study centers	MDD	DSM-IV diagnostic criteria for MDD	IG: Paroxetine (n=104) CG: Placebo (n=102) 8 weeks	Mean age: 12.0 (A, C) Age range: 7 to 17  Female: 47%  White: 79%  Baseline depression CDRS-R Mean (SD) Total IG: 60.7 (9.37) CG: 62.6 (8.96)  Comorbid conditions Psychiatric comorbidity: 22.7% Most common: ADHD 15.3%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie, 2008 <sup>57</sup> Companion: Kennard, 2018 <sup>58</sup>	United States RCT Clinic	MDD	Primary diagnosis of MDD for at least 4 weeks	IG1: Fluoxetine continuation (n=50) CG: Placebo (n=52) 12 weeks of acute treatment, 6 months of continuation treatment	Mean age: Acute treatment: 11.8 Continuation: 11.5 (A, C) Age range: 7 to 18  Female: Acute treatment: 42% Continuation: 36%  White: Acute treatment: 75% Continuation: 71%  Baseline depression Entered acute treatment (n=168) CDRS-R, mean (SD): 57.6 (7.3) CGI-S moderate, %: 30.4 CGI-S marked, %: 56.5 CGI-S severe, %: 13.1  Entered continuation (n=102), mean (SD): CDRS-R: 57.7 (7.6) CGI-S: 4.8 (0.6) CGAS: 51.8 (5.7)  Comorbid conditions Entered continuation (n=102): Comorbid anxiety disorder, mean (SD): 26 (25.5) Comorbid behavior disorder, mean (SD): 45 (44.1) Comorbid dysthymia, mean (SD): 34 (33.3)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Findling, 2009 <sup>47</sup> Companion: Hirschtritt, 2012 <sup>67</sup>	United States RCT Clinic	Mix	MDD or other DDs	IG: Fluoxetine (n=18) CG: Placebo (n=16) 8 weeks	Mean age: 16.5 (A) Age range: 12 to 17  Female: 15%  White: 73%  Baseline depression CDRS-R Mean (SD) IG: 53.0 (2.32) CG: 53.94 (2.46)	Some concerns	Some concerns
GlaxoSmithKline, 1998 <sup>48</sup> Index	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18  Female: IG1: 62% IG2: 59% CG: 66%  White: IG1: 83% IG2: 87% CG: 81%  Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
GlaxoSmithKline, 1998 <sup>48</sup> Index (continued)					Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%  Anxiety disorder IG1: 19% IG2: 26% CG: 28%  Externalizing disorder IG1: 25% IG2: 26% CG: 20%		
GlaxoSmithKline, 1998 <sup>48</sup> Companion: March, 2004 <sup>3</sup> Companion Curry, 2006 <sup>4</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2009 <sup>8</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADs total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31  Oppositional defiant disorder ADHD: 29.03 No ADHD: 10.61	Some concerns	Some concerns

A, C = adolescent/child; ADHD = attention-deficit/hyperactivity disorder; BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-III-R =

Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; N = number; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; WSAS = Work and Social Adjustment Scale.

**Table D-33. KQ 2b: Subpopulation analysis of fluoxetine for relapse prevention versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:	RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
Emslie, 2008 <sup>57</sup> Index	United States RCT Clinic	MDD	Primary diagnosis of MDD for at least 4 weeks	IG1: Fluoxetine continuation (n=50) CG: Placebo (n=52) 12 weeks acute treatment, 6 months of continuation treatment	Mean age: Acute treatment: 11.8 Continuation: 11.5 (A, C) Age range: 7 to 18  Female: Acute treatment: 42% Continuation: 36%  White: Acute treatment: 75% Continuation: 71%  Baseline depression Entered acute treatment (n=168) CDRS-R, mean (SD): 57.6 (7.3) CGI-S moderate, %: 30.4 CGI-S marked, %: 56.5 CGI-S severe, %: 13.1  Entered continuation (n=102), mean (SD): CDRS-R: 57.7 (7.6) CGI-S: 4.8 (0.6) CGAS: 51.8 (5.7)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics: Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie, 2008 <sup>57</sup> Index (continued)					Comorbid conditions Entered continuation (n=102): Comorbid anxiety disorder, mean (SD): 26 (25.5) Comorbid behavior disorder, mean (SD): 45 (44.1) Comorbid dysthymia, mean (SD): 34 (33.3)		

A, C = adolescent/child; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.



**Table D-34. KQ 2b: Subpopulation analysis of TCAs versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality—Harms
GlaxoSmithKline, 1998 <sup>48</sup>	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18  Female: IG1: 62% IG2: 59% CG: 66%  White: IG1: 83% IG2: 87% CG: 81%  Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)  Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:				RoB Study Quality— Benefits	RoB Study Quality—Harms		
					Mean Age	% Female	% White	Baseline Depression Severity				
					Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases						
GlaxoSmithKline, 1998 <sup>48</sup> (continued)					Anxiety disorder							
					IG1: 19%							
					IG2: 26%							
					CG: 28%							
					Externalizing disorder							
					IG1: 25%							
					IG2: 26%							
					CG: 20%							
CG = control group; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.												

**Table D-35. KQ 3a and b: Fluoxetine plus CBT versus placebo**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Index	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Curry, RCT 2006 <sup>4</sup>	United States Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Emslie, 2006 <sup>5</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kennard, 2006 <sup>6</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2006 <sup>68</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54% Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Vitiello, 2006 <sup>7</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2009 <sup>8</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADs total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31  Oppositional defiant disorder ADHD: 29.03 No ADHD: 10.61	Some concerns	Some concerns

A = adolescent; ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; IG = intervention group; KQ

= Key Question; MDD = major depressive disorder; NR = not reported; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-36. KQ 3a and b: Omega-3 versus other therapies**

Table 2. RoB, GRA and b: Omega-3 versus other therapies								
Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		RoB Study Quality— Benefits	RoB Study Quality—Harms
					Mean Age % Female % White	Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
Fristad, 2009 <sup>27</sup>	RCT	Mix	Diagnosis of current MDD, dysthymic disorder, or DD NOS	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	Mean age: 11.6 (A,C) Age range: 7 to 14  Female: 43%  White: 57%  Baseline depression CDRS-R, mean (SD) IG1: 38 (9) IG2: 42 (9) IG3: 44 (12) CG: 44 (13)  PTSD, n (%) 7 (9.7%)  Anxiety disorders, n (%) 54 (75.0)  ADHD, n (%) 41 (56.9)  Disruptive behavior disorder, n (%) 22 (30.6)		Some concerns	Not applicable

**Table D-37. KQ 5a: CBT versus other psychotherapy**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Index	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD	IG1: Individual CBT (n=37) IG2: Systemic behavior family therapy (n=35) CG: Nondirective supportive therapy (n=35) 12 to 16 weeks	Mean age: IG1: 15.7 IG2: 15.4 CG: 15.7 (A) Age range: 13 to 18  Female: IG1: 76% IG2: 77% CG: 74%  White: IG1: 76% IG2: 87% CG: 86%  Baseline depression BDI, mean (SD) IG1: 24.3 (8.1) IG2: 22.6 (8.2) CG: 25.7 (7.8)  Comorbid diagnosis Dysthymic disorder (%) IG1: 16.2 IG2: 25.7 CG: 25.7  Anxiety disorder (%) IG1: 37.8 IG2: 28.6 CG: 28.6	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Index (continued)					Disruptive disorder (%) IG1: 16.2 IG2: 22.9 CG: 22.9		
Brent, 1997 <sup>12</sup> Companion: Brent, 1998 <sup>13</sup>	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD	IG1: Individual CBT (n=37) IG2: Systemic behavior family therapy (n=35) CG: Nondirective supportive therapy (n=35) 12 to 16 weeks	Mean age: IG: 15.7 IG2: 15.4 CG: 15.7 (A) Age range: 13 to 18  Female: IG1: 76% IG2: 77% CG: 74%  White: IG1: 76% IG2: 87% CG: 86%  Baseline depression BDI, mean (SD) IG1: 24.3 (8.1) IG2: 22.6 (8.2) CG: 25.7 (7.8)  Comorbid diagnosis Dysthymic disorder (%) IG1: 16.2 IG2: 25.7 CG: 25.7	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics: Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Companion: Brent, 1998 <sup>13</sup> (continued)					Anxiety disorder (%) IG1: 37.8 IG2: 28.6 CG: 28.6  Disruptive disorder (%) IG1: 16.2 IG2: 22.9 CG: 22.9		
Brent, 1997 <sup>12</sup> Companion: Barbe, 2004 <sup>36</sup>	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD	IG1: Individual CBT (n=37) IG2: Systemic behavior family therapy (n=35) CG: Nondirective supportive therapy (n=35) 12 to 16 weeks	Mean age: IG1: 15.7 IG2: 15.4 CG: 15.7 (A) Age range: 13 to 18  Female: IG1: 76% IG2: 77% CG: 74%  White: IG1: 76% IG2: 89% CG: 86%	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms	
Brent, 1997 <sup>12</sup> Companion: Barbe, 2004 <sup>36</sup> (continued)					Baseline depression BDI, mean (SD) IG1: 24.3 (8.1) IG2: 22.6 (8.2) CG: 25.7 (7.8)			
					Comorbid conditions Dysthymic disorder (%) IG1: 16.2 IG2: 25.7 CG: 25.7			
					Anxiety disorder (%) IG1: 37.8 IG2: 28.6 CG: 28.6			
					Disruptive disorder (%) IG1: 16.2 IG2: 22.9 CG: 22.9			

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Companion: Barbe, 2004 <sup>69</sup>	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD	IG1: Individual CBT (n=37) IG2: Systemic behavior family therapy (n=NR) CG: Nondirective supportive therapy (n=35) 12-16 weeks for acute treatment; followup to 2 years	Mean age: IG1: 15.7 IG2: 15.4 CG: 15.7 (A) Age range: 13 to 18  Female: IG1: 76% IG2: 77% CG: 74%  White: IG1: 76% IG2: 89% CG: 86%  Baseline depression BDI, mean (SD) IG1: 24.3 (8.1) IG2: 22.6 (8.2) CG: 25.7 (7.8)  Prior traumatic exposure IG1: 6 IG2: 1 CG: 4  Comorbid conditions Dysthymic disorder (%) IG1: 16.2 IG2: 25.7 CG: 25.7	High	High



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
Brent, 1997 <sup>12</sup> Companion: Barbe, 2004 <sup>69</sup> (continued)					Anxiety disorder (%)			
					IG1: 37.8			
					IG2: 28.6			
					CG: 28.6			
					Disruptive disorder (%)			
					IG1: 16.2			
					IG2: 22.9			
					CG: 22.9			

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 1997 <sup>12</sup> Companion: 2014 <sup>70</sup>	United States RCT Clinic	MDD	Met criteria for DSM-III-R MDD, presence of MDD, measured by K-SADS-PL; score on 13 depression items from the School Age Schedule for Affective Disorders and Schizophrenia, present and lifetime versions (DEP13); and BDI score were all taken at weeks 0, 6, and 12	IG1: Individual CBT (n=37) IG2: Systemic behavior family therapy (n=35) CG: Nondirective supportive therapy (n=35) 12 to 16 weeks	Mean age: 15.6 (A) Age range: 13 to 18  Female: 78%  White: 84%  Baseline depression BDI, mean (SD) IG1: 24.3 (8.1) IG2: 22.6 (8.2) CG: 25.7 (7.8)  Comorbid conditions Dysthymic disorder (%) IG1: 16.2 IG2: 25.7 CG: 25.7  Anxiety disorder (%) IG1: 37.8 IG2: 28.6 CG: 28.6  Disruptive disorder (%) IG1: 16.2 IG2: 22.9 CG: 22.9	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Goodyer, 2017 <sup>16</sup> Index	England RCT Clinic	MDD	DSM-IV unipolar major depressive disorder	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Mean age: 15.6 (A) Age range: 11 to 17  Female: 75% White: 85%  Baseline depression SSRI prescribed before trial entry, n/N (%) IG1: 32/125 (21) IG2: 28/155 (18) CG: 29/153 (19)  PTSD diagnosis IG1: 12 (7.8%) IG2: 14 (9%) CG: 6 (3.9%)	Some concerns	Some concerns
Goodyer, 2017 <sup>16</sup> Companion: Goodyer, 2017 <sup>17</sup>	England RCT Clinic	MDD	DSM-IV unipolar MDD	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Mean age: 15.6 (A) Age range: 11 to 17  Female: 75% White: 85%  Baseline depression SSRI prescribed before trial entry, n/N (%) IG1: 32/125 (21) IG2: 28/155 (18) CG: 29/153 (19)  Prior traumatic event exposure MFQ, mean (SD) IG1: 46.2 (10.3) IG2: 45.4 (10.8) CG: 46.2 (10.6)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Goodyer, 2017 <sup>16</sup> Companion: O'Keeffe, 2018 <sup>18</sup>	England RCT Clinic	MDD	DSM-IV unipolar MDD	IG1: CBT (n=155) IG2: Short-term psychoanalytical therapy (n=157) CG: Brief psychosocial intervention (n=158) 36 weeks	Mean age: 15.6 (A) Age range: 11 to 17  Female: 75%  White: 85%  Baseline depression SSRI prescribed before trial entry, n/N (%) IG1: 32/125 (21) IG2: 28/155 (18) CG: 29/153 (19)  Prior traumatic event exposure MFQ, mean (SD) IG1: 46.2 (10.3) IG2: 45.4 (10.8) CG: 46.2 (10.6)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Rosello, 1999 <sup>10</sup>	United States (Puerto Rico) RCT University clinic	Mix	Diagnosis for MDD, dysthymia, or both	IG1: Interpersonal psychotherapy (n=23) IG2: CBT (n=25) CG: Wait list control (n=23) 12 weeks	Mean age: 14.7 (A) Age range: 13 to 18  Female: 54  White: NR  Baseline depression CDI score pretreatment, Mean (SD): IG1: 21.21 (7.53) IG2: 20.12 (6.95) CG: 20.13 (5.99)  Comorbid condition "Double depression" (N) IG1: 21 IG2: 16 CG: 17	High	Not applicable

A = adolescent; BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CG = control group; DEP13 = 13 depression items from School-Age Schedule for Affective Disorders and Schizophrenia for School-Age Children; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; IG = intervention group; KQ = Key Question; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime version; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n/N = number; NR = not reported; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; SSRI = selective serotonin reuptake inhibitors.

**Table D-38. KQ 5a: Omega-3 versus other therapies**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Fristad, 2009 <sup>27</sup>	United States RCT Clinic	Mix	Diagnosis of current MDD, dysthymic disorder, or DD NOS	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	Mean age: 11.6 (A,C) Age range: 7 to 14  Female: 43%  White: 57%  Baseline depression CDRS-R, mean (SD) IG1: 38 (9) IG2: 42 (9) IG3: 44 (12) CG: 44 (13)  PTSD, n (%) 7 (9.7%)  Anxiety disorders, n (%) 54 (75.0)  ADHD, n (%) 41 (56.9)  Disruptive behavior disorder, n (%) 22 (30.6)	Some concerns	Not applicable

ADHD = attention-deficit hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; DD = depressive disorder; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; n/N = number; NOS = not otherwise specified; PEP = psychoeducational psychotherapy; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; risk of bias; SD = standard deviation.

**Table D-39. KQ 5a: Psychotherapy within-type comparisons of delivery methods or approaches**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Clarke, 1999 <sup>9</sup>	United States RCT NR	Mix	Current DSM-III-R diagnosis of major psychiatric disorder or dysthymia	IG1: Child CBT (n=45) IG2: Child CBT with separate parent sessions (n=42) CG: Wait-list control (n=36) 8 weeks	Mean age: 16.2 (A) Age range: 14 to 18  Female: 71%  White: NR  Baseline depression HAM-D: Mean (SD) Overall: 14.2 (5.7) IG1: 13.0 (5.3) IG2: 15.1 (6.0) CG: 14.5 (5.9)  BDI: Mean (SD) Overall: 25.8 (9.5) IG1: 26.5 (9.4) IG2: 26.4 (8.7) CG: 24.2 (10.8)  CBCL depression: Mean (SD) IG1: 14.5 (4.0) IG2: 16.1 (5.5) CG: 14.9 (4.9)  Comorbid diagnosis Current anxiety disorder: 23.6% History of nonaffective disorder: 23.6%	Some concerns	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Gunlicks-Stoessel, 2016 <sup>71</sup>	United States RCT Psychiatric institute	Mix	DSM-IV diagnosis of MDD, dysthymic disorder, DDNOS, or adjustment disorder with depressed mood (K-SADS-PL)	IG: Adaptation interpersonal psychotherapy (n=9) CG: Adaptation interpersonal psychotherapy (n=6) 16 weeks	Mean age: 15.2 (A) Age range: 12 to 17  Female: 87%  White: 87%  Baseline depression MDD: 11 MDD and dysthymic disorder: 1 DDNOS: 3  CDS-R (baseline) Mean (SD) IG: 52.00 (13.00) CG: 45.17 (8.82)  Comorbid conditions Anxiety disorder: 3	Some concerns	Not applicable



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Jelalian, 2016 <sup>72</sup>	United States RCT Research clinics/hospital	Mix	DSM-IV criteria for current MDD or dysthymia	IG: CBT plus healthy lifestyle enhancement (n=24) CG: CBT (n=9) 24 weeks (18 sessions)	Mean age: IG: 15.3 CG: 14.4 (A) Age range: 12 to 18  Female: IG: 71% CG: 78%  Not Latino: IG: 67% CG: 67%  Not minority: IG: 42% CG: 56%  Baseline depression Depressed mood Mean (SD) Total 22.6 (11.4) IG: 25.0 (12.0) CG: 22.0 (11.0)	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Nelson, 2004 <sup>73</sup>	United States RCT Clinic	MDD	Met the DSM-IV criteria for depression based on K- SADS-P	IG1: CBT over ITV (n=14) IG2: CBT Face to face (n=14) 24 weeks (18 sessions)	Mean age: 10.3 (A, C) Age range: 8 to 14  Female: 29%  White: 71%  Baseline depression BDI IG: 7.92 (6.74) CG: 10.93 (9.53)  CDI IG: 14.36 (9.85) CG: 13.57 (8.75)  Comorbid conditions Bipolar symptoms: 4 Oppositional behaviors: 12 ADHD: 19 PDD: 5 Suicidal ideation in the past: 17	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Rohde, 1994 <sup>74</sup>	United States RCT NR	MDD	Diagnosis of MDD based on DSM-III	IG: CBT group for adolescents (N1=13 and N2=31) IG2: CBT group for adolescents with a separate group for parents (N1=9 and N2=29) CG: Waiting list (N1=9 and N2=24) N1: 14 2-hour sessions for adolescents; 7 2- hour sessions for parents N2: 16 2-hour sessions for adolescents; 9 2- hour sessions for parents	Mean age: IG: 16.3 CG: 16.3 (A) Age range: 14 to 18  Female: IG: 65% CG: 74%  White: IG: 87% CG: 99%  Baseline depression BDI Sample 1 Low severity IG1: 11.8 (6.1) IG2: 20.6 (8.6) CG: 22.0 (7.8)  High severity IG1: 33.5 (5.7) IG2: 26.0 (9.1) CG: 28.8 (5.6)  Sample 2 Low severity IG1: 24.2 (6.8) IG2: 21.7 (5.8) CG: 18.6 (7.8)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms	
Rohde, 1994 <sup>74</sup> (continued)					High severity IG1: 34.1 (7.2) IG2: 31.3 (7.6) CG: 33.2 (7.9)			
					CES-D Sample 1 Low severity IG1: 11.0 (6.2) IG2: 13.6 (7.1) CG: 13.8 (2.9)			
					High severity IG1: 17.4 (3.2) IG2: 14.0 (5.0) CG: 17.0 (3.4)			
					Sample 2 Low severity IG1: 36.9 (9.0) IG2: 35.2 (5.5) CG: 33.7 (8.9)			
					High severity IG1: 47.5 (5.0) IG2: 45.9 (5.6) CG: 45.9 (5.8)			

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
Rohde, 1994 <sup>74</sup> (continued)					Baseline Depression Severity			
					Prior Traumatic Event Exposure			
					Diagnosed Comorbid Conditions or Diseases			
					HDRS			
					Sample 2			
					Low severity			
					IG1: 12.0 (4.3)			
					IG2: 10.3 (3.3)			
					CG: 12.6 (4.1)			
					High severity			
					IG1: 16.1 (5.9)			
					IG2: 19.5 (4.4)			
					CG: 18.5 (5.8)			

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Spirito, 2015 <sup>75</sup>	United States RCT NR	Mix	Met DSM-IV criteria for current MDE	IG: Parent-adolescent- CBT (n=16) CG: Adolescent only- CBT (n=8) 12 weeks	Mean age IG: 14.7 CG: 14.0 (A) Age range: 11 to 17  Female IG: 88% CG: 75%  White: NR  Baseline depression BDI IG: 29.32 CG: 19.13  Prior traumatic event CTQ IG: 44.50 CG: 42.25  Comorbid conditions Suicide attempt IG: 50% CG: 0%  MSI-BPD IG: 6.38 (2.13) CG: 4.50 (1.14)	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Trowell, 2007 <sup>76</sup> Index	United Kingdom, Greece, Finland RCT Clinic and children's hospitals	MDD	Met criteria for MDD and/or Dysthymia on the Kiddie-SADS	IG1: Individual therapy (n=35) IG2: Family therapy (n=37) 9 months	Mean age: 11.7 (A, C) Age range: 9 to 15  Female: 38%  White: 87%  Baseline depression Depression: 100% MDD: 91.7%  Comorbid conditions Dysthymia: 55.6% Double depression: 47.2%	High	High
Trowell, 2007 <sup>76</sup> Companion: Garoff, 2012 <sup>77</sup>	United Kingdom, Greece, Finland RCT Clinic and children's hospitals	Mix	Met criteria for MDD and/or dysthymia on the K-SADS	IG1: Individual therapy (FIPP) (n=35) IG2: Family therapy (SIFT) (n=34) 9 months	Mean age: 11.7 (A, C) Age range: 9 to 15  Female: 38%  White: 87%  Baseline depression Depression: 100% MDD: 91.7%  Comorbid conditions Dysthymia: 55.6% Double depression: 47.2%	High	High

ADHD = attention-deficit/hyperactivity disorder; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory-II; CBCL = child behavior checklist; CBT = cognitive behavioral therapy; CDS-R = Carroll Depression Scales - Revised; CES-D = Center for Epidemiologic Studies Depression Scale; CG = control group; CTQ = Child Trauma Questionnaire; DDNOS = depressive disorder not otherwise specified; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FIPP = focused individual psychodynamic psychotherapy; HAM-D = Hamilton Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; IG = intervention group; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version; KQ = Key Question; MDE = major depressive episode; MSI-BPD = McLean Screening Instrument for Borderline Personality Disorder; n/N = number; NR = not reported; PDD = persistent depressive disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; SIFT = systems integrative family therapy.

**Table D-40. KQ 5a: Psychotherapy versus pharmacotherapy**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Iftene, 2015 <sup>78</sup>	Romania RCT Clinic	MDD	Diagnosed with MDD based on DSM-IV	IG1: Sertraline (n=33) IG2: Group rational emotive behavior therapy/CBT (n=28) IG3: Sertraline plus group rational emotive behavior therapy/CBT (n=27) 16 weeks	Mean age: IG1: 15.3 IG2: 15.1 IG3: 15.3 (A, C) Age range: 11 to 17  Female IG2: 20% IG2: 12% IG3: 15%  White: NR  Baseline depression CDI Mean (SD) IG1: 23.60 (5.82) IG2: 23.60 (5.82) IG3: 23.48 (5.14)  Comorbid conditions Any psychiatric condition IG1: 16 IG2: 13 IG3: 15  Anxiety IG1: 7 IG2: 5 IG3: 7	Some concerns	Some concerns



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics: Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Iftene, 2015 <sup>78</sup> (continued)					Tics and Tourette's disorder IG1: 4 IG2: 2 IG3: 4  Disruptive behavior IG1: 2 IG2: 6 IG3: 3		
March, 2004 <sup>3</sup> Index	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Curry, 2006 <sup>4</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Emslie, 2006 <sup>5</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kennard, 2006 <sup>6</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2006 <sup>68</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54% Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Vitiello, 2006 <sup>7</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2009 <sup>8</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADs total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31  Oppositional defiant disorder ADHD: 29.03 No ADHD: 10.61	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Melvin, 2006 <sup>79</sup>	Australia RCT Clinic	Mix	DSM-IV based diagnosis of MDD, dysthymic disorder, or DDNOS	IG1: CBT (n=22) IG2: Sertraline (n=26) IG3: Combined (n=25) 12 weeks	<p>Mean age: IG1: 15.0 IG2: 15.5 CG: 15.3 (A) Age range: 12 to 18</p> <p>Female: IG1: 68% IG2: 73% CG: 55%</p> <p>White: NR</p> <p>Baseline depression Reynolds Adolescent Depression Scale (RADs), cutoff ≥76: mean (SD) IG1: 83.77 (13.80) IG2: 84.92 (11.20) CG: 83.96 (15.01)</p> <p>Comorbid conditions Anxiety disorders: IG1: 36.4% IG2: 34.6% CG: 40.0%</p> <p>Dysthymic disorder: IG1: 4.5% IG2: 7.7% CG: 12.0%</p>	High	High



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
Melvin, 2006 <sup>79</sup> (continued)						Conduct disorder/ODD: IG: 9.1% IG: 11.5% CG: 4%		

A, C = adolescent/child; ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; DDNOS = depressive disorder not otherwise specified; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; NR = not reported; ODD = oppositional defiant disorder; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-41. KQ 5a: Psychotherapy plus pharmacotherapy versus psychotherapy**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:	RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
Bernstein, 2000 <sup>80</sup> Index	United States RCT NR	MDD	Diagnosis of MDD from the DICA-R-A and/or DICA-R-P	IG: Imipramine+CBT (n=31) CG: Placebo+CBT (n=32) 8 weeks	Mean age: 13.9 (A) Age range: 12 to 18  Female: 60%  White: 91%  Baseline depression CDRS-R Mean (SD) IG: 46.8 (9.5) CG: 52.5 (10.8)  BDI Mean (SD) IG: 12.2 (10.1) CG: 15.7 (11.3)	Some concerns	Some concerns
Bernstein, 2000 <sup>80</sup> Companion: Bernstein, 2000 <sup>81</sup>	United States RCT NR	MDD	Diagnosis of MDD from the DICA-R-A and/or DICA-R-P	IG: Imipramine+CBT (n=31) CG: Placebo+CBT (n=32) 8 weeks	Mean age: 13.9 (A) Age range: 12 to 18  Female: 60%  White: 91%  Baseline depression CDRS-R Mean (SD) IG: 46.8 (9.5) CG: 52.5 (10.8)  BDI Mean (SD) IG: 12.2 (10.1) CG: 15.7 (11.3)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Deas, 2000 <sup>82</sup>	United States RCT Hospital outpatient psychiatry institute	MDD and alcohol use disorder	PDD	IG: Sertraline plus group CBT (n=5) CG: Placebo plus group CBT (n=5) 12 weeks	Mean age: 16.6 (A) Age range: NR  Female: 20%  White: 80%  Baseline depression HAM-D Mean (SD) 20.6 (5.4)  Comorbid conditions Alcohol use disorder: 100% Days drinking in past 90 days: 29% (±27) Drinks per drinking day: 8.6 (±4.9)	Low	Low

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Dietz, 2008 <sup>83</sup>	United States Controlled clinical trials Clinic	Mix	DSM-IV diagnosis of a depressive disorder (MDD, dysthymic disorder, DDNOS)	IG: Family-based interpersonal psychotherapy (n=10) CG: Family-based interpersonal psychotherapy plus antidepressant medication (n=6)  Note: Open trial	Mean age: 10.7 (C) Age range: 9 to 12	Female: 62%	White: 94%	High	Not applicable
					Baseline depression CDRS-R IG: 43.6 (6.87) CG: 42.7 (2.42)		Comorbid conditions Passive suicidal ideation: 56% Engaged in self-injurious behavior: 19% Anxiety disorder: 33% Subthreshold levels of anxiety: 47% ADHD: 25% Began stimulant medication prior to treatment for depression: 20%		

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Iftene, 2015 <sup>78</sup>	Romania RCT Clinic	MDD	Diagnosed with MDD based on DSM-IV	IG1: Sertraline (n=33) IG2: Group rational emotive behavior therapy/CBT (n=28) IG3: Sertraline plus group rational emotive behavior therapy/CBT (n=27) 16 weeks	Mean age: IG1: 15.3 IG2: 15.1 IG3: 15.3 (A, C) Age range: 11 to 17			Some concerns	Some concerns
					Female				
					IG2: 20%				
					IG2: 12%				
					IG3: 15%				
					White: NR				
					Baseline depression CDI				
					Mean (SD)				
					IG1: 23.60 (5.82)				
					IG2: 23.60 (5.82)				
					IG3: 23.48 (5.14)				
					Comorbid conditions				
					Any psychiatric condition				
					IG1: 16				
					IG2: 13				
					IG3: 15				
					Anxiety				
					IG1: 7				
					IG2: 5				
					IG3: 7				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Iftene, 2015 <sup>78</sup> (continued)							Tics and Tourette's disorder IG1: 4 IG2: 2 IG3: 4  Disruptive behavior IG1: 2 IG2: 6 IG3: 3		
March, 2004 <sup>3</sup> Index	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17		Female: 54%  Black: 13% Hispanic: 9%	Some concerns	Some concerns
							Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7		

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Curry, 2006 <sup>4</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Emslie, 2006 <sup>5</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kennard, 2006 <sup>6</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2006 <sup>68</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54% Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Vitiello, 2006 <sup>7</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2009 <sup>8</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADS total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31  Oppositional defiant disorder ADHD: 29.03 No ADHD: 10.61	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Melvin, 2006 <sup>79</sup>	Australia RCT Clinic	Mix	DSM-IV based diagnosis of MDD, dysthymic disorder, or DDNOS	IG1: CBT (n=22) IG2: Sertraline (n=26) IG3: Combined (n=25) 12 weeks	Mean age: IG1: 15.0 IG2: 15.5 CG: 15.3 (A) Age range: 12 to 18			High	High
					Female: IG1: 68% IG2: 73% CG: 55%				
					White: NR				
					Baseline depression Reynolds Adolescent Depression Scale (RADS), cutoff ≥76: mean (SD) IG1: 83.77 (13.80) IG2: 84.92 (11.20) CG: 83.96 (15.01)				
					Comorbid conditions Anxiety disorders: IG1: 36.4% IG2: 34.6% CG: 40.0%				
					Dysthymic disorder: IG1: 4.5% IG2: 7.7% CG: 12.0%				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity				
					Prior Traumatic Event Exposure				
					Diagnosed Comorbid Conditions or Diseases				
Melvin, 2006 <sup>79</sup> (continued)					Conduct disorder/ODD: IG: 9.1% IG: 11.5% CG: 4%				

A = adolescent; ADHD = attention-deficit/hyperactivity disorder; BDI = Beck Depression Inventory; C = child; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; DDNOS = depressive disorder not otherwise specified; DICA-R-A = Diagnostic Interview for Children and Adolescents – Revised- Adolescent; DICA-R-P = Diagnostic Interview for Children and Adolescents – Revised- Parent; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; n/N = number; NR = not reported; ODD = oppositional defiant disorder; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-42. KQ 5a: Psychotherapy plus pharmacotherapy versus pharmacotherapy**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Clarke, 2005 <sup>84</sup>	United States RCT Clinic	MDD	Research- ascertained DSM-IV episode of MDD	IG: Collaborative care, brief individual CBT and TAU SSRIs (n=77) CG: TAU SSRIs (n=75) Up to 12 weeks	Mean age: IG: 15.3 CG: 15.3 (A) Age range: 12 to 18  Female: IG: 78% CG: 77%  White: IG: 87% CG: 85%  Baseline depression HAM-D: Mean (SD) IG: 21.1 (6.8) CG: 21.8 (5.8)	Some concerns	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Iftene, 2015 <sup>78</sup>	Romania RCT Clinic	MDD	Diagnosed with MDD based on DSM-IV	IG1: Sertraline (n=33) IG2: Group rational emotive behavior therapy/CBT (n=28) IG3: Sertraline plus group rational emotive behavior therapy/CBT (n=27) 16 weeks	Mean age: IG1: 15.3 IG2: 15.1 IG3: 15.3 (A, C) Age range: 11 to 17  Female IG2: 20% IG2: 12% IG3: 15%  White: NR  Baseline depression CDI Mean (SD) IG1: 23.60 (5.82) IG2: 23.60 (5.82) IG3: 23.48 (5.14)  Comorbid conditions Any psychiatric condition IG1: 16 IG2: 13 IG3: 15  Anxiety IG1: 7 IG2: 5 IG3: 7	Some concerns	Some concerns



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Iftene, 2015 <sup>78</sup> (continued)					Tics and Tourette's disorder IG1: 4 IG2: 2 IG3: 4  Disruptive behavior IG1: 2 IG2: 6 IG3: 3		
Kim, 2012 <sup>85</sup>	South Korea RCT Hospital outpatient center	MDD	Diagnosed as having MDD by a psychiatrist	IG: CBT plus bupropion (n=35) CG: Bupropion (n=37) 8 weeks of treatment, 4-week posttreatment followup	Mean age: IG: 16.2 CG: 15.9 (A, C) Age range: 13 to 18  Female: 0%  White: NR  Baseline depression BDI mean (SD) IG: 32.7 (8.8) CG: 33.3 (8.7)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Index	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Curry, 2006 <sup>4</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Emslie, 2006 <sup>5</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kennard, 2006 <sup>6</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratochvil, 2006 <sup>68</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54% Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Vitiello, 2006 <sup>7</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2009 <sup>8</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADs total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31  Oppositional defiant disorder ADHD: 29.03 No ADHD: 10.61	Some concerns	Some concerns



Melvin, 2006 <sup>79</sup>	Australia RCT Clinic	Mix	DSM-IV based diagnosis of MDD, dysthymic disorder, or DDNOS	IG1: CBT (n=22) IG2: Sertraline (n=26) IG3: Combined (n=25) 12 weeks	Mean age: IG1: 15.0 IG2: 15.5 CG: 15.3 (A) Age range: 12 to 18  Female: IG1: 68% IG2: 73% CG: 55%  White: NR  Baseline depression Reynolds Adolescent Depression Scale (RADS), cutoff ≥76: mean (SD) IG1: 83.77 (13.80) IG2: 84.92 (11.20) CG: 83.96 (15.01)  Comorbid conditions Anxiety disorders: IG1: 36.4% IG2: 34.6% CG: 40.0%  Dysthymic disorder: IG1: 4.5% IG2: 7.7% CG: 12.0%  Conduct disorder/ODD: IG: 9.1% IG: 11.5% CG: 4%	High	High
Wilkinson, 2008 <sup>86</sup>	United Kingdom RCT Clinics	MDD	Current DSM- IV MDD	IG: SSRI and psychosocial TAU plus CBT (n=15) CG: SSRI plus psychosocial TAU (n=11) 28 weeks	Mean age: IG: 15.2 CG: 15.4 (A) Age range: 11 to 17  Female: IG: 77% CG: 60%	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:	RoB Study Quality—Benefits	RoB Study Quality—Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
					White: NR		
					Baseline depression MFQ IG: 43.8 (8.1) CG: 42.5 (10.1)		
Wilkinson, 2011 <sup>87</sup>	United Kingdom RCT Clinic	MDD	DSM-IV MDD	IG: SSRI (n = 79) CG: SSRI plus CBT (n = 85) 28 weeks	Mean age: 14.2 (A) Age range: 11 to 17  Female: 78% (calculated)  White: NR  Baseline Depression Children's Depression Rating Scale-Revised (Total Score) Mean (SD) 59.9 (9.5)  Comorbid Depression Number of Comorbid disorders Mean (SD) 1.2 (0.9)  Suicide Attempt In Past Month Mean (SD) 32 (17)  Nonsuicidal Self-injury in past month Mean (SD) 65 (34)	High	High

A = adolescent; A, C = adolescent/child; ADHD = attention-deficit/hyperactivity disorder; CDI = Children's Depression Inventory; CDS-R = Carroll Depression Scales - Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; DDNOS = depressive disorder not otherwise specified; DSM-IV = Diagnostic and Statistical

Manual of Mental Disorders, Fourth Edition; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; NR = not reported; ODD = oppositional defiant disorder; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; SSRI = selective serotonin reuptake inhibitors; TAU = treatment as usual.

**Table D-43. KQ 5a: Omega-3 versus other therapies**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Fristad, 2009 <sup>27</sup>	United States RCT Clinic	Mix	Diagnosis of current MDD, dysthymic disorder, or DD NOS	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	Mean age: 11.6 (A,C) Age range: 7 to 14  Female: 43%  White: 57%  Baseline depression CDRS-R, mean (SD) IG1: 38 (9) IG2: 42 (9) IG3: 44 (12) CG: 44 (13)  PTSD, n (%) 7 (9.7%)  Anxiety disorders, n (%) 54 (75.0)  ADHD, n (%) 41 (56.9)  Disruptive behavior disorder, n (%) 22 (30.6)	Some concerns	Not applicable

ADHD = attention-deficit hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; DD = depressive disorder; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; n/N = number; NOS = not otherwise specified; PEP = psychoeducational psychotherapy; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; risk of bias; SD = standard deviation.

**Table D-44. KQ 5a: SSRIs versus SNRIs**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Atkinson, 2014 <sup>38</sup>	United States, Finland, France, Germany, Slovakia, Estonia, Russia, Ukraine, and South Africa RCT 65 psychiatric clinical sites	Mix	MDD or other depressive disorders	IG1: Duloxetine (n=117) IG2: Fluoxetine (n=117) CG: Placebo (n=103) 10 weeks	Mean age: IG1: 13.1 IG2: 13.1 CG: 13.3 (A, C) Age range: 11 to 17  Female: IG1: 55% IG2: 52% CG: 50%  White: IG1: 80% IG2: 83% CG: 81%  Baseline depression CDS-R mean (SE) IG1: 59.2 (10.5) IG2: 58.8 (10.6) CG: 50.2 (11.7)  CGI-S IG1: 4.5 (0.6) IG2: 4.5 (0.6) CG: 4.6 (0.7)  Comorbid conditions Dysmenorrhea (females only): 6.8% Seasonal allergy: 6.2% Asthma: 5.9% Anxiety: 2.4% ADD/ADHD: 2.4% Oppositional defiant disorder: 2.4%	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Emslie 2014 <sup>46</sup>	United States, Canada, Mexico, and Argentina RCT 60 psychiatric clinical sites	Mix	MDD or other depressive disorders	IG1: Duloxetine 60 mg QD (n=108) IG2: Duloxetine 30 mg QD (n=116) IG3: Fluoxetine 20 mg QD (n=117) CG: Placebo (n=122) 10 weeks	Mean age: IG1: 12.9 IG2: 12.9 IG3: 13.0 CG: 13.1 (A, C) Age range: 11 to 17			High	High
					Female: IG1: 56% IG2: 41% IG3: 52% CG: 57%				
					White: IG1: 53% IG2: 54% IG3: 59% CG: 52%				
					Baseline depression CDS-R mean (SE) IG1: 59.3 (10.9) IG2: 59.8(11.0) IG3: 57.9(10.1) CG: 58.2(9.4)				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms	
Emslie 2014 <sup>46</sup> (continued)					CGI-S IG1: 4.6 (0.7) IG2: 4.6 (0.7) IG3: 4.6 (0.6) CG: 4.5 (0.6)  Comorbid conditions Asthma: 8.2% Dysmenorrhea (females only): 5.1% Insomnia: 4.5% Oppositional defiant disorder: 4.1% Generalized anxiety disorder: 2.2%			

A, C = adolescent/child; ADD= Attention-Deficit Disorder; ADHD = attention-deficit/hyperactivity disorder; CDS-R = Carroll Depression Scales - Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; RCT = randomized controlled trial; RoB = risk of bias; SE = standard error.

**Table D-45. KQ 5a: SSRIs versus TCAs**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
GlaxoSmithKline, 1998 <sup>48</sup>	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18  Female: IG1: 62% IG2: 59% CG: 66%  White: IG1: 83% IG2: 87% CG: 81%  Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)  Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%	High	Not applicable



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
GlaxoSmithKline, 1998 <sup>48</sup> (continued)					Anxiety disorder IG1: 19% IG2: 26% CG: 28%  Externalizing disorder IG1: 25% IG2: 26% CG: 20%		
GlaxoSmithKline, 1998 <sup>48</sup> Companion: Le Noury, 2015 <sup>49</sup>	United States and Canada MDD RCT Academic psychiatry centers		Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18  Female: IG1: 62% IG2: 59% CG: 66%  White: IG1: 83% IG2: 87% CG: 81%	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms	
GlaxoSmithKline, 1998 <sup>48</sup> Companion: Le Noury, 2015 <sup>49</sup> (continued)					Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)  Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%  Anxiety disorder IG1: 19% IG2: 26% CG: 28%  Externalizing disorder IG1: 25% IG2: 26% CG: 20%			

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
GlaxoSmithKline, 1998 <sup>48</sup> Companion: Le Noury, 2016 <sup>51</sup>	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 6 months	Mean age: IG1: 14.8 IG2: 14.8 CG: 15.0 (A) Age range: 12 to 18  Female: IG1: 65% IG2: 46% CG: 68%  White: IG1: 84% IG2: 92% CG: 81% (calculated)  Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)	High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Weihs, 2018 <sup>55</sup>	United States, Mexico RCT Hospitals, academic institutions, private clinics, and clinical trial research centers	MDD	Meeting DSM- IV-TR criteria for MDD	IG1: Desvenlafaxine (25, 35, or 50 mg/d) (n=115) IG2: Fluoxetine (20 mg/d) (n=113) CG: Placebo (n=112) 8 weeks	Mean age: Children: 9.4 Adolescent: 14.8 (A, C) Age range: 7 to 17  Female: 54% (calculated)  White: 65% (calculated)  Baseline depression CDRS-R total score: Mean (SD) 56.5 (8.9)  CGI-S score: Mean (SD) 4.5 (0.6)  Comorbid diagnosis ADHD IG1: 12.2% IG2: 13.4% CG: 5.4  Nonsuicidal self-injurious behavior IG1: 7.0% IG2: 8.0% CG: 12.5%  Insomnia IG1: 7.0% IG2: 6.3% CG: 8.0%	High	Uncertain

A, C = adolescent/child; ADHD = attention-deficit/hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, TR; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-46. KQ 5a: Pharmacotherapy dose comparisons**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Atkinson, 2018 <sup>59</sup>	United States and Chile RCT NR	MDD	Met DSM -IV-TR criteria for MDD as the primary diagnosis	IG1: Low-dose desvenlafaxine (n=122) IG2: High-dose desvenlafaxine (n=121) CG: Placebo (n=120) 8 weeks	Mean age: IG1: 13.1 IG2: 12.9 CG: 13.2 (A, C) Age range: 7 to 17  Female: 57%  White: IG1: 70% IG2: 64% CG: 71%  Baseline depression IG1: 86 (70.49) IG2: 78 (64.46) CG: 85 (70.83)  Comorbid conditions Psych. condition other than MDD, % IG1: 23.0 IG2: 27.3 CG: 24.2  ADHD, % IG1: 9.8 IG2: 9.9 CG: 7.5	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms	
Atkinson, 2018 <sup>59</sup> (continued)					Self-injurious behavior, % IG1: 4.9 IG2: 9.1 CG: 6.7  Insomnia, % IG1: 7.4 IG2: 5.8 CG: 4.2			
Durgam, 2018 <sup>40</sup>	United States RCT Study centers	MDD	Diagnosis of MDD for a minimum of 6 weeks (based on DSM-IV-TR criteria and confirmed by K- SADS-PL)	IG1: Vilazodone 15 mg/d (n=175) IG2: Vilazodone 30 mg/d (n=180) CG: Placebo (n=174) 10 weeks	Mean age: IG1: 14.9 IG2: 14.6 CG: 14.9 (A) Age range: 12 to 17  Female: IG1: 59% IG2: 60% CG: 60%  White: IG1: 66% IG2: 67% CG: 64%  Baseline depression CDRS-R total score, mean (SD) IG1: 57.8 (8.7) IG2: 56.8 (8.5) CG: 57.5 (8.6)  CGI-S score, mean (SD) IG1: 4.6 (0.6) IG2: 4.6 (0.6) CG: 4.5 (0.6)	Some concerns	Some concerns	

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Emslie 2014 <sup>46</sup>	United States, Canada, Mexico, and Argentina RCT 60 psychiatric clinical sites	Mix	MDD or other depressive disorders	IG1: Duloxetine 60 mg QD (n=108) IG2: Duloxetine 30 mg QD (n=116) IG3: Fluoxetine 20 mg QD (n=117) CG: Placebo (n=122) 10 weeks	Mean age: IG1: 12.9 IG2: 12.9 IG3: 13.0 CG: 13.1 (A, C) Age range: 11 to 17  Female: IG1: 56% IG2: 41% IG3: 52% CG: 57%  White: IG1: 53% IG2: 54% IG3: 59% CG: 52%  Baseline depression CDS-R mean (SE) IG1: 59.3 (10.9) IG2: 59.8(11.0) IG3: 57.9(10.1) CG: 58.2(9.4)  CGI-S IG1: 4.6 (0.7) IG2: 4.6 (0.7) IG3: 4.6 (0.6) CG: 4.5 (0.6)	High	High

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
Emslie 2014 <sup>46</sup> (continued)						Comorbid conditions Asthma: 8.2% Dysmenorrhea (females only): 5.1% Insomnia: 4.5% Oppositional defiant disorder: 4.1% Generalized anxiety disorder: 2.2%		

A, C = adolescent/child; ADHD = attention-deficit/hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised; CDS-R = Carroll Depression Scales - Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, TR; IG = intervention group; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime version; KQ = Key Question; MDD = major depressive disorder; mg/d = milligram per day; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation; SE = standard error.



**Table D-47. KQ 5a: Treatment-resistant depression interventions**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:	RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases		
Brent, 2008 <sup>88</sup> Index	United States RCT Academic or community clinics	MDD	Active treatment for MDD according to the DSM-IV	IG1: Switch to a second, different SSRI (citalopram, or fluoxetine, 20-40 mg) (n=85) IG2: Switch to a different SSRI plus CBT (n=83) IG3: Switch to 150- 225 mg venlafaxine (n=83) IG4: Switch to venlafaxine plus CBT (n=83) 12 weeks	Mean age: IG1+IG2: 16.0 IG3+IG4: 15.8 (A) Age range: 12 to 18  Female: 70% White: 82%  Baseline depression CDRS-R average score (95% CI): 59 (58-60) Depression duration ≥2 yrs (%): 56.3  Comorbid conditions N (%) Anxiety (including PTSD) IG1+IG2: 59 (36.4) IG3+IG4: 60 (36.4) p=0.99  IG1+IG3: 60 (35.9) IG2+IG4: 59 (36.9) p=0.86  Dysthymia IG1+IG2: 45 (27.1) IG3+IG4: 53 (32.1) p=0.32  IG1+IG3: 51 (30.5) IG2+IG4: 47 (28.7) p=0.71	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 2008 <sup>88</sup> Index (continued)					ADHD IG1+IG2: 26 (15.8) IG3+IG4: 26 (15.7) p=0.98  IG1+IG3: 23 (13.8) IG2+IG4: 29 (17.7) p=0.33		
Brent, 2008 <sup>88</sup> Companion: Asarnow, 2009 <sup>89</sup>	United States RCT Academic or community clinics	MDD	Active treatment for MDD according to the DSM-IV	IG1: Switch to a second, different SSRI (citalopram, or fluoxetine, 20-40 mg) (n=85) IG2: Switch to a different SSRI plus CBT (n=83) IG3: Switch to 150- 225 mg venlafaxine (n=83) IG4: Switch to venlafaxine plus CBT (n=83) 12 weeks	Mean age: IG1+IG2: 16.0 IG3+IG4: 15.8 (A) Age range: 12 to 18  Female: 70% White: 82%  Baseline depression CDRS-R average score (95% CI): 59 (58-60) Depression duration ≥2 yrs (%): 56.3  Comorbid conditions Comorbidity, N (%) Anxiety (including PTSD) IG1+IG2: 59 (36.4) IG3+IG4: 60 (36.4) p=0.99  IG1+IG3: 60 (35.9) IG2+IG4: 59 (36.9) p=0.86	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality—Benefits	RoB Study Quality—Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases				
Brent, 2008 <sup>88</sup> Companion: Asarnow, 2009 <sup>89</sup> (continued)					Dysthymia: IG1+IG2: 45 (27.1) IG3+IG4: 53 (32.1) p=0.32  IG1+IG3: 51 (30.5) IG2+IG4: 47 (28.7) p=0.71  ADHD: IG1+IG2: 26 (15.8) IG3+IG4: 26 (15.7) p=0.98  IG1+IG3: 23 (13.8) IG2+IG4: 29 (17.7) p=0.33				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 2008 <sup>88</sup> Companion: Brent, 2009 <sup>90</sup>	United States RCT Academic or community clinics	MDD	Active treatment for MDD according to the DSM-IV	IG1: Switch to a second, different SSRI (citalopram, or fluoxetine, 20-40 mg) (n=85) IG2: Switch to a different SSRI plus CBT (n=83) IG3: Switch to 150- 225 mg venlafaxine (n=83) IG4: Switch to venlafaxine plus CBT (n=83) 12 weeks	Mean age: IG1+IG2: 16.0 IG3+IG4: 15.8 (A) Age range: 12 to 18  Female: 70%  White: 82%  Baseline depression CDRS-R average score (95% CI): 59 (58-60) Depression duration ≥2 yrs (%): 56.3  Comorbid conditions N (%) Anxiety (including PTSD) IG1+IG2: 59 (36.4) IG3+IG4: 60 (36.4) p=0.99  IG1+IG3: 60 (35.9) IG2+IG4: 59 (36.9) p=0.86  Dysthymia: IG1+IG2: 45 (27.1) IG3+IG4: 53 (32.1) p=0.32	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 2008 <sup>88</sup> Companion: Brent, 2009 <sup>90</sup> (continued)					IG1+IG3: 51 (30.5) IG2+IG4: 47 (28.7) p=0.71  ADHD: IG1+IG2: 26 (15.8) IG3+IG4: 26 (15.7) p=0.98  IG1+IG3: 23 (13.8) IG2+IG4: 29 (17.7) p=0.33		
Heiligenstein, 2006 <sup>91</sup>	Unites States RCT Clinic	MDD	Primary diagnosis of nonpsychotic MDD (single or recurrent) as defined by DSM-IV criteria	IG: Dose-titration of fluoxetine dose from 20 mg/day to 40-60 mg/day (n=14) CG: Continued treatment with fluoxetine at fixed dose of 20 mg/day (n=15) 10 weeks	Mean age: IG: 13.6 CG: 12.3 (A, C) Age range: 8 to 17  Female: IG: 36% CG: 40%  White: 90%  Baseline depression CDRS-R: IG: 46.9 (12.7) CG: 42.7 (9.6)  CGI-S: IG: 3.9 (0.8) CG: 3.6 (0.8)	Some concerns	Some concerns

A, C = adolescent/child; ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CI = confidence interval; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RoB = risk of bias; SSRI = selective serotonin reuptake inhibitors; yrs = years.

**Table D-48. KQ 5b: Subpopulation analysis of psychotherapy within-type comparisons of delivery methods or approaches**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Rohde, 1994 <sup>74</sup>	United States RCT NR	MDD	Diagnosis of MDD based on DSM-III	IG: CBT group for adolescents (N1=13 and N2=31) IG2: CBT group for adolescents with a separate group for parents (N1=9 and N2=29) CG: Waiting list (N1=9 and N2=24) N1: 14 2-hour sessions for adolescents; 7 2- hour sessions for parents N2: 16 2-hour sessions for adolescents; 9 2- hour sessions for parents	Mean age: IG: 16.3 CG: 16.3 (A) Age range: 14 to 18  Female: IG: 65% CG: 74%  White: IG: 87% CG: 99%  Baseline depression BDI Sample 1 Low severity IG1: 11.8 (6.1) IG2: 20.6 (8.6) CG: 22.0 (7.8)  High severity IG1: 33.5 (5.7) IG2: 26.0 (9.1) CG: 28.8 (5.6)  Sample 2 Low severity IG1: 24.2 (6.8) IG2: 21.7 (5.8) CG: 18.6 (7.8)	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms	
Rohde, 1994 <sup>74</sup> (continued)					High severity IG1: 34.1 (7.2) IG2: 31.3 (7.6) CG: 33.2 (7.9)			
					CES-D Sample 1 Low severity IG1: 11.0 (6.2) IG2: 13.6 (7.1) CG: 13.8 (2.9)			
					High severity IG1: 17.4 (3.2) IG2: 14.0 (5.0) CG: 17.0 (3.4)			
					Sample 2 Low severity IG1: 36.9 (9.0) IG2: 35.2 (5.5) CG: 33.7 (8.9)			
					High severity IG1: 47.5 (5.0) IG2: 45.9 (5.6) CG: 45.9 (5.8)			



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms	
Rohde, 1994 <sup>74</sup> (continued)					HDRS Sample 2 Low severity IG1: 12.0 (4.3) IG2: 10.3 (3.3) CG: 12.6 (4.1)  High severity IG1: 16.1 (5.9) IG2: 19.5 (4.4) CG: 18.5 (5.8)			

A = adolescent; BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CES-D = Center for Epidemiologic Studies Depression Scale; CG = control group; DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition; HDRS = Hamilton Rating Scale for Depression; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias.

**Table D-49. KQ 5b: Subpopulation analysis of psychotherapy versus pharmacotherapy**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Index	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Curry, 2006 <sup>4</sup> Index	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2009 <sup>8</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADs total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31  Oppositional defiant disorder ADHD: 29.03 No ADHD: 10.61	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Foster, 2018 <sup>92</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADS total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
March, 2004 <sup>3</sup>						Oppositional defiant disorder		
Companion:						ADHD: 29.03		
Foster, 2018 <sup>92</sup>						No ADHD: 10.61		
(continued)								

A = adolescent; ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; NR = not reported; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-50. KQ 5b: Subpopulation analysis of psychotherapy plus pharmacotherapy versus psychotherapy**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Index	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4 Disruptive behavior: 23.5 ADHD: 13.7	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Curry, 2006 <sup>4</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratovichil, 2009 <sup>8</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADs total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
March, 2004 <sup>3</sup>						Oppositional defiant disorder		
Companion:						ADHD: 29.03		
Kratochvil, 2009 <sup>8</sup>						No ADHD: 10.61		
(continued)								

A = adolescent; ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; NR = not reported; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-51. KQ 5b: Subpopulation analysis of psychotherapy plus pharmacotherapy versus pharmacotherapy**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Curry, 2006 <sup>4</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: 14.6 (A) Age range: 12 to 17  Female: 54%  Black: 13% Hispanic: 9%  Baseline depression CDRS-R raw score, mean (SD): 60 (10.4) CDRS-R normed t score, mean (SD): 76 (6.43) CGI-S, mean (SD): 4.77 (0.83)  Comorbid conditions Anxiety: 27.4% Disruptive behavior: 23.5% ADHD: 13.7%	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Kratochvil, 2009 <sup>8</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADs total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31  Oppositional defiant disorder ADHD: 29.03 No ADHD: 10.61	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Foster, 2018 <sup>92</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADs total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31  Oppositional defiant disorder ADHD: 29.03 No ADHD: 10.61	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
March, 2004 <sup>3</sup> Companion: Foster, 2019 <sup>93</sup>	United States RCT Clinic	MDD	DSM-IV diagnosis of MDD	IG1: Fluoxetine+CBT (n=107) IG2: Fluoxetine (n=109) IG3: CBT (n=111) CG: Placebo (n=112) 12 weeks	Mean age: ADHD: 14.6 No ADHD: NR (A) Age range: 12 to 17  Female: ADHD: 34% No ADHD: 58%  White: ADHD: 81% No ADHD: 73%  Baseline depression CDRS-R total, mean (SD) ADHD: 57.58 (9.87) No ADHD: 60.52 (10.43)  RADs total, mean (SD) ADHD: 74.46 (12.61) No ADHD: 80.01 (14.48)  Comorbid diagnosis Anxiety disorder ADHD: 19.35 No ADHD: 28.72  Dysthymia ADHD: 17.74 No ADHD: 9.31	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			
					Mean Age	% Female	RoB Study Quality— Benefits	RoB Study Quality— Harms
					% White	Baseline Depression Severity		
						Prior Traumatic Event Exposure		
						Diagnosed Comorbid Conditions or Diseases		
March, 2004 <sup>3</sup>						Oppositional defiant disorder		
Companion:						ADHD: 29.03		
Foster, 2019 <sup>93</sup>						No ADHD: 10.61		
(continued)								

A = adolescent; ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; KQ = Key Question; IG = intervention group; MDD = major depressive disorder; NR = not reported; RADS = Reactive Airways Dysfunction Syndrome; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-52. KQ 5b: Subpopulation analysis of SSRIs versus TCAs**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
GlaxoSmithKline, 1998 <sup>48</sup>	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18			High	Not applicable
					Female: IG1: 62% IG2: 59% CG: 66%				
					White: IG1: 83% IG2: 87% CG: 81%				
					Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)				
					Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%				



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
GlaxoSmithKline, 1998 <sup>48</sup> (continued)					Anxiety disorder IG1: 19% IG2: 26% CG: 28%				
					Externalizing disorder IG1: 25% IG2: 26% CG: 20%				
GlaxoSmithKline, 1998 <sup>48</sup> Companion: Keller, 2001 <sup>50</sup> Index	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18  Female: IG1: 62% IG2: 59% CG: 66%  White: IG1: 83% IG2: 87% CG: 81%  Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)			High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
GlaxoSmithKline, 1998 <sup>48</sup> Companion: Keller, 2001 <sup>50</sup> Index (continued)							Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%		
							Anxiety disorder IG1: 19% IG2: 26% CG: 28%		
							Externalizing disorder IG1: 25% IG2: 26% CG: 20%		

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
GlaxoSmithKline, 1998 <sup>48</sup> Companion: Le Noury, 2015 <sup>49</sup>	United States and Canada RCT Academic psychiatry centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 8 weeks	Mean age: IG1: 14.8 IG2: 14.9 CG: 15.1 (A) Age range: 12 to 18			High	Not applicable
					Female: IG1: 62% IG2: 59% CG: 66%				
					White: IG1: 83% IG2: 87% CG: 81%				
					Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)				
					Comorbid conditions Any concomitant diagnosis IG1: 41% IG2: 50% CG: 45%				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
GlaxoSmithKline, 1998 <sup>48</sup> Companion: Le Noury, 2015 <sup>49</sup> (continued)					Anxiety disorder IG1: 19% IG2: 26% CG: 28%				
					Externalizing disorder IG1: 25% IG2: 26% CG: 20%				
GlaxoSmithKline, 1998 <sup>48</sup> Companion: Le Noury, 2016 <sup>51</sup>	United States and Canada RCT Study centers	MDD	Met DSM-IV criteria for major depression for at least 8 weeks	IG1: Paroxetine (n=93) IG2: Imipramine (n=95) CG: Placebo (n=87) 6 months	Mean age: IG1: 14.8 IG2: 14.8 CG: 15.0 (A) Age range: 12 to 18  Female: IG1: 65% IG2: 46% CG: 68%  White: IG1: 84% IG2: 92% CG: 81% (calculated)  Baseline depression HAM-D: Mean (SD) IG1: 18.98 (0.43) IG2: 18.11 (0.43) CG: 18.97 (0.44)			High	Not applicable

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White		
					Baseline Depression Severity	Prior Traumatic Event Exposure	Diagnosed Comorbid Conditions or Diseases		
Weihls, 2018 <sup>55</sup>	United States, Mexico RCT Hospitals, academic institutions, private clinics, and clinical trial research centers	MDD	Meeting DSM-IV-TR criteria for MDD	IG1: Desvenlafaxine (25, 35, or 50 mg/d) (n=115) IG2: Fluoxetine (20 mg/d) (n=113) CG: Placebo (n=112) 8 weeks	Mean age: Children: 9.4 Adolescent: 14.8 (A, C) Age range: 7 to 17	Female: 54% (calculated)	White: 65% (calculated)	High	Uncertain
					Baseline depression CDRS-R total score: Mean (SD) 56.5 (8.9)				
					CGI-S score: Mean (SD) 4.5 (0.6)				
					Comorbid diagnosis ADHD				
					IG1: 12.2%				
					IG2: 13.4%				
					CG: 5.4				
					Nonsuicidal self-injurious behavior				
					IG1: 7.0%				
					IG2: 8.0%				
					CG: 12.5%				
					Insomnia				
					IG1: 7.0%				
					IG2: 6.3%				
					CG: 8.0%				

A = adolescent; A, C = adolescent/child; ADHD = attention-deficit/hyperactivity disorder; CDS-R = Carroll Depression Scales - Revised; CG = control group; CGI-S = Clinical Global Impression Scale-Severity Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, TR; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

**Table D-53. KQ 5b: Subpopulation analysis of pharmacotherapy dose comparisons**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Atkinson, 2018 <sup>59</sup>	United States and Chile RCT NR	MDD	Met DSM-IV-TR criteria for MDD as the primary diagnosis	IG1: Low-dose desvenlafaxine (n=122) IG2: High-dose desvenlafaxine (n=121) CG: Placebo (n=120) 8 weeks	Mean age: IG1: 13.1 IG2: 12.9 CG: 13.2 (A, C) Age range: 7 to 17  Female: 57%  White: IG1: 70% IG2: 64% CG: 71%  Baseline depression IG1: 86 (70.49) IG2: 78 (64.46) CG: 85 (70.83)  Comorbid conditions Psych. condition other than MDD, % IG1: 23.0 IG2: 27.3 CG: 24.2  ADHD, % IG1: 9.8 IG2: 9.9 CG: 7.5	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:				RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age	% Female	% White	Baseline Depression Severity		
Atkinson, 2018 <sup>59</sup> (continued)					Self-injurious behavior, %					
					IG1: 4.9					
					IG2: 9.1					
					CG: 6.7					
					Insomnia, %					
					IG1: 7.4					
					IG2: 5.8					
					CG: 4.2					
A, C = adolescent/child; ADHD = attention-deficit/hyperactivity disorder; CG = control group; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, TR; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; n = number; RCT = randomized controlled trial; RoB = risk of bias.										

**Table D-54. KQ 5b: Subpopulation analysis of TRD interventions**

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 2008 <sup>88</sup> Index	United States RCT Academic or community clinics	MDD	Active treatment for MDD according to the DSM-IV	IG1: Switch to a second, different SSRI (citalopram, or fluoxetine, 20-40 mg) (n=85) IG2: Switch to a different SSRI plus CBT (n=83) IG3: Switch to 150-225 mg venlafaxine (n=83) IG4: Switch to venlafaxine plus CBT (n=83) 12 weeks	Mean age: IG1+IG2: 16.0 IG3+IG4: 15.8 (A) Age range: 12 to 18  Female: 70% White: 82%  Baseline depression CDRS-R average score (95% CI): 59 (58-60) Depression duration ≥2 yrs (%): 56.3  Comorbid conditions N (%) Anxiety (including PTSD) IG1+IG2: 59 (36.4) IG3+IG4: 60 (36.4) p=0.99  IG1+IG3: 60 (35.9) IG2+IG4: 59 (36.9) p=0.86  Dysthymia IG1+IG2: 45 (27.1) IG3+IG4: 53 (32.1) p=0.32  IG1+IG3: 51 (30.5) IG2+IG4: 47 (28.7) p=0.71	Some concerns	Some concerns



Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics: Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 2008 <sup>88</sup> Index (continued)					ADHD IG1+IG2: 26 (15.8) IG3+IG4: 26 (15.7) p=0.98  IG1+IG3: 23 (13.8) IG2+IG4: 29 (17.7) p=0.33		
Brent, 2008 <sup>88</sup> Companion: Asarnow, 2009 <sup>89</sup>	United States RCT Academic or community clinics	MDD	Active treatment for MDD according to the DSM-IV	IG1: Switch to a second, different SSRI (citalopram, or fluoxetine, 20-40 mg) (n=85) IG2: Switch to a different SSRI plus CBT (n=83) IG3: Switch to 150-225 mg venlafaxine (n=83) IG4: Switch to venlafaxine plus CBT (n=83) 12 weeks	Mean age: IG1+IG2: 16.0 IG3+IG4: 15.8 (A) Age range: 12 to 18  Female: 70%  White: 82%  Baseline depression CDRS-R average score (95% CI): 59 (58-60) Depression duration ≥2 yrs (%): 56.3  Comorbid conditions Comorbidity, N (%) Anxiety (including PTSD) IG1+IG2: 59 (36.4) IG3+IG4: 60 (36.4) p=0.99	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:			RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White	Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases			
Brent, 2008 <sup>88</sup> Companion: Asarnow, 2009 <sup>89</sup> (continued)					IG1+IG3: 60 (35.9) IG2+IG4: 59 (36.9) p=0.86  Dysthymia: IG1+IG2: 45 (27.1) IG3+IG4: 53 (32.1) p=0.32  IG1+IG3: 51 (30.5) IG2+IG4: 47 (28.7) p=0.71  ADHD: IG1+IG2: 26 (15.8) IG3+IG4: 26 (15.7) p=0.98  IG1+IG3: 23 (13.8) IG2+IG4: 29 (17.7) p=0.33				

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases	RoB Study Quality— Benefits	RoB Study Quality— Harms
Brent, 2008 <sup>88</sup> Companion: Brent, 2009 <sup>90</sup>	United States RCT Academic or community clinics	MDD	Active treatment for MDD according to the DSM-IV	IG1: Switch to a second, different SSRI (citalopram, or fluoxetine, 20-40 mg) (n=85) IG2: Switch to a different SSRI plus CBT (n=83) IG3: Switch to 150-225 mg venlafaxine (n=83) IG4: Switch to venlafaxine plus CBT (n=83) 12 weeks	Mean age: IG1+IG2: 16.0 IG3+IG4: 15.8 (A) Age range: 12 to 18  Female: 70%  White: 82%  Baseline depression CDRS-R average score (95% CI): 59 (58-60) Depression duration ≥2 yrs (%): 56.3  Comorbid conditions N (%) Anxiety (including PTSD) IG1+IG2: 59 (36.4) IG3+IG4: 60 (36.4) p=0.99  IG1+IG3: 60 (35.9) IG2+IG4: 59 (36.9) p=0.86	Some concerns	Some concerns

Author, Year	Study Country Study Design Study Setting	Type of Depression (MDD or Mix)	Type of Depression/ Severity	Intervention and Comparison (n) Length of Intervention	Patient Characteristics:		RoB Study Quality— Benefits	RoB Study Quality— Harms
					Mean Age % Female % White Baseline Depression Severity Prior Traumatic Event Exposure Diagnosed Comorbid Conditions or Diseases			
Brent, 2008 <sup>88</sup> Companion: Brent, 2009 <sup>90</sup> (continued)					Dysthymia: IG1+IG2: 45 (27.1) IG3+IG4: 53 (32.1) p=0.32  IG1+IG3: 51 (30.5) IG2+IG4: 47 (28.7) p=0.71  ADHD: IG1+IG2: 26 (15.8) IG3+IG4: 26 (15.7) p=0.98  IG1+IG3: 23 (13.8) IG2+IG4: 29 (17.7) p=0.33			

A = adolescent; ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CI = confidence interval; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; n/N = number; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RoB = risk of bias; SSRI = selective serotonin reuptake inhibitors; yrs = years.

## Appendix E. Evidence Tables

Table E-1. KQ 1a: Benefits of CBT versus pill placebo.....	3
Table E-2. KQ 1a: Benefits of CBT versus wait-list control.....	27
Table E-3. KQ 1a: Benefits of CBT (delivered to adolescent and parent) versus wait-list control.....	29
Table E-4. KQ 1a: Benefits of CBT+TAU versus TAU/UC.....	30
Table E-5. KQ 1a: Benefits of CBT (modified) versus UC.....	35
Table E-6. KQ 1a: Benefits of CBT versus active control .....	36
Table E-7. KQ 1a: Benefits of relapse prevention CBT + continued antidepressant medication management versus continued medication management.....	43
Table E-8. KQ 1a: Benefits of IPT versus wait-list control.....	51
Table E-9. KQ 1a: Benefits of IPT versus active control (clinical monitoring) .....	52
Table E-10. KQ 1a: Benefits of family-based IPT versus active control .....	53
Table E-11. KQ 1a: Benefits of attachment-based family therapy versus wait-list control .....	55
Table E-12. KQ 1a: Benefits of attachment-based family therapy versus treatment as usual.....	56
Table E-13. KQ 1a: Benefits of family therapy versus placebo .....	57
Table E-14. KQ 1a: Benefits of family therapy versus active control.....	58
Table E-15. KQ 1a: Benefits of PCIT versus active control.....	62
Table E-16. KQ 1a: Benefits of short-term psychoanalytic therapy versus active control.....	63
Table E-17. KQ 1a: Benefits of exercise versus active control .....	67
Table E-18. KQ 1a: Benefits of spirituality versus wait-list.....	69
Table E-19. KQ 1a: Benefits of omega-3 versus pill placebo .....	70
Table E-20. KQ 2a: Benefits of SSRIs versus placebo.....	71
Table E-21. KQ 2a: Benefits of fluoxetine for relapse prevention versus placebo .....	107
Table E-22. KQ 2a: Benefits of SNRIs versus placebo .....	111
Table E-23. KQ 2a: Benefits of TCAs versus placebo .....	116

Table E-24. KQ 2a: Benefits of MAOIs versus placebo .....	131
Table E-25. KQ 2a: Benefits of venlafaxine plus active control versus placebo plus active control .....	132
Table E-26. KQ 3a: Benefits of fluoxetine plus CBT versus placebo .....	133
Table E-27. KQ 3a: Benefits of CBT versus other psychotherapy .....	158
Table E-28. KQ 5a: Benefits of CBT versus other psychotherapy .....	159
Table E-29. KQ 5a: Benefits of psychotherapy within-type comparisons of delivery methods or approaches .....	167
Table E-30. KQ 5a: Benefits of psychotherapy versus pharmacotherapy .....	177
Table E-31. KQ 5a: Benefits of psychotherapy plus pharmacotherapy versus psychotherapy .....	203
Table E-32. KQ 5a: Benefits of psychotherapy plus pharmacotherapy versus pharmacotherapy.....	230
Table E-33. KQ 5a: Benefits of omega-3 versus other therapies .....	263
Table E-34. KQ 5a: Benefits of SSRIs versus SNRIs .....	264
Table E-35. KQ 5a: Benefits of SSRIs versus TCAs.....	267
Table E-36. KQ 5a: Benefits of pharmacotherapy dose comparisons .....	272
Table E-37. KQ 5a: Benefits of treatment-resistant depression interventions.....	277

**Table E-1. KQ 1a: Benefits of CBT versus pill placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS <sup>92</sup>	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Depression symptoms, ITT (n=439) Adjusted CDRS-R total score 6 weeks, adjusted mean (SD) IG1: 38.10 (7.78) IG2: 39.80 (7.37) IG3: 44.63 (8.30) CG: 44.90 (7.32)  12 weeks, adjusted mean (SD) IG1: 33.79 (8.24) IG2: 36.30 (8.18) IG3: 42.06 (9.18) CG: 41.77 (7.99)  Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement: IG1>CG (p=0.001); IG1=IG2 (p=0.13); IG1>IG3 (p=0.001); IG2>IG3 (p=0.001); IG2>CG (p=0.002); IG3=CG (p=0.97)	Response CGI-I positive response rate, ITT (n=439) 12 weeks, % response rate (95% CI) adjusted for clinical site IG1: 71.0 (62 to 80) IG2: 60.6 (51 to 70) IG3: 43.2 (34 to 52) CG: 34.8 (26 to 44) Regression analyses found treatment was statistically significant factor in  CGI-I positive response (p=0.001) RR (calculated): 2.45; 95% CI, 0.31 to 19.7  12 weeks, statistically comparing	NR	No mortality from completed suicides	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Across all 12 weeks: Time-by-treatment interaction based on CDRS-R random regression slope coefficients: <math>p=0.001</math>; Statistically comparing improvement: IG1&gt;CG (<math>p=0.001</math>); IG1&gt;IG2 (<math>p=0.02</math>); IG1&gt;IG3 (<math>p=0.001</math>); IG2&gt;IG3 (<math>p=0.01</math>); IG2=CG (<math>p=0.10</math>); IG3=CG (<math>p=0.40</math>)</p> <p>Hedge g effect sizes relative to placebo (G4) IG1: 0.98 IG2: 0.68 IG3: -0.03</p> <p>Hedge g effect sizes relative to placebo (CG) derived from ORs for dichotomized CGI-I IG1: 0.84 IG2: 0.58 IG3: 0.20 CG: NA</p>	<p>response: IG1&gt;CG (<math>p=0.001</math>); IG2&gt;CG (<math>p=0.001</math>); IG3=CG (<math>p=0.20</math>); IG1=IG2 (<math>p=0.11</math>); IG1&gt;IG3 (<math>p=0.001</math>); IG2&gt;IG3 (<math>p=0.01</math>)</p>			



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Number needed to treat (NNT) (95% CI)  IG1: 3 (2 to 4)  IG2: 4 (3 to 8)  IG3: 12 (5 to 23)  CG: NA</p> <p>RADS total score  6 weeks, adjusted mean (SD)  IG1: 60.90 (11.59)  IG2: 63.41 (12.44)  IG3: 69.10 (13.59)  CG: 69.43 (10.94)</p> <p>12 weeks, adjusted mean (SD)  IG1: 56.95 (12.24)  IG2: 60.58 (13.07)  IG3: 67.96 (14.18)  CG: 66.68 (11.41)</p> <p>Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement :  IG1&gt;CG (p=0.001);  IG1=IG2 (p=0.11);  IG1&gt;IG3 (p=0.001);  IG2&gt;IG3 (p=0.003);  IG2&gt;CG (p=0.003);  IG3=CG (p=0.94)</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Across all 12 weeks: Time-by-treatment interaction based on RADS random regression slope coefficients: <math>p=0.001</math>; Statistically comparing improvement :</p> <p>IG1&gt;CG (<math>p=0.001</math>); IG1&gt;IG2 (<math>p=0.002</math>); IG1&gt;IG3 (<math>p=0.001</math>); IG2&gt;IG3 (<math>p=0.03</math>); IG2=CG (<math>p=0.34</math>); IG3=CG (<math>p=0.21</math>)</p> <p>NOTE: Means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	<p>Moderation analysis of C-GAS (functional status) by family income, least squares mean (SD) ITT, n=439 at 12 weeks</p> <p>Patients with &lt;\$75,000 (low-to-middle income) IG1: 32.7 (8.7) IG2: 35.3 (8.7) IG3: 43.0 (8.8) CG: 41.4 (9.0)</p> <p>Within the &lt;\$75,000 group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG IG1: 0.98 (p&lt;0.05) IG2: 0.69 (p&lt;0.05) IG3: -0.18 (p=NS)</p> <p>Patients with ≥\$75,000 (high income) IG1: 33.7 (9.6) IG2: 38.0 (9.1) IG3: 35.1 (9.0) CG: 41.7 (9.2)</p> <p>Within the ≥\$75,000 group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1=IG3: p=NS IG1&gt;CG: p&lt;0.05 IG2=IG3: p=NS IG2=CG: p=NS IG3&gt;CG: p&lt;0.05</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Effect size for active treatments vs. CG IG1: 0.85 (p&lt;0.05) IG2: 0.40 IG3: 0.72 (p&lt;0.05)</p> <p>Moderation analysis of C-GAS (functional status) by CGI-S, least squares mean (SD) ITT, n=439 at 12 weeks Patients with mild/moderate CGI-S IG1: 30.9 (7.3) IG2: 35.6 (7.1) IG3: 36.9 (6.9) CG: 38.4 (7.1)</p> <p>Within the mild/moderate CGI-S group, statistical comparisons of how groups compared with one another at 12 weeks:</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						IG1>IG2: p<0.001 IG1>IG3: p<0.001 IG1>CG: p<0.001 IG2=IG3: p=NS IG2>CG: p<0.001 IG3=CG: p=NS  Effect size for active treatments vs. CG IG1: 1.04 (p<0.05) IG2: 0.39 (p<0.05) IG3: 0.21  Patients with marked/severe CGI-S IG1: 35.4 (8.8) IG2: 36.8 (9.3) IG3: 44.0 (9.4) CG: 43.2 (9.6)  Within the marked/severe CGI-S group, statistical comparisons of how groups compared with one another at 12 weeks:

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						IG1=IG2: p=NS IG1>IG3: p<0.001 IG1>CG: p<0.001 IG2>IG3: p<0.001 IG2>CG: p<0.001 IG3=CG: p=NS  Effect size for active treatments vs. CG IG1: 0.84 (p<0.05) IG2: 0.69 (p<0.05) IG3: -0.08  Moderation analysis of CNCEQ (depressive cognitive distortions) Low CNCEQ IG1: 33.2 (7.9) IG2: 35.5 (7.8) IG3: 39.4 (7.6) CG: 41.1 (7.5)  Within the low CNCEQ group, statistical comparisons of how groups compared with one another at 12 weeks:

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						IG1=IG2: p=NS IG1>IG3: p<0.001 IG1>CG: p<0.001 IG2>IG3: p<0.001 IG2>CG: p<0.001 IG3=CG: p=NS  Effect size for active treatments vs. CG IG1: 1.03 (p<0.05) IG2: 0.73 (p<0.05) IG3: 0.22  High CNCEQ IG1: 32.3 (9.8) IG2: 35.9 (10.1) IG3: 41.8 (10.0) CG: 40.6 (10.4)  Within the high CNCEQ group, statistical comparisons of how groups compared with one another at 12 weeks:  IG1>IG2: p<0.001 IG1>IG3: p<0.001 IG1>CG: p<0.001 IG2>IG3: p<0.001 IG2>CG: p<0.001 IG3=CG: p=NS  Effect size for active treatments vs. CG IG1: 0.82 (p<0.05) IG2: 0.46 (p<0.05) IG3: -0.12



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	<p>Loss of MDD diagnosis (K-SADS-P/L) Completers analysis only (n=379): 12 weeks, % IG1: 85.3 IG2: 78.6 IG3: 61.1 CG: 60.4 Overall treatment effect: <math>p \leq 0.0001</math></p> <p>Statistical comparisons found mixed findings in terms of how groups compared with one another, OR (95% CI): IG1=IG2: 1.7 (0.79 to 3.61) (<math>p=0.18</math>); IG1&gt;IG3: 4.3 (2.06 to 8.94) (<math>p=0.0001</math>); IG1&gt;CG: 4.1 (2.00 to 8.44) (<math>p=0.0001</math>); IG2&gt;IG3: 2.5 (1.31 to 4.93) (<math>p=0.006</math>); IG2&gt;CG: 2.4 (1.27 to 4.67) (<math>p=0.007</math>); IG3=CG: 1.0 (0.52 to 1.77) (<math>p=0.89</math>)</p>	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS (continued)			<p>Remission, adjusted for site (CDRS-R) ITT (n=439): 12 weeks, %</p> <p>IG1: 37 IG2: 23 IG3: 16 CG: 17</p> <p>Overall treatment effect: p=0.0007</p> <p>Statistical comparisons found that IG1 was associated with higher remission rates than all other groups, OR (95% CI): IG1&gt;IG2: 2.1 (1.12 to 3.84) (p=0.02); IG1&gt;IG3: 3.3 (1.71 to 6.42) (p=0.0004); IG1&gt;CG: 3.0 (1.58 to 5.79) (p=0.0009)</p> <p>In contrast; IG2; IG3, and CG did not differ statistically from one another (all p &gt;0.05). See comparisons below, OR (95% CI): IG2=IG3: 1.6 (0.80 to 3.19) (p=0.19) IG2=CG: 1.5 (0.74 to 2.88) (p=0.28) IG3=CG: 0.9 (0.44 to 1.88) (p=0.80)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	Functional status (C-GAS) ITT (n=439): 6 weeks, unadjusted mean (SD) IG1: 62.4 (11.2) IG2: 59.9 (10.58) IG3: 56.7 (9.66) CG: 57.0 (9.22)  12 weeks, unadjusted mean (SD) IG1: 66.6 (11.91) IG2: 62.1 (11.91) IG3: 60.0 (11.47) CG: 59.3 (12.72) Time effect in all groups: p<0.0001 Treatment-by-time interaction: p<0.0001  Random-effects regression model (RRM) statistical comparisons of how groups compared with one another at 12 weeks :	Global burden of psychiatric problems (HoNOSCA) ITT (n=439): 12 weeks, unadjusted mean (SD) IG1: 9.5 (5.97) IG2: 10.9 (6.35) IG3: 11.7 (6.09) CG: 11.2 (6.15)  Time effect in all groups: p<0.0001 Treatment-by-time interaction: p<0.0234  Random-effects regression model (RRM) statistical comparisons of how groups compared with one another : IG1=IG2: p=0.1257 IG1>IG3: p=0.0027 IG1>CG: p=0.0393 IG2=IG3: p=0.1310 IG2=CG: p=0.5861 IG3=CG: p=0.3344	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				IG1>IG2: p=0.0450 IG1>IG3: p<0.0001 IG1>CG: p<0.0001 IG2>IG3: p=0.0032 IG2>CG: p=0.0381 IG3=CG: p=0.3805  12 weeks, mean change from baseline (SD) IG1: 16.7 (12.31) IG2: 12.6 (12.31) IG3: 9.7 (12.12) CG: 9.9 (12.38) Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): p<0.0001  GLM statistical comparisons of how groups compared with one another : IG1>IG2: p<0.01 IG1>IG3: p<0.0001 IG1>CG: p<0.0001 IG2>IG3: p=NR IG2=CG: p=NS IG3=CG: p=NS	12 weeks, mean change from baseline (SD) G1: -6.3 (5.69) G2: -5.1 (5.74) G3: -3.6 (5.58) G4: -4.2 (5.71) Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): p<0.01  GLM statistical comparisons of how groups compared with one another at 12 weeks : IG1=IG2: p=NS IG1>IG3: p<0.001 IG1>CG: p<0.01 IG2>IG3: p<0.05 IG2=CG: p=NS IG3=CG: p=NR  HoNOSCA subscores: Treatment-by-time interaction was statistically significant only for item 10 (level of functioning with peers; p=0.0004), whose effect	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				<p>Rate of nonimpaired patients (C-GAS &gt;70) 12 weeks, % IG1: 34.6 IG2: 20.2 IG3: 13.5 CG: 18.7</p> <p>Between-group difference: p=0.002 Statistically significant treatment effects of how groups compared with one another: IG1&gt;IG2: p=0.020 IG1&gt;IG3: p=0.0004 IG1&gt;CG: p=0.009 IG2=IG3: p=NS IG2=CG: p=NS IG3=CG: p=NS</p> <p>Patients not likely to be clinically referred in community (C-GAS&gt;60) 12 weeks, % IG1: 64.5 IG2: 50.5 IG3: 45.0 CG: 35.7 Between-group difference: p=0.0003</p>	<p>remained significant even after applying a Bonferroni correction for multiple comparisons.</p> <p>QoL (PQ-LES-Q) ITT (n=439): 12 weeks, unadjusted mean (SD) IG1: 54.7 (11.21) IG2: 51.2 (10.43) IG3: 47.4 (10.84) CG: 48.2 (9.91) Time effect in all groups: p&lt;0.0001 Treatment-by-time interaction: p&lt;0.0001</p> <p>Random-effects regression model (RRM) statistical comparisons of how groups compared with one another at 12 weeks: IG1&gt;IG2: p=0.0004 IG1&gt;IG3: p&lt;0.0001 IG1&gt;CG: p&lt;0.0001 IG2=IG3: p=0.2766 IG2=CG: p=0.7215 IG3=CG: p=0.4630</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				Statistically significant treatment effects of how groups compared with one another: IG1>IG2: p<0.038 IG1>IG3: p<0.004 IG1>CG: p<0.0001 IG2=IG3: p=NS IG2>CG: p=0.023 IG3=CG: p=NS	12 weeks, mean change from baseline (SD) IG1: 9.6 (10.14) IG2: 6.6 (10.23) IG3: 4.2 (10.01) CG: 5.2 (10.16) Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): p<0.001  Treatment-by-time interaction: p<0.0001 GLM statistical comparisons of how groups compared with one another: IG1>IG2: p<0.05 IG1>IG3: p<0.0001 IG1>CG: p<0.001 IG2>IG3: p=NS IG2=CG: p=NS IG3=CG: p=NS	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	<p>Subgroup Analysis #1: ADHD vs. no ADHD Depression symptoms, ITT (n=429) 12 weeks Main linear RRM effect analyses for overall sample Main effect of time (linear): <math>p&lt;0.001</math> Treatment-by-time interaction: <math>p=0.018</math> ADHD-by-treatment-by-time interaction: <math>p=0.026</math> (confirmed that ADHD status prior to treatment or having an ADHD diagnosis before study entry moderated improvement in depression)</p> <p>Linear RRM effect analyses: ADHD subgroup Main effect of time (linear): <math>p&lt;0.001</math> Treatment-by-time interaction: <math>p=0.038</math></p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Linear RRM effect analyses: No ADHD subgroup Main effect of time (linear): <math>p \leq 0.001</math> Treatment-by-time interaction: <math>p &lt; 0.001</math></p> <p>CDRS-R total score (adjusted for fixed and random effects) 12 weeks, mean (SD) ADHD subgroup IG1 (n=15): 37.08 (9.42) IG2 (n=14): 33.29 (6.42) IG3 (n=14): 35.95 (6.34) CG (n=19): 43.31 (5.65)</p> <p>No ADHD subgroup IG1 (n=92): 33.30 (8.14) IG2 (n=95): 36.83 (8.11) IG3 (n=97): 42.35 (8.96) CG (n=93): 41.39 (8.07)</p>



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Improvement was observed in all arms of both ADHD and no-ADHD subgroups, but patients had different patterns of between-group differences depending on their subgroup.</p> <p>Between-group differences: ADHD subgroup at 12 weeks</p> <p>IG1=IG2=IG3&gt;CG (p=0.046, 0.024, 0.013, respectively)</p> <p>Change trajectories did not differ between arms (p&gt;0.05).</p> <p>Effect sizes IG1 vs. CG: 1.0 IG2 vs. CG: 0.6 IG3 vs. CG: -0.1</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Between-group differences: No-ADHD subgroup at 12 weeks  <math>IG1 &gt; (IG2 &gt; IG3) = CG</math>  (p-values <math>&lt; 0.05</math> for significant differences and <math>&gt; 0.05</math> for nonsignificant differences)</p> <p>Change trajectories:  <math>IG1 &gt; IG2</math>; <math>IG3</math>, and <math>CG</math> (<math>p &lt; 0.009</math>), meaning trajectory in <math>IG1</math> was faster on average than in all other arms. <math>IG2 = CG</math> (<math>p = 0.425</math>) and <math>IG3 = CG</math> (<math>p = 0.065</math>), but <math>IG2 &gt; IG3</math> (<math>p = 0.008</math>). In short; <math>IG3</math> had the most gradual improvement trajectory among active treatments.</p> <p>Effect sizes  <math>IG1</math> vs. <math>CG</math>: 0.8  <math>IG2</math> vs. <math>CG</math>: 1.7  <math>IG3</math> vs. <math>CG</math>: 1.2</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Depression symptoms, ITT (n=327) 36 weeks: Main linear RRM effect analyses for overall sample Main effect of time (linear): <math>p &lt; 0.001</math> ADHD-by-treatment-by-time interaction: <math>p = 0.004</math> ADHD-by-treatment-by-time interaction (squared): <math>p = 0.004</math> (confirmed that ADHD status prior to treatment or having an ADHD diagnosis before study entry moderated improvement in depression at this timepoint)</p> <p>Between-group differences: ADHD subgroup at 36 weeks</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS						<p>Paired contrasts found no between-group differences in mean total CDRS-R scores within this subgroup.</p> <p>Change trajectories: No significant treatment-by-time (squared) or treatment-by-time interactions</p> <p>Between-group differences: No-ADHD subgroup at 36 weeks Paired contrasts found no between-group differences in mean total CDRS-R scores within this subgroup.</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS						<p>Change trajectories: Treatment-by-time (squared) interaction: <math>p &lt; 0.001</math> (suggesting significant different by arm)</p> <p>IG1 &gt; IG2 and IG3 (<math>p &lt; 0.05</math>), meaning trajectory in IG1 was faster on average than other IG arms.</p> <p>Subgroup Analysis #2: ADHD psychostimulant medication vs. none among patients with ADHD</p> <p>Depression symptoms, ITT (n=62 with ADHD)</p> <p>CDRS-R total score (adjusted for fixed and random effects) 12 weeks:</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS						Data values NR, but CDRS-R scores did not differ significantly among the 20/63 patients taking a psychostimulant vs. the 43/63 patients who did not (p=0.056). Treatment-by-psychostimulant use interaction was not significant (p>0.05).

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions Scale-Improvement Scale; CGI-S = Clinical Global Impressions Scale-Severity Scale; CI = confidence interval; CGI-Q = children's negative cognitive error questionnaire; G = group; GLM = generalized linear modeling; HoNOSCA = Health of Nation Outcome Scale – Children and Adolescents; IG = intervention group; ITT = intent to treat; K-SADS-P/L = Kiddie Schedule for Affective Disorders and Schizophrenia; KQ = Key Question; MDD = major depressive disorder; NA = not applicable; NNT = number needed to treat; NS = not significant; OR = odds ratio; PQ-LES-Q = Parent-Child Interaction Therapy Emotion Development; QoL = quality of life; RADS = Reactive Airways Dysfunction Syndrome; RRM = random-effects regression model; SD = standard deviation; TADS = Treatment among Adolescents with Depression.

**Table E-2. KQ 1a: Benefits of CBT versus wait-list control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 1999 <sup>9</sup>	IG1: child CBT IG2: child CBT with separate parent sessions CG: wait-list control	At 8 Weeks: HAM-D: G1: 4.6 (4.8) G2: 6.7 (7.1) G3: 7.7 (7.0)  BDI: G1: 10.1 (9.1) G2: 13.3 (10.9) G3: 16.0 (11.2)  CBCL Depression G1: 11.5 (4.7) G2: 11.7 (6.7) G3: 9.0 (5.9)	Recovery Rates at 8 weeks: G1: 24/37 (64.9%) IG2: 22/32 (68.8%) G3: 13/27 (48.1%) G1+G2 vs. G3: p<0.05; Cohen's h=0.38 (small to medium effect); OR, 2.15 (95% CI, 1.01 to 4.59)  Trend for treated males to have better outcomes than treated females (81.0% vs. 60.4%, p=0.096)	At 8 Weeks: GAF: Pre: G1: 60.4 (6.8) G2: 54.4 (8.2) CG: 58.3 (7.2)  Post: G1: 71.0 (11.7) G2: 69.9 (14.9) CG: 64.5 (11.8)  Group x time: IG1 & 2 combined vs. CG: p<0.05	NR	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Rosello, 1999 <sup>10</sup>	IG1: IPT IG2: CBT CG: Wait list control	CDI score, baseline, Mean (SD): IG1: 21.21 (7.53) IG2: 20.12 (6.95) CG: 20.13 (5.99)  CDI score 12 weeks, Mean (SD): IG1: 10.79 (6.51) IG2: 13.28 (7.61) CG: 15.83 (6.83) P-value for CDI pre vs. post: p>0.01  CDI score 3 months Mean (SD): IG1: 13.75 (9.52) IG2: 8.90 (6.84) CG: NR F value for CDI post-tx vs. followup: F=0.02	Patients in functional range (CS change) at 12 weeks, %: IG1: 82 IG2: 59  Effect size at 12 weeks (size (%): IG1: 0.73 (77) IG2: 0.43 (67)  Decrease in severely depressed adolescents, baseline vs. 12 weeks, %: IG1: 45 IG2: 24 CG: 27  Decrease in severely depressed adolescents, baseline vs. 3 months, %: IG1: 39 IG2: 30 CG: NR	NR	F values for pre/post treatment comparisons on CDI: IG1 vs. IG2: 2.61 IG1 vs. CG: 11.62 (p<0.01) IG2 vs. CG: 2.58 (p<0.05)	NR

BDI = Beck Depression Inventory; CBCL = child behavior checklist; CBT = cognitive behavioral therapy; CG = control group; G = group; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; SD = standard deviation.



**Table E-3. KQ 1a: Benefits of CBT (delivered to adolescent and parent) versus wait-list control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 1999 <sup>9</sup>	IG1: child CBT IG2: child CBT with separate parent sessions CG: wait-list control	At 8 Weeks: HAM-D: G1: 4.6 (4.8) G2: 6.7 (7.1) G3: 7.7 (7.0)  BDI: G1: 10.1 (9.1) G2: 13.3 (10.9) G3: 16.0 (11.2)  CBCL Depression G1: 11.5 (4.7) G2: 11.7 (6.7) G3: 9.0 (5.9)	Recovery Rates at 8 weeks: G1: 24/37 (64.9%) IG2: 22/32 (68.8%) G3: 13/27 (48.1%) G1+G2 vs. G3: p<0.05; Cohen's h=0.38 (small to medium effect); OR, 2.15 (95% CI, 1.01 to 4.59)  Trend for treated males to have better outcomes than treated females (81.0% vs. 60.4%, p=0.096)	At 8 Weeks: GAF: Pre: G1: 60.4 (6.8) G2: 54.4 (8.2) CG: 58.3 (7.2)  Post: G1: 71.0 (11.7) G2: 69.9 (14.9) CG: 64.5 (11.8)  Group x time: IG1 & 2 combined vs. CG: p<0.05	NR	NA

BDI = Beck Depression Inventory; CBCL = child behavior checklist; CBT = cognitive behavioral therapy; CG = control group; G = group; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question.

**Table E-4. KQ 1a: Benefits of CBT+TAU versus TAU/UC**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 2002 <sup>11</sup>	IG: Group CBT (Adolescent Coping With Depression Course)+Usual care CG: Usual care	Depressive symptoms ITT (n=88; IG: 41 and CG: 47) CES-D 8 weeks, mean (SD) IG: 26.7 (12.6) CG: 29.3 (12.8)  12 months, mean (SD) IG: 22.4 (9.2) CG: 23.8 (13.8)  24 months, mean (SD) IG: 24.3 (11.6) CG: 26.3 (12.9)  Treatment-by-time (main effect): F=0.42, p=0.52  HAM-D 8 weeks, mean (SD) IG: 5.5 (5.2) CG: 6.0 (5.1)  12 months, mean (SD) IG: 4.3 (4.2) CG: 3.3 (5.0)  24 months, mean (SD) IG: 4.1 (4.1) CG: 4.4 (5.1) Treatment-by-time (main effect): F=0.26, p=0.61	Cumulative recovery from index depressive diagnosis ITT (n=152; IG: 77 and CG: 75) 8 weeks, calculated N (%) IG: 45 (57.9) CG: 40 (53.2) Between-group p=NS  12 months, calculated N (%) IG: 55 (71.1) CG: 62 (82.1) Between-group p=NS  24 months, calculated N (%) IG: 69 (89.5) CG: 69 (92.3) Between-group p=NS  Cumulative recovery from index depressive diagnosis (combined with more stringent criteria of ≥8 weeks of "well-time" (few	Global functioning ITT (n=88; IG: 41 and CG: 47) GAF 8 weeks, mean (SD) IG: 66.8 (12.5) CG: 66.8 (11.5)  12 months, mean (SD) IG: 74.6 (12.9) CG: 76.8 (10.2)  24 months, mean (SD) IG: 73.9 (12.4) CG: 76.3 (10.8) Treatment-by-time (main effect): F=0.16, p=0.69	NA	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 2002 <sup>11</sup> (continued)		CBCL Depression 8 weeks, mean (SD) IG: 10.2 (5.8) CG: 8.9 (5.1)  12 months, mean (SD) IG: 8.2 (6.4) CG: 8.4 (5.4)  24 months, mean (SD) IG: 8.4 (7.4) CG: 8.0 (5.5) Treatment-by-time (main effect): $F=0.02$ , $p=0.88$  CBCL Internalizing 8 weeks, mean (SD) IG: 18.5 (11.8) CG: 16.2 (9.0)  12 months, mean (SD) IG: 15.6 (13.0) CG: 15.2 (8.4)  24 months, mean (SD) IG: 16.4 (15.5) CG: 15.0 (9.4) Treatment-by-time (main effect): $F=0.07$ , $p=0.80$  CBCL Externalizing 8 weeks, mean (SD) IG: 16.1 (12.4) CG: 14.4 (8.5)	or no depressive symptoms ITT (n=152; IG: 77 and CG: 75)  8 weeks, calculated N (%) IG: 24 (31.6) CG: 22 (29.8) Between-group $p=NS$			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 2002 <sup>11</sup> (continued)		12 months, mean (SD) IG: 12.0 (11.3) CG: 12.7 (9.6)				
		24 months, mean (SD) IG: 13.6 (15.6) CG: 10.8 (10.9) Treatment-by-time (main effect): F=2.12, p=0.15				
Clarke 2016 <sup>94</sup>	IG: TAU+ CBT CG: self-selected TAU	ITT (n=212; IG=106; CG=106) CDRS (week 12) Mean (SD) IG: 33.56 (10.35) CG: 40.67 (13.21)  CDRS (week 52) IG: 30.14 (11.26) CG: 28.24 (10.54)  CDRS (week 104) IG: 28.11 (9.88) CG: 29.17 (10.79)  CDRS Effect Size through 52 weeks d=0.278 -2.25 (-4.45~0.05)  CDRS Effect Size (52-104 weeks) d=0.145 -1.30 (-3.73~1.14)	ITT (n=212; IG=106; CG=106)  Weeks to Recovery Mean (95% CI), Median IG: 22.6 (18.7-26.5), 15 CG: 30.0 (25.3 - 34.7), 23  MD Recovery: Baseline n (%) IG: 0 (0%) CG: 0 (0%)  MD Recovery: Week 12 n (%) IG: 31 (31.3%) CG: 12 (12.1%)  MD Recovery: Week 52 n (%) IG: 79 (79.8%) CG: 68 (68.7%)	ITT (n=212; IG=106; CG=106)  CGAS (baseline) Mean (SD) IG: 58.38 (6.12) CG: 57.33 (6.88)  CGAS (week 12) Mean (SD) IG: 69.23 (8.86) CG: 63.91 (10.23)  CGAS (week 52) IG: 72.33 (9.97) CG: 74.10 (10.81)  CGAS (week 104) IG: 76.86 (11.03) CG: 76.45 (11.09)  CGAS Effect Size (thru 52 weeks) d=0.431 4.2 (1.55~6.86)  CGAS Effect Size (52-104 weeks) d=0.016 0.13 (-2.08~2.34)	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke 2016 <sup>94</sup> (continued)			<p>MD Recovery: Week 104 n (%) IG: 88 (88.9%) CG: 78 (78.8%)</p> <p>MD Recovery(thru 52 weeks) NNT=10 1.60 (1.15~2.21)</p> <p>MD Recovery (52-104 weeks) NNT=10 1.59(1.17~2.17)</p> <p>MD Response: Baseline n (%) IG: 0 (0%) CG: 0 (0%)</p> <p>MD Response: Week 12 n (%) IG: 68 (68.7%) CG: 47 (47.5%)</p> <p>MD Response: Week 52 n (%) IG: 90 (90.9%) CG: 87 (87.9%)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke 2016 <sup>94</sup> (continued)			MD Response: Week 104 n (%) IG: 93 (93.9%) CG: 91 (91.9%)  MD Recovery(thru 52 weeks) NNT=34 1.39 (1.03~1.87)  MD Recovery (52-104 weeks) NNT=50 1.38(1.03~1.27)			

CBCL-Depression = child behavior checklist - depression; CBT = cognitive behavioral therapy; CES-D = Center for Epidemiologic Studies Depression Scale; CG = control group; CGAS = Children's Global Assessment Scale; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; ITT = intent to treat; KQ = Key Question; MD = major depression; NA = not applicable; NR = not reported; NS = not significant; SD = standard deviation; TAU = treatment as usual.

**Table E-5. KQ 1a: Benefits of CBT (modified) versus UC**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Shirk, 2014 <sup>14</sup>	IG: Modified Cognitive Behavioral Therapy (m-CBT) CG: Usual care	BDI-II at intake (ITT): Mean (SD) IG: 29.85 (10.56) CG: 32.21 (12.99)  BDI-II at 16 weeks (ITT): Mean (SD) IG: 21.35 (11.62) CG: 19.38 (13.47) Tx group: F(1,42).06, p.81 Tx* time: F(1,42) 1.76, p.19	Remitted depression dx at 16 weeks (ITT): IG: 50.0% CG: 48.0%	NR	NR	"Owing to the limited number of males in the sample (7) and the fact that no males had observations for Sessions 8 or 12 in the m-CBT group, only data from females were analyzed."  BDI-II at 16 weeks (females): Tx group: F(1,54).09, p.12 Tx*time: F(5,128) 1.80, p.12

BDI-II = Beck Depression Inventory-II; CG = control group; IG = intervention group; ITT = intent to treat; m-CBT = modified cognitive behavioral therapy; KQ = Key Question; NR = not reported; SD = standard deviation; tx = treatment.

**Table E-6. KQ 1a:Benefits of CBT versus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Brent, 1997 <sup>12</sup> Index article	IG1: Individual CBT IG2: SBFT CG: Nondirective supportive therapy (NST)	MDD episode, % 6 weeks IG1: 60.0 IG2: 65.5 CG: 63.3 p=0.90  12-16 weeks IG1: 17.1 IG2: 32.3 CG: 42.4 Difference among 3 groups: X2=5.22; df=2; p=0.07 Pairwise difference (IG1 vs. CG): X2=5.23; df=1; p=0.02  BDI, mean (SD) 6 weeks IG1: 10.7 (11.1) IG2: 13.7 (9.3) CG: 13.4 (10.7) p=0.44  12-16 weeks IG1: 5.7 (8.6) IG2: 9.1 (9.1) CG: 9.8 (11.4) p=0.19 Difference among 3 groups: X2=5.70; df=2; p=0.06 IG1 showing more rapid response than CG: X2=5.10; df=1; p=0.02	Overall achievement of clinical response Overall achievement of clinical response data were estimated using software from Figure 2.  Overall difference: X2=5.28; df=2; p=0.07 Pairwise difference (IG1 vs. IG2): X2=4.84; df=1; p=0.03 IG1: 66.3 IG2: 39.6 CG: 42.9  Overall achievement of remission (%) 6 weeks IG1: 16.7 IG2: 6.2 CG: 16.7 p=0.37  12-16 weeks IG1: 60.0 IG2: 29.0 CG: 36.4	CGAS <60 (%) 6 weeks IG1: 34.3 IG2: 37.9 CG: 43.3 p=0.76  12-16 weeks IG1: 25.7 IG2: 35.5 CG: 33.3 p=0.66  No significant treatment x time interaction on the CGAS (treatment=NS, time <.01)	NR	NR



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Brent, 1997 <sup>12</sup> Index article (continued)		DEP13, mean (SD) 6 weeks IG1: 2.1 (0.7) IG2: 2.1 (0.6) CG: 2.1 (0.5) p=0.91  12-16 weeks IG1: 1.5 (0.5) IG2: 1.7 (0.6) CG: 1.8 (0.8) p=0.15 Difference among 3 groups: X <sup>2</sup> =6.15; df=2; p=0.05 IG1 showing more rapid response than IG2: X <sup>2</sup> =4.74; df=1; p=0.03 IG1 showing more rapid response than CG: X <sup>2</sup> =4.84; df=1; p=0.03	Rate of remission (%) IG1: 60.0 IG2: 37.9 CG: 39.4 Overall difference: X <sup>2</sup> =5.96; df=2; p=0.05 Pairwise difference (IG1 vs. IG2): X <sup>2</sup> =4.50; df=1; p=0.03 Pairwise difference (IG1 vs. CG): X <sup>2</sup> =4.30; df=1; p=0.04			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	MFQ score, n patients, Mean (SD) Comparisons are Treatment effect (95% CI) Baseline IG1: 154, 46.2 (10.3) IG2: 156, 45.4 (10.8) CG: 155, 46.2 (10.6)  6 Weeks IG1: 104, 35.2 (11.3) IG2: 107, 34.9 (13.2) CG: 99, 36.5 (14.3)  12 Weeks IG1: 106, 31.6 (13.3) IG2: 108, 33.1 (14.2) CG: 112, 34.1 (14.4)  36 Weeks IG1: 104, 24.2 (15.1) IG2: 109, 26.6 (15.7) CG: 105, 30.5 (16.1) IG1 vs. IG2: 0.179 (-3.731 to 4.088) p=0.929 IG1+IG2 vs. CG: -3.234 (-6.611 to 0.143) p=0.061	MFQ score: Response rate Freq (%); time since randomization mean (min, max) Baseline IG1: 154 (100); NR IG2: 156 (100); NR CG: 155 (100); NR  6 Weeks IG1: 104 (68); 12.3 (7, 41) IG2: 107 (69); 11.1 (6, 21) CG: 99 (64); 11.0 (6, 25)  12 Weeks IG1: 106 (69); 19.0 (11, 38) IG2: 108 (69); 17.6 (12, 28) CG: 112 (72); 17.6 (12,33)  36 Weeks IG1: 104 (68); 42.9 (35-63) IG2: 109 (70); 41.5 (31, 52) CG: 105 (68); 42.3 (36, 54)	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article (continued)		52 Weeks IG1: 111, 25.0 (18.0) IG2: 110, 23.0 (15.9) CG: 105, 25.1 (16.2) IG1 vs. IG2: 0.307 (-3.161 to 3.774) p=0.862 IG1+IG2 vs. CG: -2.806 (-5.790 to 0.177) 0.065 p=0.065  86 Weeks IG1: 123, 22.3 (15.7) IG2: 114, 21.8 (15.5) CG: 116, 23.6 (16.2) IG1 vs. IG2: 0.578 (-2.948 to 4.104) p=0.748 IG1+IG2 vs. CG: -1.898 (-4.922 to 1.126) p=0.219	52 Weeks IG1: 111 (72); 60.3 (48, 92) IG2: 110 (71); 59.3 (50, 85) CG: 105 (68); 59.2 (51, 76)  86 Weeks IG1: 123 (80); 94.9 (82, 147) IG2: 114 (73); 95.1 (69, 149) CG: 116 (75); 95.4 (73, 132)  Patients with MDD diagnosis and ≥1 antisocial behavior symptom, N (%) or n/N (%) Comparisons are Treatment effect (95% CI) Baseline IG1: 154 (100) IG2: 156 (100) CG: 155 (100)  6 Weeks IG1: 57/95 (60) IG2: 62/99 (63) CG: 63/143 (44)			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article (continued)			12 Weeks IG1: 46/98 (47) IG2: 54/99 (55) CG: 57/105 (54)			
			36 Weeks IG1: 28/89 (31) IG2: 35/98 (36) CG: 42/95 (44) IG1 vs. IG2: 0.064 (– 0.078 to 0.206) p=0.375 IG1+IG2 vs. CG: –0.043 (–0.160 to 0.073) p=0.465			
			52 Weeks IG1: 23/90 (26) IG2: 23/87 (27) CG: 27/92 (29) IG1 vs. IG2: 0.018 (– 0.084 to 0.120) p=0.727 IG1+IG2 vs. CG: –0.053 (–0.142 to 0.035) p=0.239			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article (continued)			86 Weeks IG1: 24/95 (25) IG2: 14/92 (15) CG: 27/99 (27) IG1 vs. IG2: -0.057 (-0.157 to 0.043) p=0.261 IG1+IG2 vs. CG: -0.065 (-0.152 to 0.022) p=0.145			
Goodyer, 2017 <sup>16</sup> Index article Companion article: Goodyer, 2017 <sup>17</sup>	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	See Goodyer, 2017 <sup>16</sup> Index article	221 (77%) of 286 patients were in diagnostic remission by week 86  The proportion of patients in diagnostic remission by 36, 52, or 86 weeks did not differ significantly between groups (data not shown)	NR	15 (11%) of the 140 patients in remission at wk 36 had relapsed by wk 86  Proportion between groups, n/N (%): IG1: 8/49 (16.3) IG2: 2/48 (4.2) CG: 5/43 (11.6) p=0.149	NR
Rohde, 2004 <sup>15</sup> Index article	G1: Adolescent Coping with Depression course (CWD-A) G2: Life skills/tutoring (LS) condition	Diagnostic outcome for MDD at posttreatment: n(%) G1: 27 (61.4) G2: 38 (80.9)  Diagnostic outcome for MDD at 6-month followup: n(%) G1: 19 (46.3) G2: 18 (40.0)  Diagnostic outcome for MDD at 12-month followup: n(%) G1: 15 (36.6) G2: 17 (37.0)	MDD recovery at 6-month CG: 54% IG: 60% Not significant, details NR  MDD recovery at 12-month: IG: 63% CG: 3% Not significant, details NR	CGAS score at posttreatment: mean (SD) G1: 56.3 (10.2) G2: 55.1 (8.8)  CGAS score at 6-month: G1: 59.1 (12.5) G2: 58.2 (10.0)  CGAS score at 12-month: G1: 60.2 (11.8) G2: 60.1 (11.5)  SAS-R score at posttreatment: G1: 26.4 (15.6) G2: 30.6 (11.9)	No significant main effects in MDD outcome for condition by time or condition by time by gender interactions were obtained.	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Rohde, 2004 <sup>15</sup> Index article (continued)		BDI-II score at posttreatment: mean (SD) G1: 9.6 (10.7) G2: 11.5 (11.1)  H BDI-II score at 6-month followup: mean (SD) G1: 10.6 (11.7) G2: 10.2 (9.9)  BDI-II score at 12-month followup: mean (SD) G1: 9.9 (10.4) G2: 7.5 (8.0)  DRS score at posttreatment: mean (SD) G1: 6.0 (6.3) G2: 8.3 (5.4)  HDRS score at 6-month followup: mean (SD) G1: 5.5 (6.3) G2: 5.7 (6.5)  HDRS at 12-month followup: mean (SD) G1: 5.6 (6.4) G2: 4.1 (5.1)		SAS-R score at 6-month: G1: 28.7 (17.4) G2: 29.8 (15.9)  SAS-R score at 12-month: G1: 28.6 (15.2) G2: 29.5 (15.1)		

BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory-II; CBT = cognitive behavioral therapy; CG = control group; CGAS = Children's Global Assessment Scale; CI = confidence interval; CWD-A = Adolescent Coping with Depression course; DEP13 = 13 depression items from School-Age Schedule for Affective Disorders and Schizophrenia for School-Age Children; HDRS = Hamilton Rating Scale for Depression; IG = intervention group; KQ = Key Question; LS = life skills/tutoring condition; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n/N = number; NA = not applicable; NR = not reported; NS = not significant; NST = nondirective supportive therapy; SAS-R = Social Adjustment Scale for Children-Reporting; wk = week.

**Table E-7. KQ 1a: Benefits of relapse prevention CBT + continued antidepressant medication management versus continued medication management**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Kennard, 2008 <sup>20</sup>	IG: Relapse prevention CBT plus continued antidepressant medication management CG: Continued antidepressant medication management	Depressive symptom severity, ITT (N=46) CDRS-R, mean (SD) 36 weeks IG: 27.4 (8.9) CG: 33.6 (14.1) No between-group difference: p=0.09	NA	Global functioning, ITT (N=46) CGAS, mean (SD) 36 weeks IG: 64.8 (9.7) CG: 63.5 (10.1) No between-group difference: p=0.68	Estimated probability of relapse, ITT (N=46) CDRS-R, % probability 16 weeks IG: 4 CG: 8  20 weeks IG: 5 CG: 15  24 weeks IG: 8 CG: 21  36 weeks IG: 15 CG: 37 Across 16 to 36 weeks Significantly greater risk for relapse in CG than IG after adjusting for baseline CDRS-R total score and age HR (95% CI) for CG vs. IG: 8.80 (1.01 to 76.89), p=0.049	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Kennard, 2008 <sup>20</sup> (continued)					<p>Client satisfaction, ITT (N=46)</p> <p>Patient CSQ-8, mean (SD) 36 weeks</p> <p>IG: 3.98 (0.05)</p> <p>CG: 3.58 (0.43)</p> <p>Significant between-group difference (IG&gt;CG): p=0.001</p> <p>Parent CSQ-8, mean (SD) 36 weeks</p> <p>IG: 3.88 (0.42)</p> <p>CG: 3.67 (0.42)</p> <p>No between-group difference: p=0.09</p> <p>Parents whose children received CBT reported higher levels of satisfaction than those parents whose children received medication only</p> <p>Medication discontinuation when deemed clinically appropriate, ITT (N=46) 24 weeks, n (%)</p> <p>IG: 8 (36.4)</p> <p>CG: 7 (29.2)</p> <p>No between-group difference: p=0.60</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Kennard, 2014 <sup>21</sup> Index article	IG: Relapse prevention CBT plus continued antidepressant medication management CG: Continued antidepressant medication management	NA	Estimated probability of remission, ITT (N=144) CDRS-R, % probability 12 weeks IG: 68 CG: 59  18 weeks IG: 79 CG: 71  24 weeks IG: 86 CG: 80  30 weeks IG: 90 CG: 84 No significant between-group difference at any timepoint: p=NR	NA	Estimated probability of relapse, ITT (N=115 who achieved remission at any time during the study) CDRS-R, % probability 12 weeks IG: 1 CG: 3 No between-group difference (p=NS)  18 weeks IG: 3.5 CG: 10 No between-group difference (p=NS)  24 weeks IG: 7 CG: 20.5 Significantly greater risk for relapse in CG arm than IG arm (log-rank p=0.028; false-discovery-rate-adjusted p=0.049 to account for multiple testing)	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Kennard, 2014 <sup>21</sup> Index article (continued)			Time to remission, mean weeks (SE) IG: 11.33 (0.95) CG: 13.67 (1.17) No significant between-group differences at any timepoint when using log-rank test (p=NR) and when using Cox regression model, adjusted for baseline CDRS-R score, age group, and sex (HR [95% CI]: 1.26 [0.87 to 1.82], p=NS)		30 weeks IG: 9 CG: 26.5 Significantly greater risk for relapse in CG arm than IG arm (log-rank p=0.011; false-discovery-rate-adjusted p=0.043 to account for multiple testing)  Time to relapse Across 12 to 30 weeks, mean weeks (SE) IG: 28.77 (0.48) CG: 27.13 (0.68) Effect size: Hodges g=0.439 Significantly longer time to relapse in IG arm than CG arm (log-rank p=0.009)  Full relapse (CDRS-R score ≥40), N=45 patients who relapsed (IG=17; CG=28) Across 12 to 30 weeks, n (%) IG: 9 (52.9) CG: 15 (53.6) Clinical deterioration (CDRS-R score ≤40 but clinician noted significant deterioration that would	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Kennard, 2014 <sup>21</sup> Index article (continued)					<p>suggest full relapse if patient's treatment was not altered), N=45 patients who relapsed (IG=17; CG=28)  Across 12 to 30 weeks, n (calculated %)  IG: 8 (47.1)  CG: 13 (46.4)</p> <p>Proportion of patients with time spent well (Adolescent Longitudinal Interval Follow-Up Evaluation), ITT (N=144)  Across 12 to 30 weeks, calculated n (%)  IG: 42 (55.9)  CG: 32 (46.2)  Effect size: Hodges g=0.395  Significantly higher rate of adolescents in IG arm who spent time well than in CG arm (p=0.02 adjusted for CDRS-R score at randomization, age group, and sex)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Kennard, 2014 <sup>21</sup> Index article (continued)					Duration of time spent well (Adolescent Longitudinal Interval Follow-Up Evaluation), ITT (N=144) Across 12 to 30 weeks, mean weeks (SD) IG: 16.0 (9.1) CG: 12.8 (9.5) Effect size: Hodges g=0.342 Significantly more time spent well by IG arm than CG arm (p=0.041 adjusted for CDRS-R score at randomization, age group, and sex)	
Kennard, 2014 <sup>21</sup> Index article Companion article: Emslie, 2015 <sup>22</sup>	IG: Relapse prevention CBT plus continued antidepressant medication management CG: Continued antidepressant medication management	NA	Estimated probability of remission, ITT (N=144) CDRS-R, % probability 52 weeks IG: 94 CG: 89  78 weeks IG: 96 CG: 92 NR if between-group difference at either timepoint	NA	Estimated probability of relapse, ITT (N=121 who achieved remission at any time during the study) CDRS-R, % probability 52 weeks IG: 27 CG: 49  Significantly lower risk for relapse in IG arm than CG arm (log-rank p=0.021; false-discovery-rate-adjusted p=0.021 to account for multiple testing) 78 weeks IG: 36 CG: 62	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Kennard, 2014 <sup>21</sup> Index article Companion article: Emslie, 2015 <sup>22</sup> (continued)			<p>Time to remission across 78 weeks, mean weeks (SE) IG: 14.26 (2.13) CG: 18.37 (2.94) Effect size: Hodges g=0.258 No significant between-group differences (log-rank test p=0.122)</p> <p>Cox regression model, adjusted for baseline CDRS-R score, age group, and sex, also found no significant between-group difference (HR [95% CI], 1.255 [0.874 to 1.801], p=0.220)</p>		<p>Significantly lower risk for relapse in IG arm than CG arm (log-rank p=0.008; false-discovery-rate-adjusted p=0.015 to account for multiple testing)</p> <p>Cox regression model, adjusted for CDRS-R score at randomization, age group, and sex, also found significantly lower risk of relapse in IG arm than CG arm (HR [95% CI]: 0.467 [0.264 to 0.823], p=0.009)</p> <p>Time to relapse Across 78 weeks, mean weeks (SE) IG: 64.40 (2.68) CG: 50.93 (3.61) Effect size: Hodges g=0.499 Significantly longer time to relapse in IG arm than CG arm (log-rank p=0.007)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Kennard, 2014 <sup>21</sup> Index article Companion article: Emslie, 2015 <sup>22</sup> (continued)					<p>Proportion of patients with time spent well (Adolescent Longitudinal Interval Follow-Up Evaluation), ITT (N=144) Across 78 weeks, calculated n (%) IG: 44 (59.3) CG: 34 (48.8) Effect size: Hodges g=0.341 Significantly higher rate of adolescents in IG arm who spent time well than in CG arm (p=0.043 adjusted for CDRS-R score at randomization, age group, and sex)</p> <p>Duration of time spent well (Adolescent Longitudinal Interval Follow-Up Evaluation), ITT (N=144) Across 78 weeks, mean weeks (SD) IG: 38.3 (2.82) CG: 30.4 (2.95) Effect size: Hodges g=0.308</p> <p>No between-group difference in time spent well by IG arm vs. CG arm (p=0.066 adjusted for CDRS-R score at end of acute phase, age group, and sex)</p>	

CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGAS = Children's Global Assessment Scale; CI = confidence interval; CSQ-8 = Client Satisfaction Questionnaire-8 item; HR = Hamilton Rating; IG = intervention group; ITT = intent to treat; KQ = Key Question; NA = not applicable; NR = not reported; NS = not significant; SD = standard deviation; SE = standard error.

**Table E-8. KQ 1a: Benefits of IPT versus wait-list control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Rosello, 1999 <sup>10</sup>	IG1: IPT IG2: CBT CG: Wait list control	CDI score, baseline, Mean (SD): IG1: 21.21 (7.53) IG2: 20.12 (6.95) CG: 20.13 (5.99)  CDI score 12 weeks, Mean (SD): IG1: 10.79 (6.51) IG2: 13.28 (7.61) CG: 15.83 (6.83) P-value for CDI pre vs. post: p>0.01  CDI score 3 months Mean (SD): IG1: 13.75 (9.52) IG2: 8.90 (6.84) CG: NR F value for CDI post-tx vs. followup: F=0.02	Patients in functional range (CS change) at 12 weeks, %: IG1: 82 IG2: 59  Effect size at 12 weeks (size (%): IG1: 0.73 (77) IG2: 0.43 (67)  Decrease in severely depressed adolescents, baseline vs. 12 weeks, %: IG1: 45 IG2: 24 CG: 27  Decrease in severely depressed adolescents, baseline vs. 3 months, %: IG1: 39 IG2: 30 CG: NR	NR	F values for pre/post treatment comparisons on CDI: IG1 vs. IG2: 2.61 IG1 vs. CG: 11.62 (p<0.01) IG2 vs. CG: 2.58 (p<0.05)	NR

CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CG = control group; CS =clinical significance; IG = intervention group; IPT = interpersonal psychotherapy; KQ = Key Question; NR = not reported; SD = standard deviation; tx = treatment.

**Table E-9. KQ 1a: Benefits of IPT versus active control (clinical monitoring)**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Mufson, 1999 <sup>23</sup>	IG: IPT-A CG: Clinical Monitoring	Depression diagnosis at termination IG: 3/24 CG: 10/24  Depression symptoms ITT (n=48; 24 G1 and 24 G2) HRSD 12 weeks mean (SD) IG: 6.3 (7.7) IG: 11.8 (8.9) F=6.0; df=1,45; p=0.02  BDI 12 weeks mean (SD) IG: 5.9 (8.1) CG: 12.9 (12.6) F=4.2; df=1,44; p=0.05  Completers (n=32; 21 G1 and 11 G2) HRSD 12 weeks mean (SD) IG: 4.9 (5.7) CG: 11.5 (9.4) F=7.2; df=1,28; p=0.01  BDI 12 weeks mean (SD) IG: 4.4 (5.9) CG: 9.4 (12.4) F=2.4; df=1,29; p=0.14	HRSD≤6 and BDI≤9 at week 12.  Results (week 12) IG: 75% CG: 46% X <sup>2</sup> =4.3, p=0.04	SAS-SR week 12 Overall ITT (n=48; 24 G1 and 24 G2) HRSD 12 weeks mean (SD) IG: 1.9(0.63) CG: 2.2 (0.70) F=7.1; df=1,44; p=0.01  CGI week 12 Completers (n=40, 24 G1 and 16 G2) IG: 2.4 (1.6) CG: 4.2 (1.1) F 1,37=18.8, p<0.001 IG vs. CG "improved" rating X <sup>2</sup> =16.7, p<0.001	NR	NR

BDI = Beck Depression Inventory; CG = control group; CGI = Clinical Global Impressions Scale; G = group; HRSD = Hamilton Rating Scale for Depression; IG = intervention group; IPT-A = interpersonal psychotherapy for depressed adolescents; ITT = intent to treat; KQ = Key Question; NR = not reported; SAS-SR = Social Adjustment Scale for Children-Self-Report; SD = standard deviation.



**Table E-10. KQ 1a: Benefits of family-based IPT versus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Dietz, 2015 <sup>24</sup>	IG: Family Based Interpersonal psychotherapy (FB-IPT) CG: Child-centered therapy (CCT)	CDRS-R Pretreatment IG: 44.3 (1.4) CG: 47.2 (2.6)  Posttreatment IG: 26.7 (1.1) CG: 34.5 (2.8) t=3.01, p=0.003  IG had significantly lower posttreatment CDRS-R scores than CG (R <sup>2</sup> =0.35, ΔR <sup>2</sup> =0.22; B=-8.15, SE=2.61, t[37]=-3.13, p=0.002, F2=0.28)  IG exhibited a greater decrease in CDRS-R scores from pre- to posttreatment compared to IG (R <sup>2</sup> =0.18, ΔR <sup>2</sup> =0.12; B=-6.98, SE=3.15, t[37]=-2.21, p=0.03, F2=0.22)  MFQ-P Pretreatment IG: 19.8 (2.2) CG: 26.9 (3.6)	CDRS-R Remission n (%) IG: 16 (66%) CG: 4 (31%) X <sup>2</sup> (1, n=38)=4.17, p=0.04	SAS-SR, Peer Impairment Pretreatment IG: 10.3 (1.2) CG: 10.6 (1.3)  Posttreatment IG: 6.8 (0.9) CG: 9.7 (1.7) t=1.74, p=0.08  IG had a significantly greater decrease in peer impairment than CG (R <sup>2</sup> =0.34, ΔR <sup>2</sup> =0.15; B=-4.36, SE=1.71, t[37]=-2.55, p=0.01, F2=0.18)  SAS-SR, Social Impairment Pretreatment IG: 12.1 (1.3) CG: 11.6 (1.4)  Posttreatment IG: 7.7 (0.9) CG: 11.6 (1.6) t=2.25, p=0.03  IG had a significantly greater decrease in social impairment than CG (R <sup>2</sup> =0.36, ΔR <sup>2</sup> =0.22; B=-6.32, SE=1.92, t[37]=-3.30, p=0.001, F2=0.28)	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Dietz, 2015 <sup>24</sup> (continued)		<p>Posttreatment IG: 5.8 (1.1) CG: 11.4 (1.6) t=32.90, p=0.004</p> <p>IG had significantly lower posttreatment parent- reported MFQ scores than CG (R<sup>2</sup>=0.32, ΔR<sup>2</sup>=0.15; B=-5.23, SE=2.12, t[37]=-2.47, p=0.01, F<sub>2</sub> =0.18)</p> <p>MFQ-C Pretreatment IG: 24.9 (4.5) CG: 23.6 (4.6)</p> <p>Posttreatment IG: 5.6 (1.2) CG: 12.1 (2.9) t=2.49, p=0.01</p> <p>IG had significantly lower posttreatment preadolescent-reported MFQ scores than CG (R<sup>2</sup>=0.22, ΔR<sup>2</sup>=0.11; B=-7.54, SE=2.77, t[37]=-2.72, p=0.007, F<sub>2</sub>=0.12)</p>				

CCT = child-centered therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; FB-IPT = family based interpersonal psychotherapy; IG = intervention group; KQ = Key Question; MFQ = Mood and Feelings Questionnaire; MFQ-C = Mood and Feelings Questionnaire-Child; MFQ-P = Mood and Feelings Questionnaire-Parent; SAS-SR = Social Adjustment Scale for Children-Self-Report.

**Table E-11. KQ 1a: Benefits of attachment-based family therapy versus wait-list control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Diamond, 2002 <sup>25</sup> Index article	IG: ABFT CG: Wait-list control	Condition-by-time interaction in depressive symptoms (HAM-D): F=5.2 p=0.005 effect size: 1.21  HAM-D at 12 weeks, Mean (SD): IG: 10.3 (8.7) CG: 15.3 (6.7)	BDI score ≤9 at 12 weeks, %: IG: 62 CG: 19 p=0.01  BDI score ≤9 at 6 weeks, %: IG: 56 CG: 19 p=0.03  Patients no longer meeting MDD criteria at 12 weeks, N (%): IG: 13 (81) CG: 7/15 (47)	NR	Anxiety, STAIC score, Mean (SD) IG: 38.2 (7.6) CG: 45.7 (6.6)  Condition-by-time interaction difference in anxiety symptoms in IG: F=8.6 p=0.007 ES=1.24	NR

ABFT = attachment-based family therapy; BDI = Beck Depression Inventory; CG = control group; ES = estimate; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; NR = not reported; SD = standard deviation; STAIC = State-Trait Anxiety Inventory for Children.

**Table E-12. KQ 1a: Benefits of attachment-based family therapy versus treatment as usual**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Israel, 2013 <sup>26</sup>	IG: ABFT CG: TAU	12 wk HAM-D score, mean (SD) IG: 12.5 (7.2) CG: 19.4 (5.2) Effect size (Cohen's d): 1.08 z=-2.05 p=0.04  12 wk BDI score, mean (SD) IG: 22.8 (12) CG: 31.2 (8.8) Effect size: 0.8 z=-1.02 p=0.23	HAM-D clinical recovery, % IG: 27 CG: 11	NR	NR	NR

ABFT = attachment-based family therapy; BDI = Beck Depression Inventory; CG = control group; IG = intervention group; HAM-D = Hamilton Depression Rating Scale; KQ = Key Question; NR = not reported; SD = standard deviation; TAU = treatment as usual.

**Table E-13. KQ 1a: Benefits of family therapy versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Fristad, 2009 <sup>27</sup>	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	CDSR-R score at endpoint IG1: 26 (10) IG2: 30 (9) IG3: 31 (9) CG: 31 (11)	Remitted IG1: 76.5% IG2: 61.1% IG3: 43.8% CG: 55.6%	NR	NR	History of maternal depression significantly moderated the effects of PEP+PBO versus PBO (p = 0.02) but not the placebo-controlled effects of combined or Ω3 alone.

CG = control group; CDSR-R =; IG = intervention group; KQ = Key Question; NR = not reported; PBO = placebo; PEP = psychoeducational psychotherapy.

**Table E-14. KQ 1a: Benefits of family therapy versus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Brent, 1997 <sup>12</sup> Index article	IG1: Individual CBT IG2: SBFT CG: NST	MDD episode, % 6 weeks IG1: 60.0 IG2: 65.5 CG: 63.3 p=0.90  12-16 weeks IG1: 17.1 IG2: 32.3 CG: 42.4 Difference among 3 groups: X2=5.22; df=2; p=0.07 Pairwise difference (IG1 vs. CG): X2=5.23; df=1; p=0.02  BDI, mean (SD) 6 weeks IG1: 10.7 (11.1) IG2: 13.7 (9.3) CG: 13.4 (10.7) p=0.44  12-16 weeks IG1: 5.7 (8.6) IG2: 9.1 (9.1) CG: 9.8 (11.4) p=0.19 Difference among 3 groups: X2=5.70; df=2; p=0.06	Overall achievement of clinical response Overall achievement of clinical response data were estimated using software from Figure 2.  Overall difference: X2=5.28; df=2; p=0.07 Pairwise difference (IG1 vs. IG2): X2=4.84; df=1; p=0.03 IG1: 66.3 IG2: 39.6 CG: 42.9  Overall achievement of remission (%) 6 weeks IG1: 16.7 IG2: 6.2 CG: 16.7 p=0.37  12-16 weeks IG1: 60.0 IG2: 29.0 CG: 36.4	CGAS <60 (%) 6 weeks IG1: 34.3 IG2: 37.9 CG: 43.3 p=0.76  12-16 weeks IG1: 25.7 IG2: 35.5 CG: 33.3 p=0.66  No significant treatment x time interaction on the CGAS (treatment=NS, time <.01)	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Brent, 1997 <sup>12</sup> Index article (continued)		IG1 showing more rapid response than CG: $X^2=5.10$ ; $df=1$ ; $p=0.02$  DEP13, mean (SD) 6 weeks IG1: 2.1 (0.7) IG2: 2.1 (0.6) CG: 2.1 (0.5) $p=0.91$  12-16 weeks IG1: 1.5 (0.5) IG2: 1.7 (0.6) CG: 1.8 (0.8) $p=0.15$ Difference among 3 groups: $X^2=6.15$ ; $df=2$ ; $p=0.05$ IG1 showing more rapid response than IG2: $X^2=4.74$ ; $df=1$ ; $p=0.03$ IG1 showing more rapid response than CG: $X^2=4.84$ ; $df=1$ ; $p=0.03$	Rate of remission (%) IG1: 60.0 IG2: 37.9 CG: 39.4  Overall difference: $X^2=5.96$ ; $df=2$ ; $p=0.05$ Pairwise difference (IG1 vs. IG2): $X^2=4.50$ ; $df=1$ ; $p=0.03$ Pairwise difference (IG1 vs. CG): $X^2=4.30$ ; $df=1$ ; $p=0.04$			
Poole, 2018 <sup>28</sup> Companion: Poole, 2017 <sup>29</sup>	IG: BEST MOOD family systems therapy CG: PAST family group therapy	SMFQ, mean (SE) (Cohen's d) Post-treatment IG: 13.23 (1.47) (0.83) CG: 13.33 (1.44) (0.8) Group by time $p=0.55$ 12 weeks IG: 15.58 (1.49) (0.46) CG: 14.11 (1.4) (0.51) Group-by-time $p=0.6$	NR	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Tompson, 2017 <sup>30</sup> Index Study	IG: FFT-CD CG: Individual supportive psychotherapy (IP)	CDRS-R score posttreatment, mean (SD) IG: 30.85 (11.31) CG: 34.42 (12.48)  CDI-CR score, posttreatment, mean (SD) IG: 7.30 (8.99) CG: 9.72 (8.14)  CDI-PR score, posttreatment, mean (SD) IG: 16.22 (7.83) CG: 17.82 (8.68)	Adequate response, % with CDRS-R $\geq 50\%$ ITT IG: 77.4 CG: 59.9 OR: 2.29; NNT=5.72; t=1.97; p=0.0498 Completer IG: 79.6 CG: 59.7 OR: 2.64; NNT=5.01; $\chi^2=5.37$ ; df=1; p=0.0205  Remission, % with CDRS-R scores $\leq 28$ ITT IG: 52.3 CG: 37.3 OR: 1.84; NNT=6.70; =1.63; p=0.1043 Completer IG: 53.7 CG: 35.5 OR: 2.11; NNT=5.50; $\chi^2=3.89$ ; df=1; p=0.0486	CGAS score posttreatment, mean (SD) IG: 63.70 (9.61) CG: 64.65 (10.74)  SAS-CR score posttreatment, mean (SD) IG: 42.09 (12.50) CG: 45.68 (12.21)	MASC-CR score posttreatment, mean (SD) IG: 47.17 (21.93) CG: 49.70 (19.51)  CBC-IP score posttreatment, mean (SD) IG: 59.77 (11.98) CG: 61.63 (10.60)  CBC-EP score posttreatment, mean (SD) IG: 54.77 (10.91) CG: 56.57 (9.45)	No significant effects for demographic (age group, gender, race, family composition, family income) and clinical variables (syndromal vs. subsyndromal depression, baseline CDRS score, comorbid anxiety disorder, comorbid disruptive behavior disorder, chronicity, current antidepressant medication) (no details reported)
Tompson, 2017 <sup>30</sup> Companion: Asarnow <sup>31</sup>	IG: FFT-CD CG: Individual supportive psychotherapy (IP)		Recurrence was relatively rare but was more common among youths receiving IP (details NR)			

BDI = Beck Depression Inventory; CBC-EP = Child Behavior Checklist – Externalizing Problems; CBC-IP = Child Behavior Checklist – Internalizing Problems; CBT = cognitive behavioral therapy; CDI-CR = Children's Depression Inventory-Child Report; CDI-PR = Children's Depression Inventory-Parent Report; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGAS = Children's Global Assessment Scale; DEP13 = 13 depression items from School-Age Schedule for Affective Disorders and Schizophrenia for School-Age Children; FFT-CD = family-focused treatment for childhood depression; IG = intervention group; IP = interpersonal therapy; IP = individual supportive psychotherapy; ITT = intent to treat; KQ = Key Question; MASC-CR = Multidimensional Anxiety Scale for Children-C\_R\_; MDD = major depressive disorder; NNT =



number needed to treat; NR = not reported; NS = not significant; NST = nondirective supportive therapy; OR = odds ratio; SAS-SR = Social Adjustment Scale for Children-Self-Report; SBFT = systemic behavior family therapy; SD = standard deviation.

**Table E-15. KQ 1a: Benefits of PCIT versus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Luby, 2012 <sup>32</sup>	IG: Parent Child Interaction Therapy CG: Psycho-education	<p>PFC-S score Post-treatment ITT Mean (SD) IG: 30.1 (11.3) CG: 33.7 (10.6) Differences Not significant</p> <p>Completers Post-treatment Mean IG: 26.0 CG: 30.5 Differences Not significant</p> <p>PAPA MDD Severity ITT Post-treatment Mean (SD) IG: 7.6 (4.0) CG: 7.5 (4.7) Differences Not significant</p> <p>Completers Post-treatment Mean IG: 6.7 CG: 6.2 Differences Not significant</p>	NR	<p>HBQ functional impairment-self ITT Post-treatment IG: 0.64 (0.43) CG: 0.61 (0.47) Differences Not significant</p> <p>HBQ-P functional impairment-family ITT Post-treatment IG: 0.93 (0.56) CG: 1.08 (0.71) Differences Not significant</p> <p>PECFAS ITT Post-treatment IG: 50.0 (25.5) CG: 55.3 (29.0) Differences Not significant</p> <p>BRIEF Inhibit+Emotional Control T score ITT Post-treatment IG: 72.4 (13.5) CG: 70.6 (14.5) p&lt;0.05</p> <p>Completers Post-treatment IG: 70.3 CG: 69.1 p&lt;0.05</p>	NR	NR

BRIEF = Behavior Rating Inventory of Executive Function-Preschool Version ; CG = control group; HBQ = Health Behaviors Questionnaire; HBQ-P = Health Behaviors Questionnaire-Parent; IG = intervention group; ITT = intent to treat; KQ = Key Question; MDD = major depressive disorder; NR = not reported; PAPA = Preschool Age Psychiatric Assessment; PECFAS = Preschool And Early Childhood Functional Assessment Scale; PFC-S = Preschool Feeling Checklist - Scale; SD = standard deviation.

**Table E-16. KQ 1a: Benefits of short-term psychoanalytic therapy versus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	MFQ score, n patients, Mean (SD) Comparisons are Treatment effect (95% CI) Baseline IG1: 154, 46.2 (10.3) IG2: 156, 45.4 (10.8) CG: 155, 46.2 (10.6)  6 Weeks IG1: 104, 35.2 (11.3) IG2: 107, 34.9 (13.2) CG: 99, 36.5 (14.3)  12 Weeks IG1: 106, 31.6 (13.3) IG2: 108, 33.1 (14.2) CG: 112, 34.1 (14.4)  36 Weeks IG1: 104, 24.2 (15.1) IG2: 109, 26.6 (15.7) CG: 105, 30.5 (16.1) IG1 vs. IG2: 0.179 (-3.731 to 4.088) p=0.929 IG1+IG2 vs. CG: -3.234 (-6.611 to 0.143) p=0.061	MFQ score: Response rate Freq (%); time since randomization mean (min, max) Baseline IG1: 154 (100); NR IG2: 156 (100); NR CG: 155 (100); NR  6 Weeks IG1: 104 (68); 12.3 (7, 41) IG2: 107 (69); 11.1 (6, 21) CG: 99 (64); 11.0 (6, 25)  12 Weeks IG1: 106 (69); 19.0 (11, 38) IG2: 108 (69); 17.6 (12, 28) CG: 112 (72); 17.6 (12,33)  36 Weeks IG1: 104 (68); 42.9 (35-63) IG2: 109 (70); 41.5 (31, 52) CG: 105 (68); 42.3 (36, 54)	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article (continued)		52 Weeks IG1: 111, 25.0 (18.0) IG2: 110, 23.0 (15.9) CG: 105, 25.1 (16.2) IG1 vs. IG2: 0.307 (-3.161 to 3.774) p=0.862 IG1+IG2 vs. CG: -2.806 (-5.790 to 0.177) 0.065 p=0.065  86 Weeks IG1: 123, 22.3 (15.7) IG2: 114, 21.8 (15.5) CG: 116, 23.6 (16.2) IG1 vs. IG2: 0.578 (-2.948 to 4.104) p=0.748 IG1+IG2 vs. CG: -1.898 (-4.922 to 1.126) p=0.219	52 Weeks IG1: 111 (72); 60.3 (48, 92) IG2: 110 (71); 59.3 (50, 85) CG: 105 (68); 59.2 (51, 76)  86 Weeks IG1: 123 (80); 94.9 (82, 147) IG2: 114 (73); 95.1 (69, 149) CG: 116 (75); 95.4 (73, 132)  Patients with MDD diagnosis and ≥1 antisocial behavior symptom, N (%) or n/N (%) Comparisons are Treatment effect (95% CI) Baseline IG1: 154 (100) IG2: 156 (100) CG: 155 (100)  6 Weeks IG1: 57/95 (60) IG2: 62/99 (63) CG: 63/143 (44)			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article (continued)			12 Weeks IG1: 46/98 (47) IG2: 54/99 (55) CG: 57/105 (54)			
			36 Weeks IG1: 28/89 (31) IG2: 35/98 (36) CG: 42/95 (44) IG1 vs. IG2: 0.064 (−0.078 to 0.206) p=0.375 IG1+IG2 vs. CG: −0.043 (−0.160 to 0.073) p=0.465			
			52 Weeks IG1: 23/90 (26) IG2: 23/87 (27) CG: 27/92 (29) IG1 vs. IG2: 0.018 (−0.084 to 0.120) p=0.727 IG1+IG2 vs. CG: −0.053 (−0.142 to 0.035) p=0.239			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article (continued)			86 Weeks IG1: 24/95 (25) IG2: 14/92 (15) CG: 27/99 (27) IG1 vs. IG2: -0.057 (-0.157 to 0.043) p=0.261 IG1+IG2 vs. CG: -0.065 (-0.152 to 0.022) p=0.145			
Goodyer, 2017 <sup>16</sup> Index article Companion article: Goodyer, 2017 <sup>17</sup>	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	See Goodyer, 2017 <sup>16</sup> Index article	221 (77%) of 286 patients were in diagnostic remission by week 86  The proportion of patients in diagnostic remission by 36, 52, or 86 weeks did not differ significantly between groups (data not shown)	NR	15 (11%) of the 140 patients in remission at wk 36 had relapsed by wk 86  Proportion between groups, n/N (%): IG1: 8/49 (16.3) IG2: 2/48 (4.2) CG: 5/43 (11.6) p=0.149	NR

CBT = cognitive behavioral therapy; CG = control group; CI = confidence interval; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n/N = number; NR = not reported; SD = standard deviation.

**Table E-17. KQ 1a: Benefits of exercise versus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Hughes 2013 <sup>33</sup>	IG: aerobic exercise CG: nonstrenuous exercise group	CDRS (week 12) Week 12 Mean (95% CI) Completers Only IG: 24.1 (20.8 to 27.5) CG: 28.3 (24.6 to 32.2) p=0.071  QIDS-clinician report: Week 12 Mean (95% CI) Completers Only IG: 4.4 (2.7 to 6.0) CG: 5.6 (3.8 to 7.4) p=0.305  QIDS-self report: Week 12 Mean (95% CI) Completers Only IG: 2.9 (1.2 to 4.5) CG: 4.5 (2.7 to 6.3) p=0.174  QIDS-parent report: Week 12 Mean (95% CI) Completers Only IG: 4.1 (2.4 to 5.9) CG: 5.2 (3.3 to 7.1) p=0.420	Remission (week 12) Completers only IG: 86% CG: 50% $\chi^2=3.9$ , df=1, p=0.049  Remission (week 26) Completers only IG: 100% CG: 70% p=0.06  Remission (week 52) Completers only IG: 100% CG: 88% p=0.33	C-GAS (week 12) Week 12 Mean (95% CI) Completers Only Equal improvement over time for both groups Baseline=61.6 (59.5 to 66.7) to week 12=71.1 (55.8 to 63.7)], F(2, 23)=83, p<0.001	Response (week 12) Completers only IG: 100% CG: 67% $\chi^2=5.52$ , df=1, p=0.019  Response (week 26) Completers only IG: 100% CG: 80% p=0.14  Response (week 52) Completers only IG: 100% CG: 88% p=0.33	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Hughes 2013 <sup>33</sup> (continued)		CGI-severity Week 12 Mean (95% CI) Completers Only IG: 1.4 (1.0 to 1.9) CG: 2.1 (1.6 to 2.5) p=0.04  CGI-improvement Week 12 Mean (95% CI) Completers Only IG: 1.2 (0.9 to 1.6) CG: 1.8 (1.4 to 2.3) p=0.04				

CDRS = Children's Depression Rating Scale; CG = control group; C-GAS = Children's Global Assessment Scale; CGI = Clinical Global Impressions Scale; CI = confidence interval; IG = intervention group; KQ = Key Question; NR = not reported; QIDS = Quick Inventory for Depressive Symptomatology.



**Table E-18. KQ 1a: Benefits of spirituality versus wait-list**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Rickhi, 2015 <sup>34</sup>	IG: LEAP online non-faith based spirituality program CG: Wait-list	CDRS-R ITT (n=31; IG: 18 and CG: 13) 8 weeks, mean (SE) IG: 44.94 (2.86) CG: 58.93 (3.37) Between-group p=0.0038  16 weeks, mean (SE) IG: 36.54 (2.77) CG: 44.97 (3.26) Between-group p=NR  24 weeks, mean (SE) IG: 34.37 (3.22) CG: 42.28 (3.79) Between-group p=NR	NA	NA	NA	NA

CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; IG = intervention group; ITT = intent to treat; LEAP = Listen-Empathize-Agree-Partner; KQ = Key Question; NA = not applicable; NR = not reported; SE = standard error.

**Table E-19. KQ 1a: Benefits of omega-3 versus pill placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Fristad, 2009 <sup>27</sup>	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	CDSR-R score at endpoint IG1: 26 (10) IG2: 30 (9) IG3: 31 (9) CG: 31 (11)	Remitted IG1: 76.5% IG2: 61.1% IG3: 43.8% CG: 55.6%	NR	NR	History of maternal depression significantly moderated the effects of PEP+PBO versus PBO (p = 0.02) but not the placebo-controlled effects of combined or Ω3 alone.
Nemets, 2006 <sup>35</sup>	G1: Omega-3 fatty acids G2: Placebo	CDRS scores extracted from Figure 1 2 weeks G1: 56.29 G2: 62.23 Between-group p=NS  4 weeks G1: 43.02 G2: 54.46 Between-group p=NS  8 weeks G1: 36.45 G2: 56.04 Between-group p=0.04  12 weeks G1: 33.68 G2: 54.43 Between-group p=0.03  16 weeks G1: 32.09 G2: 52.81 Between-group p=0.03	% of participants met remission criteria at exit G1: 40% G2: 0%  >50% reduction in CDRS scores G1: 7/10 G2: 0/10	NR	NR	NR

CDRS = Children's Depression Rating Scale; CG = control group; IG = intervention group; KQ = Key Question; NR = not reported.

**Table E-20. KQ 2a: Benefits of SSRIs versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Atkinson 2014 <sup>38</sup>	IG1: duloxetine IG2: fluoxetine CG: placebo	CDRS-R at 10 weeks (Mixed Effects Model with ITT sample IG1: 113; IG2: 113; CG: 103) IG1: 35.0 IG2: 35.6 CG: 35.0  Mean change at 10 weeks IG1: -24.3 IG2: -23.7 CG: -24.3  Mean change at LOCF IG1: -21.9 IG2: -22.0 CG: -22.7  CDRS-R at 36 weeks (Mixed Effects Model; CG transitioned to duloxetine or fluoxetine) IG1: 26.0 IG2: 25.7 CG: 25.1  CGI-S at 10 weeks (Mixed Effects Model with ITT sample IG1: 113; IG2: 113; CG: 103) IG1: 2.7 IG2: 2.7 CG: 2.6	Probability of CDRS-R treatment response at 10 weeks IG1: 67% IG2: 63% CG: 62% No significant differences  Probability of CDRS-R remission at 10 weeks IG1: 41% IG2: 33% CG: 41% No significant differences  Probability of CDRS-R treatment response at 36 weeks IG1: 72% IG2: 83% CG: NR (CG patients transitioned to duloxetine or fluoxetine) No significant differences  Probability of CDRS-R remission at 36 weeks No significant differences	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Atkinson 2014 <sup>38</sup> (continued)		CGI-S at 36 weeks (Mixed Effects Model; CG patients transitioned to IG1 or IG2) IG1: 1.9 IG2: 1.8 CG: 1.6				
Berard, 2006 <sup>39</sup>	IG: paroxetine CG: placebo	K-SADS-L Responders at Week 12 (LOCF; IG: 171; CG: 88), LSM (SE) IG: -9.33 (0.54) CG: -8.92 (0.70) Difference (95% CI): -0.41 (-2.01 to 1.19) p=0.616  MADRS Total at Week 12 (LOCF; IG: 177; CG: 91), LSM (SE) IG: -13.6 (0.82) CG: -12.8 (1.08) Difference (95% CI): -0.80 (-3.28 to 1.67) p=0.520	MADRS Responders at Week 12 (LOCF; IG: 177; CG: 91), n % IG: 107 (60.5%) CG: 53 (58.2%) AOR (95% CI): 1.11 (0.65 to 1.88) p=0.702  CGI-I Responders at Week 12 (LOCF; IG: 172; CG: 89), n (%) IG: 119 (69.2%) CG: 51 (57.3%) OR (95% CI): 1.74 (1.01 to 2.99) p=0.045	NR	NR	Older adolescent patients treated with paroxetine showed significant improvement on the reported sadness item from the MADRS (adjusted difference from placebo 0.61 points, p = 0.042)  The treatment difference in CGI-I responder rate for paroxetine versus placebo in the two age subgroups was significant only in the older adolescent group (at weeks 8 [p = 0.014] and 12 [p = 0.040])

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Berard, 2006 <sup>39</sup> (continued)		BDI at Week 12 (LOCF; IG: 174; CG: 90), LSM (SE) IG: -12.50 (0.82) CG: -12.07 (1.08) Difference (95% CI): -0.43 (-2.92 to 2.06) p=0.734  CGI-S at Week 12 (LOCF; IG: 172; CG: 89), LSM – Median IG: 2.0 CG: 2.0 p=0.847  MFQ at Week 12 (LOCF; IG: 169; CG: 88), LSM (SE) IG: -16.42 (1.18) CG: -15.68 (1.54) Difference (95% CI): -0.74 (-4.27 to 2.80) p=0.681				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup>	IG1: Vilazodone 15 mg/d IG2: Vilazodone 30 mg/d CG: Placebo	CDRS-R Week 8 score, mean (SD) IG1: 33.8 (12.0) IG2: 32.5 (11.5) CG: 34.0 (12.9)  Least squares change from baseline in total score, mean (SD): IG1: -22.9 (0.9) IG2: -24.2 (0.9) CG: -22.5 (0.9)  LS mean difference (LSMD) vs. Placebo (95% CI) IG1: -0.5 (-3.0 to 2.0) IG2: -1.7 (-4.2 to 0.7)  Adjusted p-value (vs. CG) IG1: 0.7162 IG2: 0.3267  P-value (vs. CG) IG1: 0.7162 IG2: 0.1634  CGI-S total score Week 8 score, mean (SD) IG1: 2.7 (1.2) IG2: 2.7 (1.1) CG: 2.9 (1.2)	CDRS-R response Responders, n (%) IG1: 83 (56.1) IG2: 103 (63.2) CG: 80 (55.9)  OR (95% CI) (vs. CG) IG1: 1.0 (0.5 to 2.1) IG2: 1.6 (0.8 to 3.2)  P-value (vs. CG) IG1: 0.9907 IG2: 0.2115  CDRS-R remission Remitters, n (%) IG1: 62 (41.9) IG2: 72 (44.2) CG: 63 (44.1)  OR (95% CI) IG1: 1.0 (0.5 to 2.0) IG2: 1.1 (0.5 to 2.2)  P-value (vs. CG) IG1: 0.9477 IG2: 0.8232  CGI-I response, score of 1 or 2	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup> (continued)		LS change from baseline, mean (SD): IG1: -1.8 (0.1) IG2: -1.9 (0.1) CG: -1.6 (0.1)	Responders, n (%) IG1: 98 (56.3) IG2: 112 (62.2) CG: 92 (54.1)			
		LS mean difference (LSMD) vs. Placebo (95% CI) IG1: -0.2 (-0.5 to 0.0) IG2: -0.3 (-0.5 to 0.0)	OR (95% CI) (vs. CG) IG1: 1.1 (0.7 to 1.7) IG2: 1.4 (0.9 to 2.1)			
		Adjusted p-value (vs. CG) IG1: 0.7162 IG2: 0.3267	P-value (vs. CG) IG1: 0.6811 IG2: 0.1248			
		P-value (vs. CG) IG1: 0.0852 IG2: 0.0323	CGI-I response, score of 1 Responders, n (%) IG1: 52 (29.9) IG2: 52 (28.9) CG: 34 (20.0)			
		CGI-I total score Week 8 score, mean (SD) IG1: 2.2 (1.2) IG2: 2.2 (1.0) CG: 2.4 (1.1)	OR (95% CI) (vs. CG) IG1: 1.7 (1.0 to 2.8) IG2: 1.6 (1.0 to 2.7)			
		Least squares change from baseline in total score, mean (SD): IG1: 2.3 (0.1) IG2: 2.2 (0.1) CG: 2.4 (0.1)	P-value (vs. CG) IG1: 0.0353 IG2: 0.0547			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup> (continued)		LS mean difference (LSMD) vs. Placebo (95% CI) IG1: -0.1 (-0.4 to 0.1) IG2: -0.2 (-0.5 to 0.0)  P-value (vs. CG) IG1: 0.3072 IG2: 0.0563				
Emslie, 1997 <sup>41</sup>	IG: Fluoxetine 20 mg/d CG: Placebo	CDI/BDI, mean (SD; range) IG: 9.9 (12.0; 0 to 56) CG: 11.2 (10.8; 0 to 42)  WSAS, mean (SD; range) IG: 13.1 (12.0; 0 to 42) CG: 16.7 (13.5; 0 to 46)  CDRS-R avg exit score at 8 wks, Avg (U per wk improvement) IG: 32.2 (2.75) CG: 43.6 (1.27)	CDSR-R 8 Wk Remission, N (%) IG: 15 (31) CG: 11 (23)  CDRS-R total score, Mean (SD; range) IG: 38.4 (14.8; 19 to 71) CG: 47.1 (17.0; 17 to 78)  Analysis of covariance: F=10.58 Df=1, 93 p=0.002	CGAS total score, Mean (SD; range) IG: 63.9 (12.9; 40 to 89) CG: 60.1 (14.8; 40 to 95)	NR	No significant drug by age interactions (F=0.12, df=1, 92, p=0.73) No significant drug by sex interaction (F=.001; df=1, 92; p=0.96)



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 1997 <sup>41</sup> (continued)			CGI Response to treatment at 8 wks (score of 1 or 2), N (%) IG: 27 (56) CG: 16 (33) $\chi^2=5.097$ df=1 p=0.02  Completers, n/N(%) IG: 25/34 (74) CG: 15/26 (58) $\chi^2=1.66$ p=0.20			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article	IG: Fluoxetine 10-20 mg/day CG: Placebo	Depressive symptom severity, modified ITT CDRS-R total score, mean (SD) (IG=109; CG=105) 9 weeks IG: 35.1 (13.5) CG: 40.2 (13.5) Difference in mean change (95% CI): 7.1 (3.3 to 10.9) Effect size: Cohen's d=0.51 Significant treatment-by-time interaction: p <0.001 Significant treatment effect: p=0.006 Significantly greater mean change in IG arm than CG arm: p <0.001  CDRS-R mood and behavior subscores (IG=109; CG=105) Across 9 weeks Mean improvement was significantly greater in IG arm than CG arm at weeks 1-9 (p <0.05) CDRS-R somatic subscores (IG=109; CG=105)	Remission, modified ITT CDRS-R, calculated n (%) (IG=109; CG=105) 9 weeks IG: 45 (41.3) CG: 21 (19.8) Significantly higher remission rate in IG arm than CG arm: p <0.01	Global functioning, modified ITT (IG=104; CG=86) GAF, mean (SD) 9 weeks IG: 64.8 (12.4) CG: 63.9 (9.8) Difference in mean change (95% CI): -2.2 (-1.0 to 5.4) Effect size: Cohen's d=0.20 No between-group difference: p=0.176	Response, modified ITT CDRS-R (IG=109; CG=105) 9 weeks "A comparison of results with response defined over a range from ≥20% to ≥70% reduction in CDRS-R score...indicates fluoxetine would be significantly superior to placebo if response had been defined as ≥20%, ≥40%, ≥50%, or ≥60% reduction in CDRS-R total score."  CGI-I, calculated n (%) (IG=109; CG=106) 9 weeks IG: 57 (52.3) CG: 39 (36.8) Significantly more patients in IG arm rated as much or very much improved (CGI-I score=1 or 2) than CG arm: p=0.028  Anxiety symptom severity, modified ITT HAM-A, mean (SD) (IG=106; CG=94) 9 weeks IG: 5.4 (4.7) CG: 7.4 (5.2)	Depressive symptom severity, modified ITT CDRS-R, mean (SD) (IG=109; CG=105) 9 weeks No significant between-group differences in mean change in CDRS-R among subgroups based on age category (p=0.371), sex (p=0.632), or family history of depression (p=0.493).  Response, modified ITT CDRS-R (IG=109; CG=105) 9 weeks No significant between-group differences in response rates among subgroups based on age category (p=0.629), sex (p=0.897), or family history of depression (p=0.809).

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article (continued)		<p>Across 9 weeks IG arm was superior to CG arm at weeks 2, 5, 7, and 9 (p &lt;0.05) CDRS-R subjective subscores (IG=109; CG=105) IG arm was superior to CG arm at weeks 2, 3, 7, and 9 (p &lt;0.05)</p> <p>MADRS, mean (SD) (IG=109; CG=105) 9 weeks IG: 11.2 (9.0) CG: 13.9 (8.2) Difference in mean change (95% CI): 2.8 (0.4 to 5.2) Effect size: Cohen's d=0.31 Significantly greater mean change in IG arm than CG arm: p=0.023</p> <p>CGI-S, mean (SD) (IG=109; CG=106) 9 weeks IG: 2.9 (1.2) CG: 3.4 (1.1)</p>			<p>Change from baseline to 9 weeks, mean (SD) IG: -4.8 (5.2) CG: -3.7 (5.2) Difference in mean change (95% CI): 1.2 (-0.3 to 2.6) Effect size: Cohen's d=0.22 No between-group difference: p=0.115</p>	<p>CGI-I (IG=109; CG=106) 9 weeks No significant between-group differences in response rates among subgroups based on age category (p=0.959), sex (p=0.379), or family history of depression (p=0.290).</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article (continued)		<p>Difference in mean change (95% CI): 0.6 (0.3 to 1.0) Effect size: Cohen's d=0.54 Significantly greater mean improvement in IG arm than CG arm: p&lt;0.001</p> <p>BDI (adolescents 13 to &lt;18 only), mean change from baseline (SD) (arm N's=NR) 9 weeks IG: -4.6 (8.2) CG: -5.3 (7.8) No between-group difference: p=0.700</p> <p>CDI (children 8 to &lt;13 only), mean change from baseline (SD) (arm N's=NR) 9 weeks IG: -2.4 (9.0) CG: -2.8 (6.8) No between-group difference: p=0.822</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2006 <sup>43</sup>	IG: Paroxetine CG: Placebo	CDRS-R total Adjusted Mean Difference (95% CI) Total 0.80 (-3.09 to 4.69) p=0.684	Remission (CGI-score of "very much improved") IG: 20.8% CG: 18.0% p=0.617  CDRS-R total score <28 IG: 22.8% CG: 28.0% p=0.249	GAF Median Difference (95% CI) 1.33 (-2.19, 4.86) p=0.456	NR	CDRS-R total Adjusted Mean Difference (95% CI)  Child Subgroup 5.27 (-0.08 to -10.63) p=0.054  Adolescent -2.55 (-8.23 to -3.13) p=0.375  Statistically significant treatment by age group interaction, p=0.049  No differences in the effect of paroxetine versus placebo on depressive symptoms found for gender, baseline depression severity, or presence/absence of psychiatric comorbidity.

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2009 <sup>44</sup> Index article	IG: escitalopram CG: placebo	Response (Continuous) CDRS-R Change (ITT, LOCF) LSM (SEM) IG: -22.1 (1.22) CG: -18.8 (1.27) LSMD (95% CI) -3.356 (-6.226 to -0.486)  CGI-I (Response) Risk Difference % (95% CI) 11.4 (0.5 to 22.3)  CDRS-R (Severity) Mean Change (95% CI) -3.4 (-6.2 to -0.5)  CGI-I (Symptom Improvement) Mean Change (95% CI) -0.4 (-0.6 to -0.1)  CGI-S (Symptom Severity) Mean Change (95% CI) -0.4 (-0.6 to -0.1)	Response (Dichotomous) CGI-I ≤2 IG: 64.3% (99) CG: 52.9% (83) p=0.03  Remission (Dichotomous) CDRS-R ≤28 IG: 41.6% (64) CG: 35.7% (56) p=0.15	CGAS Mean Change (95% CI) 2.2 (-0.4 to 4.8)	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2009 <sup>44</sup> Index article Companion article: Findling, 2013 <sup>45</sup>	IG: escitalopram CG: placebo	CGI at week 24, LS mean (SE) LOCF (IG=154; CG=157) IG: 2.2 (0.1) CG: 2.5 (0.1) p<0.05 Observed Cases (IG=39; CG=40) IG: 1.7 (0.1) CG: 1.5 (0.2)  CGI-S Change from baseline at week 24, LS mean (SE) LOCF (IG=154; CG=157) IG: -1.8 (0.1) CG: -1.4 (0.1) p<0.01  OC (IG=39; CG=40) IG: -2.5 (0.2) CG: -2.5 (0.2)	CGI-I≤2 at week 24 IG: 65% CG: 52% p<0.05  CDRS-R≥50% adjusted at week 24 IG: 66% CG: 50% p<0.05  Remission (CDRS-R≤28) at week 24 LOCF IG: 51% CG: 36% p<0.05	CGAS Change from baseline at week 24, LS mean (SE) LOCF (IG=149; CG=152) IG: 15.3 (1.2) CG: 11.7 (1.3) p<0.05  Change from baseline at week 24, LS mean (SE) OC (IG=40; CG=39) IG: 23.7 (2.0) CG: 18.7 (2.12)	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie 2014 <sup>46</sup>	IG1: duloxetine 60 mg QD IG2: duloxetine 30 mg QD IG3: fluoxetine 20 mg QD CG: placebo	CDRS-R at 10 weeks (Mixed Effects Model; IG1: 105; IG2: 114; IG3: 112; CG: 117) IG1: 35.0 IG2: 34.4 IG3: 36.4 CG: 37.4  Mean change at 10 weeks (MMRM) IG1: -23.9 IG2: -24.6 IG3: -22.6 CG: -21.6  Mean change at 10 weeks (LOCF) IG1: -22.4 IG2: -22.0 IG3: -21.1 CG: -19.4  CDRS-R at 36 weeks (Mixed Effects Model; CG transitioned to duloxetine or fluoxetine) IG1: 24.3 IG2: 25.1 IG3: 25.0 CG: 25.8	Probability of CDRS-R treatment response at 10 weeks IG1: 69% IG2: 69% IG3: 61% CG: 60% p=NS  Probability of CDRS-R remission at 10 weeks IG1: 40% IG2: 46% IG3: 32% CG: 30%  IG2 was statistically higher (p<0.05) than placebo Remission rates at the last two nonmissing acute treatment visits were significantly (p<0.05) greater for duloxetine 60 mg (26%) than for placebo (14%).	NR	NR	NR



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie 2014 <sup>46</sup> (continued)		<p>CGI-S at 10 weeks (Mixed Effects Model with ITT sample NR for all groups)</p> <p>IG1: 3.1 IG2: 3.1 IG3: 3.1 CG: NR</p> <p>Note: Mean CGI-S scores at the 10-week time point (MMRM) did not statistically differ among treatment groups (3.1 for all treatment groups).</p> <p>CGI-S at 36 weeks (Mixed Effects Model; NR for all groups; CG patients transitioned to IG1 or IG2)</p> <p>IG1: 1.8 IG2: 2.0 IG3: 1.8 CG: 1.9 (transitioned to duloxetine)</p>	<p>Probability of CDRS-R treatment remission at 36 weeks</p> <p>IG1: 81% IG2: NR IG3: 74% CG: NR (CG patients transitioned to duloxetine)</p> <p>No significant differences between groups</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Findling, 2009 <sup>47</sup> Index article	IG: Fluoxetine CG: Placebo	<p>CDRS-R Difference in Change (95% CI) End of Study -4.23 (-12.95 to 4.49), p=0.33, F=0.98 p=0.14 for every followup week during trial Beginning at week 5, placebo had greater mean decrease in CDRS-R than fluoxetine group through end of study.</p> <p>CGI-S Difference in Change (95% CI) -0.11 (-0.95 to 0.73), p=0.33, F=0.98</p> <p>CGI-I Difference in Change (95% CI) -0.17 (-1.12 to 0.77), p=0.79, F=0.14</p> <p>BDI Difference in Change (95% CI) 4.70 (-5.23 to 14.63), p=0.34, F=0.95</p>	<p>Response Rated very much improved (CGI-I score of 1 or 2) IG: 50% CG: 38% Response rate very much improved (CGI-I score of 1 or 2) IG: 50% CG: 38% RR (calculated): 1.30 95% CI, 0.96 to 1.76</p>	<p>CGAS Difference in Change (95% CI) 1.85 (-8.67 to 12.37), p=0.72</p>	NR	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article	IG1: paroxetine IG2: imipramine CG: placebo	NR	Remission Week 8 (LOCF: IG1=90; IG2=94; CG=87) IG1: 63.3% IG2: 50.0% CG: 46.0%  Week 8 (OC: IG1=67; IG2=56; CG=66) IG1: 76.1% IG2: 64.3% CG: 57.6%  Sustained Response During 8 Weeks of Treatment RR (95% CI) IG1 vs. CG 1.383 (0.946 to 2.022), p=0.095  IG2 vs. CG 1.272 (0.864 to 1.877), p=0.222	AFC Total Score: Week 8 Mean (SE) LOCF (IG1=60; IG2=57; CG=62) IG1: 14.70 (2.80), p=0.148 (vs. CG) IG2: 11.57 (2.92), p=0.546 (vs. CG) CG: 9.30 (2.75)  OC (IG1=58; IG2=52; CG=60) IG1: 14.37 (2.83), p=0.184 (vs. CG) IG2: 13.37 (3.04), p=0.297 (vs. CG) CG: 9.32 (2.80)	There were no deaths reported during treatment or 30 days following treatment completion.  SPP Total Scale Week 8 Mean (SE) LOCF (IG1=61; IG2=60; CG=63) IG1: 13.25 (2.33), p=0.542 IG2: 13.07 (2.41), p=0.586 CG: 11.36 (2.27)  OC (IG1=60; IG2=55; CG=60) IG1: 12.93 (2.31), p=0.930 IG2: 13.25 (2.46), p=0.853 CG: 12.66 (2.30)  SIP Total Score Week 8 Mean (SE) LOCF (IG1=63; IG2=60; CG=65) IG1: -11.36 (1.55), p=0.463 IG2: -12.92 (1.62), p=0.143 CG: -9.85 (1.51)  OC (IG1=62; IG2=55; CG=62) IG1: -11.19 (1.57), p=0.786 IG2: -13.45 (1.70), p=0.193 CG: -10.61 (1.57)	Responders by subgroup at Week 8  Features of Atypical Depression IG1: 86% (19/22) IG2: 67% (10/15) CG: 75% (6/8) Treatment p-value=0.356 Covariate p-value=0.023 Treatment-by covariate p-Value=0.503  Melancholic Features IG1: 55% (18/33) IG2: 52% (17/33) IG3: 49% (17/35) Treatment p-value=0.413 Covariate p-value=0.025 Treatment-by covariate p-Value=0.797  Anxiety Disorder IG1: 75% (9/12) IG2: 33% (7/21) CG: 48% (10/21) Treatment p-value=0.116

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article (continued)						Covariate p-value=0.208 Treatment-by covariate p-Value=0.114  Any Comorbid Disorder IG1: 70% (21/30) IG2: 54% (20/37) CG: 47% (16/34) Treatment p-value=0.227 Covariate p-value=0.440 Treatment-by covariate p-Value=0.436  Age at Onset<12 IG1: 50% (11/22) IG2: 63% (15/24) CG: 58% (7/12) Treatment p-value=0.904 Covariate p-value=0.569 Treatment-by covariate p-Value=0.217

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article (continued)						<p>Age at Onset≥12  IG1: 71% (47/66)  IG2: 57% (39/69)  CG: 55% (41/74)  Treatment p-value=0.904  Covariate p-value=0.569  Treatment-by covariate p-Value=0.217</p> <p>Number of Depressive Episodes≤1  IG1: 68% (50/73)  IG2: 55% (41/74)  CG: 61% (41/67)  Treatment p-value=0.260  Covariate p-value=0.311  Treatment-by covariate p-Value=0.118</p> <p>Number of Depressive Episodes&gt;1  IG1: 56% (9/16)  IG2: 68% (13/19)  CG: 37% (7/19)  Treatment p-value=0.260  Covariate p-value=0.311  Treatment-by covariate p-Value=0.118</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup>	IG1: paroxetine IG2: imipramine CG: placebo	HAM-D Change: Week 8 OC: IG1=67; IG2=56; CG=66 Least Squares Mean (95% CI), SEM IG1: -12.2 (-13.1 to -10.5), 0.88 IG2: -10.6 (-12.5 to -8.7), 0.97 CG: -10.5 (-12.3 to -8.8), 0.88 ANCOVA p=0.26  LOCF: IG1=90; IG2=94; CG=87 Least Squares Mean (95% CI), SEM IG1: -10.7 (-12.3 to -9.1), 0.81 IG2: -9.0 (-10.5 to -7.4), 0.81 CG: -9.1 (-10.7 to -7.5), 0.83 ANCOVA p=0.20  Multiple Imputation (MI): IG1=90; IG2=94; CG=87 Least Squares Mean (95% CI), SEM IG1: -12.5 (-14.2 to -10.9), 0.83 IG2: -11.1 (-12.9 to -9.4), 0.89 CG: -10.7 (-12.4 to -9.1), 0.83 ANCOVA p=0.24	HAM-D Response: Week 8 OC (IG1=67; IG2=56; CG=66) % (Criteria Met/Not Met) IG1: 80.6% (54/13) IG2: 73.2% (41/15) CG: 65.2% (43/23) p=0.13  LOCF (IG1=90; IG2=94; CG=87) n (%) IG1: 66.7% (60/30) IG2: 58.5% (55/39) CG: 55.2% (48/39) p=0.27  MI (IG1=90; IG2=94; CG=87) n (%) IG1: 73.3% (66/24) IG2: 70.2% (66/28) CG: 70.1% (61/26) p=0.24	CGI: Week 8 OC (IG1=67; IG2=56; CG=66) Least Squares Mean (95% CI), SEM IG1: 1.9 (1.6 to 2.2), 0.15 IG2: 2.2 (1.8 to 2.5), 0.17 CG: 2.4 (2.1 to 2.7), 0.16 p=0.09  LOCF (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: 2.4 (2.1 to 2.7), 0.16 IG2: 2.7 (2.4 to 3.0), 0.15 CG: 2.7 (2.4 to 3.0), 0.16 p=0.16  MI (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: 1.9 (1.6 to 2.2), 0.14 IG2: 2.2 (1.9 to 2.5), 0.15 CG: 2.4 (2.1 to 2.6), 0.14 p=0.24  AFC - Week 8 OC (IG1=58; IG2=52; CG=60) Least Squares Mean (95% CI), SEM IG1: 14.4 (8.8 to 19.9), 2.83 IG2: 13.3 (7.3 to 19.4), 3.04 CG: 9.3 (3.8 to 14.8), 2.81 p=0.32	SPP: Week 8 OC (IG1=60; IG2=55; CG=60) Least Squares Mean (95% CI), SEM IG1: 12.9 (8.3 to 17.5), 2.31 IG2: 13.2 (8.4 to 18.1), 2.46 CG: 12.7 (6.9 to 15.9), 2.30 p=0.88  LOCF (IG1=61; IG2=60; CG=63) Least Squares Mean (95% CI), SEM IG1: 13.2 (8.6 to 17.8), 2.33 IG2: 13.1 (8.3 to 17.8), 2.41 CG: 11.4 (6.9 to 15.9), 2.27 p=0.88  MI (IG1=61; IG2=60; CG=65) Least Squares Mean (95% CI), SEM IG1: 15.4 (10.7 to 20.0), 2.35 IG2: 14 (8.9 to 19.2), 2.60 CG: 14.7 (10.0 to 19.4), 2.39 p=0.92  SIP - Week 8 OC (IG1=62; IG2=55; CG=62) Least Squares Mean (95% CI), SEM IG1: -11.2 (-14.3 to -8.1), 1.57 IG2: -13.5 (-16.9 to -10.2), 1.70	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)		K-SADS-L: Week 8 OC (IG1=67; IG2=56; CG=66) Least Squares Mean (95% CI), SEM IG1: --12.1 (--13.8 to -- 10.3) 0.91 IG2: --10.7 (--12.7 to -- 8.7) 0.82 CG: --10.7 (--12.5 to -- 8.9) 0.92 p=0.46		LOCF (IG1=60; IG2=57; CG=62) Least Squares Mean (95% CI), SEM IG1: 14.7 (9.2 to 20.2), 2.80 IG2: 11.6 (5.8 to 17.3), 2.92 CG: 9.3 (8.1 to 17.2), 2.76 p=0.39  MI (IG1=60; IG2=57; CG=62) Least Squares Mean (95% CI), SEM IG1: 14.0 (8.7 to 19.3), 2.65 IG2: 14.5 (9.4 to 19.6), 2.60 CG: 9.1 (4.2 to 14.1), 2.52 p=0.24	CG: --10.6 (--13.7 to --7.5), 1.57 p=0.24  LOCF (IG1=63; IG2=60; CG=65) Least Squares Mean (95% CI), SEM IG1: --11.4 (--14.4 to --8.3), 1.55 IG2: --13.0 (--16.2 to --9.8), 1.62 CG: --9.9 (--12.9 to --6.9), 1.51 p=0.23  MI (IG1=63; IG2=60; CG=65) Least Squares Mean (95% CI), SEM IG1: --11.5 (--14.2 to --8.7), 1.39 IG2: --13.9 (--16.8 to --10.9), 1.50 CG: --10.1 (--13.0 to --7.1), 1.48 p=0.19	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)		<p>LOCF (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: --11.4 (--13.1 to -- 9.8) 0.84 IG2: --9.5 (--11.1 to -- 7.9) 0.82 CG: --9.4 (--11.0 to --7.8) 0.83 p=0.13</p> <p>MI (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: --12.3 (--13.9 to -- 10.6) 0.84 IG2: --11.5 (--13.3 to -- 9.7) 0.91 CG: --10.9 (--12.6 to -- 9.2) 0.86 p=0.45</p>				



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup>	IG1: Paroxetine IG2: Imipramine CG: Placebo	NR	Response at some time point (defined as remission [HAM-D <8] in Table 3) ITT: IG1=93; IG2=95; CG=87 IG1: 61 IG2: 57 CG: 47  Completed Responders defined as HAM-D <8 (+ potential responders) ITT: IG1=93; IG2=95; CG=87 IG1: 15 (+3) IG2: 12 (+1) CG: 12 (+9)	NR	Acute phase relapse (HAM-D) ITT: IG1=93; IG2=95; CG=87 IG1: 6 IG2: 5 CG: 3  Continuation phase relapse (HAM-D) ITT: IG1=93; IG2=95; CG=87 IG1: 19 IG2: 10 CG: 7  Total relapses (HAM-D) ITT: IG1=93; IG2=95; CG=87 IG1: 25 (41%) IG2: 15 (26%) CG: 10 (21%)	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS <sup>92</sup>	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Depression symptoms, ITT (n=439) Adjusted CDRS-R total score 6 weeks, adjusted mean (SD) IG1: 38.10 (7.78) IG2: 39.80 (7.37) IG3: 44.63 (8.30) CG: 44.90 (7.32)  12 weeks, adjusted mean (SD) IG1: 33.79 (8.24) IG2: 36.30 (8.18) IG3: 42.06 (9.18) CG: 41.77 (7.99)  Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement : IG1>CG (p=0.001); IG1=IG2 (p=0.13); IG1>IG3 (p=0.001); IG2>IG3 (p=0.001); IG2>CG (p=0.002); IG3=CG (p=0.97)  Across all 12 weeks: Time-by-treatment interaction based on CDRS-R random	Response CGI-I positive response rate, ITT (n=439) 12 weeks, % response rate (95% CI) adjusted for clinical site IG1: 71.0 (62 to 80) IG2: 60.6 (51 to 70) IG3: 43.2 (34 to 52) CG: 34.8 (26 to 44) Regression analyses found treatment was statistically significant factor in CGI-I positive response (p=0.001)  RR (calculated): 2.45 95% CI, 0.31 to 19.7  12 weeks, statistically comparing response : IG1>CG (p=0.001); IG2>CG (p=0.001); IG3=CG (p=0.20); IG1=IG2 (p=0.11); IG1>IG3 (p=0.001); IG2>IG3 (p=0.01)	NR	No mortality from completed suicides	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>regression slope coefficients: <math>p=0.001</math>; Statistically comparing improvement :</p> <p>IG1&gt;CG (<math>p=0.001</math>); IG1&gt;IG2 (<math>p=0.02</math>); IG1&gt;IG3 (<math>p=0.001</math>); IG2&gt;IG3 (<math>p=0.01</math>); IG2=CG (<math>p=0.10</math>); IG3=CG (<math>p=0.40</math>)</p> <p>Hedge g effect sizes relative to placebo (G4) IG1: 0.98 IG2: 0.68 IG3: -0.03</p> <p>Hedge g effect sizes relative to placebo (CG) derived from ORs for dichotomized CGI-I IG1: 0.84 IG2: 0.58 IG3: 0.20 CG: NA</p> <p>NNT (95% CI) IG1: 3 (2 to 4) IG2: 4 (3 to 8) IG3: 12 (5 to 23) CG: NA</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>RADS total score 6 weeks, adjusted mean (SD) IG1: 60.90 (11.59) IG2: 63.41 (12.44) IG3: 69.10 (13.59) CG: 69.43 (10.94)</p> <p>12 weeks, adjusted mean (SD) IG1: 56.95 (12.24) IG2: 60.58 (13.07) IG3: 67.96 (14.18) CG: 66.68 (11.41)</p> <p>Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement : IG1&gt;CG (p=0.001); IG1=IG2 (p=0.11); IG1&gt;IG3 (p=0.001); IG2&gt;IG3 (p=0.003); IG2&gt;CG (p=0.003); IG3=CG (p=0.94)</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Across all 12 weeks: Time-by-treatment interaction based on RADS random regression slope coefficients: <math>p=0.001</math>; Statistically comparing improvement :</p> <p>IG1&gt;CG (<math>p=0.001</math>); IG1&gt;IG2 (<math>p=0.002</math>); IG1&gt;IG3 (<math>p=0.001</math>); IG2&gt;IG3 (<math>p=0.03</math>); IG2=CG (<math>p=0.34</math>); IG3=CG (<math>p=0.21</math>)</p> <p>NOTE: Means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	<p>Loss of MDD diagnosis (K-SADS-P/L) Completers analysis only (n=379): 12 weeks, % IG1: 85.3 IG2: 78.6 IG3: 61.1 CG: 60.4 Overall treatment effect: <math>p \leq 0.0001</math></p> <p>Statistical comparisons found mixed findings in terms of how groups compared with one another, OR (95% CI): IG1=IG2: 1.7 (0.79 to 3.61) (<math>p=0.18</math>); IG1&gt;IG3: 4.3 (2.06 to 8.94) (<math>p=0.0001</math>); IG1&gt;CG: 4.1 (2.00 to 8.44) (<math>p=0.0001</math>); IG2&gt;IG3: 2.5 (1.31 to 4.93) (<math>p=0.006</math>); IG2&gt;CG: 2.4 (1.27 to 4.67) (<math>p=0.007</math>); IG3=CG: 1.0 (0.52 to 1.77) (<math>p=0.89</math>)</p>	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS (continued)			<p>Remission, adjusted for site (CDRS-R) ITT (n=439): 12 weeks, % IG1: 37 IG2: 23 IG3: 16 CG: 17 Overall treatment effect: p=0.0007</p> <p>Statistical comparisons found that IG1 was associated with higher remission rates than all other groups, OR (95% CI): IG1&gt;IG2: 2.1 (1.12 to 3.84) (p=0.02); IG1&gt;IG3: 3.3 (1.71 to 6.42) (p=0.0004); IG1&gt;CG: 3.0 (1.58 to 5.79) (p=0.0009)</p> <p>In contrast; IG2; IG3, and CG did not differ statistically from one another (all p &gt;0.05). See comparisons below, OR (95% CI): IG2=IG3: 1.6 (0.80 to 3.19) (p=0.19) IG2=CG: 1.5 (0.74 to 2.88) (p=0.28) IG3=CG: 0.9 (0.44 to 1.88) (p=0.80)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	<p>Functional status (C-GAS) ITT (n=439): 6 weeks, unadjusted mean (SD) IG1: 62.4 (11.2) IG2: 59.9 (10.58) IG3: 56.7 (9.66) CG: 57.0 (9.22)</p> <p>12 weeks, unadjusted mean (SD) IG1: 66.6 (11.91) IG2: 62.1 (11.91) IG3: 60.0 (11.47) CG: 59.3 (12.72) Time effect in all groups: p&lt;0.0001 Treatment-by-time interaction: p&lt;0.0001</p> <p>RRM statistical comparisons of how groups compared with one another at 12 weeks : IG1&gt;IG2: p=0.0450 IG1&gt;IG3: p&lt;0.0001 IG1&gt;CG: p&lt;0.0001 IG2&gt;IG3: p=0.0032 IG2&gt;CG: p=0.0381 IG3=CG: p=0.3805</p>	<p>Global burden of psychiatric problems (HoNOSCA) ITT (n=439): 12 weeks, unadjusted mean (SD) IG1: 9.5 (5.97) IG2: 10.9 (6.35) IG3: 11.7 (6.09) CG: 11.2 (6.15) Time effect in all groups: p&lt;0.0001 Treatment-by-time interaction: p&lt;0.0234</p> <p>RRM statistical comparisons of how groups compared with one another : IG1=IG2: p=0.1257 IG1&gt;IG3: p=0.0027 IG1&gt;CG: p=0.0393 IG2=IG3: p=0.1310 IG2=CG: p=0.5861 IG3=CG: p=0.3344</p> <p>12 weeks, mean change from baseline (SD) G1: -6.3 (5.69) G2: -5.1 (5.74) G3: -3.6 (5.58) G4: -4.2 (5.71)</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				12 weeks, mean change from baseline (SD) IG1: 16.7 (12.31) IG2: 12.6 (12.31) IG3: 9.7 (12.12) CG: 9.9 (12.38) Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): $p < 0.0001$ GLM statistical comparisons of how groups compared with one another : IG1>IG2: $p < 0.01$ IG1>IG3: $p < 0.0001$ IG1>CG: $p < 0.0001$ IG2>IG3: $p = \text{NR}$ IG2=CG: $p = \text{NS}$ IG3=CG: $p = \text{NS}$ Rate of nonimpaired patients (C-GAS >70) 12 weeks, % IG1: 34.6 IG2: 20.2 IG3: 13.5 CG: 18.7	Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): $p < 0.01$ GLM statistical comparisons of how groups compared with one another at 12 weeks : IG1=IG2: $p = \text{NS}$ IG1>IG3: $p < 0.001$ IG1>CG: $p < 0.01$ IG2>IG3: $p < 0.05$ IG2=CG: $p = \text{NS}$ IG3=CG: $p = \text{NR}$ HoNOSCA subscores: Treatment-by-time interaction was statistically significant only for item 10 (level of functioning with peers; $p = 0.0004$ ), whose effect remained significant even after applying a Bonferroni correction for multiple comparisons. QoL (PQ-LES-Q) ITT (n=439): 12 weeks, unadjusted mean (SD) IG1: 54.7 (11.21) IG2: 51.2 (10.43) IG3: 47.4 (10.84) CG: 48.2 (9.91)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				<p>Between-group difference: p=0.002</p> <p>Statistically significant treatment effects of how groups compared with one another :</p> <p>IG1&gt;IG2: p&lt;0.020</p> <p>IG1&gt;IG3: p&lt;0.0004</p> <p>IG1&gt;CG: p&lt;0.009</p> <p>IG2=IG3: p=NS</p> <p>IG2=CG: p=NS</p> <p>IG3=CG: p=NS</p> <p>Patients not likely to be clinically referred in community (C-GAS &gt;60)</p> <p>12 weeks, %</p> <p>IG1: 64.5</p> <p>IG2: 50.5</p> <p>IG3: 45.0</p> <p>CG: 35.7</p> <p>Between-group difference: p=0.0003</p> <p>Statistically significant treatment effects of how groups compared with one another :</p> <p>IG1&gt;IG2: p&lt;0.038</p> <p>IG1&gt;IG3: p&lt;0.004</p> <p>IG1&gt;CG: p&lt;0.0001</p> <p>IG2=IG3: p=NS</p> <p>IG2&gt;CG: p=0.023</p> <p>IG3=CG: p=NS</p>	<p>Time effect in all groups: p&lt;0.0001</p> <p>Treatment-by-time interaction: p&lt;0.0001</p> <p>RRM statistical comparisons of how groups compared with one another at 12 weeks :</p> <p>IG1&gt;IG2: p=0.0004</p> <p>IG1&gt;IG3: p&lt;0.0001</p> <p>IG1&gt;CG: p&lt;0.0001</p> <p>IG2=IG3: p=0.2766</p> <p>IG2=CG: p=0.7215</p> <p>IG3=CG: p=0.4630</p> <p>12 weeks, mean change from baseline (SD)</p> <p>IG1: 9.6 (10.14)</p> <p>IG2: 6.6 (10.23)</p> <p>IG3: 4.2 (10.01)</p> <p>CG: 5.2 (10.16)</p> <p>Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): p&lt;0.001</p> <p>Treatment-by-time interaction: p&lt;0.0001</p> <p>GLM statistical comparisons of how groups compared with one another :</p> <p>IG1&gt;IG2: p&lt;0.05</p> <p>IG1&gt;IG3: p&lt;0.0001</p> <p>IG1&gt;CG: p&lt;0.001</p> <p>IG2&gt;IG3: p=NS</p> <p>IG2=CG: p=NS</p> <p>IG3=CG: p=NS</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Wagner, 2004 <sup>52</sup> Index article Companion article: Forest, 2001 <sup>53</sup>	G1: Citalopram G2: Placebo	CDRS-R Changes at Week 8 (LOCF) G1: -21.7 (1.6) G2: -16.5 (1.6) LSMD -4.6 (95% CI, -0.3, -9.0, p=0.038)  CGI-I Score at Week 8 (LOCF) G1: 2.6 (0.1) G2: 2.8 (0.1) LSMD -0.2  CGI-S Changes at Week 8 (LOCF) G1: -1.3 (0.1) G2: -1.1 (0.1) LSMD -0.2  K-SADS-P Changes at Week 8 (LOCF) G1: -9.1 (0.9) G2: -7.2 (0.9) LSMD -1.9	CDRS-R Response (score ≤28) at Week 8 (LOCF), % IG: 36 CG: 24 (p <0.05)	CGAS Change at Week 8 G1: 14.3 (1.5) G2: 11.8 (1.4) LSMD 2.0	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Wagner, 2006 <sup>54</sup>	G1: escitalopram G2: placebo	Change to CDRS-R at Week 8 (IG: 129; CG: 132) LOCF IG: -21.9 CG: -20.2 p=0.310 OC IG: -23.9 CG: -20.8 p=0.084  Change to CGI-S at Week 8 (IG: 129; CG: 132) LOCF IG: -1.6 CG: -1.3 p=0.057  OC IG: -1.8 CG: -1.4 p=0.014  CGI-I at Week 8 (IG: 129; CG: 132) LOCF IG: 2.3 CG: 2.5 p=0.169  OC IG: 2.1 CG: 2.4 p=0.110	CGI-I=1 or 2 response rate at Week 8 LOCF G1: 63% calculated G2: 52% calculated  OC IG: 72.1 CG: 57.8 p=0.05	Change to CGAS at Week 8 (IG: 129; CG: 132) LOCF IG: 15.6 CG: 12.7 p=0.065  OC IG: 16.8 CG: 13.6 p=0.046	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Weihs, 2018 <sup>55</sup>	IG1: Desvenlafaxine (25, 35, or 50 mg/d) IG2: Fluoxetine (20 mg/d) CG: Placebo	Change in CDRS-R from baseline to Week 8 (ITT): Adjusted mean change (SE) in total score IG1: -22.6 (1.17) IG2: -24.8 (1.17) CG: -23.1 (1.18) Adjusted mean difference as compared to placebo (95% CI) IG1: -0.47 (-3.23 to 2.30), p<0.05 IG2: 1.71 (-1.06 to 4.48) No significant differences Change in CGI-S score from baseline to Week 8 (completers): Adjusted mean change (SE) in total score IG1 (n=99): -1.70 (0.11) IG2 (n=101): -1.88 (0.12) CG (n=99): -1.71 (0.12) Adjusted mean difference as compared to placebo (95% CI) IG1: -0.01 (-0.29 to 0.27), p=0.944 IG2: 0.18 (-0.11 to 0.46), p=0.224	CGI-I score: % very much improved, much improved, minimally improved, no change IG1: 23.2, 45.5, 21.2, 9.1, CMH test p=0.852 (vs. CG) IG2: 30.7, 47.5, 16.8, 4.0, CMH test p=0.095 (vs. CG) CG: 27.3, 35.4, 32.3, 4.0 CGI-I response at Week 8 (ITT): IG1: 68.7% IG2: 78.2% CG: 62.6%, p=0.343 Adjusted OR (95% CI) vs. CG IG1: 0.751 (0.249 to 0.871), p=0.343 IG2: 0.465 (0.249 to 0.871), p=0.017	NR	NR	

AFC = Autonomous Functioning Checklist; ANCOVA = analysis of covariance; AOR = adjusted odds ratio; BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDI-S = Children's Depression Inventory-Severity; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGAS = Children's Global Assessment Scale; CGI = Clinical Global Impressions Scale; CGI-I = Clinical Global Impressions Scale-Improvement Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; CI = confidence interval; CMH test = Cochran-Mantel-Haenszel test; GAF = Global Assessment of Functioning; GLM = generalized linear modeling; HAM-A = Hamilton Depression Rating Scale; HAM-D = Hamilton Depression Rating Scale; HoNOSCA = Health of Nation Outcome Scale – Children and Adolescents; IG = Intervention group; ITT = intent to treat; K-SADS-L = Kiddie Schedule for Affective Disorders and Schizophrenia-Lifetime; K-SADS-P = Kiddie Schedule for

Affective Disorders and Schizophrenia-Parent; K-SADS-P/L = Kiddie Schedule for Affective Disorders and Schizophrenia; KQ = Key Question; LOCF: last observation carried forward; LOCF = last observation carried forward; LS = life skills/tutoring condition; LSM = least squares mean; LSMD = least squares mean difference; MADRS = Montgomery-Asberg Depression Rating Scale; MFQ = Mood and Feelings Questionnaire; MI = multiple imputation; n/N = number; NNT = number needed to treat; NR = not reported; OC = observed cases; OR = odds ratio; PQ-LES-Q = Parent-Child Interaction Therapy Emotion Development; QD = every day; QoL = quality of life; RADS = Reactive Airways Dysfunction Syndrome; RR = relative risk; RRM = random-effects regression model; SD = standard deviation; SE = standard error; SEM = structural equation modeling; SIP = suicidal ideation protocol; SPP = Self Perception Profile; TADS = Treatment among Adolescents with Depression; wk(s) = week(s).

**Table E-21. KQ 2a: Benefits of fluoxetine for relapse prevention versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup>	IG: Continued treatment with fluoxetine at current dose (20-60 mg/day) CG: Switch to placebo	Depressive symptom severity, modified ITT CDRS-R total score: mean change from baseline [19 weeks] (SD) (IG=20; CG=20) 19 to 51 weeks IG: 8.2 (12.4) CG: 14.7 (14.5) No between-group difference: p=0.139  CDRS-R mood subscores: mean change from baseline [19 weeks] (SD) (IG=20; CG=20) 19 to 51 weeks IG: 2.3 (4.6) CG: 5.5 (5.1) Significantly smaller increase (worsening) in CDRS mood subscale score in IG arm than CG arm: p=0.048  CDRS-R somatic subscores: mean change from baseline [19 weeks] (SD) (IG=20; CG=20) 19 to 51 weeks IG: 2.7 (4.4) CG: 3.1 (4.3) No between-group difference: p=0.803	NA	Global functioning, modified ITT (IG=20; CG=18) GAF, mean change from baseline [19 weeks] (SD) 19 to 51 weeks IG: -7.3 (13.1) CG: -7.9 (14.7) No between-group difference: p=0.888	Estimated probability of relapse, ITT (N=40) CDRS-R primary analysis (total score >40 for ≥2 weeks history of worsening depressive symptoms or relapse in opinion of treating physician), % probability 19 to 51 weeks IG: 34 CG: 60 Lower risk for relapse in IG arm than CG arm, but unclear if difference was statistically significant (p=NR)  Time to relapse 19 to 51 weeks, mean days (SE) IG: 180.7 (17.0) CG: 71.2 (9.5) Significantly longer time to relapse in IG arm than CG arm (p=0.046)  CDRS-R secondary analysis (total score >40 for ≥2 weeks history of worsening depressive symptoms or relapse in opinion of treating physician), % probability 19 to 51 weeks IG: 21 CG: 47	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup> (continued)		<p>CDRS-R subjective subscores: mean change from baseline [19 weeks] (SD) (IG=20; CG=20) 19 to 51 weeks IG: 0.5 (1.5) CG: 2.8 (3.9) Significantly smaller increase (worsening) in CDRS mood subscale score in IG arm than CG arm: p=0.018</p> <p>CDRS-R behavior subscores: mean change from baseline [19 weeks] (SD) (IG=20; CG=20) 19 to 51 weeks IG: 2.7 (3.9) CG: 3.4 (3.3) No between-group difference: p=0.578</p> <p>MADRS, mean change from baseline [19 weeks] (SD) (IG=20; CG=20) 19 to 51 weeks IG: 3.6 (7.9) CG: 8.2 (10.4) No between-group difference: p=0.128</p>			<p>Lower risk for relapse in IG arm than CG arm, but unclear if difference was statistically significant (p=NR) Time to relapse 19 to 51 weeks, mean days (SE) IG: 203.0 (13.0) CG: 37.2 (2.1) Significantly longer time to relapse in IG arm than CG arm (p=0.032)</p> <p>Anxiety symptom severity, modified ITT HAM-A, mean change from baseline (SD) (IG=20; CG=19) 19 to 51 weeks IG: 1.3 (2.5) CG: 2.1 (3.9) No between-group difference: p=0.448</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup> (continued)		CGI-S, mean change from baseline [19 weeks] (SD) (IG=20; CG=20) 19 to 51 weeks IG: 0.5 (1.2) CG: 1.0 (1.6) No between-group difference: p=0.274  CGI-I, mean change from baseline [week 1 of entire trial] (SD) (IG=20; CG=20) 19 to 51 weeks IG: 1.9 (1.2) CG: 3.2 (1.8) Significantly greater maintenance of improvement in IG arm than CG arm: p=0.011  BDI (adolescents 13 to <18 only), mean change from baseline [19 weeks] (SD) (IG=12; CG=6) 9 weeks IG: 0.7 (3.6) CG: 6.0 (8.4) No between-group difference: p=0.0704  CDI (children 8 to <13 only), mean change from baseline [19 weeks] (SD) (IG=8; CG=13) 19 to 51 weeks IG: 1.6 (1.9) CG: 3.8 (7.9) No between-group difference: p=0.447				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2008 <sup>57</sup> Index article	IG1: Fluoxetine continuation CG: Placebo	Participants reporting residual depressive symptoms after acute treatment, %: IG1: 67 CG: 25	NR	NR	Relapse, % IG1: 42.0 CG: 69.2 X2=7.67; df=1; p=0.007 Odds of relapse for CG vs. IG1: 3.2 times (95% CI, 1.2-8.2) Unadjusted risk of relapse, RR (95% CI): 2.1 (1.3-3.6) X2=3.1; df=1; p=0.0044 Adjusted risk of relapse, RR (95% CI): 2.2 (1.2-3.8) X2=7.7; df=1; p=0.0055 Full relapse, % IG1: 22.0 CG: 48.1 X2=7.59; df=1; p=0.007  Survival curves for time to relapse and full relapse: only in Figure 2 and Figure 3	
Emslie, 2008 <sup>57</sup> Index article Companion article: Kennard, 2018 <sup>58</sup>	See Emslie, 2008 <sup>57</sup> Index article	CDRS-R at week 12 (randomization): 22.83) IG1: NR CG: NR	NR	NR	NR	NR

BDI = Beck Depression Inventory; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-I = Clinical Global Impressions Scale-Improvement Scale; GAF = Global Assessment of Functioning; HAM-A = Hamilton Depression Rating Scale; IG = intervention group; ITT = intent to treat; KQ = Key Question; MADRS = Montgomery-Asberg Depression Rating Scale; NA = not applicable; NR = not reported; RR = relative risk; SD = standard deviation; SE = standard error.

**Table E-22. KQ 2a: Benefits of SNRIs versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Atkinson, 2018 <sup>59</sup>	IG1: Low-dose Desvenlafaxine IG2: High-dose Desvenlafaxine CG: Placebo	CDRS-R, Week 8 Change from baseline, mean (SD) IG1: -23.7 (1.1) IG2: -24.4 (1.1) CG: -22.9 (1.1)  Adjusted mean difference vs. placebo (95% CI) IG1: 0.85 [-2.23, 3.94] IG2: 1.52 [-1.56, 4.61] p=NS  CGI-S, Week 8 Adjusted mean change (SE) IG1: -1.51 (0.11) IG2: -1.65 (0.11) CG: -1.49 (0.11)  Difference in adjusted means, placebo active (95% CI) IG1: 0.015 (-0.29 to 0.32) p=0.923 IG2: 0.161 (-0.14 to 0.47) p=0.302	CGI-I response, Week 8 Responders, proportion (%) IG1: 59/105 (56.2) IG2: 66/106 (62.3) CG: 57/102 (55.9) Adjusted OR (Wald 95% CI) IG1: 0.97 (0.56, 1.69) p=0.925 IG2: 0.76 (0.44, 1.33) p=0.342  CGI-I, Week 8 1: Very much improved (%) IG1: 20 (19.0) IG2: 27 (25.5) CG: 22 (21.6)  2: Much improved (%) IG1: 39 (37.1) IG2: 39 (36.8) CG: 35 (34.3)  3: Minimally improved (%) IG1: 26 (24.8) IG2: 23 (21.7) CG: 29 (28.4)  4: No change (%) IG1: 19 (18.1) IG2: 16 (15.1) CG: 16 (15.7)	NR	NR	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie 2007 <sup>60</sup>	IG: venlafaxine ER (112.5 mg, 150 mg, or 22mg based on weight) CG: Placebo	<p>Study 1</p> <p>Change in CDRS-R from baseline to week 8 (ITT; IG1: 68; CG: 73))</p> <p>Adjusted mean change (SE) in total score</p> <p>IG1: -18.1 (1.6)</p> <p>CG: -16.1 (1.4)</p> <p>p = 0.34</p> <p>Mean CDRS-R at followup</p> <p>IG1: 36.3</p> <p>CG: 38.3</p> <p>Study 2</p> <p>Change in CDRS-R from baseline to week 8 (ITT; IG1: 101; CG: 92))</p> <p>Adjusted mean change (SE) in total score</p> <p>IG1: -24.6 (1.3)</p> <p>CG: -22.8 (1.4)</p> <p>p = 0.39</p> <p>Mean CDRS-R at followup</p> <p>IG1: 32.7</p> <p>CG: 34.5</p>	<p>Study 1</p> <p>CDRS-R responder rates at 8 weeks (ITT; IG1: 68; CG: 73)</p> <p>IG1: 43/68 (63%)</p> <p>CG: 37/73 (51%)</p> <p>p = 0.174</p> <p>Study 2</p> <p>CDRS-R responder rates at 8 weeks (ITT; IG1: 101; CG: 92)</p> <p>IG1: 77/101 (76%)</p> <p>CG: 62/92 (67%)</p> <p>p = 0.200</p>	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie 2014 <sup>46</sup>	IG1: duloxetine 60 mg QD IG2: duloxetine 30 mg QD IG3: fluoxetine 20 mg QD CG: placebo	CDRS-R at 10 weeks (Mixed Effects Model; IG1: 105; IG2: 114' IG3: 112; CG: 117) IG1: 35.0 IG2: 34.4 IG3: 36.4 CG: 37.4  Mean change at 10 weeks IG1: -23.9 IG2: -24.6 IG3: -22.6 CG: -21.6  Mean change at LOCF IG1: -22.4 IG2: -22.0 IG3: -21.1 CG: -19.4  CDRS-R at 36 weeks (Mixed Effects Model; CG transitioned to duloxetine or fluoxetine) IG1: 24.3 IG2: 25.1 IG3: 25.0 CG: 25.8	Probability of treatment response at 10 weeks IG1: 69% IG2: 69% IG3: 61% CG: 60% No significant differences  Probability of remission at 10 weeks IG1: 40% IG2: 46% IG3: 32% CG: 14% IG2 was statistically higher ( p<0.05) than placebo Remission rates at the last two nonmissing acute treatment visits was significantly ( p<0.05) greater for duloxetine 60 mg (26%) than for placebo (14%).	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie 2014 <sup>46</sup> (continued)			Probability of treatment remission at 36 weeks IG1: 81% IG2: NR IG3: 74% CG: NR (CG patients transitioned to duloxetine) No significant differences between groups			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Weihs, 2018 <sup>55</sup>	IG1: Desvenlafaxine (25, 35, or 50 mg/d) IG2: Fluoxetine (20 mg/d) CG: Placebo	Change in CDRS-R from baseline to week 8 (ITT): Adjusted mean change (SE) in total score IG1: -22.6 (1.17) IG2: -24.8 (1.17) CG: -23.1 (1.18) Adjusted mean difference as compared to placebo (95% CI) IG1: -0.47 (-3.23 to 2.30), p<0.05 IG2: 1.71 (-1.06 to 4.48), p<0.01  Change in CGI-S score from baseline to week 8 (completers): Adjusted mean change (SE) in total score IG1 (n=99): -1.70 (0.11) IG2 (n=101): -1.88 (0.12) CG (n=99): -1.71 (0.12)  Adjusted mean difference as compared to placebo (95% CI) IG1: -0.01 (-0.29 to 0.27), p=0.944 IG2: 0.18 (-0.11 to 0.46), p=0.224	CGI-I score: % very much improved, minimally improved, no change IG1: 23.2%, 45.5, 21.2, 9.1, CMH test p=0.852 IG2: 30.7%, 47.5, 16.8, 4.0, CMH test p=0.095 CG: 27.3%, 35.4, 32.3, 4.0  CGI-I response at week 8 (ITT): IG1: 68.7%, IG2: 78.2% CG: 62.6%  Adjusted OR (95% CI) vs. CG IG1: 0.751 (0.249 to 0.871), p=0.343 IG2: 0.465 (0.249 to 0.871), p=0.017	NR	NR	

AOR = adjusted odds ratio; CDRS-R = Children's Depression Rating Scale-Revised; CGI-I = Clinical Global Impressions Scale-Improvement Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; CI = confidence interval; CMH = Cochran-Mantel-Haenszel row-mean score-difference test; IG = intervention group; ITT = intent to treat; KQ = Key Question; mg/d = milligram per day; MMRM = mixed effect model repeat measurement; NR = not reported; QD = every day; SD = standard deviation; SE = standard error.

**Table E-23. KQ 2a: Benefits of TCAs versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Geller, 1989 <sup>61</sup>	IG: Nortriptyline CG: Placebo	NA	Response rate (CDRS) Completers analysis (n=50; IG: 26 and CG: 24) 8 weeks, N (%) IG: 8 (30.8) CG: 4 (16.7) Between-group difference: $\chi$ -squared: 1.36; df=1; p=0.24	NA	NA	
Geller, 1992 <sup>62</sup>	IG: Nortriptyline CG: Placebo	CDRS Change score (SD) IG: 0.2 (11.6) CG: -0.6 (8.6) Change (%) IG: -33.6 (23.5) CG: -35.8 (16.7) t=0.37, p=0.71  9-item KSADS Change score (SD) IG: 0.95 (0.88) CG: 0.76 (0.69)  Change (%) IG: -37.90 (23.90) CG: -44.00 (16.50) t=1.04, p=0.30	Responder based on CDRS score of <20 IG: 30.8% CG: 16.7% X <sup>2</sup> =1.36, df=1, p=0.24  Responder based on K-SADS-P scores 1 or 2 IG: 46.2% CG: 58.3% X <sup>2</sup> =0.74, df=1, p=0.39	KGAS Change score (SD) IG: 81.0 (20.5) CG: 83.9 (17.6) Change (%) IG: 55.7 (59.1) CG: 59.2 (49.9) t=-0.23, p=0.82	NR	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article	IG1: paroxetine IG2: imipramine CG: placebo	Sustained Response During 8 Weeks of Treatment RR (95% CI) IG1 vs. CG 1.383 (0.946 to 2.022), p=0.095  IG2 vs. CG 1.272 (0.864 to 1.877), p=0.222	Remission Week 8 (LOCF: IG1=90; IG2=94; CG=87) IG1: 63.3% IG2: 50.0% CG: 46.0%  Week 8 (OC: IG1=67; IG2=56; CG=66) IG1: 76.1% IG2: 64.3% CG: 57.6%	AFC Total Score -Week 8 Mean (SE) LOCF (IG1=60; IG2=57; CG=62) IG1: 14.70 (2.80), p=0.148 IG2: 11.57 (2.92), p=0.546 CG: 9.30 (2.75)  OC (IG1=58; IG2=52; CG=60) IG1: 14.37 (2.83), p=0.184 IG2: 13.37 (13.04), p=0.297 CG: 9.32 (2.80)	There were no deaths reported during treatment or 30 days following treatment completion.  SPP Total Scale Week 8 Mean (SE) LOCF (IG1=61; IG2=60; CG=63) IG1: 13.25 (2.33), p=0.542 IG2: 13.07 (2.41), p=0.586 CG: 11.36 (2.27)  OC (IG1=60; IG2=55; CG=60) IG1: 12.93 (2.31), p=0.930 IG2: 13.25 (2.46), p=0.853 CG: 12.66 (2.30)  SIP Total Score Week 8 Mean (SE) LOCF (IG1=63; IG2=60; CG=65) IG1: -11.36 (1.55), p=0.463 IG2: -12.92 (1.62), p=0.143 CG: -9.85 (1.51)  OC (IG1=62; IG2=55; CG=62) IG1: -11.19 (1.57), p=0.786 IG2: -13.45 (1.70), p=0.193 CG: -10.61 (1.57)	Responders by subgroup at Week 8  Features of Atypical Depression IG1: 86% (19/22) IG2: 67% (10/15) CG: 75% (6/8) Treatment p-value=0.356 Covariate p-value=0.023 Treatment-by covariate p-Value=0.503  Melancholic Features IG1: 55% (18/33) IG2: 52% (17/33) IG3: 49% (17/35) Treatment p-value=0.413 Covariate p-value=0.025 Treatment-by covariate p-Value=0.797  Anxiety Disorder IG1: 75% (9/12) IG2: 33% (7/21) CG: 48% (10/21)

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article (continued)						<p>Treatment p-value=0.116 Covariate p-value=0.208 Treatment-by covariate p-value=0.114</p> <p>Any Comorbid Disorder IG1: 70% (21/30) IG2: 54% (20/37) CG: 47% (16/34) Treatment p-value=0.227 Covariate p-value=0.440 Treatment-by covariate p-value=0.436</p> <p>Age at Onset&lt;12 IG1: 50% (11/22) IG2: 63% (15/24) CG: 58% (7/12) Treatment p-value=0.904 Covariate p-value=0.569 Treatment-by covariate p-value=0.217</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article (continued)						<p>Age at Onset≥12  IG1: 71% (47/66)  IG2: 57% (39/69)  CG: 55% (41/74)  Treatment p-value=0.904  Covariate p-value=0.569  Treatment-by covariate p-value=0.217</p> <p>Number of Depressive Episodes≤1  IG1: 68% (50/73)  IG2: 55% (41/74)  CG: 61% (41/67)  Treatment p-value=0.260  Covariate p-value=0.311  Treatment-by covariate p-value=0.118</p> <p>Number of Depressive Episodes&gt;1  IG1: 56% (9/16)  IG2: 68% (13/19)  CG: 37% (7/19)  Treatment p-value=0.260  Covariate p-value=0.311  Treatment-by covariate p-value=0.118</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup>	IG1: paroxetine IG2: imipramine CG: placebo	Response (mean HAM-D score of $\leq 8$ or $\geq 50\%$ reduction in baseline HAM-D score at Week 8) LOCF (IG1=90; IG2=94; CG=87) % IG1: 66.7% (p=0.11) IG2: 58.5% (p=0.61) CG: 55.2%  HAM-D $\leq 8$ at Week 8 LOCF (IG1=90; IG2=94; CG=87) % IG1: 63.3% (p=0.02) IG2: 50.0% (p=0.57) CG: 46.0%  Ham-D Depressed Mood Item Baseline LOCF (IG1=90; IG2=94; CG=87) Mean (SE) IG1: 2.99 (0.08) IG2: 2.79(0.08) CG: 2.86 (0.08)		CGI score of 1 (very much improved) or 2 (much improved) LOCF (IG1=90; IG2=94; CG=87) % Week 8 IG1: 65.6% (p=0.02) IG2: 52.1% (p=0.64) CG: 48.3%  Mean CGI Score LOCF (IG1=90; IG2=94; CG=87) Mean (SE) Week 8 IG1: 2.37 (0.16), p=0.09 IG2: 2.70 (0.15), p=0.90 CG: 2.73 (0.16)	NR	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup> (continued)		<p>Week 8  LOCF (IG1=9; IG2=94;  CG=87) [Note: n of 9 in  table 2 is likely a typo]  Mean (SE)  IG1: 0.99 (0.14),  p=0.001  IG2: 1.17(0.14), p=0.14  CG: 1.53 (0.14)</p> <p>KSADS-L depressed  mood item  LOCF (IG1=83; IG2=87;  CG=85)  Mean (SE)  Baseline  IG1: 4.57 (0.09)  IG2: 4.29(0.09)  CG: 4.63(0.09)</p> <p>Week 8  IG1: 2.37 (0.18), p=0.05  IG2: 2.52(0.18), p=0.87  CG: 2.90 (0.18)</p> <p>KSADS-L 9-item  depression scale  LOCF (IG1=83; IG2=88;  CG=85)  Mean (SE)  Baseline  IG1: 28.25 (0.52)  IG2: 27.54(0.51)  CG: 28.24(0.52)</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup> (continued)		Week 8 IG1: 16.59 (0.84), p=0.07 IG2: 17.99(0.83), p=0.98 CG: 19.27 (0.83)				
		HAM-D Total Score LOCF (IG1=90; IG2=94; CG=87) Mean (SE) Baseline IG1: 18.98 (0.43) IG2: 18.11(0.43) CG: 18.97(0.44)				
		Week 8 IG1: 8.24 (0.81), p=0.13 IG2: 9.2(0.81), p=0.87 CG: 9.88 (0.83)				

GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup>	IG1: paroxetine IG2: imipramine CG: placebo	HAM-D Change - Week 8 OC: IG1=67; IG2=56; CG=66 Least Squares Mean (95% CI), SEM IG1: --12.2 (--13.1 to --10.5), 0.88 IG2: --10.6 (--12.5 to --8.7), 0.97 CG: --10.5 (--12.3 to --8.8), 0.88 ANCOVA=0.26  Last Observation Carried Forward (LOCF): IG1=90; IG2=94; CG=87 Least Squares Mean (95% CI), SEM IG1: --10.7 (--12.3 to --9.1), 0.81 IG2: --9.0 (--10.5 to --7.4), 0.81 CG: --9.1 (--10.7 to --7.5), 0.83 ANCOVA=0.20  MI: IG1=90; IG2=94; CG=87 Least Squares Mean (95% CI), SEM IG1: --12.5 (--14.2 to --10.9), 0.83 IG2: --11.1 (--12.9 to --9.4), 0.89 CG: --10.7 (--12.4 to --9.1), 0.83 ANCOVA=0.24	NR	CGI - Week 8 OC (IG1=67; IG2=56; CG=66) Least Squares Mean (95% CI), SEM IG1: 1.9 (1.6 to 2.2) 0.15 IG2: 2.2 (1.8 to 2.5) 0.17 CG: 2.4 (2.1 to 2.7) 0.16 p=0.09  LOCF (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: 2.4 (2.1 to 2.7) 0.16 IG2: 2.7 (2.4 to 3.0) 0.15 CG: 2.7 (2.4 to 3.0) 0.16 p=0.16  MI (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: 1.9 (1.6 to 2.2) 0.14 IG2: 2.2 (1.9 to 2.5) 0.15 CG: 2.4 (2.1 to 2.6) 0.14 p=0.24  AFC - Week 8 OC (IG1=58; IG2=52; CG=60) Least Squares Mean (95% CI), SEM IG1: 14.4 (8.8 to 19.9) 2.83	SPP - Week 8 OC (IG1=60; IG2=55; CG=60) Least Squares Mean (95% CI), SEM IG1: 12.9 (8.3 to 17.5) 2.31 IG2: 13.2 (8.4 to 18.1) 2.46 CG: 12.7 (6.9 to 15.9) 2.30 p=0.88  LOCF (IG1=61; IG2=60; CG=63) Least Squares Mean (95% CI), SEM IG1: 13.2 (8.6 to 17.8) 2.33 IG2: 13.1 (8.3 to 17.8) 2.41 CG: 11.4 (6.9 to 15.9) 2.27 p=0.88  MI (IG1=61; IG2=60; CG=65) Least Squares Mean (95% CI), SEM IG1: 15.4 (10.7 to 20.0) 2.35 IG2: 14 (8.9 to 19.2) 2.60 CG: 14.7 (10.0 to 19.4) 2.39 p=0.92  SIP - Week 8 OC (IG1=62; IG2=55; CG=62) Least Squares Mean (95% CI), SEM IG1: --11.2 (--14.3 to --8.1) 1.57 IG2: --13.5 (--16.9 to --10.2)
--	---	---	----	---	---

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
				IG2: 13.3 (7.3 to 19.4) 3.04 CG: 9.3 (3.8 to 14.8) 2.81 p=0.32		



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)		HAM-D Response - Week 8 OC (IG1=67; IG2=56; CG=66) % (Criteria Met) IG1: 80.6% (54/13) IG2: 73.2% (41/15) CG: 65.2% (43/23) $\chi^2=0.13$  LOCF (IG1=90; IG2=94; CG=87) n (%) IG1: 66.7% (60/30) IG2: 58.5% (55/39) CG: 55.2% (48/39) $\chi^2=0.27$  MI (IG1=90; IG2=94; CG=87) n (%) IG1: 73.3% (66/24) IG2: 70.2% (66/28) CG: 70.1% (61/26) $\chi^2=0.24$  K-SADS-L - Week 8 OC (IG1=67; IG2=56; CG=66) Least Squares Mean (95% CI), SEM IG1: --12.1 (--13.8 to -- 10.3) 0.91 IG2: --10.7 (--12.7 to -- 8.7) 0.82 CG: --10.7 (--12.5 to -- 8.9) 0.92 p=0.46		LOCF (IG1=60; IG2=57; CG=62) Least Squares Mean (95% CI), SEM IG1: 14.7 (9.2 to 20.2) 2.80 IG2: 11.6 (5.8 to 17.3) 2.92 CG: 9.3 (8.1 to 17.2) 2.76 p=0.39  MI (IG1=60; IG2=57; CG=62) Least Squares Mean (95% CI), SEM IG1: 14.0 (8.7 to 19.3) 2.65 IG2: 14.5 (9.4 to 19.6) 2.60 CG: 9.1 (4.2 to 14.1) 2.52 p=0.24	CG: --10.6 (--13.7 to --7.5) p=0.24  LOCF (IG1=63; IG2=60; CG=65) Least Squares Mean (95% CI), SEM IG1: --11.4 (--14.4 to --8.3) 1.55 IG2: --13.0 (--16.2 to --9.8) 1.62 CG: --9.9 (--12.9 to --6.9) 1.51 p=0.23  MI (IG1=63; IG2=60; CG=65) Least Squares Mean (95% CI), SEM IG1: --11.5 (--14.2 to --8.7) 1.39 IG2: --13.9 (--16.8 to --10.9) 1.50 CG: --10.1 (--13.0 to --7.1) p=0.19	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)		LOCF (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: --11.4 (--13.1 to -- 9.8) 0.84 IG2: --9.5 (--11.1 to -- 7.9) 0.82 CG: --9.4 (--11.0 to --7.8) 0.83 p=0.13				
		MI (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: --12.3 (--13.9 to -- 10.6) 0.84 IG2: --11.5 (--13.3 to -- 9.7) 0.91 CG: --10.9 (--12.6 to -- 9.2) 0.86 p=0.45				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup>	IG1: Paroxetine IG2: Imipramine CG: Placebo	NR	Response at some time point (defined as remission in Table 3) ITT: IG1=93; IG2=95; CG=87 IG1: 61 IG2: 57 CG: 47  Completed Responders defined as HAM-D <8 (+ potential responders) ITT: IG1=93; IG2=95; CG=87 IG1: 15 (+3) IG2: 12 (+1) CG: 12 (+9)	NR	Acute phase relapse ITT: IG1=93; IG2=95; CG=87 IG1: 6 IG2: 5 CG: 3  Continuation phase relapse ITT: IG1=93; IG2=95; CG=87 IG1: 19 IG2: 10 CG: 7  Total Relapses ITT: IG1=93; IG2=95; CG=87 IG1: 25 (41%) IG2: 15 (26%) CG: 10 (21%)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Klein, 1998 <sup>63</sup>	IG: Desipramine CG: Placebo	<p>HAM-D After Treatment Mean (SD) IG: 10.83 (2.1) CG: 14.61 (2.1) F=1.67, p=0.21</p> <p>Number of MDD Symptoms After Treatment Mean (SD) IG: 2.30 (2.5) CG: 3.92 (2.5) F=3.5, p=0.07</p> <p>BDI After Treatment Mean (SD) IG: 12.0 (9.6) CG: 15.92 (9.6) F=1.2, p=0.28</p> <p>SCL-90-R After Treatment Mean (SD) IG: 0.91 (0.7) CG: 1.42 (0.7) F=4.1, p=0.05</p>	<p>No longer meeting MDD criteria based on K-SADS IG: 72% CG: 50% p=NS</p> <p>CGI (Overall improvement, considered to have improved to a clinically meaning degree) IG: 67% CG: 50% p=0.31</p>	<p>SAICA-Area After Treatment Mean (SD) IG: 2.46 (0.5) CG: 2.38 (0.5) F=0.21, p=0.65</p> <p>SAICA-Category After Treatment Mean (SD) IG: 2.46 (0.4) CG: 2.38 (0.4) F=0.34, p=0.56</p> <p>C-GAS Mean (SD) IG: 66.9 (13.2) CG: 68.0 (13.2) F=0.1, p=0.81</p>	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Kye, 1996 <sup>64</sup>	IG: AMI CG: Placebo	HAM-D After Treatment ITT Mean (SD) IG: 8.0 (4.9) CG: 8.8 (4.5) pooled t test, t 29, -0.44, p=NS  Completers ITT Mean (SD) IG: 4.7 (6.3) CG: 7.8 (5.5) Mann-Whitney U 39.0, p=NS  K-SADS IG: 15.7 (5.3) CG: 15.6 (4.7) Pooled t test, t 29=0.95, p=NS  Drug X Treatment Effect X2=0.52, df=12, p=NS	HAM-D score <6 ITT IG: 10/18 CG: 2/13 FET, p <0.14  Completers IG: 9/12 CG: 3/10 FET, p <0.09  50% decrease in HAM-D ITT IG: 13/18 CG: 11/13 FET, p=NS  Completers IG: 11/12 CG: 9/10 FET, p=NS  CGI Mean Change (SD) ITT IG: -1.7 (1.1) CG: -0.2 (1.9) p<0.03  Completers IG: -2.0 (0.9) CG: -0.7 (1.5) Mann-Whitney U 67.0, p <0.07	NR	NR	NR

AFC = Autonomous Functioning Checklist; AMI = amitriptyline; ANCOVA = analysis of covariance; BDI = Beck Depression Inventory; CDRS = Children's Depression Rating Scale; CG = control group; CGAS = Children's Global Assessment Scale; CGI = Clinical Global Impressions Scale; FET = Fisher's Exact Test; HAM-D = Hamilton Depression Rating Scale; IG = Intervention group; ITT = intent to treat; KGAS = Kiddie Global Assessment Scale; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; K-SADS-L = Kiddie Schedule for Affective Disorders and Schizophrenia-Lifetime; K-SADS-P = Kiddie Schedule for Affective Disorders and Schizophrenia-Parent; KQ = Key Question; LOCF = last observation carried forward; MI = multiple imputation; n/N = number; NA = not applicable; NR = not reported; OC = observed cases; RR = relative risk;

SAICA = Social Adjustment Inventory for Children and Adolescents; SCL-90 = Symptom Checklist 90 item; SD = standard deviation; SE = standard error; SEM = structural equation modeling; SIP = suicidal ideation protocol; SPP = Self Perception Profile.

**Table E-24. KQ 2a: Benefits of MAOIs versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
DelBello, 2014 <sup>65</sup>	IG: STS CG: Placebo	CDRS-R total Week 12 change from baseline arithmetic mean (SD) IG: -21.4 (16.61) CG: -21.5 (16.47) p=0.72  CGI-S at week 12 IG: 3.00 CG: 3.01 no difference	CGI Responders at Week 12 (<3) IG: 85 (58.6%) CG: 89 (59.3%) p=0.8992	NR	NR	NR

CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI = Clinical Global Impressions Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; IG = intervention group; KQ = Key Question; NR = not reported; SD = standard deviation; STS = Selegiline Transdermal system.

**Table E-25. KQ 2a: Benefits of venlafaxine plus active control versus placebo plus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Mandoki 1997 <sup>66</sup>	IG: venlafaxine and therapy CG: placebo and therapy	<p>CDI No change over time F=1.66 (p=0.1903) No medication effect F=0.83 (p=0.3709)</p> <p>CBCL Change over time F=17.36 (p=0.0001) No medication effect F=3.29 (p=0.0804)</p> <p>HAM-D Change over time F=30.62 (p=0.0001) No medication effect F=0.47 (p=0.4988)</p> <p>CDRS Change over time F=8.42 (p=0.0101) No medication effect F=0.54 (p=0.4793)</p> <p>No treatment x age or treatment x severity of illness interactions</p>	NR	NR	NR	NR

CBCL = Child Behavior Checklist; CDI = Children's Depression Inventory; CDRS = Children's Depression Rating Scale; CG = control group; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; KQ = Key Question; NR = not reported.



**Table E-26. KQ 3a: Benefits of fluoxetine plus CBT versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS <sup>92</sup>	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Depression symptoms, ITT (n=439) Adjusted CDRS-R total score 6 weeks, adjusted mean (SD) IG1: 38.10 (7.78) IG2: 39.80 (7.37) IG3: 44.63 (8.30) CG: 44.90 (7.32)  12 weeks, adjusted mean (SD) IG1: 33.79 (8.24) IG2: 36.30 (8.18) IG3: 42.06 (9.18) CG: 41.77 (7.99)  Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement: IG1>CG (p=0.001); IG1=IG2 (p=0.13); IG1>IG3 (p=0.001); IG2>IG3 (p=0.001); IG2>CG (p=0.002); IG3=CG (p=0.97)  Across all 12 weeks: Time-by-treatment interaction based on CDRS-R random	Response CGI-I positive response rate, ITT (n=439) 12 weeks, % response rate (95% CI) adjusted for clinical site IG1: 71.0 (62 to 80) IG2: 60.6 (51 to 70) IG3: 43.2 (34 to 52) CG: 34.8 (26 to 44) Regression analyses found treatment was statistically significant factor in CGI-I positive response (p=0.001)  RR (calculated): 2.45 95% CI, 0.31 to 19.7  12 weeks, statistically comparing response: IG1>CG (p=0.001); IG2>CG (p=0.001); IG3=CG (p=0.20); IG1=IG2 (p=0.11); IG1>IG3 (p=0.001); IG2>IG3 (p=0.01)	NR	No mortality from completed suicides	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>regression slope coefficients: <math>p=0.001</math>; Statistically comparing improvement :</p> <p>IG1&gt;CG (<math>p=0.001</math>); IG1&gt;IG2 (<math>p=0.02</math>); IG1&gt;IG3 (<math>p=0.001</math>); IG2&gt;IG3 (<math>p=0.01</math>); IG2=CG (<math>p=0.10</math>); IG3=CG (<math>p=0.40</math>)</p> <p>Hedge g effect sizes relative to placebo (G4) IG1: 0.98 IG2: 0.68 IG3: -0.03</p> <p>Hedge g effect sizes relative to placebo (CG) derived from ORs for dichotomized CGI-I IG1: 0.84 IG2: 0.58 IG3: 0.20 CG: NA</p> <p>NNT (95% CI) IG1: 3 (2 to 4) IG2: 4 (3 to 8) IG3: 12 (5 to 23) CG: NA</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>RADS total score 6 weeks, adjusted mean (SD) IG1: 60.90 (11.59) IG2: 63.41 (12.44) IG3: 69.10 (13.59) CG: 69.43 (10.94)</p> <p>12 weeks, adjusted mean (SD) IG1: 56.95 (12.24) IG2: 60.58 (13.07) IG3: 67.96 (14.18) CG: 66.68 (11.41)</p> <p>Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement : IG1&gt;CG (p=0.001); IG1=IG2 (p=0.11); IG1&gt;IG3 (p=0.001); IG2&gt;IG3 (p=0.003); IG2&gt;CG (p=0.003); IG3=CG (p=0.94)</p> <p>Across all 12 weeks: Time-by-treatment interaction based on RADS random regression slope coefficients: p=0.001; Statistically comparing improvement:</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		IG1>CG (p=0.001); IG1>IG2 (p=0.002); IG1>IG3 (p=0.001); IG2>IG3 (p=0.03); IG2=CG (p=0.34); IG3=CG (p=0.21)				
		NOTE: Means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	<p>Moderation analysis of C-GAS (functional status) by family income, least squares mean (SD) ITT, n=439 at 12 weeks</p> <p>Patients with &lt;\$75,000 (low-to-middle income) IG1: 32.7 (8.7) IG2: 35.3 (8.7) IG3: 43.0 (8.8) CG: 41.4 (9.0)</p> <p>Within the &lt;\$75,000 group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Effect size for active treatments vs. CG IG1: 0.98 (p&lt;0.05) IG2: 0.69 (p&lt;0.05) IG3: -0.18 (p=NS)</p> <p>Patients with ≥\$75,000 (high income) IG1: 33.7 (9.6) IG2: 38.0 (9.1) IG3: 35.1 (9.0) CG: 41.7 (9.2)</p> <p>Within the ≥\$75,000 group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1=IG3: p=NS IG1&gt;CG: p&lt;0.05 IG2=IG3: p=NS IG2=CG: p=NS IG3&gt;CG: p&lt;0.05</p> <p>Effect size for active treatments vs. CG IG1: 0.85 (p&lt;0.05) IG2: 0.40 IG3: 0.72 (p&lt;0.05)</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Moderation analysis of C-GAS (functional status) by CGI-S, least squares mean (SD)</p> <p>ITT, n=439 at 12 weeks</p> <p>Patients with mild/moderate CGI-S</p> <p>IG1: 30.9 (7.3)</p> <p>IG2: 35.6 (7.1)</p> <p>IG3: 36.9 (6.9)</p> <p>CG: 38.4 (7.1)</p> <p>Within the mild/moderate CGI-S group, statistical comparisons of how groups compared with one another at 12 weeks:</p> <p>IG1&gt;IG2: p&lt;0.001</p> <p>IG1&gt;IG3: p&lt;0.001</p> <p>IG1&gt;CG: p&lt;0.001</p> <p>IG2=IG3: p=NS</p> <p>IG2&gt;CG: p&lt;0.001</p> <p>IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG</p> <p>IG1: 1.04 (p&lt;0.05)</p> <p>IG2: 0.39 (p&lt;0.05)</p> <p>IG3: 0.21</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Patients with marked/severe CGI-S IG1: 35.4 (8.8) IG2: 36.8 (9.3) IG3: 44.0 (9.4) CG: 43.2 (9.6)</p> <p>Within the marked/severe CGI-S group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG IG1: 0.84 (p&lt;0.05) IG2: 0.69 (p&lt;0.05) IG3: -0.08</p> <p>Moderation analysis of CNCEQ (depressive cognitive distortions)</p>



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Low CNCEQ IG1: 33.2 (7.9) IG2: 35.5 (7.8) IG3: 39.4 (7.6) CG: 41.1 (7.5)</p> <p>Within the low CNCEQ group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG IG1: 1.03 (p&lt;0.05) IG2: 0.73 (p&lt;0.05) IG3: 0.22</p> <p>High CNCEQ IG1: 32.3 (9.8) IG2: 35.9 (10.1) IG3: 41.8 (10.0) CG: 40.6 (10.4)</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Within the high CNCEQ group, statistical comparisons of how groups compared with one another at 12 weeks:</p> <p>IG1&gt;IG2: <math>p&lt;0.001</math>  IG1&gt;IG3: <math>p&lt;0.001</math>  IG1&gt;CG: <math>p&lt;0.001</math>  IG2&gt;IG3: <math>p&lt;0.001</math>  IG2&gt;CG: <math>p&lt;0.001</math>  IG3=CG: <math>p=NS</math></p> <p>Effect size for active treatments vs. CG  IG1: 0.82 (<math>p&lt;0.05</math>)  IG2: 0.46 (<math>p&lt;0.05</math>)  IG3: -0.12</p>
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	<p>Loss of MDD diagnosis (K-SADS-P/L)</p> <p>Completers analysis only (n=379): 12 weeks, % IG1: 85.3 IG2: 78.6 IG3: 61.1 CG: 60.4 Overall treatment effect: <math>p \leq 0.0001</math></p> <p>Statistical comparisons found mixed findings in terms of how groups compared with one another, OR (95% CI): IG1=IG2: 1.7 (0.79 to 3.61) (<math>p=0.18</math>); IG1&gt;IG3: 4.3 (2.06 to 8.94) (<math>p=0.0001</math>); IG1&gt;CG: 4.1 (2.00 to 8.44) (<math>p=0.0001</math>); IG2&gt;IG3: 2.5 (1.31 to 4.93) (<math>p=0.006</math>); IG2&gt;CG: 2.4 (1.27 to 4.67) (<math>p=0.007</math>); IG3=CG: 1.0 (0.52 to 1.77) (<math>p=0.89</math>)</p>	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS (continued)			<p>Remission, adjusted for site (CDRS-R) ITT (n=439): 12 weeks, % IG1: 37 IG2: 23 IG3: 16 CG: 17 Overall treatment effect: p=0.0007</p> <p>Statistical comparisons found that IG1 was associated with higher remission rates than all other groups, OR (95% CI): IG1&gt;IG2: 2.1 (1.12 to 3.84) (p=0.02); IG1&gt;IG3: 3.3 (1.71 to 6.42) (p=0.0004); IG1&gt;CG: 3.0 (1.58 to 5.79) (p=0.0009)</p> <p>In contrast; IG2; IG3, and CG did not differ statistically from one another (all p &gt;0.05). See comparisons below, OR (95% CI): IG2=IG3: 1.6 (0.80 to 3.19) (p=0.19) IG2=CG: 1.5 (0.74 to 2.88) (p=0.28) IG3=CG: 0.9 (0.44 to 1.88) (p=0.80)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	<p>First response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks Data values NR, but between-group comparisons reported (NR which were statistically significant) HR (95% CI): 3.0 (2.1 to 4.3) for IG1 vs. CG HR (95% CI): 2.2 (1.6 to 3.2) for IG2 vs. CG</p> <p>First response (based on CBT clinician-assigned CGI-I=1 or 2), calculated N (%) Across 12 weeks Data values NR, but between-group comparisons reported (NR if statistically significant) HR (95% CI): 2.0 (1.4 to 2.7) for IG1 vs. IG3</p> <p>Time to first response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks (Phase I) IG1: ≥5 weeks IG2: ≥6 weeks CG: ≥11 weeks Between-group comparisons IG1 and IG2&gt;CG:</p>	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS (continued)			<p>Stable response (based on pharmacotherapist-assigned CGI-I=1 or 2), calculated N (%)</p> <p>6 weeks IG1: 37 (34.3) IG2: 25 (23.3) CG: 7 (6.6)</p> <p>12 weeks IG1: 75 (70.0) IG2: 68 (62.1) CG: 43 (38) HR (95% CI) for IG1 vs. CG: 3.1 (2.0 to 4.8) HR (95% CI) for IG2 vs. CG: 2.0 (1.3 to 3.1) HR (95% CI) for IG1 vs. IG2: 1.5 (1.0 to 2.1)</p> <p>Stable response (based on CBT clinician-assigned CGI-I=1 or 2), calculated N (%)</p> <p>6 weeks IG1: 48 (45) IG3: 25 (22.4)</p> <p>12 weeks IG1: 93 (87.1) IG3: 56 (50.8) HR (95% CI) for IG1 vs. IG3: 2.7 (1.9 to 3.9) (p&lt;0.05)</p>		<p>Significantly faster onset of benefit in both IG1 and IG2 (p&lt;0.001) IG1=IG2: Trend toward faster improvement in IG1 (p=0.0585) HR (95% CI): 1.3 (1.0 to 1.8)</p> <p>Time to first response in ≥50% patients (based on CBT clinician-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks (Phase I) IG1: ≥6 weeks IG3: ≥8 weeks Between-group comparisons IG1&gt;IG3: Significantly faster onset of benefit in IG1 (p&lt;0.001)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS (continued)					<p>Time to stable response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks (Phase I) IG1: ≥9 weeks IG2: ≥11 weeks CG: NA (only 38% patients had reached stable response by 12 weeks)</p> <p>Between-group comparisons IG1&gt;CG: Significantly faster onset of benefit in IG1 (p&lt;0.001) IG2&gt;CG: Significantly faster onset of benefit in IG2 (p=0.001) IG1&gt;IG2: Significantly faster onset of benefit in IG1 (p=0.034)</p> <p>Time to stable response in ≥50% patients (based on CBT clinician-assigned CGI-I=1 or 2): Between-group comparisons IG1&gt;IG3: Significantly faster onset of benefit in IG1 (p&lt;0.001)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	Functional status (C-GAS) ITT (n=439): 6 weeks, unadjusted mean (SD) IG1: 62.4 (11.2) IG2: 59.9 (10.58) IG3: 56.7 (9.66) CG: 57.0 (9.22)  12 weeks, unadjusted mean (SD) IG1: 66.6 (11.91) IG2: 62.1 (11.91) IG3: 60.0 (11.47) CG: 59.3 (12.72) Time effect in all groups: p<0.0001 Treatment-by-time interaction: p<0.0001  Random-effects regression model (RRM) statistical comparisons of how groups compared with one another at 12 weeks: IG1>IG2: p=0.0450 IG1>IG3: p<0.0001 IG1>CG: p<0.0001 IG2>IG3: p=0.0032 IG2>CG: p=0.0381 IG3>CG: p=0.3805	Global burden of psychiatric problems (HoNOSCA) ITT (n=439): 12 weeks, unadjusted mean (SD) IG1: 9.5 (5.97) IG2: 10.9 (6.35) IG3: 11.7 (6.09) CG: 11.2 (6.15) Time effect in all groups: p<0.0001 Treatment-by-time interaction: p<0.0234  RRM statistical comparisons of how groups compared with one another: IG1=IG2: p=0.1257 IG1>IG3: p=0.0027 IG1>CG: p=0.0393 IG2=IG3: p=0.1310 IG2=CG: p=0.5861 IG3=CG: p=0.3344  12 weeks, mean change from baseline (SD) G1: -6.3 (5.69) G2: -5.1 (5.74) G3: -3.6 (5.58) G4: -4.2 (5.71) Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): p<0.01	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				<p>12 weeks, mean change from baseline (SD)  IG1: 16.7 (12.31)  IG2: 12.6 (12.31)  IG3: 9.7 (12.12)  CG: 9.9 (12.38)</p> <p>Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): <math>p &lt; 0.0001</math></p> <p>GLM statistical comparisons of how groups compared with one another:  IG1&gt;IG2: <math>p &lt; 0.01</math>  IG1&gt;IG3: <math>p &lt; 0.0001</math>  IG1&gt;CG: <math>p &lt; 0.0001</math>  IG2&gt;IG3: <math>p = \text{NR}</math>  IG2=CG: <math>p = \text{NS}</math>  IG3=CG: <math>p = \text{NS}</math></p> <p>Rate of nonimpaired patients (C-GAS &gt;70) 12 weeks, %  IG1: 34.6  IG2: 20.2  IG3: 13.5  CG: 18.7</p>	<p>GLM statistical comparisons of how groups compared with one another at 12 weeks:  IG1=IG2: <math>p = \text{NS}</math>  IG1&gt;IG3: <math>p &lt; 0.001</math>  IG1&gt;CG: <math>p &lt; 0.01</math>  IG2&gt;IG3: <math>p &lt; 0.05</math>  IG2=CG: <math>p = \text{NS}</math>  IG3=CG: <math>p = \text{NR}</math></p> <p>HoNOSCA subscores: Treatment-by-time interaction was statistically significant only for item 10 (level of functioning with peers; <math>p = 0.0004</math>), whose effect remained significant even after applying a Bonferroni correction for multiple comparisons.</p> <p>QoL (PQ-LES-Q)  ITT (n=439):  12 weeks, unadjusted mean (SD)  IG1: 54.7 (11.21)  IG2: 51.2 (10.43)  IG3: 47.4 (10.84)  CG: 48.2 (9.91)  Time effect in all groups: <math>p &lt; 0.0001</math>  Treatment-by-time interaction: <math>p &lt; 0.0001</math></p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				<p>Between-group difference: <math>p=0.002</math> Statistically significant treatment effects of how groups compared with one another : IG1&gt;IG2: <math>p&lt;0.020</math> IG1&gt;IG3: <math>p&lt;0.0004</math> IG1&gt;CG: <math>p&lt;0.009</math> IG2=IG3: <math>p=NS</math> IG2=CG: <math>p=NS</math> IG3=CG: <math>p=NS</math></p> <p>Patients not likely to be clinically referred in community (C-GAS &gt;60) 12 weeks, % IG1: 64.5 IG2: 50.5 IG3: 45.0 CG: 35.7 Between-group difference: <math>p=0.0003</math></p> <p>Statistically significant treatment effects of how groups compared with one another: IG1&gt;IG2: <math>p&lt;0.038</math> IG1&gt;IG3: <math>p&lt;0.004</math> IG1&gt;CG: <math>p&lt;0.0001</math> IG2=IG3: <math>p=NS</math> IG2&gt;CG: <math>p=0.023</math> IG3=CG: <math>p=NS</math></p>	<p>RRM statistical comparisons of how groups compared with one another at 12 weeks: IG1&gt;IG2: <math>p=0.0004</math> IG1&gt;IG3: <math>p&lt;0.0001</math> IG1&gt;CG: <math>p&lt;0.0001</math> IG2=IG3: <math>p=0.2766</math> IG2=CG: <math>p=0.7215</math> IG3=CG: <math>p=0.4630</math></p> <p>12 weeks, mean change from baseline (SD) IG1: 9.6 (10.14) IG2: 6.6 (10.23) IG3: 4.2 (10.01) CG: 5.2 (10.16) Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): <math>p&lt;0.001</math></p> <p>Treatment-by-time interaction: <math>p&lt;0.0001</math> GLM statistical comparisons of how groups compared with one another: IG1&gt;IG2: <math>p&lt;0.05</math> IG1&gt;IG3: <math>p&lt;0.0001</math> IG1&gt;CG: <math>p&lt;0.001</math> IG2&gt;IG3: <math>p=NS</math> IG2=CG: <math>p=NS</math> IG3=CG: <math>p=NS</math></p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratovichil, 2009 <sup>8</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	<p>Subgroup Analysis #1: ADHD vs. no ADHD Depression symptoms, ITT (n=429) 12 weeks Main linear RRM effect analyses for overall sample Main effect of time (linear): p&lt;0.001 Treatment-by-time interaction: p=0.018 ADHD-by-treatment-by-time interaction: p=0.026 (confirmed that ADHD status prior to treatment or having an ADHD diagnosis before study entry moderated improvement in depression)</p> <p>Linear RRM effect analyses: ADHD subgroup Main effect of time (linear): p&lt;0.001 Treatment-by-time interaction: p=0.038</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Linear RRM effect analyses: No ADHD subgroup Main effect of time (linear): <math>p \leq 0.001</math> Treatment-by-time interaction: <math>p &lt; 0.001</math></p> <p>CDRS-R total score (adjusted for fixed and random effects) 12 weeks, mean (SD) ADHD subgroup IG1 (n=15): 37.08 (9.42) IG2 (n=14): 33.29 (6.42) IG3 (n=14): 35.95 (6.34) CG (n=19): 43.31 (5.65)</p> <p>No ADHD subgroup IG1 (n=92): 33.30 (8.14) IG2 (n=95): 36.83 (8.11) IG3 (n=97): 42.35 (8.96) CG (n=93): 41.39 (8.07) Improvement was observed in all arms of both ADHD and no-ADHD subgroups.</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>but patients had different patterns of between-group differences depending on their subgroup.</p> <p>Between-group differences: ADHD subgroup at 12 weeks 12 weeks IG1=IG2=IG3&gt;CG (p=0.046, 0.024, 0.013, respectively)</p> <p>Change trajectories did not differ between arms (p&gt;0.05).</p> <p>Effect sizes IG1 vs. CG: 1.0 IG2 vs. CG: 0.6 IG3 vs. CG: -0.1</p> <p>Between-group differences: No-ADHD subgroup at 12 weeks</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>IG1&gt;(IG2&gt;IG3)=CG (p-values &lt;0.05 for significant differences and &gt;0.05 for nonsignificant differences)</p> <p>Change trajectories: IG1&gt;IG2; IG3, and CG (p&lt;0.009), meaning trajectory in IG1 was faster on average than in all other arms. IG2=CG (p=0.425) and IG3=CG (p=0.065), but IG2&gt;IG3 (p=0.008). In short; IG3 had the most gradual improvement trajectory among active treatments.</p> <p>Effect sizes IG1 vs. CG: 0.8 IG2 vs. CG: 1.7 IG3 vs. CG: 1.2</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Depression symptoms, ITT (n=327) 36 weeks: Main linear RRM effect analyses for overall sample Main effect of time (linear): <math>p &lt; 0.001</math> ADHD-by-treatment-by-time interaction: <math>p = 0.004</math> ADHD-by-treatment-by-time interaction (squared): <math>p = 0.004</math> (confirmed that ADHD status prior to treatment or having an ADHD diagnosis before study entry moderated improvement in depression at this timepoint)</p> <p>Between-group differences: ADHD subgroup at 36 weeks Paired contrasts found no between-group differences in mean total CDRS-R scores within this subgroup.</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Change trajectories: No significant treatment-by-time (squared) or treatment-by-time interactions</p> <p>Between-group differences: No-ADHD subgroup at 36 weeks Paired contrasts found no between-group differences in mean total CDRS-R scores within this subgroup.</p> <p>Change trajectories: Treatment-by-time (squared) interaction: <math>p &lt; 0.001</math> (suggesting significant different by arm) IG1 &gt; IG2 and IG3 (<math>p &lt; 0.05</math>), meaning trajectory in IG1 was faster on average than other IG arms.</p>



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						Subgroup Analysis #2: ADHD psychostimulant medication vs. none among patients with ADHD Depression symptoms, ITT (n=62 with ADHD) CDRS-R total score (adjusted for fixed and random effects) 12 weeks: Data values NR, but CDRS-R scores did not differ significantly among the 20/63 patients taking a psychostimulant vs. the 43/63 patients who did not (p=0.056). Treatment-by-psychostimulant use interaction was not significant (p>0.05).

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; C-GAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions Scale-Improvement Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; CI = confidence interval; CNCEQ = children's negative cognitive error questionnaire; GLM = generalized linear modeling; HoNOSCA = Health of Nation Outcome Scale – Children and Adolescents; HR = Hamilton Rating; IG = intervention group; ITT = intent to treat; K-SADS-P/L = Kiddie Schedule for Affective Disorders and Schizophrenia; KQ = Key Question; NA = not applicable; NNT = number needed to treat; NS = not significant; OR = odds ratio; PQ-LES-Q = Parent-Child Interaction Therapy Emotion Development; RADS = Reactive Airways Dysfunction Syndrome; RR = relative risk; RRM = random-effects regression model; SD = standard deviation; TADS = Treatment among Adolescents with Depression.

**Table E-27. KQ 3a: Benefits of CBT versus other psychotherapy**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Fristad, 2009 <sup>27</sup>	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	CDSR-R score at endpoint IG1: 26 (10) IG2: 30 (9) IG3: 31 (9) CG: 31 (11)	Remitted IG1: 76.5% IG2: 61.1% IG3: 43.8% CG: 55.6%	NR	NR	History of maternal depression significantly moderated the effects of PEP+PBO versus PBO (p = 0.02) but not the placebo-controlled effects of combined or $\Omega 3$ alone.

CBT = cognitive behavioral therapy; CDSR-R = Children's Depression Rating Scale-Revised; CG = control group; IG = intervention group; KQ = Key Question; NR = not reported; PBO = placebo; PEP = psychoeducational psychotherapy.

**Table E-28. KQ 5a: Benefits of CBT versus other psychotherapy**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Brent, 1997 <sup>12</sup> Index article	IG1: Individual CBT IG2: SBFT CG: NST	MDD episode, % 6 weeks IG1: 60.0 IG2: 65.5 CG: 63.3 p=0.90  12-16 weeks IG1: 17.1 IG2: 32.3 CG: 42.4 Difference among 3 groups: X2=5.22; df=2; p=0.07 Pairwise difference (IG1 vs. CG): X2=5.23; df=1; p=0.02  BDI, mean (SD) 6 weeks IG1: 10.7 (11.1) IG2: 13.7 (9.3) CG: 13.4 (10.7) p=0.44  12-16 weeks IG1: 5.7 (8.6) IG2: 9.1 (9.1) CG: 9.8 (11.4) p=0.19 Difference among 3 groups: X2=5.70; df=2; p=0.06 IG1 showing more rapid response than CG: X2=5.10; df=1; p=0.02	Overall achievement of clinical response Overall achievement of clinical response data were estimated using software from Figure 2.  Overall difference: X2=5.28; df=2; p=0.07 Pairwise difference (IG1 vs. IG2): X2=4.84; df=1; p=0.03 IG1: 66.3 IG2: 39.6 CG: 42.9  Overall achievement of remission (%) 6 weeks IG1: 16.7 IG2: 6.2 CG: 16.7 p=0.37  12-16 weeks IG1: 60.0 IG2: 29.0 CG: 36.4  Rate of remission (%) IG1: 60.0 IG2: 37.9 CG: 39.4 Overall difference: X2=5.96; df=2; p=0.05	CGAS <60 (%) 6 weeks IG1: 34.3 IG2: 37.9 CG: 43.3 p=0.76  12-16 weeks IG1: 25.7 IG2: 35.5 CG: 33.3 p=0.66  No significant treatment x time interaction on the CGAS (treatment=NS, time <.01)	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Brent, 1997 <sup>12</sup> Index article (continued)		DEP13, mean (SD) 6 weeks IG1: 2.1 (0.7) IG2: 2.1 (0.6) CG: 2.1 (0.5) p=0.91  12-16 weeks IG1: 1.5 (0.5) IG2: 1.7 (0.6) CG: 1.8 (0.8) p=0.15 Difference among 3 groups: X2=6.15; df=2; p=0.05 IG1 showing more rapid response than IG2: X2=4.74; df=1; p=0.03 IG1 showing more rapid response than CG: X2=4.84; df=1; p=0.03	Pairwise difference (IG1 vs. IG2): X2=4.50; df=1; p=0.03 Pairwise difference (IG1 vs. CG): X2=4.30; df=1; p=0.04			
Brent, 1997 <sup>12</sup> Index article Companion article: Brent, 1998 <sup>13</sup>	IG1: Individual CBT IG2: SBFT CG: NST	See index article (Brent 1997)	See index article (Brent 1997))	See index article (Brent 1997)	See index article (Brent 1997)	See index article (Brent 1997)

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Brent, 1997 <sup>12</sup> Index article Companion article: Barbe, 2004 <sup>36</sup>	IG1: Individual CBT IG2: SBFT CG: Nondirective supportive therapy (NST)	No significant treatment x time interactions on BDI or DEP 13	<p>Likelihood of being depressed at the end of treatment (%): Currently suicidal: 53.8 Nonsuicidal: 27.1 <math>\chi^2=3.81</math> <math>p=0.05</math></p> <p>There was no difference in achievement of remission, or significant treatment x time interactions on BDI or DEP 13</p> <p>Lifetime suicidal subjects had higher rates of MDD at the end of treatment than lifetime nonsuicidal subjects (%): Lifetime: 42.1 Non-lifetime: 23.0 <math>\chi^2=4.07</math> <math>df=1</math> <math>p=0.04</math></p>	There were no group differences in the proportion of subjects with CGAS <60 at the end of treatment Suicidal: 38.5 Nonsuicidal: 29.4	NR	<p>Remission: No MDD at end of treatment</p> <p>Currently Suicidal CBT 87% SBFT 68.4% NST 35.7%</p> <p>Currently Nonsuicidal CBT 85% SBFT 67% NST 73.7</p> <p>Response to treatment depends on the treatment they received: For CBT and SBFT lifetime suicidality did not moderate treatment response, but for NST the response of subjects with suicidal history was much less favorable than for nonsuicidal subjects. <math>p=0.03</math></p>
Brent, 1997 <sup>12</sup> Index article Companion article: Barbe, 2004 <sup>69</sup>	IG1: Individual CBT IG2: SBFT CG: NST	At the end of acute treatment, there was not a difference in slope of decline of depression (interviewer or self-rated) History of abuse: 44.4% No abuse: 27.1% Fisher exact $p=0.40$	Response at the end of acute treatment: History of abuse: 33.3% No abuse: 55.2% Fisher exact $p=0.30$	Functional status (CGAS) at the end of acute treatment: History of abuse: 77.8% No abuse: 69.5% Fisher exact $p=1.0$	Likelihood to have a second episode of depression: History of abuse: 90% No abuse: 39.7% Fisher exact $p=0.005$	<p>No MDD at end of treatment (12-16 weeks) % Sexual Abuse CBT 2/5=40% NST 2/4=50%</p> <p>No Sexual Abuse CBT 4/30=13.3% NST 13/31=41.9%</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Brent, 1997 <sup>12</sup> Index article Companion article: Dietz, 2014 <sup>70</sup>	IG1: Individual CBT IG2: SBFT CG: Nondirective supportive therapy (NST)	Adolescent diagnosis of MDD post-treatment (%): IG1: 8 IG2: 15 CG: 16.7 $\chi^2$ (df=2, n=63)=0.85	Adolescent remission status post-treatment (%): IG1: 80.0 IG2: 50.0 CG: 50.0 $\chi^2$ (df=2, n=63)=5.76	NR	NR	NR
Goodyer, 2017 <sup>16</sup> Index article	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	MFQ score, n patients, Mean (SD) Comparisons are Treatment effect (95% CI) Baseline IG1: 154, 46.2 (10.3) IG2: 156, 45.4 (10.8) CG: 155, 46.2 (10.6)  6 Weeks IG1: 104, 35.2 (11.3) IG2: 107, 34.9 (13.2) CG: 99, 36.5 (14.3)  12 Weeks IG1: 106, 31.6 (13.3) IG2: 108, 33.1 (14.2) CG: 112, 34.1 (14.4)	MFQ score: Response rate Freq (%); time since randomization mean (min, max) Baseline IG1: 154 (100); NR IG2: 156 (100); NR CG: 155 (100); NR  6 Weeks IG1: 104 (68); 12.3 (7, 41) IG2: 107 (69); 11.1 (6, 21) CG: 99 (64); 11.0 (6, 25)  12 Weeks IG1: 106 (69); 19.0 (11, 38) IG2: 108 (69); 17.6 (12, 28) CG: 112 (72); 17.6 (12,33)	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article (continued)		36 Weeks IG1: 104, 24.2 (15.1) IG2: 109, 26.6 (15.7) CG: 105, 30.5 (16.1) IG1 vs. IG2: 0.179 (-3.731 to 4.088) p=0.929 IG1+IG2 vs. CG: -3.234 (-6.611 to 0.143) p=0.061  52 Weeks IG1: 111, 25.0 (18.0) IG2: 110, 23.0 (15.9) CG: 105, 25.1 (16.2) IG1 vs. IG2: 0.307 (-3.161 to 3.774) p=0.862 IG1+IG2 vs. CG: -2.806 (-5.790 to 0.177) 0.065 p=0.065  86 Weeks IG1: 123, 22.3 (15.7) IG2: 114, 21.8 (15.5) CG: 116, 23.6 (16.2) IG1 vs. IG2: 0.578 (-2.948 to 4.104) p=0.748 IG1+IG2 vs. CG: -1.898 (-4.922 to 1.126) p=0.219	36 Weeks IG1: 104 (68); 42.9 (35-63) IG2: 109 (70); 41.5 (31, 52) CG: 105 (68); 42.3 (36, 54)  52 Weeks IG1: 111 (72); 60.3 (48, 92) IG2: 110 (71); 59.3 (50, 85) CG: 105 (68); 59.2 (51, 76)  86 Weeks IG1: 123 (80); 94.9 (82, 147) IG2: 114 (73); 95.1 (69, 149) CG: 116 (75); 95.4 (73, 132)			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article (continued)			<p>Patients with MDD diagnosis and <math>\geq 1</math> antisocial behavior symptom, N (%) or n/N (%)</p> <p>Comparisons are Treatment effect (95% CI)</p> <p>Baseline</p> <p>IG1: 154 (100)</p> <p>IG2: 156 (100)</p> <p>CG: 155 (100)</p> <p>6 Weeks</p> <p>IG1: 57/95 (60)</p> <p>IG2: 62/99 (63)</p> <p>CG: 63/143 (44)</p> <p>12 Weeks</p> <p>IG1: 46/98 (47)</p> <p>IG2: 54/99 (55)</p> <p>CG: 57/105 (54)</p> <p>36 Weeks</p> <p>IG1: 28/89 (31)</p> <p>IG2: 35/98 (36)</p> <p>CG: 42/95 (44)</p> <p>IG1 vs. IG2: 0.064 (–0.078 to 0.206)</p> <p>p=0.375</p> <p>IG1+IG2 vs. CG: –0.043 (–0.160 to 0.073)</p> <p>p=0.465</p>			



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article (continued)			52 Weeks IG1: 23/90 (26) IG2: 23/87 (27) CG: 27/92 (29) IG1 vs. IG2: 0.018 (−0.084 to 0.120) p=0.727 IG1+IG2 vs. CG: −0.053 (−0.142 to 0.035) p=0.239  86 Weeks IG1: 24/95 (25) IG2: 14/92 (15) CG: 27/99 (27) IG1 vs. IG2: −0.057 (−0.157 to 0.043) p=0.261 IG1+IG2 vs. CG: −0.065 (−0.152 to 0.022) p=0.145			
Goodyer, 2017 <sup>16</sup> Index article Companion article: Goodyer, 2017 <sup>17</sup>	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	See Goodyer, 2017 <sup>16</sup> Index article	221 (77%) of 286 patients were in diagnostic remission by week 86  The proportion of patients in diagnostic remission by 36, 52, or 86 weeks did not differ significantly between groups (data not shown)	NR	15 (11%) of the 140 patients in remission at wk 36 had relapsed by wk 86  Proportion between groups, n/N (%): IG1: 8/49 (16.3) IG2: 2/48 (4.2) CG: 5/43 (11.6) p=0.149	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Rosello, 1999 <sup>10</sup>	IG1: IPT IG2: CBT CG: Wait list control	CDI score, baseline, Mean (SD): IG1: 21.21 (7.53) IG2: 20.12 (6.95) CG: 20.13 (5.99)  CDI score 12 weeks, Mean (SD): IG1: 10.79 (6.51) IG2: 13.28 (7.61) CG: 15.83 (6.83) P-value for CDI pre vs. post: $p > 0.01$  CDI score 3 months Mean (SD): IG1: 13.75 (9.52) IG2: 8.90 (6.84) CG: NR F value for CDI post-tx vs. followup: $F = 0.02$	Patients in functional range (CS change) at 12 weeks, %: IG1: 82 IG2: 59  Effect size at 12 weeks (size (%): IG1: 0.73 (77) IG2: 0.43 (67)  Decrease in severely depressed adolescents, baseline vs. 12 weeks, %: IG1: 45 IG2: 24 CG: 27  Decrease in severely depressed adolescents, baseline vs. 3 months, %: IG1: 39 IG2: 30 CG: NR	NR	F values for pre/post treatment comparisons on CDI: IG1 vs. IG2: 2.61 IG1 vs. CG: 11.62 ( $p < 0.01$ ) IG2 vs. CG: 2.58 ( $p < 0.05$ )	NR

BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CG = control group; CGAS = Children's Global Assessment Scale; CS = clinically significant; DEP13 = 13 depression items from School-Age Schedule for Affective Disorders and Schizophrenia for School-Age Children; IG = intervention group; KQ = Key Question; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n/N = number; NR = not reported; NS = not significant; NST = nondirective supportive therapy; SBFT = systemic behavior family therapy; SD = standard deviation; wk(s) = week(s).

**Table E-29. KQ 5a: Benefits of psychotherapy within-type comparisons of delivery methods or approaches**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 1999 <sup>9</sup>	IG1: child CBT IG2: child CBT with separate parent sessions CG: wait-list control	At 8 Weeks: HAM-D: G1: 4.6 (4.8) G2: 6.7 (7.1) G3: 7.7 (7.0)  BDI: G1: 10.1 (9.1) G2: 13.3 (10.9) G3: 16.0 (11.2)  CBCL Depression G1: 11.5 (4.7) G2: 11.7 (6.7) G3: 9.0 (5.9)	Recovery Rates at 8 weeks: G1: 24/37 (64.9%) IG2: 22/32 (68.8%) G3: 13/27 (48.1%) G1+G2 vs. G3: p<0.05; Cohen's h=0.38 (small to medium effect); OR, 2.15 (95% CI, 1.01 to 4.59)  Trend for treated males to have better outcomes than treated females (81.0% vs. 60.4%, p=0.096)	At 8 Weeks: GAF: Pre: G1: 60.4 (6.8) G2: 54.4 (8.2) CG: 58.3 (7.2)  Post: G1: 71.0 (11.7) G2: 69.9 (14.9) CG: 64.5 (11.8)  Group x time: IG1 & 2 combined vs. CG: p<0.05	NR	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Gunlicks-Stoessel, 2016 <sup>71</sup>	IG: IPT-AP CG: adaptation interpersonal psychotherapy (IPT-A)	ITT (n=15; IG=9; CG=6) CDS-R: 16 weeks Mean (SD) IG: 31.33 (6.37) CG: 30.33 (8.47) F=0.01; eta squared=.00 Significant decrease over time: t(14)=6.19, p=0.000	NA	ITT (n=15; IG=9; CG=6) CGAS (baseline) Mean (SD) IG: 54.44 (7.86) CG: 60.33 (6.06)  CGAS (week 16) Mean (SD) IG: 69.94 (7.49) CG: 67.28 (6.46) F=.14; eta squared=.01 Significant increase over time: t(14)=-5.12, p=0.000	ITT (n=15; IG=9; CG=6) Mean (SD)  Conflict Behavior Questionnaire (CBQ) Adolescent report on Mother's behavior (baseline) IG: 13.83 (6.48) CG: 12.59 (7.59) Adolescent report on Mother's behavior (Week 16) IG: 7.61 (4.46) CG: 7.13 (7.25) F=.05; eta squared=.00 Significant decrease over time: [t(14)=2.43, p=0.029]  Adolescent report on Mother-Adolescent dyadic behavior (baseline) IG: 7.44 (4.48) CG: 6.82 (2.56)  Adolescent report on Mother-Adolescent dyadic behavior (Week 16) IG: 3.50 (2.34) CG: 3.65 (1.36) F=.07; eta squared=.01 Significant decrease over time: [t(14)=4.00, p=0.001]	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Gunlicks-Stoessel, 2016 <sup>71</sup> (continued)					<p>Adolescent report on Father's behavior (baseline) IG: 13.94 (4.31) CG: 16.49 (5.89)</p> <p>Adolescent report on Father's behavior (Week 16) IG: 8.87 (3.25) CG: 15.12 (8.87) F=3.77; eta squared=.24; p&lt;0.10 Significant decrease over time: [t(14)=3.09, p=0.008]</p> <p>Adolescent report on Father-Adolescent dyadic behavior (baseline) IG: 7.79 (3.31) CG: 8.93 (3.80)</p> <p>Adolescent report on Father-Adolescent dyadic behavior (Week 16) IG: 5.97 (2.11) CG: 8.81 (4.63) F=2.10; eta squared=.15</p> <p>Mother report on Adolescent's behavior (baseline) IG: 15.78 (7.61) CG: 16.71 (4.51)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Gunlicks-Stoessel, 2016 <sup>71</sup> (continued)					<p>Mother report on Adolescent's behavior (Week 16) IG: 12.47 (7.12) CG: 16.27 (7.38) F=.87; eta squared=.07</p> <p>Mother report on Mother-Adolescent dyadic behavior (baseline) IG: 4.89 (2.37) CG: 5.09 (2.94)</p> <p>Mother report on Mother-Adolescent dyadic behavior(Week 16) IG: 3.26 (1.99) CG: 6.20 (3.36) F=4.82; eta squared=.29, p&lt;0.05</p>	
Jelalian, 2016 <sup>72</sup>	IG:CBT plus Healthy Lifestyle Enhancement CG: CBT	<p>BDI (Completers) Mean (SD) Pretreatment IG: 22.0 (11.0) CG: 25.0 (12.0)</p> <p>12 weeks IG: 9.3 (12.7) CG:7.0 (5.9)</p> <p>24 weeks (end of treatment) IG: 9.0 (10.9) CG:6.9 (7.5)</p> <p>48 weeks (followup) IG: 10.3 (14.4) CG:6.0 (5.6)</p>	NR	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Nelson, 2004 <sup>73</sup>	IG1: CBT over ITV IG2: CBT Face to face	CDI Group X Time Interaction $p < 0.05$ , $WL=0.83$ , $F=5.40$  Marginal Means (T2) IG1:6.71 (2.38) IG2:11.64 (2.38) ETA=0.17  BDI Group X Time Interaction NS, $WL=0.94$ , $F=1.50$  Marginal Means (T2) IG1:4.91 (2.27) IG2:10.57 (2.27) ETA=0.06	NR	NR	NR	BASC subscales available  Assuming T1 and T2 are timepoints; assuming you want marginal means
Rohde, 1994 <sup>74</sup>	IG:CBT group for adolescents IG2: CBT group for adolescents with a separate group for parents CG: Waiting-list	Only provide subgroup information	NR	NR	NR	NR
Spirito, 2015 <sup>75</sup>	IG: Parent-Adolescent-CBT CG: Adolescent Only-CBT	BDI (Adolescent Only) Treatment Effect Slope z score: -0.74, NS  Treatment maintenance Treatment Effect Slope z score: 0.45, NS	NR	NR	NR	NR





First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Trowell, 2007 <sup>76</sup> Index article (continued)		Dysthymia (change over baseline, end of treatment, and followup) IG1: $\chi^2=32.308$ ; df=2; p<0.001 IG2: $\chi^2=19.425$ ; df=2; p<0.001  Double Depression (end of therapy) n (%) IG1: 3 (8.6%) IG2: 6 (16.2%)  Double Depression(6 month followup) n (%) IG1: 0 (0%) IG2: 4 (10.8%)  Dysthymia (change over baseline, end of treatment, and followup) IG1: $\chi^2=30.512$ ; df=2; p<0.001 IG2: $\chi^2=14.389$ ; df=2; p=0.001	Depression (followup) IG1: 0 (0%) IG2: 8.1% Difference not statistically significant			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Trowell, 2007 <sup>76</sup> Index article (continued)		CDI (end of therapy) mean (SD) IG1: 15.23 (9.47) IG2: 10.76 (7.72)				
		CDI(6 month followup) mean (SD) IG1: 9.74 (6.15) IG2: 9.08 (7.82)				
		MFQ (end of therapy) mean (SD) IG1: 7.88 (6.87) IG2: 6.11 (5.05)				
		MFQ (6 month followup) mean (SD) IG1: 5.54 (4.74) IG2: 4.92 (4.70)				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Trowell, 2007 <sup>76</sup> Index article Companion article: Garoff, 2012 <sup>77</sup>	IG1: Individual Therapy (FIPP) IG2: Family Therapy (SIFT)	NR	NR	ITT (N=72; IG1=35 and IG2=37) FAD and BICS outcomes not reported for IG1 and IG2 separately.  FAD (end of treatment) Mean (SD) IG1 and IG2: 2.0 (0.4)  FADS (change over baseline, end of treatment, and followup) Significant decrease (p=0.03) The treatment group did not show significant within-subjects (p=0.98) or between-subjects (p=0.23) effects (Individual or family therapy was examined as a between-subjects factor)  BICS (end of treatment) Mean (SD) IG2: 5.3 (1.5)  BICS (change over baseline, end of treatment, and followup) Significant decrease (p=0.01)	NR	FAD significant interactions with gender p=0.01 and clinical severity p=0.01  BICS significant interactions with age p=0.04

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Trowell, 2007 <sup>76</sup> Index article Companion article: Garoff, 2012 <sup>77</sup> (continued)				BISS (end of treatment) Mean (SD) IG2: 2.8 (1.0) p=0.44		

BASC = Behavior Assessment System for Children; BDI = Beck Depression Inventory; BICS = Bayesian Information Criterion Score; CBCL = child behavior checklist; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; C-GAS = Children's Global Assessment Scale; ETA = Eta-squared; FAD = functional assessment of depression; FIPP = focused individual psychodynamic psychotherapy; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; IPT-AP = adaptation interpersonal psychotherapy; ITT = intent to treat; ITV = interactive televideo; KQ = Key Question; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; SD = standard deviation; SIFT = systems integrative family therapy.

**Table E-30. KQ 5a: Benefits of psychotherapy versus pharmacotherapy**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Iftene, 2015 <sup>78</sup>	IG1: Sertraline IG2: Group Rational Emotive Behavior Therapy/CBT IG3: Sertraline plus Group Rational Emotive Behavior Therapy/CBT	CDI Posttreatment IG1:15.39 (8.76) IG2:15.92 (6.49) IG3: 16.80 (8.78)  No significant differences amount the three conditions, F(2, 84)=0.177, p >0.05	Clinical response rate at posttreatment IG1:60.60% IG2:67.85% IG3:53.84% NS	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS <sup>92</sup>	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Depression symptoms, ITT (n=439) Adjusted CDRS-R total score 6 weeks, adjusted mean (SD) IG1: 38.10 (7.78) IG2: 39.80 (7.37) IG3: 44.63 (8.30) CG: 44.90 (7.32)  12 weeks, adjusted mean (SD) IG1: 33.79 (8.24) IG2: 36.30 (8.18) IG3: 42.06 (9.18) CG: 41.77 (7.99)  Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement : IG1>CG (p=0.001); IG1=IG2 (p=0.13); IG1>IG3 (p=0.001); IG2>IG3 (p=0.001); IG2>CG (p=0.002); IG3=CG (p=0.97)  Across all 12 weeks: Time-by-treatment interaction based on CDRS-R random	Response CGI-I positive response rate, ITT (n=439) 12 weeks, % response rate (95% CI) adjusted for clinical site IG1: 71.0 (62 to 80) IG2: 60.6 (51 to 70) IG3: 43.2 (34 to 52) CG: 34.8 (26 to 44) Regression analyses found treatment was statistically significant factor in CGI-I positive response (p=0.001)  RR (calculated): 2.45 95% CI, 0.31 to 19.7  12 weeks, statistically comparing response: IG1>CG (p=0.001); IG2>CG (p=0.001); IG3=CG (p=0.20); IG1=IG2 (p=0.11); IG1>IG3 (p=0.001); IG2>IG3 (p=0.01)	NR	No mortality from completed suicides	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>regression slope coefficients: <math>p=0.001</math>; Statistically comparing improvement :</p> <p>IG1&gt;CG (<math>p=0.001</math>); IG1&gt;IG2 (<math>p=0.02</math>); IG1&gt;IG3 (<math>p=0.001</math>); IG2&gt;IG3 (<math>p=0.01</math>); IG2=CG (<math>p=0.10</math>); IG3=CG (<math>p=0.40</math>)</p> <p>Hedge g effect sizes relative to placebo (G4) IG1: 0.98 IG2: 0.68 IG3: -0.03</p> <p>Hedge g effect sizes relative to placebo (CG) derived from ORs for dichotomized CGI-I IG1: 0.84 IG2: 0.58 IG3: 0.20 CG: NA</p> <p>NNT (95% CI) IG1: 3 (2 to 4) IG2: 4 (3 to 8) IG3: 12 (5 to 23) CG: NA</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>RADS total score 6 weeks, adjusted mean (SD) IG1: 60.90 (11.59) IG2: 63.41 (12.44) IG3: 69.10 (13.59) CG: 69.43 (10.94)</p> <p>12 weeks, adjusted mean (SD) IG1: 56.95 (12.24) IG2: 60.58 (13.07) IG3: 67.96 (14.18) CG: 66.68 (11.41)</p> <p>Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement : IG1&gt;CG (p=0.001); IG1=IG2 (p=0.11); IG1&gt;IG3 (p=0.001); IG2&gt;IG3 (p=0.003); IG2&gt;CG (p=0.003); IG3=CG (p=0.94)</p> <p>Across all 12 weeks: Time-by-treatment interaction based on RADS random regression slope coefficients: p=0.001;</p>				



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		Statistically comparing improvement : IG1>CG (p=0.001); IG1>IG2 (p=0.002); IG1>IG3 (p=0.001); IG2>IG3 (p=0.03); IG2=CG (p=0.34); IG3=CG (p=0.21)  NOTE: Means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	<p>Moderation analysis of C-GAS (functional status) by family income, least squares mean (SD) ITT, n=439 at 12 weeks</p> <p>Patients with &lt;\$75,000 (low-to-middle income)  IG1: 32.7 (8.7)  IG2: 35.3 (8.7)  IG3: 43.0 (8.8)  CG: 41.4 (9.0)</p> <p>Within the &lt;\$75,000 group, statistical comparisons of how groups compared with one another at 12 weeks:  IG1=IG2: p=NS  IG1&gt;IG3: p&lt;0.001  IG1&gt;CG: p&lt;0.001  IG2&gt;IG3: p&lt;0.001  IG2&gt;CG: p&lt;0.001  IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>IG1: 0.98 (p&lt;0.05) IG2: 0.69 (p&lt;0.05) IG3: -0.18 (p=NS)</p> <p>Patients with ≥\$75,000 (high income) IG1: 33.7 (9.6) IG2: 38.0 (9.1) IG3: 35.1 (9.0) CG: 41.7 (9.2)</p> <p>Within the ≥\$75,000 group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1=IG3: p=NS IG1&gt;CG: p&lt;0.05 IG2=IG3: p=NS IG2=CG: p=NS IG3&gt;CG: p&lt;0.05</p> <p>Effect size for active treatments vs. CG IG1: 0.85 (p&lt;0.05) IG2: 0.40 IG3: 0.72 (p&lt;0.05)</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Moderation analysis of C-GAS (functional status) by CGI-S, least squares mean (SD)</p> <p>ITT, n=439 at 12 weeks</p> <p>Patients with mild/moderate CGI-S</p> <p>IG1: 30.9 (7.3)</p> <p>IG2: 35.6 (7.1)</p> <p>IG3: 36.9 (6.9)</p> <p>CG: 38.4 (7.1)</p> <p>Within the mild/moderate CGI-S group, statistical comparisons of how groups compared with one another at 12 weeks:</p> <p>IG1&gt;IG2: p&lt;0.001</p> <p>IG1&gt;IG3: p&lt;0.001</p> <p>IG1&gt;CG: p&lt;0.001</p> <p>IG2=IG3: p=NS</p> <p>IG2&gt;CG: p&lt;0.001</p> <p>IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG</p> <p>IG1: 1.04 (p&lt;0.05)</p> <p>IG2: 0.39 (p&lt;0.05)</p> <p>IG3: 0.21</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Patients with marked/severe CGI-S IG1: 35.4 (8.8) IG2: 36.8 (9.3) IG3: 44.0 (9.4) CG: 43.2 (9.6)</p> <p>Within the marked/severe CGI-S group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG IG1: 0.84 (p&lt;0.05) IG2: 0.69 (p&lt;0.05) IG3: -0.08</p> <p>Moderation analysis of CNCEQ (depressive cognitive distortions)</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Low CNCEQ IG1: 33.2 (7.9) IG2: 35.5 (7.8) IG3: 39.4 (7.6) CG: 41.1 (7.5)</p> <p>Within the low CNCEQ group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG IG1: 1.03 (p&lt;0.05) IG2: 0.73 (p&lt;0.05) IG3: 0.22</p> <p>High CNCEQ IG1: 32.3 (9.8) IG2: 35.9 (10.1) IG3: 41.8 (10.0) CG: 40.6 (10.4)</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Within the high CNCEQ group, statistical comparisons of how groups compared with one another at 12 weeks:</p> <p>IG1&gt;IG2: p&lt;0.001  IG1&gt;IG3: p&lt;0.001  IG1&gt;CG: p&lt;0.001  IG2&gt;IG3: p&lt;0.001  IG2&gt;CG: p&lt;0.001  IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG  IG1: 0.82 (p&lt;0.05)  IG2: 0.46 (p&lt;0.05)  IG3: -0.12</p>
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	Loss of MDD diagnosis (K-SADS-P/L) Completers analysis only (n=379): 12 weeks, % IG1: 85.3 IG2: 78.6 IG3: 61.1 CG: 60.4 Overall treatment effect: $p \leq 0.0001$  Statistical comparisons found mixed findings in terms of how groups compared with one another, OR (95% CI): IG1=IG2: 1.7 (0.79 to 3.61) ( $p=0.18$ ); IG1>IG3: 4.3 (2.06 to 8.94) ( $p=0.0001$ ); IG1>CG: 4.1 (2.00 to 8.44) ( $p=0.0001$ ); IG2>IG3: 2.5 (1.31 to 4.93) ( $p=0.006$ ); IG2>CG: 2.4 (1.27 to 4.67) ( $p=0.007$ ); IG3=CG: 1.0 (0.52 to 1.77) ( $p=0.89$ )	NA	NA	NA



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS (continued)			<p>Remission, adjusted for site (CDRS-R) ITT (n=439): 12 weeks, %</p> <p>IG1: 37 IG2: 23 IG3: 16 CG: 17</p> <p>Overall treatment effect: p=0.0007</p> <p>Statistical comparisons found that IG1 was associated with higher remission rates than all other groups, OR (95% CI): IG1&gt;IG2: 2.1 (1.12 to 3.84) (p=0.02); IG1&gt;IG3: 3.3 (1.71 to 6.42) (p=0.0004); IG1&gt;CG: 3.0 (1.58 to 5.79) (p=0.0009)</p> <p>In contrast; IG2; IG3, and CG did not differ statistically from one another (all p &gt;0.05). See comparisons below, OR (95% CI): IG2=IG3: 1.6 (0.80 to 3.19) (p=0.19) IG2=CG: 1.5 (0.74 to 2.88) (p=0.28) IG3=CG: 0.9 (0.44 to 1.88) (p=0.80)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	<p>Stable response (based on pharmacotherapist-assigned CGI-I=1 or 2), calculated N (%)</p> <p>6 weeks IG1: 37 (34.3) IG2: 25 (23.3) CG: 7 (6.6)</p> <p>12 weeks IG1: 75 (70.0) IG2: 68 (62.1) CG: 43 (38) HR (95% CI) for IG1 vs. CG: 3.1 (2.0 to 4.8) HR (95% CI) for IG2 vs. CG: 2.0 (1.3 to 3.1) HR (95% CI) for IG1 vs. IG2: 1.5 (1.0 to 2.1)</p> <p>Stable response (based on CBT clinician-assigned CGI-I=1 or 2), calculated N (%)</p> <p>6 weeks IG1: 48 (45) IG3: 25 (22.4)</p> <p>12 weeks IG1: 93 (87.1) IG3: 56 (50.8) HR (95% CI) for IG1 vs. IG3: 2.7 (1.9 to 3.9) (p&lt;0.05)</p>	NA	<p>First response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439)</p> <p>Across 12 weeks Data values NR, but between-group comparisons reported (NR which were statistically significant) HR (95% CI): 3.0 (2.1 to 4.3) for IG1 vs. CG HR (95% CI): 2.2 (1.6 to 3.2) for IG2 vs. CG</p> <p>First response (based on CBT clinician-assigned CGI-I=1 or 2), calculated N (%)</p> <p>Across 12 weeks Data values NR, but between-group comparisons reported (NR if statistically significant) HR (95% CI): 2.0 (1.4 to 2.7) for IG1 vs. IG3</p> <p>Time to first response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439)</p> <p>Across 12 weeks (Phase I) IG1: ≥5 weeks IG2: ≥6 weeks CG: ≥11 weeks</p>	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS (continued)					<p>Between-group comparisons IG1 and IG2&gt;CG: Significantly faster onset of benefit in both IG1 and IG2 (p&lt;0.001) IG1=IG2: Trend toward faster improvement in IG1 (p=0.0585) HR (95% CI): 1.3 (1.0 to 1.8)</p> <p>Time to first response in ≥50% patients (based on CBT clinician-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks (Phase I) IG1: ≥6 weeks IG3: ≥8 weeks Between-group comparisons IG1&gt;IG3: Significantly faster onset of benefit in IG1 (p&lt;0.001)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS (continued)					<p>Time to stable response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks (Phase I) IG1: ≥9 weeks IG2: ≥11 weeks CG: NA (only 38% patients had reached stable response by 12 weeks)</p> <p>Between-group comparisons IG1&gt;CG: Significantly faster onset of benefit in IG1 (p&lt;0.001) IG2&gt;CG: Significantly faster onset of benefit in IG2 (p=0.001) IG1&gt;IG2: Significantly faster onset of benefit in IG1 (p=0.034)</p> <p>Time to stable response in ≥50% patients (based on CBT clinician-assigned CGI-I=1 or 2): Between-group comparisons IG1&gt;IG3: Significantly faster onset of benefit in IG1 (p&lt;0.001)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	Functional status (C-GAS) ITT (n=439): 6 weeks, unadjusted mean (SD) IG1: 62.4 (11.2) IG2: 59.9 (10.58) IG3: 56.7 (9.66) CG: 57.0 (9.22)  12 weeks, unadjusted mean (SD) IG1: 66.6 (11.91) IG2: 62.1 (11.91) IG3: 60.0 (11.47) CG: 59.3 (12.72) Time effect in all groups: p<0.0001 Treatment-by-time interaction: p<0.0001  Random-effects regression model (RRM) statistical comparisons of how groups compared with one another at 12 weeks: IG1>IG2: p=0.0450 IG1>IG3: p<0.0001 IG1>CG: p<0.0001 IG2>IG3: p=0.0032 IG2>CG: p=0.0381 IG3>CG: p=0.3805	Global burden of psychiatric problems (HoNOSCA) ITT (n=439): 12 weeks, unadjusted mean (SD) IG1: 9.5 (5.97) IG2: 10.9 (6.35) IG3: 11.7 (6.09) CG: 11.2 (6.15) Time effect in all groups: p<0.0001 Treatment-by-time interaction: p<0.0234  RRM statistical comparisons of how groups compared with one another: IG1=IG2: p=0.1257 IG1>IG3: p=0.0027 IG1>CG: p=0.0393 IG2=IG3: p=0.1310 IG2=CG: p=0.5861 IG3=CG: p=0.3344  12 weeks, mean change from baseline (SD) G1: -6.3 (5.69) G2: -5.1 (5.74) G3: -3.6 (5.58) G4: -4.2 (5.71) Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): p<0.01	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				<p>12 weeks, mean change from baseline (SD)  IG1: 16.7 (12.31)  IG2: 12.6 (12.31)  IG3: 9.7 (12.12)  CG: 9.9 (12.38)  Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): <math>p &lt; 0.0001</math></p> <p>GLM statistical comparisons of how groups compared with one another:  IG1&gt;IG2: <math>p &lt; 0.01</math>  IG1&gt;IG3: <math>p &lt; 0.0001</math>  IG1&gt;CG: <math>p &lt; 0.0001</math>  IG2&gt;IG3: <math>p = \text{NR}</math>  IG2=CG: <math>p = \text{NS}</math>  IG3=CG: <math>p = \text{NS}</math></p> <p>Rate of nonimpaired patients (C-GAS &gt;70)  12 weeks, %  IG1: 34.6  IG2: 20.2  IG3: 13.5  CG: 18.7</p>	<p>GLM statistical comparisons of how groups compared with one another at 12 weeks:  IG1=IG2: <math>p = \text{NS}</math>  IG1&gt;IG3: <math>p &lt; 0.001</math>  IG1&gt;CG: <math>p &lt; 0.01</math>  IG2&gt;IG3: <math>p &lt; 0.05</math>  IG2=CG: <math>p = \text{NS}</math>  IG3=CG: <math>p = \text{NR}</math></p> <p>HoNOSCA subscores:  Treatment-by-time interaction was statistically significant only for item 10 (level of functioning with peers; <math>p = 0.0004</math>), whose effect remained significant even after applying a Bonferroni correction for multiple comparisons.</p> <p>QoL (PQ-LES-Q)  ITT (n=439):  12 weeks, unadjusted mean (SD)  IG1: 54.7 (11.21)  IG2: 51.2 (10.43)  IG3: 47.4 (10.84)  CG: 48.2 (9.91)  Time effect in all groups: <math>p &lt; 0.0001</math>  Treatment-by-time interaction: <math>p &lt; 0.0001</math></p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				<p>Between-group difference: <math>p=0.002</math> Statistically significant treatment effects of how groups compared with one another: IG1&gt;IG2: <math>p&lt;0.020</math> IG1&gt;IG3: <math>p&lt;0.0004</math> IG1&gt;CG: <math>p&lt;0.009</math> IG2=IG3: <math>p=NS</math> IG2=CG: <math>p=NS</math> IG3=CG: <math>p=NS</math></p> <p>Patients not likely to be clinically referred in community (C-GAS &gt;60) 12 weeks, % IG1: 64.5 IG2: 50.5 IG3: 45.0 CG: 35.7 Between-group difference: <math>p=0.0003</math></p> <p>Statistically significant treatment effects of how groups compared with one another: IG1&gt;IG2: <math>p&lt;0.038</math> IG1&gt;IG3: <math>p&lt;0.004</math> IG1&gt;CG: <math>p&lt;0.0001</math> IG2=IG3: <math>p=NS</math> IG2&gt;CG: <math>p=0.023</math> IG3=CG: <math>p=NS</math></p>	<p>RRM statistical comparisons of how groups compared with one another at 12 weeks: IG1&gt;IG2: <math>p=0.0004</math> IG1&gt;IG3: <math>p&lt;0.0001</math> IG1&gt;CG: <math>p&lt;0.0001</math> IG2=IG3: <math>p=0.2766</math> IG2=CG: <math>p=0.7215</math> IG3=CG: <math>p=0.4630</math></p> <p>12 weeks, mean change from baseline (SD) IG1: 9.6 (10.14) IG2: 6.6 (10.23) IG3: 4.2 (10.01) CG: 5.2 (10.16) Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): <math>p&lt;0.001</math></p> <p>Treatment-by-time interaction: <math>p&lt;0.0001</math> GLM statistical comparisons of how groups compared with one another: IG1&gt;IG2: <math>p&lt;0.05</math> IG1&gt;IG3: <math>p&lt;0.0001</math> IG1&gt;CG: <math>p&lt;0.001</math> IG2&gt;IG3: <math>p=NS</math> IG2=CG: <math>p=NS</math> IG3=CG: <math>p=NS</math></p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	<p>Subgroup Analysis #1: ADHD vs. no ADHD Depression symptoms, ITT (n=429) 12 weeks Main linear RRM effect analyses for overall sample Main effect of time (linear): p&lt;0.001 Treatment-by-time interaction: p=0.018 ADHD-by-treatment-by-time interaction: p=0.026 (confirmed that ADHD status prior to treatment or having an ADHD diagnosis before study entry moderated improvement in depression)</p> <p>Linear RRM effect analyses: ADHD subgroup Main effect of time (linear): p&lt;0.001 Treatment-by-time interaction: p=0.038</p>



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Linear RRM effect analyses: No ADHD subgroup Main effect of time (linear): <math>p \leq 0.001</math> Treatment-by-time interaction: <math>p &lt; 0.001</math></p> <p>CDRS-R total score (adjusted for fixed and random effects) 12 weeks, mean (SD) ADHD subgroup IG1 (n=15): 37.08 (9.42) IG2 (n=14): 33.29 (6.42) IG3 (n=14): 35.95 (6.34) CG (n=19): 43.31 (5.65)</p> <p>No ADHD subgroup IG1 (n=92): 33.30 (8.14) IG2 (n=95): 36.83 (8.11) IG3 (n=97): 42.35 (8.96) CG (n=93): 41.39 (8.07)</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Improvement was observed in all arms of both ADHD and no-ADHD subgroups, but patients had different patterns of between-group differences depending on their subgroup.</p> <p>Between-group differences: ADHD subgroup at 12 weeks 12 weeks IG1=IG2=IG3&gt;CG (p=0.046, 0.024, 0.013, respectively)</p> <p>Change trajectories did not differ between arms (p&gt;0.05).</p> <p>Effect sizes IG1 vs. CG: 1.0 IG2 vs. CG: 0.6 IG3 vs. CG: -0.1</p> <p>Between-group differences: No-ADHD subgroup at 12 weeks</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>IG1&gt;(IG2&gt;IG3)=CG (p-values &lt;0.05 for significant differences and &gt;0.05 for nonsignificant differences)</p> <p>Change trajectories: IG1&gt;IG2; IG3, and CG (p&lt;0.009), meaning trajectory in IG1 was faster on average than in all other arms. IG2=CG (p=0.425) and IG3=CG (p=0.065), but IG2&gt;IG3 (p=0.008). In short; IG3 had the most gradual improvement trajectory among active treatments.</p> <p>Effect sizes IG1 vs. CG: 0.8 IG2 vs. CG: 1.7 IG3 vs. CG: 1.2</p> <p>Depression symptoms, ITT (n=327) 36 weeks: Main linear RRM effect analyses for overall sample Main effect of time (linear): p&lt;0.001</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>ADHD-by-treatment-by-time interaction: <math>p=0.004</math></p> <p>ADHD-by-treatment-by-time interaction (squared): <math>p=0.004</math> (confirmed that ADHD status prior to treatment or having an ADHD diagnosis before study entry moderated improvement in depression at this timepoint)</p> <p>Between-group differences: ADHD subgroup at 36 weeks</p> <p>Paired contrasts found no between-group differences in mean total CDRS-R scores within this subgroup.</p> <p>Change trajectories: No significant treatment-by-time (squared) or treatment-by-time interactions</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Between-group differences: No-ADHD subgroup at 36 weeks Paired contrasts found no between-group differences in mean total CDRS-R scores within this subgroup.</p> <p>Change trajectories: Treatment-by-time (squared) interaction: <math>p &lt; 0.001</math> (suggesting significant different by arm) IG1 &gt; IG2 and IG3 (<math>p &lt; 0.05</math>), meaning trajectory in IG1 was faster on average than other IG arms.</p> <p>Subgroup Analysis #2: ADHD psychostimulant medication vs. none among patients with ADHD Depression symptoms, ITT (n=62 with ADHD) CDRS-R total score (adjusted for fixed and random effects)</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						12 weeks: Data values NR, but CDRS-R scores did not differ significantly among the 20/63 patients taking a psychostimulant vs. the 43/63 patients who did not (p=0.056). Treatment-by-psychostimulant use interaction was not significant (p>0.05).
March, 2004 <sup>3</sup> Index article  TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Depressive symptoms, ITT (n=427) CDRS-R Overall (across all trauma subgroups) Significant main effect of time: p<0.001 Significant treatment-by-time effect: p<0.05	NA	NA	NA	

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; C-GAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions Scale-Improvement Scale; CI = confidence interval; CNCEQ = children's negative cognitive error questionnaire; GLM = generalized linear modeling; HoNOSCA = Health of Nation Outcome Scale – Children and Adolescents; HR = hazard ratio; IG = intervention group; ITT = intent to treat; K-SADS-P/L = Kiddie Schedule for Affective Disorders and Schizophrenia; KQ = Key Question; NA = not applicable; NNT = number needed to treat; NR = not reported; NS = not significant; OR = odds ratio; PQ-LES-Q = Parent-Child Interaction Therapy Emotion Development; RADS = Reactive Airways Dysfunction Syndrome; RR = relative risk; RRM = random-effects regression model; SD = standard deviation; TADS = Treatment among Adolescents with Depression.

**Table E-31. KQ 5a: Benefits of psychotherapy plus pharmacotherapy versus psychotherapy**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Bernstein, 2000 <sup>80</sup> Index article	IG: Imipramine+CBT CG: Placebo+CBT	NR	NR	NR	NR	NR
Bernstein, 2000 <sup>80</sup> Index article Companion article: Bernstein, 2000 <sup>81</sup>	IG: Imipramine+CBT CG: Placebo+CBT	CDRS-R Mean (SD) Week 8 IG: 34.6 (8.9) CG: 45.7 (16.5) IG vs. CG, est.=2.30, SE=1.10, z=2.08, p=0.037; Cohen d=0.333  BDI Mean (SD) Week 8 IG: 6.4 (8.3) CG: 9.8 (7.8) IG vs. CG, NS	Remission based on CDRS-R score of 35 or less IG: 52% CG: 32% X <sup>2</sup> =2.05, df=1, NS	NR	NR	NR
Deas, 2000 <sup>82</sup>	IG: sertraline plus group CBT CG: placebo plus group CBT	ITT (n=10; IG=5; CG=5) HAM-D: 12 weeks Mean (SD) IG: 12.00 (4.95) CG: 10.40 (3.65) ANOVA time effect F=26.14, p<0.001  Depression Response IG: 2 CG: 4 p=0.52	NR	NR	ITT (n=10; IG=5; CG=5) DDD: 12 weeks Mean (SD) IG: 4.99 (4.48) CG: 2.81 (4.81) ANOVA time effect F=20.48, p<0.002  PDD: 12 weeks Mean (SD) IG: 5.71 (3.98) CG: 7.62 (12.42) ANOVA time effect F=8.90, p<0.02	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Dietz, 2008 <sup>83</sup>	IG: Family Based Interpersonal psychotherapy CG: Family Based Interpersonal psychotherapy plus antidepressant medication	CDRS-R Mean (SD) Pretreatment IG: 43.6 (6.87) CG: 42.7 (2.42)  Posttreatment IG: 28.8 (10.52) CG: 22.7 (4.32)  No group differences, $t(15)=7.98$ , $p < 0.001$ for baseline to followup for overall sample	NR	CGAS Mean (SD) Pretreatment IG: 58.6 (3.13) CG: 57.5 (4.18)  Posttreatment IG: 73.0 (9.77) CG: 77.5 (12.15)  No group differences, $t(16)=-6.76$ , $p < 0.000$ for baseline to followup for overall sample	NR	NR
Iftene, 2015 <sup>78</sup>	IG1: Sertraline IG2: Group Rational Emotive Behavior Therapy/CBT IG3: Sertraline plus Group Rational Emotive Behavior Therapy/CBT	CDI Posttreatment IG1: 15.39 (8.76) IG2: 15.92 (6.49) IG3: 16.80 (8.78)  No significant differences amount the three conditions, $F(2, 84)=0.177$ , $p > 0.05$	Clinical response rate at posttreatment IG1: 60.60% IG2: 67.85% IG3: 53.84% NS	NR	NR	NR



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Depression symptoms, ITT (n=439) Adjusted CDRS-R total score 6 weeks, adjusted mean (SD) IG1: 38.10 (7.78) IG2: 39.80 (7.37) IG3: 44.63 (8.30) CG: 44.90 (7.32)  12 weeks, adjusted mean (SD) IG1: 33.79 (8.24) IG2: 36.30 (8.18) IG3: 42.06 (9.18) CG: 41.77 (7.99)  Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement : IG1>CG (p=0.001); IG1=IG2 (p=0.13); IG1>IG3 (p=0.001); IG2>IG3 (p=0.001); IG2>CG (p=0.002); IG3=CG (p=0.97)  Across all 12 weeks: Time-by-treatment interaction based on CDRS-R random regression slope coefficients: p=0.001;	Response CGI-I positive response rate, ITT (n=439) 12 weeks, % response rate (95% CI) adjusted for clinical site IG1: 71.0 (62 to 80) IG2: 60.6 (51 to 70) IG3: 43.2 (34 to 52) CG: 34.8 (26 to 44) Regression analyses found treatment was statistically significant factor in CGI-I positive response (p=0.001)  RR (calculated): 2.45 95% CI, 0.31 to 19.7  12 weeks, statistically comparing response : IG1>CG (p=0.001); IG2>CG (p=0.001); IG3=CG (p=0.20); IG1=IG2 (p=0.11); IG1>IG3 (p=0.001); IG2>IG3 (p=0.01)	NR	No mortality from completed suicides	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Statistically comparing improvement :</p> <p>IG1&gt;CG (p=0.001); IG1&gt;IG2 (p=0.02); IG1&gt;IG3 (p=0.001); IG2&gt;IG3 (p=0.01); IG2=CG (p=0.10); IG3=CG (p=0.40)</p> <p>Hedge g effect sizes relative to placebo (G4) IG1: 0.98 IG2: 0.68 IG3: -0.03</p> <p>Hedge g effect sizes relative to placebo (CG) derived from ORs for dichotomized CGI-I IG1: 0.84 IG2: 0.58 IG3: 0.20 CG: NA</p> <p>NNT (95% CI) IG1: 3 (2 to 4) IG2: 4 (3 to 8) IG3: 12 (5 to 23) CG: NA</p> <p>RADS total score 6 weeks, adjusted mean (SD) IG1: 60.90 (11.59) IG2: 63.41 (12.44)</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		IG3: 69.10 (13.59) CG: 69.43 (10.94)  12 weeks, adjusted mean (SD) IG1: 56.95 (12.24) IG2: 60.58 (13.07) IG3: 67.96 (14.18) CG: 66.68 (11.41)  Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement: IG1>CG (p=0.001); IG1=IG2 (p=0.11); IG1>IG3 (p=0.001); IG2>IG3 (p=0.003); IG2>CG (p=0.003); IG3=CG (p=0.94)  Across all 12 weeks: Time-by-treatment interaction based on RADS random regression slope coefficients: p=0.001; Statistically comparing improvement: IG1>CG (p=0.001); IG1>IG2 (p=0.002); IG1>IG3 (p=0.001);				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		IG2>IG3 (p=0.03); IG2=CG (p=0.34); IG3=CG (p=0.21)  NOTE: Means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model				
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	Moderation analysis of C-GAS (functional status) by family income, least squares mean (SD) ITT, n=439 at 12 weeks  Patients with <\$75,000 (low-to-middle income) IG1: 32.7 (8.7) IG2: 35.3 (8.7) IG3: 43.0 (8.8) CG: 41.4 (9.0)  Within the <\$75,000 group, statistical comparisons of how groups compared with one another at 12 weeks:

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>IG1=IG2: p=NS  IG1&gt;IG3: p&lt;0.001  IG1&gt;CG: p&lt;0.001  IG2&gt;IG3: p&lt;0.001  IG2&gt;CG: p&lt;0.001  IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG  IG1: 0.98 (p&lt;0.05)  IG2: 0.69 (p&lt;0.05)  IG3: -0.18 (p=NS)</p> <p>Patients with ≥\$75,000 (high income)  IG1: 33.7 (9.6)  IG2: 38.0 (9.1)  IG3: 35.1 (9.0)  CG: 41.7 (9.2)</p> <p>Within the ≥\$75,000 group, statistical comparisons of how groups compared with one another at 12 weeks:  IG1=IG2: p=NS  IG1=IG3: p=NS  IG1&gt;CG: p&lt;0.05  IG2=IG3: p=NS  IG2=CG: p=NS  IG3&gt;CG: p&lt;0.05</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Effect size for active treatments vs. CG IG1: 0.85 (p&lt;0.05) IG2: 0.40 IG3: 0.72 (p&lt;0.05)</p> <p>Moderation analysis of C-GAS (functional status) by CGI-S, least squares mean (SD) ITT, n=439 at 12 weeks Patients with mild/moderate CGI-S IG1: 30.9 (7.3) IG2: 35.6 (7.1) IG3: 36.9 (6.9) CG: 38.4 (7.1)</p> <p>Within the mild/moderate CGI-S group, statistical comparisons of how groups compared with one another at 12 weeks: IG1&gt;IG2: p&lt;0.001 IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2=IG3: p=NS IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Effect size for active treatments vs. CG IG1: 1.04 (p&lt;0.05) IG2: 0.39 (p&lt;0.05) IG3: 0.21</p> <p>Patients with marked/severe CGI-S IG1: 35.4 (8.8) IG2: 36.8 (9.3) IG3: 44.0 (9.4) CG: 43.2 (9.6)</p> <p>Within the marked/severe CGI-S group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG IG1: 0.84 (p&lt;0.05) IG2: 0.69 (p&lt;0.05) IG3: -0.08</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Moderation analysis of CNCEQ (depressive cognitive distortions)</p> <p>Low CNCEQ IG1: 33.2 (7.9) IG2: 35.5 (7.8) IG3: 39.4 (7.6) CG: 41.1 (7.5)</p> <p>Within the low CNCEQ group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG IG1: 1.03 (p&lt;0.05) IG2: 0.73 (p&lt;0.05) IG3: 0.22</p>



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>High CNCEQ IG1: 32.3 (9.8) IG2: 35.9 (10.1) IG3: 41.8 (10.0) CG: 40.6 (10.4)</p> <p>Within the high CNCEQ group, statistical comparisons of how groups compared with one another at 12 weeks: IG1&gt;IG2: p&lt;0.001 IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG IG1: 0.82 (p&lt;0.05) IG2: 0.46 (p&lt;0.05) IG3: -0.12</p>
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	<p>Loss of MDD diagnosis (K-SADS-P/L) Completers analysis only (n=379): 12 weeks, % IG1: 85.3 IG2: 78.6 IG3: 61.1 CG: 60.4 Overall treatment effect: <math>p \leq 0.0001</math></p> <p>Statistical comparisons found mixed findings in terms of how groups compared with one another, OR (95% CI): IG1=IG2: 1.7 (0.79 to 3.61) (<math>p=0.18</math>); IG1&gt;IG3: 4.3 (2.06 to 8.94) (<math>p=0.0001</math>); IG1&gt;CG: 4.1 (2.00 to 8.44) (<math>p=0.0001</math>); IG2&gt;IG3: 2.5 (1.31 to 4.93) (<math>p=0.006</math>); IG2&gt;CG: 2.4 (1.27 to 4.67) (<math>p=0.007</math>); IG3=CG: 1.0 (0.52 to 1.77) (<math>p=0.89</math>)</p>	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS (continued)			<p>Remission, adjusted for site (CDRS-R) ITT (n=439): 12 weeks, %</p> <p>IG1: 37 IG2: 23 IG3: 16 CG: 17</p> <p>Overall treatment effect: p=0.0007</p> <p>Statistical comparisons found that IG1 was associated with higher remission rates than all other groups, OR (95% CI): IG1&gt;IG2: 2.1 (1.12 to 3.84) (p=0.02); IG1&gt;IG3: 3.3 (1.71 to 6.42) (p=0.0004); IG1&gt;CG: 3.0 (1.58 to 5.79) (p=0.0009)</p> <p>In contrast; IG2; IG3, and CG did not differ statistically from one another (all p &gt;0.05). See comparisons below, OR (95% CI): IG2=IG3: 1.6 (0.80 to 3.19) (p=0.19) IG2=CG: 1.5 (0.74 to 2.88) (p=0.28) IG3=CG: 0.9 (0.44 to 1.88) (p=0.80)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	First response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks Data values NR, but between-group comparisons reported (NR which were statistically significant) HR (95% CI): 3.0 (2.1 to 4.3) for IG1 vs. CG HR (95% CI): 2.2 (1.6 to 3.2) for IG2 vs. CG  First response (based on CBT clinician-assigned CGI-I=1 or 2), calculated N (%) Across 12 weeks Data values NR, but between-group comparisons reported (NR if statistically significant) HR (95% CI): 2.0 (1.4 to 2.7) for IG1 vs. IG3	NA	Time to first response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks (Phase I) IG1: ≥5 weeks IG2: ≥6 weeks CG: ≥11 weeks Between-group comparisons	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS (continued)			<p>Stable response (based on pharmacotherapist-assigned CGI-I=1 or 2), calculated N (%)</p> <p>6 weeks IG1: 37 (34.3) IG2: 25 (23.3) CG: 7 (6.6)</p> <p>12 weeks IG1: 75 (70.0) IG2: 68 (62.1) CG: 43 (38)</p> <p>HR (95% CI) for IG1 vs. CG: 3.1 (2.0 to 4.8) HR (95% CI) for IG2 vs. CG: 2.0 (1.3 to 3.1) HR (95% CI) for IG1 vs. IG2: 1.5 (1.0 to 2.1)</p> <p>Stable response (based on CBT clinician-assigned CGI-I=1 or 2), calculated N (%)</p> <p>6 weeks IG1: 48 (45) IG3: 25 (22.4)</p> <p>12 weeks IG1: 93 (87.1) IG3: 56 (50.8) HR (95% CI) for IG1 vs. IG3: 2.7 (1.9 to 3.9) (p&lt;0.05)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS (continued)					IG1 and IG2>CG: Significantly faster onset of benefit in both IG1 and IG2 (p<0.001) IG1=IG2: Trend toward faster improvement in IG1 (p=0.0585) HR (95% CI): 1.3 (1.0 to 1.8)	
					Time to first response in ≥50% patients (based on CBT clinician-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks (Phase I) IG1: ≥6 weeks IG3: ≥8 weeks Between-group comparisons IG1>IG3: Significantly faster onset of benefit in IG1 (p<0.001)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS (continued)					<p>Time to stable response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks (Phase I) IG1: ≥9 weeks IG2: ≥11 weeks CG: NA (only 38% patients had reached stable response by 12 weeks)</p> <p>Between-group comparisons IG1&gt;CG: Significantly faster onset of benefit in IG1 (p&lt;0.001) IG2&gt;CG: Significantly faster onset of benefit in IG2 (p=0.001) IG1&gt;IG2: Significantly faster onset of benefit in IG1 (p=0.034)</p> <p>Time to stable response in ≥50% patients (based on CBT clinician-assigned CGI-I=1 or 2): Between-group comparisons IG1&gt;IG3: Significantly faster onset of benefit in IG1 (p&lt;0.001)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	Functional status (C-GAS) ITT (n=439): 6 weeks, unadjusted mean (SD) IG1: 62.4 (11.2) IG2: 59.9 (10.58) IG3: 56.7 (9.66) CG: 57.0 (9.22)  12 weeks, unadjusted mean (SD) IG1: 66.6 (11.91) IG2: 62.1 (11.91) IG3: 60.0 (11.47) CG: 59.3 (12.72) Time effect in all groups: p<0.0001 Treatment-by-time interaction: p<0.0001  Random-effects regression model (RRM) statistical comparisons of how groups compared with one another at 12 weeks: IG1>IG2: p=0.0450 IG1>IG3: p<0.0001 IG1>CG: p<0.0001 IG2>IG3: p=0.0032 IG2>CG: p=0.0381 IG3>CG: p=0.3805	Global burden of psychiatric problems (HoNOSCA) ITT (n=439): 12 weeks, unadjusted mean (SD) IG1: 9.5 (5.97) IG2: 10.9 (6.35) IG3: 11.7 (6.09) CG: 11.2 (6.15) Time effect in all groups: p<0.0001 Treatment-by-time interaction: p<0.0234  Random-effects regression model (RRM) statistical comparisons of how groups compared with one another: IG1=IG2: p=0.1257 IG1>IG3: p=0.0027 IG1>CG: p=0.0393 IG2=IG3: p=0.1310 IG2=CG: p=0.5861 IG3=CG: p=0.3344  12 weeks, mean change from baseline (SD) G1: -6.3 (5.69) G2: -5.1 (5.74) G3: -3.6 (5.58) G4: -4.2 (5.71)	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				<p>12 weeks, mean change from baseline (SD) IG1: 16.7 (12.31) IG2: 12.6 (12.31) IG3: 9.7 (12.12) CG: 9.9 (12.38)</p> <p>Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): <math>p &lt; 0.0001</math></p> <p>GLM statistical comparisons of how groups compared with one another: IG1&gt;IG2: <math>p &lt; 0.01</math> IG1&gt;IG3: <math>p &lt; 0.0001</math> IG1&gt;CG: <math>p &lt; 0.0001</math> IG2&gt;IG3: <math>p = \text{NR}</math> IG2=CG: <math>p = \text{NS}</math> IG3=CG: <math>p = \text{NS}</math></p> <p>Rate of nonimpaired patients (C-GAS &gt;70) 12 weeks, % IG1: 34.6 IG2: 20.2 IG3: 13.5 CG: 18.7</p> <p>Between-group difference: <math>p = 0.002</math> Statistically significant</p>	<p>Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): <math>p &lt; 0.01</math></p> <p>GLM statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: <math>p = \text{NS}</math> IG1&gt;IG3: <math>p &lt; 0.001</math> IG1&gt;CG: <math>p &lt; 0.01</math> IG2&gt;IG3: <math>p &lt; 0.05</math> IG2=CG: <math>p = \text{NS}</math> IG3=CG: <math>p = \text{NR}</math></p> <p>HoNOSCA subscores: Treatment-by-time interaction was statistically significant only for item 10 (level of functioning with peers; <math>p = 0.0004</math>), whose effect remained significant even after applying a Bonferroni correction for multiple comparisons.</p> <p>QoL (PQ-LES-Q) ITT (n=439): 12 weeks, unadjusted mean (SD) IG1: 54.7 (11.21) IG2: 51.2 (10.43) IG3: 47.4 (10.84) CG: 48.2 (9.91)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratovichil, 2009 <sup>8</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	<p>Subgroup Analysis #1: ADHD vs. no ADHD Depression symptoms, ITT (n=429) 12 weeks Main linear RRM effect analyses for overall sample Main effect of time (linear): p&lt;0.001 Treatment-by-time interaction: p=0.018 ADHD-by-treatment-by-time interaction: p=0.026 (confirmed that ADHD status prior to treatment or having an ADHD diagnosis before study entry moderated improvement in depression)</p> <p>Linear RRM effect analyses: ADHD subgroup Main effect of time (linear): p&lt;0.001 Treatment-by-time interaction: p=0.038</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Linear RRM effect analyses: No ADHD subgroup Main effect of time (linear): <math>p \leq 0.001</math> Treatment-by-time interaction: <math>p &lt; 0.001</math></p> <p>CDRS-R total score (adjusted for fixed and random effects) 12 weeks, mean (SD) ADHD subgroup IG1 (n=15): 37.08 (9.42) IG2 (n=14): 33.29 (6.42) IG3 (n=14): 35.95 (6.34) CG (n=19): 43.31 (5.65)</p> <p>No ADHD subgroup IG1 (n=92): 33.30 (8.14) IG2 (n=95): 36.83 (8.11) IG3 (n=97): 42.35 (8.96) CG (n=93): 41.39 (8.07) Improvement was observed in all arms of both ADHD and no-ADHD subgroups, but patients had different patterns of</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>between-group differences depending on their subgroup.</p> <p>Between-group differences: ADHD subgroup at 12 weeks 12 weeks IG1=IG2=IG3&gt;CG (p=0.046, 0.024, 0.013, respectively)</p> <p>Change trajectories did not differ between arms (p&gt;0.05).</p> <p>Effect sizes IG1 vs. CG: 1.0 IG2 vs. CG: 0.6 IG3 vs. CG: -0.1</p> <p>Between-group differences: No-ADHD subgroup at 12 weeks IG1&gt;(IG2&gt;IG3)=CG (p-values &lt;0.05 for significant differences and &gt;0.05 for nonsignificant differences)</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Change trajectories: IG1&gt;IG2; IG3, and CG (p&lt;0.009), meaning trajectory in IG1 was faster on average than in all other arms. IG2=CG (p=0.425) and IG3=CG (p=0.065), but IG2&gt;IG3 (p=0.008). In short; IG3 had the most gradual improvement trajectory among active treatments.</p> <p>Effect sizes IG1 vs. CG: 0.8 IG2 vs. CG: 1.7 IG3 vs. CG: 1.2</p> <p>Depression symptoms, ITT (n=327) 36 weeks: Main linear RRM effect analyses for overall sample Main effect of time (linear): p&lt;0.001 ADHD-by-treatment-by-time interaction: p=0.004 ADHD-by-treatment-by-time interaction (squared): p=0.004 (confirmed that</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>ADHD status prior to treatment or having an ADHD diagnosis before study entry moderated improvement in depression at this timepoint)</p> <p>Between-group differences: ADHD subgroup at 36 weeks Paired contrasts found no between-group differences in mean total CDRS-R scores within this subgroup.</p> <p>Change trajectories: No significant treatment-by-time (squared) or treatment-by-time interactions</p> <p>Between-group differences: No-ADHD subgroup at 36 weeks</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Paired contrasts found no between-group differences in mean total CDRS-R scores within this subgroup.</p> <p>Change trajectories: Treatment-by-time (squared) interaction: <math>p &lt; 0.001</math> (suggesting significant different by arm) IG1 &gt; IG2 and IG3 (<math>p &lt; 0.05</math>), meaning trajectory in IG1 was faster on average than other IG arms.</p> <p>Subgroup Analysis #2: ADHD psychostimulant medication vs. none among patients with ADHD Depression symptoms, ITT (n=62 with ADHD) CDRS-R total score (adjusted for fixed and random effects) 12 weeks:</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						Data values NR, but CDRS-R scores did not differ significantly among the 20/63 patients taking a psychostimulant vs. the 43/63 patients who did not (p=0.056). Treatment-by-psychostimulant use interaction was not significant (p>0.05).
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Depressive symptoms, ITT (n=427) CDRS-R Overall (across all trauma subgroups) Significant main effect of time: p<0.001 Significant treatment-by-time effect: p<0.05	NA	NA	NA	
	G1: CBT G2: Sertraline G3: Combined	Response to treatment (OR, 95% CI) G1 vs. G3: 0.19, CI, 0.03 to 1.16 G2 vs. G3: 1.31, CI, 0.31 to 5.48 G2 vs. G1: 6.86, CI, 1.12 to 41.48  Regression model results: no significant difference in the odds of depression between treatments (OR, 6.46; CI, 0.89 to 46.77)	Proportion in full remission from MDD by posttreatment assessment (i.e. at 3 months) G1: 14% G2: NR G3: 7%	Significant difference detected in the longitudinal regression among all three study groups in the PreYFU and PreYPost interactions for both the GAF and the GARF assessments but PostYFU interaction was not significant.	Proportion of adolescents remitted from dysthymic disorder or DDNOS over time is similar for each treatment group. The odds of depression at posttreatment assessment did not differ between treatment groups (G1 v. G3: OR, 0.71; 95% CI, 0.10 to 5.12; G2 v. G3: OR, 1.14; 95% CI, 0.17 to 7.60; G2 v. G1: OR, 1.6; 95% CI, 0.23 to 11.27). The odds of	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Melvin, 2006 <sup>79</sup>		Change in the proportion depressed over time (posttreatment to followup assessment) was not significant (OR, 95% CI) G1 vs. G3: 0.02; CI, 0 to 3.45 G2 vs. G3: 2.66; CI, 0.07 to 108.11 G2 vs. G1: 84.94; CI, 0.83 to 8,718.04  RDS at posttreatment (3 months), mean (SD) G1: 66.00 (15.93) G2: 72.92 (16.84) G3: 71.64 (18.28)	Proportion in full remission from MDD by followup assessment (i.e. at 9 months) G1: NR G2: NR G3: 60% (Author commented on highest only) For G1 v. G3: OR 2.7 (95% CI, 0.60 to 12.14) For G2 v. G3: OR 3.0 (95% CI, 0.68 to 13.31)		depression for those with dysthymic disorder or DDNOS decreased significantly between postacute treatment and followup assessment (OR, 8.52; CI, 2.58 to 28.15) in contrast with the odds for those with MDD.	NR

ADHD = attention-deficit/hyperactivity disorder; ANCOVA = analysis of covariance; ANOVA = analysis of variance; BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGAS = Children's Global Assessment Scale; CI = confidence interval; CNCEQ = children's negative cognitive error questionnaire; DDD = drinks per drinking day; GLM = generalized linear modeling; HoNOSCA = Health of Nation Outcome Scale – Children and Adolescents; HR = hazard ratio; IG = intervention group; ITT = intent to treat; K-SADS-P/L = Kiddie Schedule for Affective Disorders and Schizophrenia; KQ = Key Question; MDD = major depressive disorder; NA = not applicable; NNT = number needed to treat; NR = not reported; NS = not significant; OR = odds ratio; PDD = persistent depressive disorder; PQ-LES-Q = Parent-Child Interaction Therapy Emotion Development; QoL = quality of life; RADS = Reactive Airways Dysfunction Syndrome; RRM = random-effects regression model; SD = standard deviation; SE = standard error; vs. = versus; YFU = year followup.

**Table E-32. KQ 5a: Benefits of psychotherapy plus pharmacotherapy versus pharmacotherapy**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 2005 <sup>84</sup>	IG: Collaborative care - brief individual CBT+TAU SSRIs CG: TAU SSRIs	Depressive symptoms ITT (n=152; IG: 77 and CG: 75) CES-D 6 weeks, mean (SD) IG: 20.1 (11.6) CG: 19.6 (10.2)  12 weeks, mean (SD) IG: 15.7 (11.3) CG: 16.6 (9.6)  26 weeks, mean (SD) IG: 13.7 (11.5) CG: 15.0 (11.4)  52 weeks, mean (SD) IG: 11.5 (11.0) CG: 14.9 (10.1) Treatment-by-time (linear): F=3.2, p=0.07  Effect size D: 0.170 HAM-D 6 weeks, mean (SD) IG: 11.9 (7.6) CG: 11.9 (7.3)  12 weeks, mean (SD) IG: 8.2 (6.6) CG: 8.4 (6.7)  26 weeks, mean (SD) IG: 6.5 (6.7) CG: 7.8 (6.9)	Recovery from index depressive diagnosis ITT (n=152; IG: 77 and CG: 75) 6 weeks, calculated N (%) IG: 33 (43.3) CG: 43 (56.9) χ-squared: 2.46; p=0.12  12 weeks, calculated N (%) IG: 18 (23.0) CG: 21 (27.9) χ-squared: 0.39; p=0.53  26 weeks, calculated N (%) IG: 8 (10.8) CG: 13 (17.7) χ-squared: 1.27; p=0.26  52 weeks, calculated N (%) IG: 8 (10.7) CG: 4 (5.8) χ-squared: 0.86; p=0.35 Recovery from "moderately	C-GAS ITT (n=152; IG: 77 and CG: 75) 6 weeks, mean (SD) IG: 60.4 (10.1) CG: 59.5 (9.5)  12 weeks, mean (SD) IG: 65.5 (10.0) CG: 63.7 (9.6)  26 weeks, mean (SD) IG: 68.8 (8.4) CG: 66.6 (8.7)  52 weeks, mean (SD) IG: 71.4 (8.7) CG: 68.4 (7.6) Treatment-by-time (best-fitting of linear, quadratic, and cubic models): F=1.52, p=0.22 Effect size D: 0.090 SAS-SR: Outcome data NR	Relapse among patients recovering from MDD episodes (n=135; group Ns=NR) 52 weeks, N (%) IG: 16 (NR) CG: 16 (NR) χ-squared: 0.01; p=0.76 Treatment effect controlling for age and gender: χ-squared: 0.43; p=0.51  SF-12 MCS ITT (n=152; IG1: 77 and CG: 75) 6 weeks, mean (SD) IG: 38.5 (8.6) CG: 40.5 (8.3)  12 weeks, mean (SD) IG: 40.2 (10.2) CG: 41.7 (10.9)  26 weeks, mean (SD) IG: 43.6 (11.2) CG: 41.9 (10.1)  52 weeks, mean (SD) IG: 45.4 (9.3) CG: 43.1 (10.2) Treatment-by-time-by-time (cubic): F=4.25, p=0.04 Effect size D: 0.203 SF-12 PCS	No significant moderation of any IG arm's benefit outcomes by intensity/degree of CBT participation (N of intervention sessions)

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 2005 <sup>84</sup> (continued)		52 weeks, mean (SD) IG: 4.9 (7.1) CG: 6.5 (6.6) Treatment-by-time-by-time (quadratic): F=1.0, p=0.32  Effect size D: 0.054 CBCL Depression 6 weeks, mean (SD) IG: 9.8 (4.9) CG: 9.7 (4.7)  12 weeks, mean (SD) IG: 8.6 (5.0) CG: 8.6 (4.8)  26 weeks, mean (SD) IG: 6.8 (4.1) CG: 8.3 (4.7)  52 weeks, mean (SD) IG: 6.7 (4.9) CG: 8.3 (3.9) Treatment-by-time (linear): F=1.45, p=0.23  Effect size D: 0.093 CBCL Internalizing 6 weeks, mean (SD) IG: 18.5 (10.0) CG: 18.6 (8.7)  12 weeks, mean (SD) IG: 16.2 (9.6) CG: 16.0 (9.5)	depressed" CES-D scores (CES-D ≥16) Completers analysis (n=103; IG: 53 and CG: 50)  52 weeks, N (%) still moderately depressed IG: 13 (25) CG: 22 (44) χ-squared: 4.3; p=0.04 Recovery from "seriously depressed" CES-D scores (CES-D ≥24)  Completers analysis (n=103; IG: 53 and CG: 50)  52 weeks, N (%) still seriously depressed (CES-D ≥24) Group values NR, but in contrast to analyses with lower cutoff score of 16, these analyses found no significant advantage for IG arm		ITT (n=152; IG1: 77 and CG: 75) 6 weeks, mean (SD) IG: 47.9 (7.7) CG: 46.5 (8.3)  12 weeks, mean (SD) IG: 48.7 (7.2) CG: 48.2 (7.0)  26 weeks, mean (SD) IG: 48.2 (7.5) CG: 49.9 (6.2)  52 weeks, mean (SD) IG: 49.0 (5.8) CG: 48.1 (8.5) Treatment-by-time (linear): F=0.04, p=0.84 Effect size D: 0.110 Satisfaction with care  ITT (n=152; IG1: 77 and CG: 75) 6 weeks, mean (SD) IG: 7.4 (2.5) CG: 7.0 (3.2)  12 weeks, mean (SD) IG: 6.8 (2.6) CG: 6.8 (2.9)  26 weeks, mean (SD) IG: 6.4 (2.7) CG: 6.9 (3.1)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 2005 <sup>84</sup> (continued)		<p>26 weeks, mean (SD) IG: 14.4 (8.8) CG: 15.5 (9.0)</p> <p>52 weeks, mean (SD) IG: 12.6 (9.1) CG: 15.0 (7.7) Treatment-by-time (linear): F=1.35, p=0.25</p> <p>Effect size D: 0.085 CBCL Externalizing 6 weeks, mean (SD) IG: 13.9 (9.8) CG: 13.6 (10.4)</p> <p>12 weeks, mean (SD) IG: 12.2 (8.9) CG: 14.2 (10.8)</p> <p>26 weeks, mean (SD) IG: 11.1 (8.8) CG: 14.5 (12.1)</p> <p>52 weeks, mean (SD) IG: 8.9 (6.8) CG: 10.6 (9.0) Treatment-by-time (linear): F=1.63, p=0.20</p> <p>Effect size D: 0.106 YSR Depression 6 weeks, mean (SD) IG: 11.4 (5.3) CG: 10.6 (4.4)</p>			<p>52 weeks, mean (SD) IG: 6.0 (2.6) CG: 6.7 (3.3) Treatment-by-time (linear): F=0.75, p=0.38 Effect size D: 0.032</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 2005 <sup>84</sup> (continued)		12 weeks, mean (SD) IG: 8.7 (5.0) CG: 8.7 (5.1)				
		26 weeks, mean (SD) IG: 8.1 (5.3) CG: 8.2 (4.6)				
		52 weeks, mean (SD) IG: 7.0 (5.3) CG: 8.4 (4.8) Treatment-by-time (linear): $F=2.51$ , $p=0.11$				
		Effect size $D: 0.142$ YSR Internalizing 6 weeks, mean (SD) IG: 19.0 (9.6) CG: 17.2 (8.2)				
		12 weeks, mean (SD) IG: 14.7 (9.2) CG: 15.1 (8.9)				
		26 weeks, mean (SD) IG: 13.5 (9.9) CG: 13.7 (9.0)				
		52 weeks, mean (SD) IG: 11.9 (9.8) CG: 12.9 (7.7) Treatment-by-time (linear): $F=1.02$ , $p=0.31$				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Clarke, 2005 <sup>84</sup> (continued)		Effect size D: 0.057 YSR Externalizing 6 weeks, mean (SD) IG: 14.3 (8.4) CG: 14.9 (8.6)  12 weeks, mean (SD) IG: 11.9 (7.3) CG: 14.0 (8.8)  26 weeks, mean (SD) IG: 11.2 (6.5) CG: 14.3 (9.0)  52 weeks, mean (SD) IG: 10.5 (5.7) CG: 12.9 (8.5) Treatment-by-time-by-time (quadratic): $F=3.34$ , $p=0.07$ Effect size D: 0.171				
Iftene, 2015 <sup>78</sup>	IG1: Sertraline IG2: Group Rational Emotive Behavior Therapy/CBT IG3: Sertraline plus Group Rational Emotive Behavior Therapy/CBT	CDI Posttreatment IG1:15.39 (8.76) IG2:15.92 (6.49) IG3: 16.80 (8.78)  No significant differences amount the three conditions, $F(2, 84)=0.177$ , $p>0.05$	Clinical response rate at posttreatment IG1:60.60% IG2:67.85% IG3:53.84% NS		NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Kim, 2012 <sup>85</sup>	IG: CBT plus bupropion CG: Bupropion	BDI 8 weeks IG: 15.5 (8.4) CG: 20.7 (8.5) t=2.54, p=0.01  12 weeks IG: 15.6 (7.5) CG: 20.4 (1.2) t=2.69, p<0.01  Mean BDI scores of IG were decreased compared to CG, F=5.64, p=0.02 at a trend level  4 week post-treatment followup period NS changes in BDI in IG (F=0.02, p=0.88) and CG (F=0.28, p=0.6)	NR	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Depression symptoms, ITT (n=439) Adjusted CDRS-R total score 6 weeks, adjusted mean (SD) IG1: 38.10 (7.78) IG2: 39.80 (7.37) IG3: 44.63 (8.30) CG: 44.90 (7.32)  12 weeks, adjusted mean (SD) IG1: 33.79 (8.24) IG2: 36.30 (8.18) IG3: 42.06 (9.18) CG: 41.77 (7.99)  Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement: IG1>CG (p=0.001); IG1=IG2 (p=0.13); IG1>IG3 (p=0.001); IG2>IG3 (p=0.001); IG2>CG (p=0.002); IG3=CG (p=0.97)	Response CGI-I positive response rate, ITT (n=439) 12 weeks, % response rate (95% CI) adjusted for clinical site IG1: 71.0 (62 to 80) IG2: 60.6 (51 to 70) IG3: 43.2 (34 to 52) CG: 34.8 (26 to 44) Regression analyses found treatment was statistically significant factor in CGI-I positive response (p=0.001)  RR (calculated): 2.45 95% CI, 0.31 to 19.7  12 weeks, statistically comparing response: IG1>CG (p=0.001); IG2>CG (p=0.001); IG3=CG (p=0.20); IG1=IG2 (p=0.11); IG1>IG3 (p=0.001); IG2>IG3 (p=0.01)	NR	No mortality from completed suicides	NR



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Across all 12 weeks: Time-by-treatment interaction based on CDRS-R random regression slope coefficients: <math>p=0.001</math>; Statistically comparing improvement: IG1&gt;CG (<math>p=0.001</math>); IG1&gt;IG2 (<math>p=0.02</math>); IG1&gt;IG3 (<math>p=0.001</math>); IG2&gt;IG3 (<math>p=0.01</math>); IG2=CG (<math>p=0.10</math>); IG3=CG (<math>p=0.40</math>)</p> <p>Hedge g effect sizes relative to placebo (G4) IG1: 0.98 IG2: 0.68 IG3: -0.03</p> <p>Hedge g effect sizes relative to placebo (CG) derived from ORs for dichotomized CGI-I IG1: 0.84 IG2: 0.58 IG3: 0.20 CG: NA</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		NNT (95% CI) IG1: 3 (2 to 4) IG2: 4 (3 to 8) IG3: 12 (5 to 23) CG: NA  RADS total score 6 weeks, adjusted mean (SD) IG1: 60.90 (11.59) IG2: 63.41 (12.44) IG3: 69.10 (13.59) CG: 69.43 (10.94)  12 weeks, adjusted mean (SD) IG1: 56.95 (12.24) IG2: 60.58 (13.07) IG3: 67.96 (14.18) CG: 66.68 (11.41)  Post-hoc supportive contrasts at 12 weeks, statistically comparing improvement: IG1>CG (p=0.001); IG1=IG2 (p=0.11); IG1>IG3 (p=0.001); IG2>IG3 (p=0.003); IG2>CG (p=0.003); IG3=CG (p=0.94)				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Across all 12 weeks: Time-by-treatment interaction based on RADS random regression slope coefficients: <math>p=0.001</math>; Statistically comparing improvement: IG1&gt;CG (<math>p=0.001</math>); IG1&gt;IG2 (<math>p=0.002</math>); IG1&gt;IG3 (<math>p=0.001</math>); IG2&gt;IG3 (<math>p=0.03</math>); IG2=CG (<math>p=0.34</math>); IG3=CG (<math>p=0.21</math>)</p> <p>NOTE: Means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	<p>Moderation analysis of C-GAS (functional status) by family income, least squares mean (SD) ITT, n=439 at 12 weeks</p> <p>Patients with &lt;\$75,000 (low-to-middle income) IG1: 32.7 (8.7) IG2: 35.3 (8.7) IG3: 43.0 (8.8) CG: 41.4 (9.0)</p> <p>Within the &lt;\$75,000 group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>IG1: 0.98 (p&lt;0.05) IG2: 0.69 (p&lt;0.05) IG3: -0.18 (p=NS)</p> <p>Patients with ≥\$75,000 (high income) IG1: 33.7 (9.6) IG2: 38.0 (9.1) IG3: 35.1 (9.0) CG: 41.7 (9.2)</p> <p>Within the ≥\$75,000 group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1=IG3: p=NS IG1&gt;CG: p&lt;0.05 IG2=IG3: p=NS IG2=CG: p=NS IG3&gt;CG: p&lt;0.05</p> <p>Effect size for active treatments vs. CG</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						IG1: 0.85 (p<0.05) IG2: 0.40 IG3: 0.72 (p<0.05)  Moderation analysis of C-GAS (functional status) by CGI-S, least squares mean (SD) ITT, n=439 at 12 weeks Patients with mild/moderate CGI-S IG1: 30.9 (7.3) IG2: 35.6 (7.1) IG3: 36.9 (6.9) CG: 38.4 (7.1)  Within the mild/moderate CGI-S group, statistical comparisons of how groups compared with one another at 12 weeks: IG1>IG2: p<0.001 IG1>IG3: p<0.001 IG1>CG: p<0.001 IG2=IG3: p=NS IG2>CG: p<0.001 IG3=CG: p=NS

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Effect size for active treatments vs. CG IG1: 1.04 (p&lt;0.05) IG2: 0.39 (p&lt;0.05) IG3: 0.21</p> <p>Patients with marked/severe CGI-S IG1: 35.4 (8.8) IG2: 36.8 (9.3) IG3: 44.0 (9.4) CG: 43.2 (9.6)</p> <p>Within the marked/severe CGI-S group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Effect size for active treatments vs. CG IG1: 0.84 (p&lt;0.05) IG2: 0.69 (p&lt;0.05) IG3: -0.08</p> <p>Moderation analysis of CNCEQ (depressive cognitive distortions) Low CNCEQ IG1: 33.2 (7.9) IG2: 35.5 (7.8) IG3: 39.4 (7.6) CG: 41.1 (7.5)</p> <p>Within the low CNCEQ group, statistical comparisons of how groups compared with one another at 12 weeks: IG1=IG2: p=NS IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p>



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS (continued)						<p>Effect size for active treatments vs. CG IG1: 1.03 (p&lt;0.05) IG2: 0.73 (p&lt;0.05) IG3: 0.22</p> <p>High CNCEQ IG1: 32.3 (9.8) IG2: 35.9 (10.1) IG3: 41.8 (10.0) CG: 40.6 (10.4)</p> <p>Within the high CNCEQ group, statistical comparisons of how groups compared with one another at 12 weeks: IG1&gt;IG2: p&lt;0.001 IG1&gt;IG3: p&lt;0.001 IG1&gt;CG: p&lt;0.001 IG2&gt;IG3: p&lt;0.001 IG2&gt;CG: p&lt;0.001 IG3=CG: p=NS</p> <p>Effect size for active treatments vs. CG IG1: 0.82 (p&lt;0.05) IG2: 0.46 (p&lt;0.05) IG3: -0.12</p>
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	<p>Loss of MDD diagnosis (K-SADS-P/L)</p> <p>Completers analysis only (n=379): 12 weeks, % IG1: 85.3 IG2: 78.6 IG3: 61.1 CG: 60.4 Overall treatment effect: <math>p \leq 0.0001</math></p> <p>Statistical comparisons found mixed findings in terms of how groups compared with one another, OR (95% CI): IG1=IG2: 1.7 (0.79 to 3.61) (<math>p=0.18</math>); IG1&gt;IG3: 4.3 (2.06 to 8.94) (<math>p=0.0001</math>); IG1&gt;CG: 4.1 (2.00 to 8.44) (<math>p=0.0001</math>); IG2&gt;IG3: 2.5 (1.31 to 4.93) (<math>p=0.006</math>); IG2&gt;CG: 2.4 (1.27 to 4.67) (<math>p=0.007</math>); IG3=CG: 1.0 (0.52 to 1.77) (<math>p=0.89</math>)</p>	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS (continued)			<p>Remission, adjusted for site (CDRS-R) ITT (n=439): 12 weeks, % IG1: 37 IG2: 23 IG3: 16 CG: 17 Overall treatment effect: p=0.0007</p> <p>Statistical comparisons found that IG1 was associated with higher remission rates than all other groups, OR (95% CI): IG1&gt;IG2: 2.1 (1.12 to 3.84) (p=0.02); IG1&gt;IG3: 3.3 (1.71 to 6.42) (p=0.0004); IG1&gt;CG: 3.0 (1.58 to 5.79) (p=0.0009)</p> <p>In contrast; IG2; IG3, and CG did not differ statistically from one another (all p&gt;0.05). See comparisons below, OR (95% CI): IG2=IG3: 1.6 (0.80 to 3.19) (p=0.19) IG2=CG: 1.5 (0.74 to 2.88) (p=0.28) IG3=CG: 0.9 (0.44 to 1.88) (p=0.80)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	First response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks Data values NR, but between-group comparisons reported (NR which were statistically significant) HR (95% CI): 3.0 (2.1 to 4.3) for IG1 vs. CG HR (95% CI): 2.2 (1.6 to 3.2) for IG2 vs. CG  First response (based on CBT clinician-assigned CGI-I=1 or 2), calculated N (%) Across 12 weeks Data values NR, but between-group comparisons reported (NR if statistically significant) HR (95% CI): 2.0 (1.4 to 2.7) for IG1 vs. IG3	NA	Time to first response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks (Phase I) IG1: ≥5 weeks IG2: ≥6 weeks CG: ≥11 weeks Between-group comparisons IG1 and IG2>CG: Significantly faster onset of benefit in both IG1 and IG2 (p<0.001) IG1=IG2: Trend toward faster improvement in IG1 (p=0.0585) HR (95% CI): 1.3 (1.0 to 1.8)  Time to first response in ≥50% patients (based on CBT clinician-assigned CGI-I=1 or 2), ITT (n=439) Across 12 weeks (Phase I) IG1: ≥6 weeks IG3: ≥8 weeks  Between-group comparisons IG1>IG3: Significantly faster onset of benefit in IG1 (p<0.001)  Time to stable response in ≥50% patients (based on pharmacotherapist-assigned CGI-I=1 or 2), ITT (n=439)	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article Kratochvil, 2006 <sup>68</sup> TADS (continued)			<p>Stable response (based on pharmacotherapist-assigned CGI-I=1 or 2), calculated N (%)</p> <p>6 weeks IG1: 37 (34.3) IG2: 25 (23.3) CG: 7 (6.6)</p> <p>12 weeks IG1: 75 (70.0) IG2: 68 (62.1) CG: 43 (38) HR (95% CI) for IG1 vs. CG: 3.1 (2.0 to 4.8) HR (95% CI) for IG2 vs. CG: 2.0 (1.3 to 3.1) HR (95% CI) for IG1 vs. IG2: 1.5 (1.0 to 2.1)</p> <p>Stable response (based on CBT clinician-assigned CGI-I=1 or 2), calculated N (%)</p> <p>6 weeks IG1: 48 (45) IG3: 25 (22.4)</p> <p>12 weeks IG1: 93 (87.1) IG3: 56 (50.8) HR (95% CI) for IG1 vs. IG3: 2.7 (1.9 to 3.9) (p&lt;0.05)</p>		<p>Across 12 weeks (Phase I) IG1: ≥9 weeks IG2: ≥11 weeks CG: NA (only 38% patients had reached stable response by 12 weeks)</p> <p>Between-group comparisons IG1&gt;CG: Significantly faster onset of benefit in IG1 (p&lt;0.001) IG2&gt;CG: Significantly faster onset of benefit in IG2 (p=0.001) IG1&gt;IG2: Significantly faster onset of benefit in IG1 (p=0.034)</p> <p>Time to stable response in ≥50% patients (based on CBT clinician-assigned CGI-I=1 or 2): Between-group comparisons IG1&gt;IG3: Significantly faster onset of benefit in IG1 (p&lt;0.001)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	Functional status (C-GAS) ITT (n=439): 6 weeks, unadjusted mean (SD) IG1: 62.4 (11.2) IG2: 59.9 (10.58) IG3: 56.7 (9.66) CG: 57.0 (9.22)  12 weeks, unadjusted mean (SD) IG1: 66.6 (11.91) IG2: 62.1 (11.91) IG3: 60.0 (11.47) CG: 59.3 (12.72) Time effect in all groups: p<0.0001 Treatment-by-time interaction: p<0.0001  RRM statistical comparisons of how groups compared with one another at 12 weeks : IG1>IG2: p=0.0450 IG1>IG3: p<0.0001 IG1>CG: p<0.0001 IG2>IG3: p=0.0032 IG2>CG: p=0.0381 IG3=CG: p=0.3805	Global burden of psychiatric problems (HoNOSCA) ITT (n=439): 12 weeks, unadjusted mean (SD) IG1: 9.5 (5.97) IG2: 10.9 (6.35) IG3: 11.7 (6.09) CG: 11.2 (6.15) Time effect in all groups: p<0.0001 Treatment-by-time interaction: p<0.0234  RRM statistical comparisons of how groups compared with one another IG1=IG2: p=0.1257 IG1>IG3: p=0.0027 IG1>CG: p=0.0393 IG2=IG3: p=0.1310 IG2=CG: p=0.5861 IG3=CG: p=0.3344  12 weeks, mean change from baseline (SD) G1: -6.3 (5.69) G2: -5.1 (5.74) G3: -3.6 (5.58) G4: -4.2 (5.71) Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): p<0.01:	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				<p>12 weeks, mean change from baseline (SD)  IG1: 16.7 (12.31)  IG2: 12.6 (12.31)  IG3: 9.7 (12.12)  CG: 9.9 (12.38)  Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): <math>p&lt;0.0001</math></p> <p>GLM statistical comparisons of how groups compared with one another :</p> <p>IG1&gt;IG2: <math>p&lt;0.01</math>  IG1&gt;IG3: <math>p&lt;0.0001</math>  IG1&gt;CG: <math>p&lt;0.0001</math>  IG2&gt;IG3: <math>p=NR</math>  IG2=CG: <math>p=NS</math>  IG3=CG: <math>p=NS</math></p> <p>Rate of nonimpaired patients (C-GAS &gt;70) 12 weeks, %  IG1: 34.6  IG2: 20.2  IG3: 13.5  CG: 18.7</p>	<p>GLM statistical comparisons of how groups compared with one another at 12 weeks :</p> <p>IG1=IG2: <math>p=NS</math>  IG1&gt;IG3: <math>p&lt;0.001</math>  IG1&gt;CG: <math>p&lt;0.01</math>  IG2&gt;IG3: <math>p&lt;0.05</math>  IG2=CG: <math>p=NS</math>  IG3=CG: <math>p=NR</math></p> <p>HoNOSCA subscores: Treatment-by-time interaction was statistically significant only for item 10 (level of functioning with peers; <math>p=0.0004</math>), whose effect remained significant even after applying a Bonferroni correction for multiple comparisons.</p> <p>QoL (PQ-LES-Q)  ITT (n=439):  12 weeks, unadjusted mean (SD)  IG1: 54.7 (11.21)  IG2: 51.2 (10.43)  IG3: 47.4 (10.84)  CG: 48.2 (9.91)  Time effect in all groups: <math>p&lt;0.0001</math>  Treatment-by-time interaction: <math>p&lt;0.0001</math></p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS (continued)				<p>Between-group difference: <math>p=0.002</math> Statistically significant treatment effects of how groups compared with one another: IG1&gt;IG2: <math>p&lt;0.020</math> IG1&gt;IG3: <math>p&lt;0.0004</math> IG1&gt;CG: <math>p&lt;0.009</math> IG2=IG3: <math>p=NS</math> IG2=CG: <math>p=NS</math> IG3=CG: <math>p=NS</math></p> <p>Patients not likely to be clinically referred in community (C-GAS &gt;60)</p> <p>12 weeks, % IG1: 64.5 IG2: 50.5 IG3: 45.0 CG: 35.7 Between-group difference: <math>p=0.0003</math></p> <p>Statistically significant treatment effects of how groups compared with one another: IG1&gt;IG2: <math>p&lt;0.038</math> IG1&gt;IG3: <math>p&lt;0.004</math> IG1&gt;CG: <math>p&lt;0.0001</math> IG2=IG3: <math>p=NS</math> IG2&gt;CG: <math>p=0.023</math> IG3=CG: <math>p=NS</math></p>	<p>RRM statistical comparisons of how groups compared with one another at 12 weeks: IG1&gt;IG2: <math>p=0.0004</math> IG1&gt;IG3: <math>p&lt;0.0001</math> IG1&gt;CG: <math>p&lt;0.0001</math> IG2=IG3: <math>p=0.2766</math> IG2=CG: <math>p=0.7215</math> IG3=CG: <math>p=0.4630</math></p> <p>12 weeks, mean change from baseline (SD) IG1: 9.6 (10.14) IG2: 6.6 (10.23) IG3: 4.2 (10.01) CG: 5.2 (10.16) Statistically significant treatment effects based on mean change from baseline (adjusting for baseline score as covariate): <math>p&lt;0.001</math></p> <p>Treatment-by-time interaction: <math>p&lt;0.0001</math> GLM statistical comparisons of how groups compared with one another: IG1&gt;IG2: <math>p&lt;0.05</math> IG1&gt;IG3: <math>p&lt;0.0001</math> IG1&gt;CG: <math>p&lt;0.001</math> IG2&gt;IG3: <math>p=NS</math> IG2=CG: <math>p=NS</math> IG3=CG: <math>p=NS</math></p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA	Subgroup Analysis #1: ADHD vs. no ADHD Depression symptoms, ITT (n=429) 12 weeks Main linear RRM effect analyses for overall sample Main effect of time (linear): p<0.001 Treatment-by-time interaction: p=0.018 ADHD-by-treatment-by-time interaction: p=0.026 (confirmed that ADHD status prior to treatment or having an ADHD diagnosis before study entry moderated improvement in depression)  Linear RRM effect analyses: ADHD subgroup

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Main effect of time (linear): <math>p &lt; 0.001</math> Treatment-by-time interaction: <math>p = 0.038</math></p> <p>Linear RRM effect analyses: No ADHD subgroup Main effect of time (linear): <math>p \leq 0.001</math> Treatment-by-time interaction: <math>p &lt; 0.001</math></p> <p>CDRS-R total score (adjusted for fixed and random effects) 12 weeks, mean (SD) ADHD subgroup IG1 (n=15): 37.08 (9.42) IG2 (n=14): 33.29 (6.42) IG3 (n=14): 35.95 (6.34) CG (n=19): 43.31 (5.65)</p> <p>No ADHD subgroup IG1 (n=92): 33.30 (8.14) IG2 (n=95): 36.83 (8.11)</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>IG3 (n=97): 42.35 (8.96) CG (n=93): 41.39 (8.07) Improvement was observed in all arms of both ADHD and no-ADHD subgroups, but patients had different patterns of between-group differences depending on their subgroup.</p> <p>Between-group differences: ADHD subgroup at 12 weeks 12 weeks IG1=IG2=IG3&gt;CG (p=0.046, 0.024, 0.013, respectively)</p> <p>Change trajectories did not differ between arms (p&gt;0.05).</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Effect sizes IG1 vs. CG: 1.0 IG2 vs. CG: 0.6 IG3 vs. CG: -0.1</p> <p>Between-group differences: No-ADHD subgroup at 12 weeks IG1&gt;(IG2&gt;IG3)=CG (p-values &lt;0.05 for significant differences and &gt;0.05 for nonsignificant differences)</p> <p>Change trajectories: IG1&gt;IG2; IG3, and CG (p&lt;0.009), meaning trajectory in IG1 was faster on average than in all other arms. IG2=CG (p=0.425) and IG3=CG (p=0.065), but IG2&gt;IG3 (p=0.008). In short; IG3 had the most gradual improvement trajectory among active treatments.</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						Effect sizes IG1 vs. CG: 0.8 IG2 vs. CG: 1.7 IG3 vs. CG: 1.2  Depression symptoms, ITT (n=327) 36 weeks: Main linear RRM effect analyses for overall sample Main effect of time (linear): $p < 0.001$ ADHD-by-treatment-by-time interaction: $p = 0.004$ ADHD-by-treatment-by-time interaction (squared): $p = 0.004$ (confirmed that ADHD status prior to treatment or having an ADHD diagnosis before study entry moderated improvement in depression at this timepoint)

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Between-group differences: ADHD subgroup at 36 weeks Paired contrasts found no between-group differences in mean total CDRS-R scores within this subgroup.</p> <p>Change trajectories: No significant treatment-by-time (squared) or treatment-by-time interactions</p> <p>Between-group differences: No-ADHD subgroup at 36 weeks Paired contrasts found no between-group differences in mean total CDRS-R scores within this subgroup.</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS (continued)						<p>Change trajectories: Treatment-by-time (squared) interaction: <math>p &lt; 0.001</math> (suggesting significant different by arm)  <math>IG1 &gt; IG2</math> and <math>IG3</math> (<math>p &lt; 0.05</math>), meaning trajectory in <math>IG1</math> was faster on average than other <math>IG</math> arms.</p> <p>Subgroup Analysis #2: ADHD psychostimulant medication vs. none among patients with ADHD  Depression symptoms, ITT (<math>n=62</math> with ADHD)  CDRS-R total score (adjusted for fixed and random effects)  12 weeks:  Data values NR, but CDRS-R scores did not differ significantly among the 20/63 patients</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratovichil, 2009 <sup>8</sup> TADS (continued)						taking a psychostimulant vs. the 43/63 patients who did not (p=0.056). Treatment-by-psychostimulant use interaction was not significant (p>0.05).
March, 2004 <sup>3</sup> Index article  TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Depressive symptoms, ITT (n=427) CDRS-R Overall (across all trauma subgroups) Significant main effect of time: p<0.001 Significant treatment-by-time effect: p<0.05	NA	NA	NA	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Melvin, 2006 <sup>79</sup>	G1: CBT G2: Sertraline G3: Combined	<p>Response to treatment (OR, 95% CI) G1 vs. G3: 0.19, CI, 0.03 to 1.16 G2 vs. G3: 1.31, CI, 0.31 to 5.48 G2 vs. G1: 6.86, CI, 1.12 to 41.48</p> <p>Regression model results: no significant difference in the odds of depression between treatments (OR, 6.46; CI, 0.89 to 46.77)</p> <p>Change in the proportion depressed over time (posttreatment to followup assessment) was not significant (OR, 95% CI) G1 vs. G3: 0.02; CI, 0 to 3.45 G2 vs. G3: 2.66; CI, 0.07 to 108.11 G2 vs. G1: 84.94; CI, 0.83 to 8,718.04</p> <p>RADS at posttreatment (3 months), mean (SD) G1: 66.00 (15.93) G2: 72.92 (16.84) G3: 71.64 (18.28)</p>	<p>Proportion in full remission from MDD by posttreatment assessment (i.e. at 3 months) G1: 14% G2: NR G3: 7%</p> <p>Proportion in full remission from MDD by followup assessment (i.e. at 9 months) G1: NR G2: NR G3: 60% (Author commented on highest only) For G1 v. G3: OR 2.7 (95% CI, 0.60 to 12.14) For G2 v. G3: OR 3.0 (95% CI, 0.68 to 13.31)</p>	Significant difference detected in the longitudinal regression among all three study groups in the Pre/YFU and PreYPost interactions for both the GAF and the GARF assessments but PostYFU interaction was not significant.	Proportion of adolescents remitted from dysthymic disorder or DD NOS over time is similar for each treatment group. The odds of depression at posttreatment assessment did not differ between treatment groups (G1 v. G3: OR, 0.71; 95% CI, 0.10 to 5.12; G2 v. G3: OR, 1.14; 95% CI, 0.17 to 7.60; G2 v. G1: OR, 1.6; 95% CI, 0.23 to 11.27). The odds of depression for those with dysthymic disorder or DD NOS decreased significantly between postacute treatment and followup assessment (OR, 8.52; CI, 2.58 to 28.15) in contrast with the odds for those with MDD.	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Wilkinson, 2008 <sup>86</sup>	IG:SSRI and psychosocial treatment as usual plus CBT CG: SSRI plus psychosocial treatment as usual	MFQ Intent to Treat Endpoint IG: 16.2 (14.3) CG: 19.3 (23.8) F (df 1, 20)=0.1, p=0.07	NR	NR	NR	NR

ADHD = attention-deficit/hyperactivity disorder; BDI = Beck Depression Inventory; CBCL = child behavior checklist; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CES-D = Center for Epidemiologic Studies Depression Scale; CG = control group; C-GAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impressions Scale-Improvement Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; CI = confidence interval; CNCEQ = children's negative cognitive error questionnaire; DDNOS = depressive disorder not otherwise specified; GLM = generalized linear modeling; HAM-D = Hamilton Depression Rating Scale; HoNOSCA = Health of Nation Outcome Scale – Children and Adolescents; HR = hazard ratio; IG = intervention group; ITT = intent to treat; K-SADS-P/L = Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version; KQ = Key Question; MCS = mental component score of the Short Form 12 health survey; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; N/A = not applicable; n/N = number; NA = not applicable; NNT = number needed to treat; NR = not reported; NS = not significant; OR = odds ratio; PCS = Preschool Checklist Scale; PQ-LES-Q = Parent-Child Interaction Therapy Emotion Development; RADS = Reactive Airways Dysfunction Syndrome; RR = relative risk; RRM = random-effects regression model; SAS-R = Social Adjustment Scale for Children-Reporting; SD = standard deviation; SF-12 = short form-12 items health survey; SSRI = selective serotonin reuptake inhibitors; TADS = Treatment among Adolescents with Depression; TAU = treatment as usual; YFU = year followup; YSR = Youth Self Report.

**Table E-33. KQ 5a: Benefits of omega-3 versus other therapies**

<b>First Author's Last Name; Year; Trial Name</b>	<b>Treatment Interventions and Comparators</b>	<b>Depressive Symptoms</b>	<b>Remission/ Recovery</b>	<b>Functional Impairment</b>	<b>Other Outcomes (Mortality, Relapse)</b>	<b>Subgroup(s) Examined</b>
Fristad, 2009 <sup>27</sup>	IG1: PEP (Family therapy)+omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	CDSR-R score at endpoint IG1: 26 (10) IG2: 30 (9) IG3: 31 (9) CG: 31 (11)	Remitted IG1: 76.5% IG2: 61.1% IG3: 43.8% CG: 55.6%	NR	NR	History of maternal depression significantly moderated the effects of PEP+PBO versus PBO (p = 0.02) but not the placebo-controlled effects of combined or Ω3 alone.

CG = control group; CDSR-R =; IG = intervention group; KQ = Key Question; NR = not reported; PBO = placebo; PEP =psychoeducational psychotherapy.

**Table E-34. KQ 5a: Benefits of SSRIs versus SNRIs**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Atkinson 2014 <sup>38</sup>	IG1: duloxetine IG2: fluoxetine CG: placebo	CDRS-R at 10 weeks (Mixed Effects Model with ITT sample IG1: 113; IG2L 113; CG: 103) IG1: 35.0 IG2: 35.6 CG: 35.0  Mean change at 10 weeks IG1: -24.3 IG2: -23.7 CG: -24.3  Mean change at LOCF IG1: -21.9 IG2: -22.0 CG: -22.7  CDRS-R at 36 weeks (Mixed Effects Model; CG transitioned to duloxetine or fluoxetine) IG1: 26.0 IG2: 25.7 CG: 25.1  CGI-S at 10 weeks (Mixed Effects Model with ITT sample; IG1: 113; IG2: 113; CG: 103) IG1: 2.7 IG2: 2.7 CG: 2.6	Probability of treatment response at 10 weeks IG1: 67% IG2: 63% CG: 62% No significant differences  Probability of remission at 10 weeks IG1: 41% IG2: 33% CG: 41% No significant differences  Probability of treatment response at 36 weeks IG1: 72% IG2: 83% CG: NR (CG patients transitioned to duloxetine or fluoxetine) No significant differences  Probability of remission at 36 weeks No significant differences	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Atkinson 2014 <sup>38</sup> (continued)		CGI-S at 36 weeks (Mixed Effects Model; CG patients transitioned to IG1 or IG2) IG1: 1.9 IG2: 1.8 CG: 1.6				
Emslie 2014 <sup>46</sup>	IG1: duloxetine 60 mg QD IG2: duloxetine 30 mg QD IG3: fluoxetine 20 mg QD CG: placebo	CDRS-R at 10 weeks (Mixed Effects Model; IG1: 105; IG2: 114; IG3: 112; CG: 117) IG1: 35.0 IG2: 34.4 IG3: 36.4 CG: 37.4  Mean change at 10 weeks IG1: -23.9 IG2: -24.6 IG3: -22.6 CG: -21.6  Mean change at LOCF IG1: -22.4 IG2: -22.0 IG3: -21.1 CG: -19.4  CDRS-R at 36 weeks (Mixed Effects Model; CG transitioned to duloxetine or fluoxetine) IG1: 24.3 IG2: 25.1 IG3: 25.0 CG: 25.8	Probability of treatment response at 10 weeks IG1: 69% IG2: 69% IG3: 61% CG: 60% No significant differences  Probability of remission at 10 weeks IG1: 40% IG2: 46% IG3: 32% CG: 14% IG2 was statistically higher (p<0.05) than placebo Remission rates at the last two nonmissing acute treatment visits was significantly (p<0.05) greater for duloxetine 60 mg (26%) than for placebo (14%).  Probability of treatment remission at 36 weeks IG1: 81% IG2: NR IG3: 74% CG: NR (CG patients transitioned to duloxetine) No significant differences between groups	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie 2014 <sup>46</sup> (continued)		CGI-S at 10 weeks (Mixed Effects Model with ITT sample IG1: NR; IG2: NR; CG: NR) IG1: 3.1 IG2: 3.1 IG3: 3.1 CG: NR Note: Mean CGI-S scores at the 10-week time point (MMRM) did not statistically differ among treatment groups (3.1 for all treatment groups).				
		CGI-S at 36 weeks (Mixed Effects Model; CG patients transitioned to IG1 or IG2) IG1: 1.8 IG2: 2.0 IG3: 1.8 CG: 1.9 (transitioned to duloxetine)				

ADHD = attention-deficit/hyperactivity disorder; BDI = Beck Depression Inventory; CBCL = child behavior checklist; CBT = cognitive behavioral therapy; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; CES-D = Center for Epidemiologic Studies Depression Scale; CG = control group; C-GAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; CI = confidence interval; CNCEQ = children's negative cognitive error questionnaire; DD = depressive disorder; DDNOS = depressive disorder not otherwise specified; GLM = generalized linear modeling; HAM-D = Hamilton Depression Rating Scale; HoNOSCA = Health of Nation Outcome Scale – Children and Adolescents; IG = intervention group; ITT = intent to treat; K-SADS-P/L = Kiddie Schedule for Affective Disorders and Schizophrenia; KQ = Key Question; LOCF = last observation carried forward; MCS = mental component score of the Short Form 12 health survey; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; n/N = number; NA = not applicable; NNT = number needed to treat; NR = not reported; NS = not significant; OR = odds ratio; PQ-LES-Q = Parent-Child Interaction Therapy Emotion Development; QD = every day; QoL = quality of life; RADS = Reactive Airways Dysfunction Syndrome; RR = relative risk; RRM = random-effects regression model; SAS-SR = Social Adjustment Scale for Children-Self-Report; SD = standard deviation; SF-12 = short form-12 items health survey; SSRI = selective serotonin reuptake inhibitors; TADS = Treatment among Adolescents with Depression; TAU = treatment as usual; YFU = year followup.

**Table E-35. KQ 5a: Benefits of SSRIs versus TCAs**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup>	IG1: paroxetine IG2: imipramine CG: placebo	HAM-D Change - Week 8 OC: IG1=67; IG2=56; CG=66 Least Squares Mean (95% CI), SEM IG1: -12.2 (-13.1 to -10.5), 0.88 IG2: -10.6 (-12.5 to -8.7), 0.97 CG: -10.5 (-12.3 to -8.8), 0.88 ANCOVA=0.26  LOCF: IG1=90; IG2=94; CG=87 Least Squares Mean (95% CI), SEM IG1: -10.7 (-12.3 to -9.1), 0.81 IG2: -9.0 (-10.5 to -7.4), 0.81 CG: -9.1 (-10.7 to -7.5), 0.83 ANCOVA=0.20  MI: IG1=90; IG2=94; CG=87 Least Squares Mean (95% CI), SEM IG1: -12.5 (-14.2 to -10.9), 0.83 IG2: -11.1 (-12.9 to -9.4), 0.89 CG: -10.7 (-12.4 to -9.1), 0.83 ANCOVA=0.24	NR	CGI - Week 8 OC (IG1=67; IG2=56; CG=66) Least Squares Mean (95% CI), SEM IG1: 1.9 (1.6 to 2.2) 0.15 IG2: 2.2 (1.8 to 2.5) 0.17 CG: 2.4 (2.1 to 2.7) 0.16 p=0.09  LOCF (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: 2.4 (2.1 to 2.7) 0.16 IG2: 2.7 (2.4 to 3.0) 0.15 CG: 2.7 (2.4 to 3.0) 0.16 p=0.16  MI (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: 1.9 (1.6 to 2.2) 0.14 IG2: 2.2 (1.9 to 2.5) 0.15 CG: 2.4 (2.1 to 2.6) 0.14 p=0.24  AFC - Week 8 OC (IG1=58; IG2=52; CG=60) Least Squares Mean (95% CI), SEM IG1: 14.4 (8.8 to 19.9) 2.83	SPP - Week 8 OC (IG1=60; IG2=55; CG=60) Least Squares Mean (95% CI), SEM IG1: 12.9 (8.3 to 17.5) 2.31 IG2: 13.2 (8.4 to 18.1) 2.46 CG: 12.7 (6.9 to 15.9) 2.30 p=0.88  LOCF (IG1=61; IG2=60; CG=63) Least Squares Mean (95% CI), SEM IG1: 13.2 (8.6 to 17.8) 2.33 IG2: 13.1 (8.3 to 17.8) 2.41 CG: 11.4 (6.9 to 15.9) 2.27 p=0.88  MI (IG1=61; IG2=60; CG=65) Least Squares Mean (95% CI), SEM IG1: 15.4 (10.7 to 20.0) 2.35 IG2: 14 (8.9 to 19.2) 2.60 CG: 14.7 (10.0 to 19.4) 2.39 p=0.92  SIP - Week 8 OC (IG1=62; IG2=55; CG=62) Least Squares Mean (95% CI), SEM IG1: -11.2 (-14.3 to -8.1) 1.57	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)		HAM-D Response - Week 8 OC (IG1=67; IG2=56; CG=66) % (Criteria Met) IG1: 80.6% (54/13) IG2: 73.2% (41/15) CG: 65.2% (43/23) $\chi^2=0.13$  LOCF (IG1=90; IG2=94; CG=87) n (%) IG1: 66.7% (60/30) IG2: 58.5% (55/39) CG: 55.2% (48/39) $\chi^2=0.27$  MI (IG1=90; IG2=94; CG=87) n (%) IG1: 73.3% (66/24) IG2: 70.2% (66/28) CG: 70.1% (61/26) $\chi^2=0.24$  K-SADS-L - Week 8 OC (IG1=67; IG2=56; CG=66) Least Squares Mean (95% CI), SEM IG1: -12.1 (-13.8 to -10.3) 0.91 IG2: -10.7 (-12.7 to -8.7) 0.82 CG: -10.7 (-12.5 to -8.9) 0.92 p=0.46		IG2: 13.3 (7.3 to 19.4) 3.04 CG: 9.3 (3.8 to 14.8) 2.81 p=0.32  LOCF (IG1=60; IG2=57; CG=62) Least Squares Mean (95% CI), SEM IG1: 14.7 (9.2 to 20.2) 2.80 IG2: 11.6 (5.8 to 17.3) 2.92 CG: 9.3 (8.1 to 17.2) 2.76 p=0.39  MI (IG1=60; IG2=57; CG=62) Least Squares Mean (95% CI), SEM IG1: 14.0 (8.7 to 19.3) 2.65 IG2: 14.5 (9.4 to 19.6) 2.60 CG: 9.1 (4.2 to 14.1) 2.52 p=0.24	IG2: -13.5 (-16.9 to -10.2) CG: -10.6 (-13.7 to -7.5) p=0.24  LOCF (IG1=63; IG2=60; CG=65) Least Squares Mean (95% CI), SEM IG1: -11.4 (-14.4 to -8.3) 1.55 IG2: -13.0 (-16.2 to -9.8) 1.62 CG: -9.9 (-12.9 to -6.9) 1.51 p=0.23  MI (IG1=63; IG2=60; CG=65) Least Squares Mean (95% CI), SEM IG1: -11.5 (-14.2 to -8.7) 1.39 IG2: -13.9 (-16.8 to -10.9) 1.50 CG: -10.1 (-13.0 to -7.1) p=0.19	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)		<p>LOCF (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: -11.4 (-13.1 to -9.8) 0.84 IG2: -9.5 (-11.1 to -7.9) 0.82 CG: -9.4 (-11.0 to -7.8) 0.83 p=0.13</p> <p>MI (IG1=90; IG2=94; CG=87) Least Squares Mean (95% CI), SEM IG1: -12.3 (-13.9 to -10.6) 0.84 IG2: -11.5 (-13.3 to -9.7) 0.91 CG: -10.9 (-12.6 to -9.2) 0.86 p=0.45</p>				

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup>	IG1: Paroxetine IG2: Imipramine CG: Placebo	Completed Responders defined as HAM-D <8 (+ potential responders) ITT: IG1=93; IG2=95; CG=87 IG1: 15 (+3) IG2: 12 (+1) CG: 12 (+9)	Response at some time point (defined as remission in Table 3) ITT: IG1=93; IG2=95; CG=87 IG1: 61 IG2: 57 CG: 47	NR	Acute phase relapse ITT: IG1=93; IG2=95; CG=87 IG1: 6 IG2: 5 CG: 3  Continuation phase relapse ITT: IG1=93; IG2=95; CG=87 IG1: 19 IG2: 10 CG: 7  Total Relapses ITT: IG1=93; IG2=95; CG=87 IG1: 25 (41%) IG2: 15 (26%) CG: 10 (21%)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Weihs, 2018 <sup>55</sup>	IG1: Desvenlafaxine (25, 35, or 50 mg/d) IG2: Fluoxetine (20 mg/d) CG: Placebo	Change in CDRS-R from baseline to week 8 (ITT): Adjusted mean change (SE) in total score IG1: -22.6 (1.17) IG2: -24.8 (1.17) CG: -23.1 (1.18) Adjusted mean difference as compared to placebo (95% CI) IG1: -0.47 (-3.23 to 2.30), p<0.05 IG2: 1.71 (-1.06 to 4.48), p<0.01	CGI-I score: % very much improved, minimally improved, no change IG1: 23.2%, 45.5, 21.2, 9.1, CMH test p=0.852 IG2: 30.7%, 47.5, 16.8, 4.0, CMH test p=0.095 CG: 27.3%, 35.4, 32.3, 4.0 CGI-I response at week 8 (ITT): IG1: 68.7%, IG2: 78.2% CG: 62.6% Adjusted OR (95% CI) vs. CG IG1: 0.751 (0.249 to 0.871), p=0.343 Adjusted mean difference as compared to placebo (95% CI) IG2: 0.465 (0.249 to 0.871), p=0.017 IG1: -0.01 (-0.29 to 0.27), p=0.944 IG2: 0.18 (-0.11 to 0.46), p=0.224	NR	NR	

AFC = adult family child; ANCOVA = analysis of covariance; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI = Clinical Global Impressions Scale; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; ITT = intent to treat; K-SADS-L = Kiddie Schedule for Affective Disorders and Schizophrenia-Lifetime; KQ = Key Question; LOCF = last observation carried forward; MI = multiple imputation; NR = not reported; OC = observed cases; SEM = structural equation modeling; SPP = Self Perception Profile.

**Table E-36. KQ 5a: Benefits of pharmacotherapy dose comparisons**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Atkinson, 2018 <sup>59</sup>	IG1: Low-dose Desvenlafaxine IG2: High-dose Desvenlafaxine CG: Placebo	CDRS-R, Week 8 Change from baseline, mean (SD) IG1: -23.7 (1.1) IG2: -24.4 (1.1) CG: -22.9 (1.1)  Adjusted mean difference vs. placebo (95% CI) IG1: 0.85 (-2.23, 3.94) IG2: 1.52 (-1.56, 4.61) p=NS  CGI-S, Week 8 Adjusted mean change (SE) IG1: -1.51 (0.11) IG2: -1.65 (0.11) CG: -1.49 (0.11)  Difference in adjusted means, placebo active (95% CI) IG1: 0.015 (-0.29 to 0.32) p=0.923 IG2: 0.161 (-0.14 to 0.47) p=0.302	CGI-I response, Week 8 Responders, (%) IG1: 59/105 (56.2) IG2: 66/106 (62.3) CG: 57/102 (55.9) Adjusted OR (Wald 95% CI) IG1: 0.97 (0.56, 1.69) p=0.925 IG2: 0.76 (0.44, 1.33) p=0.342  CGI-I, Week 8 1: Very much improved (%) IG1: 20 (19.0) IG2: 27 (25.5) CG: 22 (21.6)  2: Much improved (%) IG1: 39 (37.1) IG2: 39 (36.8) CG: 35 (34.3)  3: Minimally improved (%) IG1: 26 (24.8) IG2: 23 (21.7) CG: 29 (28.4)  4: No change (%) IG1: 19 (18.1) IG2: 16 (15.1) CG: 16 (15.7)	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup>	IG1: Vilazodone 15 mg/d IG2: Vilazodone 30 mg/d CG: Placebo	CDRS-R Week 8 score, mean (SD) IG1: 33.8 (12.0) IG2: 32.5 (11.5) CG: 34.0 (12.9)  Least squares change from baseline in total score, mean (SD): IG1: -22.9 (0.9) IG2: - 24.2 (0.9) CG: - 22.5 (0.9)  LS mean difference (LSMD) vs. Placebo (95% CI) IG1: -0.5 (-3.0 to 2.0) IG2: - 1.7 (-4.2 to 0.7)  Adjusted p-value IG1: 0.7162 IG2: 0.3267  P-value IG1: 0.7162 IG2: 0.1634  CGI-S total score Week 8 score, mean (SD) IG1: 2.7 (1.2) IG2: 2.7 (1.1) CG: 2.9 (1.2)	CDRS-R response Responders, n (%) IG1: 83 (56.1) IG2: 103 (63.2) CG: 80 (55.9) OR (95% CI) IG1: 1.0 (0.5 to 2.1) IG2: 1.6 (0.8 to 3.2)  P-value IG1: 0.9907 IG2: 0.2115  CDRS-R remission Remitters, n (%) IG1: 62 (41.9) IG2: 72 (44.2) CG: 63 (44.1) OR (95% CI) IG1: 1.0 (0.5 to 2.0) IG2: 1.1 (0.5 to 2.2)  P-value IG1: 0.9477 IG2: 0.8232 CGI-I response, score of 1 or 2  Responders, n (%) IG1: 98 (56.3) IG2: 112 (62.2) CG: 92 (54.1)  OR (95% CI) IG1: 1.1 (0.7 to 1.7) IG2: 1.4 (0.9 to 2.1)	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup> (continued)		LS change from baseline, mean (SD): IG1: -1.8 (0.1) IG2: -1.9 (0.1) CG: -1.6 (0.1)  LS mean difference (LSMD) vs. Placebo (95% CI) IG1: -0.2 (-0.5 to 0.0) IG2: -0.3 (-0.5 to 0.0)  Adjusted p-value IG1: 0.7162 IG2: 0.3267  P-value IG1: 0.0852 IG2: 0.0323  CGI-I total score Week 8 score, mean (SD) IG1: 2.2 (1.2) IG2: 2.2 (1.0) CG: 2.4 (1.1)  Least squares change from baseline in total score, mean (SD): IG1: 2.3 (0.1) IG2: 2.2 (0.1) CG: 2.4 (0.1)	P-value IG1: 0.6811 IG2: 0.1248  CGI-I response, score of 1 Responders, n (%) IG1: 52 (29.9) IG2: 52 (28.9) CG: 34 (20.0)  OR (95% CI) IG1: 1.7 (1.0 to 2.8) IG2: 1.6 (1.0 to 2.7)  P-value IG1: 0.0353 IG2: 0.0547			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup> (continued)		LS mean difference (LSMD) vs. Placebo (95% CI) IG1: -0.1 (-0.4 to 0.1) IG2: -0.2 (-0.5 to 0.0)  P-value IG1: 0.3072 IG2: 0.0563				
Emslie 2014 <sup>46</sup>	IG1: duloxetine 60 mg QD IG2: duloxetine 30 mg QD IG3: fluoxetine 20 mg QD CG: placebo	CDRS-R at 10 weeks (Mixed Effects Model; IG1: 105; IG2: 114; IG3: 112; CG: 117) IG1: 35.0 IG2: 34.4 IG3: 36.4 CG: 37.4  Mean change at 10 weeks IG1: -23.9 IG2: -24.6 IG3: -22.6 CG: -21.6  Mean change at LOCF IG1: -22.4 IG2: -22.0 IG3: -21.1 CG: -19.4  CDRS-R at 36 weeks (Mixed Effects Model; CG transitioned to duloxetine or fluoxetine) IG1: 24.3 IG2: 25.1 IG3: 25.0 CG: 25.8	Probability of treatment response at 10 weeks IG1: 69% IG2: 69% IG3: 61% CG: 60% No significant differences  Probability of remission at 10 weeks IG1: 40% IG2: 46% IG3: 32% CG: 14% IG2 was statistically higher (p<0.05) than placebo Remission rates at the last two nonmissing acute treatment visits was significantly (p<0.05) greater for duloxetine 60 mg (26%) than for placebo (14%).	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie 2014 <sup>46</sup> (continued)		CGI-S at 10 weeks (Mixed Effects Model with ITT sample IG1: 108; IG2: 116; CG: 122) IG1: 3.1 IG2: 3.1 IG3: 3.1 CG: NR Note: Mean CGI-S scores at the 10-week time point (MMRM) did not statistically differ among treatment groups (3.1 for all treatment groups).	Probability of treatment remission at 36 weeks IG1: 81% IG2: NR IG3: 74% CG: NR (CG patients transitioned to duloxetine) No significant differences between groups			
		CGI-S at 36 weeks (Mixed Effects Model; CG patients transitioned to IG1 or IG2) IG1: 1.8 IG2: 2.0 IG3: 1.8 CG: 1.9 (transitioned to duloxetine)				

CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-I = Clinical Global Impressions Scale-Improvement Scale; CI = confidence interval; IG = intervention group; KQ = Key Question; LOCF = last observation carried forward; LS = life skills/tutoring condition; LSMD = least squares mean difference; NR = not reported; OR = odds ratio; SD = standard deviation; SE = standard error.



**Table E-37. KQ 5a: Benefits of treatment-resistant depression interventions**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Brent, 2008 <sup>88</sup> Index article TORDIA	IG1: Switch to a second, different SSRI (citalopram, or fluoxetine, 20-40 mg) IG2: Switch to a different SSRI plus CBT IG3: Switch to venlafaxine (150-225 mg) IG4: Switch to venlafaxine plus CBT	CDRS-R total score, Mean (SD) [95% CI] Week 6 IG1+IG2: 42.3 (14.0) [40.1 to 44.6] IG3+IG4: 42.6 (13.2) [40.4 to 44.8] IG1+IG3: 41.6 (13.4) [39.5-43.7] IG2+IG4: 43.4 (13.9) [41.1 to 45.7]  Week 12 IG1+IG2: 37.9 (13.7) [35.7 to 40.1] IG3+IG4: 37.0 (13.1) [34.9 to 39.2] IG1+IG3: 38.1 (12.9) [36.0 to 40.1] IG2+IG4: 36.9 (13.9) [34.6 to 39.2]  BDI total score, Mean (SD) [95% CI] Week 6 IG1+IG2: 13.2 (11.4) [11.4 to 15.1] IG3+IG4: 13.2 (12.2) [11.3 to 15.3] IG1+IG3: 12.3 (10.8) [10.6 to 14.1] IG2+IG4: 14.2 (12.7) [12.1 to 16.2]	Adequate clinical response (CGI-I score $\leq 2$ and CDRS-R decline $\geq 50\%$ ), N (%) ITT (N=334) IG1+IG2: 79 (47.0) IG3+IG4: 80 (48.2) IG1+IG3: 68 (40.5) IG2+IG4: 91 (54.8) ITT by medication: $X^2=.05$ ; $p=0.83$ ITT by CBT: $X^2=6.89$ ; $p=0.009$  Completers (N=231) IG1+IG2: 64 (54.7) IG3+IG4: 65 (57.0) IG1+IG3: 60 (49.6) IG2+IG4: 69 (62.7)  Completers by medication: $X^2=.13$ ; $p=0.72$ Completers by CBT: $X^2=4.04$ ; $p=0.05$	CGAS total score, Mean (SD) [95% CI] Week 6 IG1+IG2: 58.9 (11.5) [57.1 to 60.8] IG3+IG4: 59.7 (9.7) [58.1 to 61.3] IG1+IG3: 59.3 (10.7) [57.6 to 61.0] IG2+IG4: 59.4 (10.7) [57.6 to 61.1]  Week 12 IG1+IG2: 63.3 (11.9) [61.3 to 65.2] IG3+IG4: 64.8 (11.1) [62.9 to 66.6] IG1+IG3: 63.0 (11.2) [61.2 to 64.8] IG2+IG4: 65.1 (11.8) [63.1 to 67.0]	NR	No relationship between outcome and the use of anxiolytics, stimulants, adjunctive supportive therapy, or the presence of comorbid attention-deficit/ hyperactivity disorder for those on venlafaxine vs. those on SSRIs.  Anxiolytics N (RR) (95% CI) G1+IG2: 7 (28.6) (6-65) IG3+IG4: 5 (80.0) (37-98)  No anxiolytics IG1+IG2: 159 (49.1) (41-57) IG3+IG4: 163 (46.0) (38-54)  Stimulants IG1+IG2: 23 (52.2) (32-73) IG3+IG4: 20 (40.0) (19-62)

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Brent, 2008 <sup>88</sup> Index article TORDIA (continued)		Week 12 IG1+IG2: 11.5 (10.9) [9.7 to 13.3] IG3+IG4: 9.9 (10.5) [8.2 to 11.6] IG1+IG3: 10.5 (9.8) [8.9 to 12.1] IG2+IG4: 11.0 (11.5) [9.0 to 12.9]  CGI-S total score, Mean (SD) [95% CI] Week 6 IG1+IG2: 3.5 (1.0) [3.3 to 3.6] IG3+IG4: 3.4 (1.1) [3.3 to 3.6] IG1+IG3: 3.4 (1.0) [3.3 to 3.6] IG2+IG4: 3.5 (1.0) [3.3 to 3.6]  Week 12 IG1+IG2: 2.9 (1.2) [2.7 to 3.1] IG3+IG4: 2.8 (1.2) [2.6 to 3.0] IG1+IG3: 3.0 (1.1) [2.8 to 3.2] IG2+IG4: 2.7 (1.2) [2.5 to 2.9]				No stimulants IG1+IG2: 143 (47.6) (39-56) IG3+IG4: 148 (48.0) (40-56)  Supportive therapy IG1+IG2: 14 (64.3) (38-85) IG3+IG4: 13 (38.5) (16-65)  No supportive therapy IG1+IG2: 152 (46.7) (39-55) IG3+IG4: 155 (47.7) (40-56)  ADHD IG1+IG2: 26 (61.5) (42-78) IG3+IG4: 26 (42.3) (25-61)  No ADHD IG1+IG2: 140 (45.7) (38-54) IG3+IG4: 139 (46.8) (39-55)
Brent, 2008 <sup>88</sup> Index article Companion article: Asarnow, 2009 <sup>89</sup> TORDIA	See Brent, 2008 <sup>88</sup> Index article TORDIA	NR	NR	NR	NR	NR

<b>First Author's Last Name; Year; Trial Name</b>	<b>Treatment Interventions and Comparators</b>	<b>Depressive Symptoms</b>	<b>Remission/ Recovery</b>	<b>Functional Impairment</b>	<b>Other Outcomes (Mortality, Relapse)</b>	<b>Subgroup(s) Examined</b>
Brent, 2008 <sup>88</sup> Index article Companion article: Brent, 2009 <sup>90</sup> TORDIA	See Brent, 2008 <sup>88</sup> Index article TORDIA	See Brent, 2008 <sup>88</sup> Index article TORDIA	See Brent, 2008 <sup>88</sup> Index article TORDIA	See Brent, 2008 <sup>88</sup> Index article TORDIA	See Brent, 2008 <sup>88</sup> Index article TORDIA	See Brent, 2008 <sup>88</sup> Index article TORDIA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup>	IG: Dose-titration of fluoxetine dose from 20 mg/day to 40-60 mg/day CG: Continued treatment with fluoxetine at fixed dose of 20 mg/day	Depressive symptom severity, modified ITT CDRS-R total score, mean (SD) (IG=14; CG=15) 19 weeks IG: 37.4 (13.2) CG: 41.2 (15.5)  Change from baseline to 19 weeks, mean (SD) IG: -9.4 (10.6) CG: -1.5 (13.7) Effect size: Cohen's d=0.65 No significantly between-group change, but trend in favor of IG arm: p=0.099  CDRS-R: any improvement, n (%) (IG=14; CG=15) 19 weeks IG: 13 (93) CG: 7 (50) Between-group difference NR  CGI-S, mean (SD) (IG=14; CG=15) 19 weeks IG: 3.4 (1.0) CG: 3.4 (1.1)	Response, modified ITT CDRS-R, n (%) (IG=14; CG=15) 19 weeks IG: 10 (71) CG: 5 (36) No between-group difference: p=0.128  CGI-S improvements of 1-to-2 points, n (calculated %) (IG=14; CG=15) 19 weeks IG: 6 (42.9) CG: 4 (26.7) Between-group difference NR	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Depressive Symptoms	Remission/ Recovery	Functional Impairment	Other Outcomes (Mortality, Relapse)	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)		Change from baseline to 19 weeks, mean (SD) IG: -0.6 (1.1) CG: -0.2 (1.1) No between-group change: p=0.401				
		CGI-I, mean (SD) (IG=14; CG=15) 19 weeks IG: 2.79 (0.97) CG: 3.29 (1.49) No between-group change: p=0.303				

ADHD = attention-deficit/hyperactivity disorder; BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impression Scale-Severity Scale; IG = intervention group; KQ = Key Question; N = number; NA = not applicable; NR = not reported; RR = relative risk; SD = standard deviation; SSRI = selective serotonin reuptake inhibitors; TORDIA = Treatment of SSRI-Resistant Depression in Adolescents trial.

## Appendix F. Harms Tables

Table F-1. KQ 1a: Harms of CBT versus pill placebo .....	F-3
Table F-2. KQ 1a: Harms of CBT+TAU versus TAU/UC .....	F-25
Table F-3. KQ 1a: Harms of CBT versus active control .....	F-27
Table F-4. KQ 1a: Harms of relapse prevention CBT+continued antidepressant medication management versus continued medication management.....	F-29
Table F-5. KQ 1a: Harms of IPT versus active control (clinical monitoring).....	F-31
Table F-6. KQ 1a: Harms of attachment-based family therapy versus wait-list control .....	F-32
Table F-7. KQ 1a: Harms of family therapy versus active control.....	F-33
Table F-8. KQ 1a: Harms of PCIT versus active control .....	F-34
Table F-9. KQ 1a: Harms of short-term psychoanalytic therapy versus active control .....	F-35
Table F-10. KQ 2a: Harms of SSRIs versus placebo.....	F-36
Table F-11. KQ 2a: Harms of fluoxetine for relapse prevention versus placebo .....	F-85
Table F-12. KQ 2a: Harms of SNRIs versus placebo .....	F-94
Table F-13. KQ 2a: Harms of TCAs versus placebo .....	F-101
Table F-14. KQ 2a: Harms of MAOIs versus placebo .....	F-120
Table F-15. KQ 2a: Harms of venlafaxine plus active control versus placebo plus active control.....	F-124
Table F-16. KQ 3a: Harms of fluoxetine plus CBT versus placebo .....	F-125
Table F-17. KQ 5a: Harms of CBT versus other psychotherapy.....	F-138
Table F-18. KQ 5a: Harms of psychotherapy versus pharmacotherapy .....	F-140
Table F-19. KQ 5a: Harms of psychotherapy plus pharmacotherapy versus psychotherapy .....	F-163
Table F-20. KQ 5a: Harms of psychotherapy plus pharmacotherapy versus pharmacotherapy .....	F-186
Table F-21. KQ 5a: Harms of SSRIs versus SNRIs .....	F-210
Table F-22. KQ 5a: Harms of SSRIs versus TCAs .....	F-214
Table F-23. KQ 5a: Harms of pharmacotherapy dose comparisons .....	F-224

Table F-24. KQ 5a: Harms of treatment-resistant depression interventions .....	F-233
--	-------

**Table F-1. KQ 1a: Harms of CBT versus pill placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, ITT (n=439) 6 weeks, adjusted mean (SD) IG1: 14.31 (12.58) IG2: 16.20 (12.42) IG3: 13.18 (11.34) CG: 16.85 (11.70)  12 weeks, adjusted mean (SD) IG1: 11.79 (11.69) IG2: 14.44 (11.13) IG3: 11.40 (10.44) CG: 15.01 (11.05)  None of the post-hoc supportive contrasts at 12 weeks comparing improvement following active treatments vs. placebo were statistically significant  Across all 12 weeks: Time-by-treatment interaction based on SIQ-Jr random regression slope coefficients: p=0.01; Statistically comparing improvement : IG1>CG (p=0.02); IG1>IG2 (p=0.002); IG1>IG3 (p=0.05); IG2=IG3 (p=0.22); IG2=CG (p=0.36); IG3=CG (p=0.76)	Early termination at 12 weeks Patient-initiated withdrawal, N (calculated %) IG1: 7 (6.54) IG2: 5 (4.59) IG3: 16 (14.41) CG: 10 (8.93) Between-group difference: p=0.18  Patient Removal due to out-of-protocol treatment in place of or in addition to study treatment, N (calculated %) IG1: 8 (7.48) IG2: 13 (11.93) IG3: 8 (7.21) CG: 13 (11.61) Between-group difference: p=0.50	Serious AEs, N (%) IG1: 9 (8.41) IG2: 13 (11.93) IG3: 5 (4.50) CG: 6 (5.36)  Serious AEs, OR (95% CI) vs. CG: IG1: 1.62 (0.56 to 4.72) IG2: 2.39 (0.87 to 6.54) IG3: 0.83 (0.25 to 2.81) CG: NA Between-groups p=0.15 NOTE: ORs ≤2 reflect little or no increased risk  Serious Psychiatric-Related AEs, ITT (n=439) N patients [N events], (calculated %) IG1: 0 IG2: 1 [1] (0.92) (worsening depression, also captured below) IG3: 0 CG: 1 [1] (0.89) (mania, also captured below)  Any Psychiatric-Related AEs, ITT (n=439) N patients [N events], (%) IG1: 12 [16] (15) IG2: 20 [23] (21) IG3: 1 [1] (1) CG: 9 [11] (9.8)	NR



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Hedge g effect sizes relative to placebo (CG) IG1: 0.28 IG2: 0.05 IG3: 0.33</p> <p>NOTE: Above means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model</p> <p>Suicide-Related AEs, N (%) IG1: 6 (5.61) IG2: 9 (8.26) IG3: 5 (4.50) CG: 4 (3.57) Suicide-Related AEs, OR (95% CI) vs. CG: IG1: 1.60 (0.44 to 5.85) IG2: 2.43 (0.73 to 8.14) IG3: 1.27 (0.33 to 4.87) CG: NA</p>		<p>These events more frequent in fluoxetine arms (IG1 and IG2) than CBT (IG3) or placebo (CG), but p=NR</p> <p>Mania, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)</p> <p>Hypomania, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p> <p>Elevated mood, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Hypersensitivity, ITT (n=439) N events (%) IG1: 0 IG2: 2 (1.83) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		Suicide attempts, N (calculated %) IG1: 4 (3.74%) IG2: 2 (1.83%) IG3: 1 (0.90%) CG: 0 N of events too small to allow statistical comparison of suicide events		Irritability, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 1 (0.92) IG3: 0 CG: 0  Anger, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0  Worsening of depression, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)  Crying, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0  Agitation, ITT (n=439) N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Akathisia, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0</p> <p>Nervousness, ITT (n=439) N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Restlessness, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)</p> <p>Hyperactivity, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Panic attacks, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 1 (0.91) CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Anxiety, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Somnolence, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Insomnia, ITT (n=439) N events (%) IG1: 5 (4.67) IG2: 3 (2.75) IG3: 0 CG: 1 (0.89)</p> <p>Nightmares, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0</p> <p>Night sweats, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Sedation, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 3 (2.75) IG3: 0 CG: 0</p> <p>Fatigue, ITT (n=439) N events (%) IG1: 2 (1.87) IG2: 1 (0.92) IG3: 0 CG: 2 (1.79)</p> <p>Tremors, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 2 (1.83) IG3: 0 CG: 0</p> <p>Abnormal behavior N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Feeling abnormal N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0 p=NR</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Nonpsychiatric AEs, ITT (n=439) Generally more frequent in fluoxetine-treated arms (IG1 and IG2) than CBT (IG3) or placebo (CG)</p> <p>Headache, ITT (n=439) N patients (%) IG1: N (5.6) IG2: N (12) IG3: 0 CG: N (9) This was the only AE occurring in ≥10% of patients in any single treatment group</p> <p>Sedation IG1: 0 IG2: 3 (2.75) IG3: 0 CG: 0</p> <p>Upper abdominal pain IG1: 0 IG2: 6 (5.5) IG3: 0 CG: 2 (1.79)</p> <p>Diarrhea IG1: 2 (1.87) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				Influenza IG1: 0 IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)  Insomnia IG1: 5 (4.67) IG2: 3 (2.75) IG3: 0 CG: 1 (0.89)  Sinusitis IG1: 0 IG2: 4 (3.67) IG3: 0 CG: 2 (1.79)  Vomiting IG1: 4 (3.74) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, observed case analysis (n=359) 12 weeks, adjusted mean (SD) IG1: 10.9 (0.3) IG2: 13.7 (0.2) IG3: 11.3 (0.3) CG: 14.5 (0.6) No between-group differences: p=NS  Comparison of change in SIQ-Jr total score from baseline to 12 weeks, observed case analysis (n=359) IG1>IG2: p=0.004 IG1>IG3: p=0.04 IG1>CG: p=0.02  Emergence or worsening of suicidal ideation (change from baseline SIQ-Jr <31 to SIQ-Jr ≥31 at 6 or 12 weeks), observed case analysis (n=374)	NA	Self-reported physical symptom severity (PSC), observed case analysis (n=364) 12 weeks, mean (SD) IG1: 11.0 (8.2) IG2: 13.0 (10.5) IG3: 18.5 (17.5) CG: 12.3 (8.9)  Statistical comparisons of medication-based arms (IG1; IG2, and CG) with IG3 found that IG3 patients reported significantly higher/worse PSC scores: IG1<IG3: p=0.0036 IG2<IG3: p=0.0328 CG<IG3: p=0.0280 No between-group differences between IG1; IG2, and CG arms (all p's=NS)	NA



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>12 weeks, n (%)</p> <p>IG1: 2/93 (2.2)</p> <p>IG2: 7/96 (7.3)</p> <p>IG3: 2/93 (2.2)</p> <p>CG: 7/92 (7.6)</p> <p>No between-group differences: p=NS</p> <p>Worsening of suicidality from baseline to 6 or 12 weeks (CDRS-R item 13 worsening by <math>\geq 1</math> point), observed case analysis (n=374)</p> <p>Calculated n (%)</p> <p>IG1: 2/93 (5.0)</p> <p>IG2: 7/96 (13.4)</p> <p>IG3: 2/93 (15.2)</p> <p>CG: 7/92 (7.2)</p> <p>No between-group differences: p=NS</p> <p>Emergence of suicidality from baseline to 6 or 12 weeks (change from CDRS-R item score=1 or 2 to <math>\geq 5</math>), observed case analysis (n=374)</p> <p>Calculated n (%)</p> <p>IG1: 0/93 (0)</p> <p>IG2: 4/96 (3.7)</p> <p>IG3: 1/93 (1.3)</p> <p>CG: 2/92 (2.6)</p> <p>No between-group differences: p=NS</p>		<p>Factor-based PSC scores (sleep, upper respiratory, pain, cardiac, panic, elimination, nausea, and skin), observed case analysis (N=364)</p> <p>12 weeks</p> <p>All treatment arms showed improvement on each of the 8 PSC factors. Pain was the only factor with a significant treatment-by-time interaction (p=NR), based on significantly more improvement compared with IG3 IG1&gt;IG3: p=0.0011 IG2&gt;IG3: p=0.0017</p> <p>Treatment-emergent physical AEs (spontaneous), ITT (n=439)</p> <p>12 weeks, N patients [N events], (calculated % patients)</p> <p>IG1: 37 [61] (34.6)</p> <p>IG2: 35 [81] (32.1)</p> <p>IG3: NR [9] (NR)</p> <p>CG: 34 [60] (30.4)</p> <p>No between-group differences in arms receiving pills (IG1; IG2, and CG), but more events reported in IG2 than IG1 or CG (p=NR).</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Suicide-Related AEs (primary analysis: C-CASA Codes 1, 2, and 6), ITT (n=439) 12 weeks, N (%) IG1: 5 (4.7) IG2: 10 (9.2) IG3: 5 (4.5) CG: 3 (2.7) Statistical comparisons of groups, OR (95% CI) IG1=IG3: p=NS IG1=CG: p=NS IG2&gt;CG: 3.7 (1.00 to 13.7), p=0.0402, meaning higher incidence in IG2</p> <p>Suicide-Related AEs (sensitivity analysis: C-CASA Codes 1, 2, 3, and 6), ITT (n=439) 12 weeks, N (%) IG1: 6 (5.6) IG2: 10 (9.2) IG3: 5 (4.5) CG: 3 (2.7) Between-group differences NR</p> <p>Suicide attempts (C-CASA Code 1), ITT (n=439) 12 weeks, N (%) IG1: 2 (1.9) IG2: 1 (1.8) IG3: 1 (0.9) CG: 0</p>		<p>Spontaneously reported physical AEs reported in ≥2% of active treatment arms and at rates at least twice that of CG, ITT (n=429) 12 weeks Sedation IG1: 1 (0.9) IG2: 3 (2.8) IG3: 0 CG: 0 IG2 vs. CG ratio: 3.00</p> <p>Insomnia IG1: 5 (4.7) IG2: 3 (2.8) IG3: 0 CG: 1 (0.9) IG1 vs. CG ratio: 5.23 IG2 vs. CG ratio: 3.08</p> <p>Vomiting IG1: 4 (3.7) IG2: 2 (1.8) IG3: 1 (0.9) CG: 1 (0.9) IG1 vs. CG ratio: 4.19</p> <p>Upper abdominal pain IG1: 1 (0.9) IG2: 6 (5.5) IG3: 0 CG: 2 (1.8) IG2 vs. CG ratio: 3.08</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Preparatory actions toward imminent suicidal behavior (C-CASA Code 2), ITT (n=439) No events at 12 weeks Self-injurious behavior: unknown intent (C-CASA Code 3), ITT (n=439) 12 weeks, N (%) IG1: 1 (0.9) IG2: 0 IG3: 0 CG: 0</p> <p>Suicidal ideation (C-CASA Code 6), ITT (n=439) 12 weeks, N (%) IG1: 3 (2.8) IG2: 8 (7.3) IG3: 4 (3.6) CG: 3 (2.7)</p> <p>Timing of suicide-related events, ITT (n=439) 12 weeks, mean days (SD) IG1: 52.0 (20.8) IG2: 38.0 (21.7) IG3: 45.4 (26.7) CG: 32.0 (15.0) No between-group differences: p=NS</p>		<p>Headache: only spontaneously reported physical AE occurring in &gt;5% of patients, ITT (N=429) 12 weeks, calculated n (%) IG1: 7 (6.8) IG2: 13 (11.9) IG3: NA CG: 12 (10.7) No between-group differences (p=NS)</p> <p>Emergence or worsening of physical symptoms (change from baseline PSC severity of 0 [not at all] or 1 [just a little] to 2 [pretty much] or 3 [very much] at 6 or 12 weeks), observed case analysis (N=374) 12 weeks, n (%) (NOTE: patients with multiple reports of same event were counted only once) Sleep disturbance: Trouble sleeping IG1: 12 (3.3) IG2: 14 (15.2) IG3: 11 (12.5) CG: 14 (15.1)</p> <p>Sleep disturbance: Feeling drowsy or too sleepy IG1: 17 (18.9) IG2: 15 (16.3) IG3: 12 (13.5) CG: 16 (17.2)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Sleep disturbance: Sleeplessness IG1: 12 (13.3) IG2: 17 (18.5) IG3: 16 (18.2) CG: 9 (9.7)</p> <p>Sleep disturbance: Nightmares or very strange dreams IG1: 11 (12.2) IG2: 17 (18.5) IG3: 7 (8.0) CG: 13 (14.0)</p> <p>Sleep disturbance: Restless or uncomfortable urge to move IG1: 2 (2.2) IG2: 9 (9.8) IG3: 5 (5.7) CG: 10 (10.8)</p> <p>Upper respiratory: Head cold or sniffles IG1: 15 (16.7) IG2: 16 (17.4) IG3: 13 (14.6) CG: 16 (17.2)</p> <p>Upper respiratory: Allergies IG1: 10 (11.1) IG2: 13 (14.1) IG3: 13 (14.6) CG: 8 (8.6)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Upper respiratory: Sore throat IG1: 8 (8.9) IG2: 6 (6.5) IG3: 9 (10.1) CG: 14 (15.1)  Upper respiratory: Dry mouth IG1: 9 (10.0) IG2: 8 (8.7) IG3: 8 (9.0) CG: 7 (7.5)  Upper respiratory: Coughing or wheezing IG1: 6 (6.7) IG2: 5 (5.4) IG3: 6 (6.8) CG: 8 (8.6)  Upper respiratory: Fever IG1: 6 (6.7) IG2: 4 (4.4) IG3: 6 (6.7) CG: 4 (4.3)  Pain: Stomach pain or ache IG1: 6 (6.7) IG2: 10 (10.9) IG3: 9 (10.1) CG: 13 (14.0)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Pain: Muscle aches or cramps IG1: 9 (10.0) IG2: 5 (5.4) IG3: 12 (13.6) CG: 12 (12.9)  Pain: Joint pain IG1: 3 (3.3) IG2: 2 (2.2) IG3: 8 (8.9) CG: 9 (9.7)  Pain: Numbness or tingling in arms or legs IG1: 3 (3.3) IG2: 3 (3.3) IG3: 5 (5.7) CG: 5 (5.4)  Cardiac: Chest pain IG1: 4 (4.4) IG2: 5 (5.4) IG3: 4 (4.6) CG: 6 (6.5)  Cardiac: Racing or pounding heart IG1: 2 (2.2) IG2: 2 (2.2) IG3: 5 (5.7) CG: 6 (6.5)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Cardiac: Heart skips beats IG1: 1 (1.1) IG2: 2 (2.2) IG3: 3 (3.4) CG: 1 (1.1)  Panic: Excessive sweating IG1: 3 (3.3) IG2: 6 (6.5) IG3: 2 (2.3) CG: 9 (9.7)  Panic: Difficulty breathing IG1: 4 (4.4) IG2: 3 (3.3) IG3: 2 (2.3) CG: 6 (6.5)  Panic: Can't hear well IG1: 3 (3.3) IG2: 2 (2.2) IG3: 4 (4.6) CG: 2 (2.2)  Elimination: Frequent urination IG1: 6 (6.7) IG2: 4 (4.4) IG3: 11 (12.5) CG: 6 (6.5)  Elimination: Feeling bloated or gassy IG1: 2 (2.2) IG2: 6 (6.5) IG3: 6 (6.8) CG: 7 (7.5)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Elimination: Pain with urination IG1: 2 (2.2) IG2: 1 (1.1) IG3: 3 (3.4) CG: 0</p> <p>Elimination: Constipation IG1: 1 (1.1) IG2: 0) IG3: 4 (4.6) CG: 3 (3.2)</p> <p>Diarrhea IG1: 4 (4.4) IG2: 5 (5.4) IG3: 6 (6.7) CG: 7 (7.5)</p> <p>Nausea or vomiting IG1: 8 (8.9) IG2: 3 (3.3) IG3: 10 (11.2) CG: 5 (5.4)</p> <p>Skin: Skin rash IG1: 6 (6.7) IG2: 4 (4.4) IG3: 9 (10.1) CG: 4 (4.3)</p> <p>Skin: Hives IG1: 0 IG2: 2 (2.2) IG3: 1 (1.1) CG: 2 (2.2)</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Other: Headache IG1: 12 (13.3) IG2: 18 (19.6) IG3: 14 (15.7) CG: 16 (17.2)</p> <p>Treatment with FLX (i.e.; IG1 or IG2) did not lead to significantly higher rates of symptom worsening or emergence on any physical symptoms (p=NR).</p> <p>Furthermore, the double-blind treatment arms (IG2 and CG) did not differ significantly on symptom worsening or emergence on any physical symptoms (p=NR).</p> <p>Worsening of Psychiatric Symptoms (CGI-I <math>\geq</math>5-7 [slightly worse, much worse, or very much worse] at 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 3 (2.8) IG3: 10 (9.0) CG: 7 (6.3) Between-group differences: IG1 and IG2 (FLX arms) had significantly lower rates of</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>worsening than IG3 and CG (non-FLX arms) (p=0.01). Ns of individual arms too small to allow statistical comparison.</p> <p>Worsening of Psychiatric Symptoms (CGI-S <math>\geq</math>1 point from baseline to 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 2 (1.8) IG3: 5 (4.5) CG: 9 (8.0) Between-group differences NR</p> <p>Treatment-emergent psychiatric AEs (spontaneously reported), ITT (N=429) 12 weeks, n (%) (NOTE: Patients may be represented in more than one arm due to patient-initiated crossover)</p> <p>Any treatment-emergent psychiatric AE IG1: 6 (5.6) IG2: 12 (11.0) IG3: 1 (0.91) CG: 5 (4.5) Between-group comparisons:</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>IG1 and IG2 (FLX arms) experienced more psychiatric AEs than IG3 or CG (non-FLX arms). IG2 experienced more psychiatric AEs than CG, but Ns too small to detect statistical significance.</p> <p>Mania spectrum (mania, hypomania, elevated mood)            IG1: 1 (0.93)            IG2: 4 (3.67)            IG3: 0            CG: 1 (0.89)</p> <p>Irritability spectrum (hypersensitivity, irritability, anger, worsening depression, crying)            IG1: 2 (1.86)            IG2: 4 (3.67)            IG3: 0            CG: 1 (0.89)</p> <p>Agitation spectrum (agitation, akathisia, nervousness, restlessness, hyperactivity)            IG1: 1 (0.93)            IG2: 2 (1.84)            IG3: 2 (1.78)            CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Anxiety (anxiety, panic attacks) IG1: 0 IG2: 2 (1.84) IG3: 1 (0.91) CG: 0</p> <p>Other (tremor, "abnormal behavior," "feeling spacy") IG1: 2 (1.84) IG2: 2 (1.84) IG3: 0 CG: 1 (0.89)</p> <p>ADS Mania subscale severity scores (clinician-reported), ITT (N=429) 12 weeks, mean (SD) IG1: 0.5 (0.8) IG2: 1.1 (1.0) IG3: 1.0 (1.2) CG: 1.1 (0.1)</p> <p>Between-group comparisons: IG1&lt;IG2: p=0.013 IG1&lt;CG: p=0.003 IG1&lt;IG3: p=0.012 IG2=IG3: p=NR</p> <p>ADS Mania change from baseline of ≥3 points, modified ITT (n=424 with ≥2 mania total scores)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				12 weeks, n (%) IG1: 21 (20) IG2: 15 (14.2) IG3: 13 (12.3) CG: 16 (15.0)  Between-group differences NR Incidence of mania or hypomania: ADS Mania scale, ITT (N=429) 12 weeks, n (calculated %) IG1: 3 (2.8) IG2: 1 (0.9) IG3: 0 CG: 1 (0.9)	

ADS = Anxiety And Depression Scale; AE = adverse event; CBT = cognitive behavioral therapy; C-CASA = Columbia Classification Algorithm of Suicide Assessment; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-I = Clinical Global Impressions Scale-Improvement Scale; CI = confidence interval; FLX = fluoxetine; IG = intervention group; ITT = intent to treat; KQ = Key Question; N = number; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; PSC = physical symptom severity; SD = standard deviation; SIQ-JR = Suicide Ideation Questionnaire-Junior High School; TADS = Treatment among Adolescents with Depression.

**Table F-2. KQ 1a: Harms of CBT+TAU versus TAU/UC**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Clarke, 2002 <sup>11</sup>	IG: Group CBT (Adolescent Coping With Depression Course)+Usual care CG: Usual care	K-SADS suicide items total score ITT (n=88; IG: 41 and CG: 47) 8 weeks, mean (SD) IG: 0.6 (1.2) CG: 0.4 (1.1)  12 months, mean (SD) IG: 0.1 (0.6) CG: 0.2 (0.6)  24 months, mean (SD) IG: 0.3 (0.9) CG: 0.3 (1.0)  Treatment-by-time (main effect): F=0.10, p=0.75	Overall withdrawal ITT (n=88; IG: 41 and CG: 47) No followup interviews completed: 2 Missed 8-week interview: 2 Missed 12-month interview: 6 Missed 24-month interview: 13 Arm-specific attrition at all timepoints: NR  Sensitivity analysis of all primary outcomes limited to patients completing all four assessments found same pattern of outcomes.	NA	No significant moderation of IG arm's K-SADS suicide symptom total score by intensity/degree of CBT participation (N of intervention sessions): F=0.46; p=0.50

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Clarke 2016 <sup>94</sup>	IG: TAU+CBT CG: self-selected AU	ITT (n=212; IG=106; CG=106) KSAD suicidal behavior (week 12) IG: 2 (2.3%) CG: 10 (1.9%) [ percent reported in table may be a typo, should be closer to 10%] KSAD suicidal behavior (week 104) IG: 1 (1.1%) CG: 1 (1.1%)	Non-Completers (Calculated) Week 6 IG: 7 (7%) CG: 7 (7%)  Week 12 IG: 15 (14%) CG: 11 (10%)  Week 26 IG: 23 (22%) CG: 16 (15%)  Week 52 IG: 19 (18%) CG: 19 (18%)  Week 78 IG: 24 (23%) CG: 24 (23%)  Week 104 IG: 13 (12%) CG: 15 (14%)	NR	NA

CBT = cognitive behavioral therapy; CG = control group; IG = intervention group; ITT = intent to treat; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; KQ = Key Question; NA = not applicable; NR = not reported.

**Table F-3. KQ 1a: Harms of CBT versus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Brent, 1997 <sup>12</sup> Index article	IG1: Individual CBT IG2: SBFT CG: NST	<p>Suicidality &gt;4 (%)</p> <p>6 weeks</p> <p>IG1: 5.7</p> <p>IG2: 3.4</p> <p>CG: 13.3</p> <p>p=0.31</p> <p>12-16 weeks</p> <p>IG1: 8.6</p> <p>IG2: 6.5</p> <p>CG: 15.2</p> <p>p=0.48</p> <p>Significant decreases in suicidality across all groups: McNemar X<sup>2</sup>=21.78 df=1 p&lt;0.001</p>	<p>Protocol deviations after randomization Never came</p> <p>IG1: 1</p> <p>IG2: 3</p> <p>CG: 0</p> <p>Censored</p> <p>IG1: 2</p> <p>IG2: 3</p> <p>CG: 5</p> <p>Open</p> <p>IG1: 1</p> <p>IG2: 3</p> <p>CG: 3</p> <p>Dropped out</p> <p>IG1: 3</p> <p>IG2: 2</p> <p>CG: 3</p>	NR	NR



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	Adverse event scores; Mean (SD); Median (range) Baseline IG1 (n=154): 5.1 (1.0); 5 (2–6) IG2 (n=156): 5.0 (1.1); 5 (2–6) CG (n=155): 5.0 (1.1); 5 (1–6)  6 weeks IG1 (n=104): 4.6 (1.3); 5 (2–6) IG2 (n=107): 4.4 (1.5); 5 (0–6) CG (n=99): 4.4 (1.5); 5 (0–6)  12 weeks IG1 (n=106): 4.0 (1.5); 4 (0–6) IG2 (n=108): 4.2 (1.6); 4 (0–6) CG (n=112): 4.2 (1.6); 4 (0–6)  36 weeks IG1 (n=104): 3.6 (1.6); 4 (0–6) IG2 (n=109): 3.6 (1.7); 4 (0–6) CG (n=105): 4.1 (1.6); 4 (0–6)  52 weeks IG1 (n=111): 3.5 (1.9); 4 (0–6) IG2 (n=110): 3.2 (1.9); 3 (0–6) CG (n=105): 3.5 (1.8); 3.5 (0–6)  86 weeks IG1 (n=123): 3.4 (1.9); 4 (0–6) IG2 (n=114): 3.2 (1.8); 3 (0–6) CG (n=116): 3.3 (1.8); 3.5 (0–6)	NR	Recent nonsuicidal self-injury is defined as within 2 weeks - so the timeframe for recent suicide attempt is likely similar	
Goodyer 2017 <sup>16</sup> Companion: O'Keeffe, 2018 <sup>18</sup> O'Keeffe, 2019 <sup>19</sup>	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention		IG1: 32% IG2: 43% CG: 36% No evidence of difference in chi-square test ( $\chi^2(4, N=453)=9.07, p=0.059$ )		

CBT = cognitive behavioral therapy; CG = control group; IG = intervention group; KQ = Key Question; NR = not reported; NST = Nondirective supportive therapy; SBFT = Systemic behavior family therapy; SD = standard deviation.

**Table F-4. KQ 1a: Harms of relapse prevention CBT+continued antidepressant medication management versus continued medication management**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Kennard, 2014 <sup>21</sup> Index article;	IG: Relapse prevention CBT plus continued antidepressant medication management CG: Continued antidepressant medication management	<p>Suicidal ideation not leading to hospitalization, ITT (N=144) Across 12 to 30 weeks, n (calculated %) IG: 0 CG: 3 (4.3) NR if any between-group difference</p> <p>Suicidal ideation leading to hospitalization, ITT (N=144) Across 12 to 30 weeks, n (calculated %) IG: 5 (6.7) CG: 0 NR if any between-group difference</p> <p>Suicidal attempt leading to hospitalization, ITT (N=144) Across 12 to 30 weeks, n (calculated %) IG: 0 CG: 1 (1.4) NR if any between-group difference</p> <p>Suicidal behavior not leading to hospitalization, ITT (N=144) Across 12 to 30 weeks, n (calculated %) IG: 1 (1.3) CG: 0 NR if any between-group difference</p>	<p>Overall withdrawal, ITT (N=144) Across 12 to 30 weeks, calculated n (calculated %) IG: 13 (17.3) CG: 17 (24.6) No between-group difference: p=NS</p> <p>Withdrawal due to AEs, ITT (N=144) Across 12 to 30 weeks, n (calculated %) IG: 2 (2.7) CG: 3 (4.3) No between-group difference: p=NR</p> <p>Medication discontinuation, ITT (N=144) Across 12 to 30 weeks, calculated n (%) IG: 53 (70.7) CG: 42 (60.9) No between-group difference: p=NS</p>	<p>Overall AEs, ITT (N=144) Across 12 to 30 weeks, n (%) IG: 2 (2.7) CG: 3 (4.3) No between-group difference (p=NS)</p> <p>Serious AEs, ITT (N=144) Across 12 to 30 weeks, n patients [n events] (calculated % patients) IG: 9 [11] (12.0) CG: 7 [7] (10.1) No between-group difference (p=NS)</p>	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Kennard, 2008 <sup>20</sup>	IG: Relapse prevention CBT plus continued antidepressant medication management CG: Continued antidepressant medication management	Suicide attempts, ITT (N=46) Across 16 to 36 weeks, n (calculated %) IG: 1 (4.5) CG: 2 (8.3) Between-group difference: NR	Overall withdrawal, ITT (N=46) Across 16 to 36 weeks, n (%) IG: 3 (13.6) CG: 3 (12.5) No between-group difference: p=0.60 Withdrawal due to AEs, ITT (N=46) Across 16 to 36 weeks, n (calculated %) IG: 0 CG: 1 (4.2)	Serious AEs, ITT (N=46) Across 16 to 36 weeks, n (calculated %) IG: 2 (9.1) CG: 2 (8.3) Between-group difference NR	NA

AE = adverse event; CBT = cognitive behavioral therapy; CG = control group; IG = intervention group; ITT = intent to treat; KQ = Key Question; NA = not applicable; NR = not reported; NS = not significant.

**Table F-5. KQ 1a: Harms of IPT versus active control (clinical monitoring)**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Mufson, 1999 <sup>23</sup>	IG: IPT-A CG: Clinical Monitoring	Suicidality IG: 2/24 CG: 4/24	Early termination Patient-initiated withdrawal IG: 1/24 CG: 3/24  Patient Removal due to noncompliance IG: 0/24 CG: 4/24  School refusal IG: 0/24 CG: 1/24  Psychotic symptoms IG: 0/24 CG: 1/24	NR	NR

CG = control group; IG = intervention group; KQ = Key Question; NR = not reported.

**Table F-6. KQ 1a: Harms of attachment-based family therapy versus wait-list control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Diamond, 2002 <sup>25</sup> Index article	IG: ABFT CG: Wait-list control	SIQ score, Mean (SD) IG: 21.0 (16.6) CG: 28.3 (22.0)  Lower levels of suicidal ideation in IG: F=3.15 p=0.09 ES=0.52	NR	NR	NR

ABFT = attachment-based family therapy; CG = control group; ES = effect size; IG = intervention group; KQ = Key Question; NR = not reported; SIQ = Suicidal Ideation Questionnaire; SD = standard deviation.

**Table F-7. KQ 1a: Harms of family therapy versus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Brent, 1997 <sup>12</sup> Index article	IG1: Individual CBT IG2: SBFT CG: NST	<p>Suicidality &gt;4 (%)</p> <p>6 weeks</p> <p>IG1: 5.7 IG2: 3.4 CG: 13.3 p=0.31</p> <p>12-16 weeks</p> <p>IG1: 8.6 IG2: 6.5 CG: 15.2 p=0.48</p> <p>Significant decreases in suicidality across all groups: McNemar <math>X^2=21.78</math> df=1 p&lt;0.001</p>	<p>Protocol deviations after randomization Never came</p> <p>IG1: 1 IG2: 3 CG: 0</p> <p>Censored</p> <p>IG1: 2 IG2: 3 CG: 5</p> <p>Open</p> <p>IG1: 1 IG2: 3 CG: 3</p> <p>Dropped out</p> <p>IG1: 3 IG2: 2 CG: 3</p>	NR	NR

CBT = cognitive behavioral therapy; CG = control group; IG = intervention group; KQ = Key Question; NR = not reported; NST = Nondirective supportive therapy; SBFT = Systemic behavior family therapy.

**Table F-8. KQ 1a: Harms of PCIT versus active control**

<b>First Author's Last Name; Year; Trial Name</b>	<b>Treatment Interventions and Comparators</b>	<b>Suicidality</b>	<b>Withdrawal From Intervention/Drop Out From Study</b>	<b>Other Harms</b>	<b>Subgroup(s) Examined</b>
Luby, 2012 <sup>32</sup>	IG: Parent Child Interaction Therapy CG: Psycho-education	NR	Dropouts after randomization IG:8 (2 before pre-treatment assessment) CG:17 (9 before pre-treatment assessment)  High dropout rate for the CG appeared to be related to the perceived need for more intensive treatment, 40.7% of CG dropped out after group assignment and prior to any participation in sessions	There were no significant adverse effects reported or observed from any study participants. No other detail.	NR

CG = control group; IG = intervention group; KQ = Key Question; NR = not reported.

**Table F-9. KQ 1a: Harms of short-term psychoanalytic therapy versus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article Companion article: Goodyer, 2017 <sup>17</sup>	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	Adverse event scores; Mean (SD); Median (range) Baseline IG1 (n=154): 5.1 (1.0); 5 (2–6) IG2 (n=156): 5.0 (1.1); 5 (2–6) CG (n=155): 5.0 (1.1); 5 (1–6)  6 weeks IG1 (n=104): 4.6 (1.3); 5 (2–6) IG2 (n=107): 4.4 (1.5); 5 (0–6) CG (n=99): 4.4 (1.5); 5 (0–6)  12 weeks IG1 (n=106): 4.0 (1.5); 4 (0–6) IG2 (n=108): 4.2 (1.6); 4 (0–6) CG (n=112): 4.2 (1.6); 4 (0–6)  36 weeks IG1 (n=104): 3.6 (1.6); 4 (0–6) IG2 (n=109): 3.6 (1.7); 4 (0–6) CG (n=105): 4.1 (1.6); 4 (0–6)  52 weeks IG1 (n=111): 3.5 (1.9); 4 (0–6) IG2 (n=110): 3.2 (1.9); 3 (0–6) CG (n=105): 3.5 (1.8); 3.5 (0–6)  86 weeks IG1 (n=123): 3.4 (1.9); 4 (0–6) IG2 (n=114): 3.2 (1.8); 3 (0–6) CG (n=116): 3.3 (1.8); 3.5 (0–6)	NR	Recent nonsuicidal self-injury is defined as within 2 weeks, so the time frame for recent suicide attempt is likely similar	CBT and short-term psychoanalytic psychotherapy vs. brief psychosocial intervention
Goodyer 2017 <sup>16</sup> Companion: O'Keeffe, 2018 <sup>18</sup> O'Keeffe, 2019 <sup>19</sup>	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention		IG1: 32% IG2: 43% CG: 36% No evidence of difference in chi-square test ( $\chi^2(4, N=453)=9.07, p=0.059$ )		

CBT = cognitive behavioral therapy; CG = control group; IG = intervention group; KQ = Key Question.



**Table F-10. KQ 2a: Harms of SSRIs versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson 2014 <sup>38</sup>	IG1: duloxetine IG2: fluoxetine CG: placebo	No statistically significant differences between any treatment groups for any outcome on the C-SSRS during acute treatment.  Any Occurrence of Suicidal Ideation at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 16 (14.2%) IG2: 16 (14.2%) CG: 15 (14.6%)  Any Occurrence of Suicidal Behaviors at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 0 IG2: 1 (0.9%) CG: 0  Any Occurrence of Suicidal Acts at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 0 IG2: 1 (0.9%) CG: 0  Any Occurrence of Nonsuicidal Self-Injurious Behavior at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 4 (3.5%) IG2: 6 (5.3%) CG: 2 (1.9%)	Discontinuation in Acute Phase (IG1: 117; IG2: 117; CG: 103) IG1: 30 (25.6%) IG2: 26 (22.2%) CG: 16 (5.5%)  Discontinuation in Extension Phase (IG1: 83; IG2: 92; CG: 86) IG1: 27 (32.5%) IG2: 27 (29.3%) CG: 17 (19.8%)  Discontinuation due to AE in Acute Phase (IG1: 117; IG2: 117; CG: 103) IG1: 9 (7.7%) IG2: 1 (0.9%) CG: 3 (2.9%)  Significantly more IG1 than IG2, p=0.019  Discontinuation due to AE in Extension Phase (IG1: 83; IG2: 92; CG: 86) IG1: 2 (2.4%) IG2: 8 (8.7%) CG: 4 (4.7%)	Patients with Serious Adverse Events (all resulted in hospitalization, 3 suicide related) IG1: 7 IG2: 6 CG: 1 (major depression)  At least one TEAE at 10 weeks IG1: 59.8% IG2: 62.4% CG: 66.0% No significant difference  At least one TEAE at 36 weeks IG1: 63.9% IG2: 62.0% CG: 72.1% (transitioned to either duloxetine or fluoxetine) No significant difference	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson 2014 <sup>38</sup> (continued)		<p>Treatment-Emergent Suicidal Ideation at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 8 (7.1%) IG2: 9 (8.0%) CG: 7 (6.8%)</p> <p>Treatment-Emergent Suicidal Behaviors at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 0 IG2: 1 (0.9) CG: 0</p> <p>Treatment-Emergent Nonsuicidal Self-Injurious Behavior at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 4 (3.5%) IG2: 6 (5.3%) CG: 1 (1.0%)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Berard, 2006 <sup>39</sup>	IG: paroxetine CG: placebo	<p>Suicide-Related Events (IG: 181; CG: 95), n (%)  IG: 8 (4.4%)  CG: 2 (2.1%)  OR (95% CI): 2.15 (0.45 to 10.33)  p=0.502</p> <p>Suicide Attempts (IG: 181; CG: 95), n (%)  IG: 3 (1.7%)  CG: 2 (2.1%)  OR (95% CI): 0.78 (0.13 to 4.77)  p=1.00</p>	<p>Overall Withdrawal  IG: 55 of 182 (30.2%)  CG: 24 of 93 (25.8%)</p> <p>Withdrawal due to AE  IG: 20 of 182 (11.0%)  CG: 7 of 93 (7.5%): n calculated</p> <p>Withdrawal due to lack of efficacy  IG: 9 of 182 (4.9%): n calculated  CG: 6 of 93 (6.5%): n calculated</p>	<p>Experienced an AE  IG: 65.9%  CG: 59.1%</p> <p>Decreased Appetite  IG: 7.7%  CG: NR</p> <p>Note: Adverse events leading to discontinuation of study medication in more than a single paroxetine patient and at a rate greater than that for placebo were headache (1.1% versus 0%), nausea (3.3% versus 1.1%), vomiting (1.1% versus 0%), agitation (1.6% versus 0%), anxiety (1.1% versus 0%), and somnolence (2.2% versus 1.1%). Four (4) patients on paroxetine and 1 on placebo required a dose reduction owing to an AE. And this Twenty-two (22; 12.1%) patients in the paroxetine group and 6 (6.5%) patients in the placebo group experienced SAEs during the treatment phase.</p>	<p>Higher incidence of AEs in paroxetine-treated patients (70.5%) compared with placebo (58.3%) in older adolescents.</p> <p>The incidence of AEs leading to withdrawal in older adolescents treated with paroxetine was also higher compared with placebo (11.5% vs. 5.6%, respectively), whereas in younger adolescents, the incidence rates were similar between treatment groups (9.9% paroxetine versus 8.8% placebo).</p> <p>The overall incidence of SAEs was higher in the paroxetine group compared with placebo; the magnitude of this difference was found to be greater in older adolescents (8.2% paroxetine vs. 2.8% placebo) than younger adolescents (8.3% paroxetine vs. 5.3% placebo).</p>

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Berard, 2006 <sup>39</sup> (continued)					8 of 181 (4.4%) paroxetine patients (younger adolescents, n=4; older adolescents, n=4) and 2 of 95 (2.1%) placebo patients (younger adolescents, n=2) who experienced a suicide-related AE (OR 2.15, 95% CI 0.45, 10.33; p=0.502). Of the events that involved a suicide attempt, 3 of 181 (1.7%) occurred in paroxetine patients (younger adolescents, n=1; older adolescents, n=2), whereas 2 of 95 (2.1%) were reported in placebo patients (OR 0.78, 95% CI 0.13, 4.77; p=1.000).

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup>	IG1: Vilazodone 15 mg/d IG2: Vilazodone 30 mg/d CG: Placebo	Incidence of suicidal ideation based on C-SSRS (%) IG1: 36.0 IG2: 31.1 CG: 33.3  Incidence of suicidal behavior based on C-SSRS (%) IG1: 1.1 IG2: 1.1 CG: 1.8  Suicide attempt, patient reported on C-SSRS, N IG1: 1 IG2: 1 CG: 2	Total premature discontinuation after randomization, N IG1: 26 IG2: 19 CG: 32  Discontinuation prior to entering safety pop. Lost to followup, N IG1: 0 IG2: 0 CG: 1  Withdrew consent, N IG1: 0 IG2: 0 CG: 1  Protocol violation, N IG1: 0 IG2: 0 CG: 1  Discontinuation prior to entering ITT pop. Withdrew consent, N IG1: 1 IG2: 0 CG: 1  Discontinuation prior to completed treatment Adverse event IG1: 9 IG2: 8 CG: 4	Any TAE, N (%) IG1: 122 (69.7) IG2: 135 (75.0) CG: 105 (61.4)  Any SAE, N (%) IG1: 2 (1.1) IG2: 3 (1.7) CG: 1 (0.6)  Discontinuation due to AEs, N (%) IG1: 9 (5.1) IG2: 8 (4.4) CG: 4 (2.3)  Nausea, N (%) IG1: 51 (29.1) IG2: 49 (27.2) CG: 14 (8.2)  Headache, N (%) IG1: 22 (12.6) IG2: 29 (16.1) CG: 27 (15.8)  Upper abdominal pain, N (%) IG1: 7 (4.0) IG2: 28 (15.6) CG: 11 (6.4)  Vomiting, N (%) IG1: 11 (6.3) IG2: 21 (11.7) CG: 6 (3.5)	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup> (continued)			<p>Withdrew consent, N IG1: 6 IG2: 8 CG: 8</p> <p>Lost to followup, N IG1: 3 IG2: 1 CG: 6</p> <p>Protocol violation, N IG1: 4 IG2: 2 CG: 3</p> <p>Insufficient therapeutic response, N IG1: 3 IG2: 0 CG: 5</p> <p>Other, N IG1: 0 IG2: 0 CG: 2</p>	<p>Diarrhea, N (%) IG1: 15 (8.6) IG2: 16 (8.9) CG: 8 (4.7)</p> <p>Dizziness, N (%) IG1: 8 (4.6) IG2: 13 (7.2) CG: 5 (2.9)</p> <p>Nasopharyngitis, N (%) IG1: 6 (3.4) IG2: 11 (6.1) CG: 6 (3.5)</p> <p>Abdominal discomfort, N (%) IG1: 7 (4.0) IG2: 8 (4.4) CG: 2 (1.2)</p> <p>Upper respiratory tract infection, N (%) IG1: 7 (4.0) IG2: 7 (3.9) CG: 4 (2.3)</p> <p>Insomnia, N (%) IG1: 5 (2.9) IG2: 7 (3.9) CG: 5 (2.9)</p> <p>Fatigue, N (%) IG1: 4 (2.3) IG2: 7 (3.9) CG: 7 (4.1)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup> (continued)				<p>Decreased appetite, N (%)</p> <p>IG1: 7 (4.0)</p> <p>IG2: 6 (3.3)</p> <p>CG: 1 (0.6)</p> <p>Somnolence, N (%)</p> <p>IG1: 8 (4.6)</p> <p>IG2: 4 (2.2)</p> <p>CG: 1 (0.6)</p>	
Emslie, 1997 <sup>41</sup>	IG: Fluoxetine (20 mg/day) CG: Placebo	NR	<p>Withdrawal due to lack of efficacy, N (IG=48; CG=48)</p> <p>IG: 7</p> <p>CG: 19</p> <p>Withdrawal due to AEs, N (IG=48; CG=48)</p> <p>IG: 4</p> <p>CG: 1</p> <p>Withdrawal due to protocol violation, N (IG=48; CG=48)</p> <p>IG: 3</p> <p>CG: 2</p>	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article	IG: Fluoxetine (20 mg/day) CG: Placebo	Self-mutilatory behavior leading to hospitalization and study discontinuation, ITT (IG=109; CG=110) 9 weeks, n (calculated %) IG: 0 CG: 1 (0.9) Between-group difference NR	Overall withdrawal, ITT (IG=109; CG=110) 9 weeks, n (calculated %) IG: 19 (17.4) CG: 42 (38.2) Significantly smaller withdrawal rate in IG arm than CG arm: p=0.001  Withdrawal due to AEs, ITT (IG=109; CG=110) 9 weeks, n (%) IG: 5 (4.6) CG: 9 (8.2) No between-group difference: p=0.408  Withdrawal due to lack of efficacy, ITT (IG=109; CG=110) 9 weeks, n (%) IG: 5 (4.6) CG: 12 (10.9) No between-group difference: p=0.128	Serious AEs, ITT (IG=109; CG=110) 9 weeks, n (calculated %) IG: 1 (0.9) CG: 4 (3.6) Between-group difference NR  Withdrawal due to AEs, ITT (IG=109; CG=110) 9 weeks, n (%) IG: 5 (4.6) CG: 9 (8.2) No between-group difference: p=0.408  "Nonsolicited" treatment-emergent AEs, ITT (IG=109; CG=110) 9 weeks No between-group difference (p=NR)  "Solicited" treatment-emergent AEs, ITT (IG=109; CG=110) 9 weeks No between-group difference (p=NR)  Trouble pronouncing words, ITT (IG=109; CG=110) 9 weeks Significantly more events in the placebo arm (CG): p=0.015	"Nonsolicited" treatment-emergent AEs, ITT (IG=109; CG=110) 9 weeks No between-group differences based on age, gender, or family history of depression (p=NR)  "Solicited" treatment-emergent AEs, ITT (IG=109; CG=110) 9 weeks No between-group differences based on age, gender, or family history of depression (p=NR)



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article (continued)				<p>Headache, ITT (IG=109; CG=110) 9 weeks No between-group difference: p=0.273</p> <p>Trouble paying attention, ITT (IG=109; CG=110) 9 weeks No between-group difference: p=0.088</p> <p>Dizziness, ITT (IG=109; CG=110) 9 weeks No between-group difference: p=0.092</p> <p>Manic reaction, ITT (IG=109; CG=110) 9 weeks IG: 1 (0.9) CG: 0 (0) No between-group difference: p=NR</p> <p>Vital signs, ITT (IG=109; CG=110) 9 weeks No between-group differences in changes from baseline in sitting HR, sitting systolic BP, sitting diastolic BP, or temperature) (p's=NR)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2006 <sup>43</sup>	IG: Paroxetine CG: Placebo	Treatment phase Suicidal behavior IG: 2/104 CG: 0  Suicidal ideation IG: 0 CG: 1/102	Withdrawals IG: 31/101 CG: 23/102  Withdrawals due to AEs IG: 9/101 CG: 2/102  Withdrawals due to lack of efficacy IG: 8/101 CG: 11/102	Patients with >1 AE, N (%) IG: 71 (70.3) CG: 62 (60.8)  Serious AEs IG: 6 CG: 1  AEs occurring at an incidence of >5% in IG and at least twice that in the placebo Increased Cough IG: 6 (5.9%) CG: 2 (2.9%)  Dyspepsia IG: 6 (5.9%) CG: 2 (2.9%)  Vomiting IG: 6 (5.9%) CG: 2 (2.0%)  Dizziness IG: 5 (5.0%) CG: 1 (1.0%)  Trauma IG: 13 (12.95%) CG: 8 (7.8%)  Respiratory disorder IG: 11 (10.9%) CG: 11 (10.9%)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2006 <sup>43</sup> (continued)				Insomnia IG: 11 (10.9%) CG: 7 (6.9%)  Somnolence IG: 10 (9.9%) CG: 7 (6.9%)  Pharyngitis IG: 8 (7.9%) CG: 6 (5.9%)  Fever IG: 7 (6.9%) CG: 4 (3.9%)  Otitis media IG: 4 (4.0%) CG: 2 (2.0%)  Sweating IG: 4 (4.0%) CG: 0  Contact dermatitis IG: 3 (3.0%) CG: 0  Dose Reduction due to AEs IG: 9/101 (8.9%) CG: 5/102 (4.9%)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2009 <sup>44</sup> Index article	IG: escitalopram CG: placebo	<p>Suicidal tendency, N IG: 1 CG: 1</p> <p>MCSSRS (worsening suicidal behavior) , N IG: 2 CG: 3</p> <p>MCSSRS (increase in suicidal ideation), N IG: 12 CG: 12</p> <p>SIQ-JR, Mean change (SD) IG: -4.6 (12.0) CG: -2.9 (10.2)</p> <p>Any suicidal behavior and/or ideation, N (%) IG: 13 (10.2%) CG: 12 (9.2%) Serious (&gt;5%)</p>	<p>Overall Attrition: 17%  Discontinuation due to adverse events, N IG: 4 CG: 1</p> <p>Most frequent, % Headache IG: 25.2 CG: 25.5</p> <p>Menstrual cramps, % IG: 10.9 CG: 15.2</p> <p>Insomnia, % IG: 10.3 CG: 6.4</p> <p>Nausea, % IG: 10.3 CG: 8.3</p> <p>Abdominal pain, % IG: 9.0 CG: 7.0</p> <p>Influenza-like symptoms, % IG: 7.1 CG: 3.2</p> <p>Rhinitis, % G1: 7.1 G2: 8.9</p>	<p>Hospitalizations, N IG: 4 CG: 1</p> <p>Inflicted injury, N IG: 2 CG: 0</p> <p>Irritability, N IG: 1 CG: 0</p> <p>Aggravated depression, N IG: 0 CG: 1</p> <p>Patients reporting adverse events, N (%) IG: 121 (78.1) CG: 118 (75.2)</p> <p>Serious adverse events, N IG: 4 CG: 2</p> <p>Death from suicide or other causes, N IG: 0 CG: 0</p> <p>Difference(s) between groups: d=0</p> <p>Weight Gain, lbs G1: 1.2 G2: 1.2</p>	None

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2009 <sup>44</sup> Index article (continued)			<p>Vomiting, % G1: 6.5 G2: 5.7</p> <p>Diarrhea, % G1: 5.2 G2: 3.2</p> <p>Upper respiratory tract infection, % G1: 5.2 G2: 7.6</p> <p>Most frequent (%) Appetite decrease G1: 2.6 G2: 3.8</p> <p>Urinary tract infection G1: 2.6 G2: 0.6</p> <p>Coughing G1: 1.3 G2: 4.5</p>	<p>Most frequent, % Inflicted injury G1: 9.0 G2: 13.4</p> <p>Pharyngitis G1: 8.4 G2: 9.6</p> <p>Fatigue G1: 7.7 G2: 8.3</p>	
Emslie, 2009 <sup>44</sup> Index article Companion article: Findling, 2013 <sup>45</sup>	IG: Escitalopram (10-20 mg) CG: Placebo	Treatment-emergent AEs suggestive of self-harm in Extension Phase (16-24 weeks), N (%) (IG=83; CG=82) IG: 5 (6.0) CG: 3 (3.7)	<p>Discontinued due to AEs in Extension Phase (16-24 weeks), N (%) (IG=83; CG=82) IG: 4 (4.8) CG: 0 (0)</p> <p>Discontinued for Suicidal Ideation in Extension Phase (16-24 weeks), N (%) (IG=83; CG=82) IG: 1 (superficial cutting on arm) CG: 0</p>	<p>Treatment-emergent AEs in Extension Phase (16-24 weeks), N (%) (IG=83; CG=82) IG: 7 (8.4) CG: 7 (8.5)</p> <p>Serious AEs in Extension Phase (16-24 weeks), N (%) (IG=83; CG=82) IG: 2 (2.4) CG: 2 (2.4)</p>	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie 2014 <sup>46</sup>	IG1: duloxetine 60 mg QD IG2: duloxetine 30 mg QD IG3: fluoxetine 20 mg QD CG: placebo	No statistically significant differences between any treatment groups for any outcome on the C-SSRS during acute treatment.  Any Occurrence of Suicidal Ideation at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 17 (16.2%) IG2: 11 (9.6%) IG3: 13 (11.6%) CG: 15 (12.8%)  Any Occurrence of Suicidal Behaviors at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)  Any Occurrence of Suicidal Acts at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)  Any Occurrence of Nonsuicidal self-injurious behavior at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 116) IG1: 3 (2.9%) IG2: 6 (5.2%) IG3: 2 (1.8%) CG: 5 (4.3%)	Discontinuation in Acute Phase (IG1:108; IG2: 116; IG3: 117 CG: 122) IG1: 33 (30.6%) IG2: 35 (30.2%) IG3: 33 (28.2%) CG: 37 (30.3%)  Discontinuation in Extension Phase (IG1: 73; IG2: 81; IG3: 84; CG: 82) IG1: 30 (41.1%) IG2: 31 (38.3%) IG3: 35 (41.7%) CG: 38 (46.3%)  Discontinuation due to AE in Acute Phase (IG1:108; IG2: 116; IG3: 117 CG: 122) IG1: 12 (11.1%) IG2: 7 (6.0%) IG3: 6 (5.1%) CG: 4 (3.3%)  Discontinuation due to AE in Extension Phase (IG1: 73; IG2: 81; IG3: 84; CG: 82) IG1: 4 (5.5%) IG2: 6 (7.4%) IG3: 3 (3.6%) CG: 7 (8.5%)	Patients with Serious Adverse Events (all resulted in hospitalization, 9 suicide related) IG1+IG2: 14 IG3: 6 CG: 2  At least one treatment-emergent adverse event (TEAE) at 10 weeks IG1: 73.1% IG2: 57.8% IG3: 61.5% CG: 58.2%  Significantly more IG1 patients experiencing at least one TEAE compared with CG ( p=0.02) and IG2 ( p=0.02).  At least one TEAE at 36 weeks IG1: 68.5% IG2: 56.8% IG3: 53.6% CG: 67.1% (transitioned to duloxetine) Greater among IG1 and CG than IG2 and IG3	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie 2014 <sup>46</sup> (continued)		<p>Treatment-emergent Suicidal Ideation at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117)</p> <p>IG1: 7 (6.7%) IG2: 6 (5.2%) IG3: 9 (8.0%) CG: 11 (9.4%)</p> <p>Treatment-emergent Suicidal Behaviors at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117)</p> <p>IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)</p> <p>Treatment-emergent Nonsuicidal self-injurious behavior at 10 weeks (IG1:104; IG2: 112; IG3: 112; CG: 115)</p> <p>IG1: 3 (2.9%) IG2: 3 (2.7%) IG3: 2 (1.8%) CG: 5 (4.3%)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Findling, 2009 <sup>47</sup> Index article	IG: Fluoxetine CG: Placebo	Discontinued due to Suicidal ideation IG: 1 CG: 1	Discontinued, N IG: 6 CG: 3  Non-Adherence, N IG:1 CG:1  Withdrew Consent, N IG:1 CG:1  Suicidal Ideation, N IG:1 CG:1  Lack of efficacy, N IG: 3 CG:0	Headache IG: 10 (56%) CG: 8 (50%)  Nasal Congestion IG: 7 (39%) CG: 6 (38%)  Drowsiness IG: 6 (33%) CG: 2 (13%)  Nausea/Vomiting IG: 5 (28%) CG: 3 (19%)  Stomach Pain IG: 2 (11%) CG: 5 (31%)  Diarrhea IG: 2 (11%) CG: 2 (13%)  Dry Mouth IG: 1 (6%) CG: 2 (13%)  Syncope/Dizziness IG: 2 (11%) CG: 1 (6%)  Insomnia IG: 1 (6%) CG: 2 (13%)	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index Companion article: Le Noury, 2015 <sup>49</sup>	IG1: paroxetine IG2: imipramine CG: placebo	Suicidal or self injurious behaviors (IG1: 93; IG2: 95; CG: 87) CSR, Keller, RIAT IG1: 7, 5, 11 IG2: 3, 3, 4 (3 definite, 1 possible) CG: 1, 1, 2 (1 definite, 1 possible)	Withdrawal for adverse events among 86 patients (IG1: 93; IG2: 95; CG: 87) CSR IG1: 11 (11.8%) IG2: 30 (31.5%) CG: 6 (6.9%)  RIAT IG1: 14 (15.0%) IG2: 31 (32.6%) CG: 6 (6.9%)  Withdrawal for protocol violations CSR IG1: 3 (3.2%) IG2: 5 (5.3%) CG: 7 (8.0%)  RIAT IG1: 1 (1.1%) IG2: 5 (5.3%) CG: 9 (10.3%)  Total dropout rate CSR IG1: 26 (28%) IG2: 38 (40%) CG: 21 (24%)  RIAT IG1: 27 (29%) IG2: 38 (40%) CG: 21 (24%)	Adverse events found in CRFs (IG1: 31; IG2: 40; CG: 22) IG1: 159 IG2: 257 CG: 77  Adverse events appendix of original trial (IG1: 31; IG2: 40; CG: 22) IG1: 136 IG2: 240 CG: 67  % underestimate in relying only on adverse event appendix (IG1: 31; IG2: 40; CG: 22) IG1: 14% IG2: 7% CG: 13%  Adverse events in SKB CSR, Keller 2001, RIAT reanalysis (IG1: 93; IG2: 95; CG: 87) CSR, Keller, RIAT  Cardiovascular IG1: 7, 5, 44 IG2: 60, 42, 130 CG: 12, 6, 32  Gastrointestinal/digestive IG1: 80, 84, 112 IG2: 108, 106, 147 CG: 59, 61, 79	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)				<p>Psychiatric IG1: NR, NR, 103 IG2: NR, NR, 63 CG: NR, NR, 24</p> <p>Respiratory IG1: 39, 33, 42 IG2: 32, 27, 22 CG: 43, 37, 39</p> <p>Neurological/ nervous system IG1: 106, 115, 101 IG2: 117, 135, 114 CG: 42, 65, 77</p> <p>Other IG1: 121, 28, 79 IG2: 51, 30, 76 CG: 30, 38, 79</p> <p>Body as whole IG1: 106, NR, NR IG2: 125, NR, NR CG: 121, NR, NR</p> <p>Total IG1: 338, 265, 481 IG2: 493, 340, 552 CG: 277, 207, 330</p> <p>Adverse events in original study and reorganized by RIAT analysis (IG1: 93; IG2: 95; CG: 87)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)				Cardiovascular IG1: 1 IG2: 3 CG: 0  Gastrointestinal IG1: 25 IG2: 20 CG: 4  Psychiatric IG1: 32 IG2: 4 CG: 6  Respiratory IG1: 2 IG2: 1 CG: 4  Neurological IG1: 7 IG2: 14 CG: 7  Other IG1: 3 IG2: 8 CG: 5  Total IG1: 70 IG2: 50 CG: 26	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup>	IG1: paroxetine IG2: imipramine CG: placebo	Emotional lability (e.g. suicidal ideation/gestures) IG1: 2 IG2: 1 CG: 1	Premature Withdrawal for AE IG1: 9 (9.7%) IG2: 30 (31.6)% CG: 6 (6.9%)	Serious Adverse Effects (resulted in hospitalization, associated with suicidal gestures, or described as serious by treating physician) IG1: 11 IG2: 5 CG: 2  Adverse Effects in ≥5% of Subjects ITT (IG1=90; IG2=94; CG=87) n (%)  Cardiovascular Tachycardia IG1: 2 (2%) IG2: 18 (19%) CG: 1 (1%)  Postural Hypotension IG1: 1 (1%) IG2: 13 (14%) CG: 1 (1%)  Vasodilatation IG1: 0 (0%) IG2: 6 (6%) CG: 2 (2%)  Chest Pain IG1: 2 (25) IG2: 5 (5%) CG: 2 (2%)	No

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup> (continued)				Digestive System Dry Mouth IG1: 19 (20%) IG2: 43 (45%) CG: 12 (14%)  Nausea IG1: 22 (23.7%) IG2: 23 (24.2%) CG: 17 (19.5%)  Constipation IG1: 5 (5.4%) IG2: 9 (9.5%) CG: 4 (4.6%)  Decreased Appetite IG1: 7 (7.5%) IG2: 2 (2.1%) CG: 4 (4.6%)  Diarrhea IG1: 7 (7.5%) IG2: 3 (3.2%) CG: 7 (8.0%)  Dyspepsia IG1: 6 (6.5%) IG2: 9 (9.5%) CG: 4 (4.6%)  Tooth Disorder IG1: 5 (5.4%) IG2: 2 (2.1%) CG: 2 (2.3%)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup> (continued)				<p>Vomiting IG1: 3 (3.2%) IG2: 8 (8.4%) CG: 6 (6.9%)</p> <p>Abdominal Pain IG1: 10 (10.8) IG2: 7 (7.4) CG: 10 (11.5)</p> <p>Nervous System Dizziness IG1: 22 (23.7%) IG2: 45 (47.4%) CG: 16 (18.4%)</p> <p>Emotional Lability IG1: 6 (6.5%) IG2: 3 (3.2%) CG: 1 (1.1%)</p> <p>Hostility IG1: 7 (7.5%) IG2: 3 (3.2%) CG: 0 (0.0%)</p> <p>Insomnia IG1: 14 (15.1%) IG2: 13 (13.7%) CG: 4 (4.6%)</p> <p>Nervousness IG1: 8 (8.6%) IG2: 6 (6.3%) CG: 5 (5.7%)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup> (continued)				<p>Somnolence IG1: 16 (17.2%) IG2: 13 (13.7%) CG: 3 (3.4%)</p> <p>Tremor IG1: 10 (10.8%) IG2: 14 (14.7%) CG: 2 (2.3%)</p> <p>Headache IG1: 32 (34.4) IG2: 38 (40.0) CG: 34 (39.1)</p> <p>Respiratory system Cough Increased IG1: 5 (5.4%) IG2: 3 (3.2%) CG: 6 (6.9%)</p> <p>Pharyngitis IG1: 5 (5.4%) IG2: 12 (12.6%) CG: 8 (9.2%)</p> <p>Respiratory Disorder IG1: 10 (10.8%) IG2: 7 (7.4%) CG: 11 (12.6%)</p> <p>Rhinitis IG1: 7 (7.5%) IG2: 3 (3.2%) CG: 5 (5.7%)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup> (continued)				<p>Sinusitis IG1: 6 (6.5%) IG2: 2 (2.1%) CG: 7 (8.0%)</p> <p>Other Sweating IG1: 1 (1.1%) IG2: 6 (6.3%) CG: 1 (1.1%)</p> <p>Abnormal Vision IG1: 1 (1.1%) IG2: 7 (7.4%) CG: 2 (2.3%)</p> <p>Asthenia IG1: 10 (10.8%) IG2: 7 (7.4%) CG: 10 (11.5%)</p> <p>Back Pain IG1: 4 (4.3%) IG2: 2 (2.1%) CG: 10 (11.5%)</p> <p>Infection IG1: 10 (10.8%) IG2: 5 (5.3%) CG: 9 (10.3%)</p> <p>Trauma IG1: 2 (2.2%) IG2: 3 (3.2%) CG: 6 (6.9%)</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, ITT (n=439) 6 weeks, adjusted mean (SD) IG1: 14.31 (12.58) IG2: 16.20 (12.42) IG3: 13.18 (11.34) CG: 16.85 (11.70)  12 weeks, adjusted mean (SD) IG1: 11.79 (11.69) IG2: 14.44 (11.13) IG3: 11.40 (10.44) CG: 15.01 (11.05)  None of the post-hoc supportive contrasts at 12 weeks comparing improvement following active treatments vs. placebo were statistically significant  Across all 12 weeks: Time-by-treatment interaction based on SIQ-Jr random regression slope coefficients: p=0.01; Statistically comparing improvement: IG1>CG (p=0.02); IG1>IG2 (p=0.002); IG1>IG3 (p=0.05); IG2=IG3 (p=0.22); IG2=CG (p=0.36); IG3=CG (p=0.76)	Early termination at 12 weeks Patient-initiated withdrawal, N (calculated %) IG1: 7 (6.54) IG2: 5 (4.59) IG3: 16 (14.41) CG: 10 (8.93) Between-group difference: p=0.18  Patient Removal due to out-of-protocol treatment in place of or in addition to study treatment, N (calculated %) IG1: 8 (7.48) IG2: 13 (11.93) IG3: 8 (7.21) CG: 13 (11.61) Between-group difference: p=0.50	Serious AEs, N (%) IG1: 9 (8.41) IG2: 13 (11.93) IG3: 5 (4.50) CG: 6 (5.36)  Serious AEs, OR (95% CI) vs. CG: IG1: 1.62 (0.56 to 4.72) IG2: 2.39 (0.87 to 6.54) IG3: 0.83 (0.25 to 2.81) CG: NA Between-groups p=0.15 NOTE: ORs ≤2 reflect little or no increased risk  Serious Psychiatric-Related AEs, ITT (n=439) N patients [N events], (calculated %) IG1: 0 IG2: 1 [1] (0.92) (worsening depression, also captured below) IG3: 0 CG: 1 [1] (0.89) (mania, also captured below)  Any Psychiatric-Related AEs, ITT (n=439) N patients [N events], (%) IG1: 12 [16] (15) IG2: 20 [23] (21) IG3: 1 [1] (1) CG: 9 [11] (9.8) These events more frequent in fluoxetine arms (IG1 and IG2) than CBT (IG3) or placebo (CG), but p=NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Hedge g effect sizes relative to placebo (CG) IG1: 0.28 IG2: 0.05 IG3: 0.33</p> <p>NOTE: Above means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model</p> <p>Suicide-Related AEs, N (%) IG1: 6 (5.61) IG2: 9 (8.26) IG3: 5 (4.50) CG: 4 (3.57)</p>		<p>Mania, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)</p> <p>Hypomania, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p> <p>Elevated mood, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Hypersensitivity, ITT (n=439) N events (%) IG1: 0 IG2: 2 (1.83) IG3: 0 CG: 0</p> <p>Irritability, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 1 (0.92) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Suicide-Related AEs, OR (95% CI) vs. CG:  IG1: 1.60 (0.44 to 5.85)  IG2: 2.43 (0.73 to 8.14)  IG3: 1.27 (0.33 to 4.87)  CG: NA</p> <p>Suicide attempts, N (calculated %)  IG1: 4 (3.74%)  IG2: 2 (1.83%)  IG3: 1 (0.90%)  CG: 0  N of events too small to allow statistical comparison of suicide events</p>		<p>Anger, ITT (n=439)  N events (%)  IG1: 0  IG2: 1 (0.92)  IG3: 0  CG: 0</p> <p>Worsening of depression, ITT (n=439)  N events (%)  IG1: 0  IG2: 1 (0.92)  IG3: 0  CG: 1 (0.89)</p> <p>Crying, ITT (n=439)  N events (%)  IG1: 1 (0.93)  IG2: 0  IG3: 0  CG: 0</p> <p>Agitation, ITT (n=439)  N events (%)  IG1: 0  IG2: 0  IG3: 0  CG: 1 (0.89)</p> <p>Akathisia, ITT (n=439)  N events (%)  IG1: 1 (0.93)  IG2: 0  IG3: 0  CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Nervousness, ITT (n=439) N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Restlessness, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)</p> <p>Hyperactivity, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Panic attacks, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 1 (0.91) CG: 0</p> <p>Anxiety, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Somnolence, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Insomnia, ITT (n=439) N events (%) IG1: 5 (4.67) IG2: 3 (2.75) IG3: 0 CG: 1 (0.89)</p> <p>Nightmares, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0</p> <p>Night sweats, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Sedation, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 3 (2.75) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Fatigue, ITT (n=439) N events (%) IG1: 2 (1.87) IG2: 1 (0.92) IG3: 0 CG: 2 (1.79)</p> <p>Tremors, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 2 (1.83) IG3: 0 CG: 0</p> <p>Abnormal behavior N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Feeling abnormal N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0 p=NR</p> <p>Nonpsychiatric AEs, ITT (n=439) Generally more frequent in fluoxetine-treated arms (IG1 and IG2) than CBT (IG3) or placebo (CG)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Headache, ITT (n=439) N patients (%) IG1: N (5.6) IG2: N (12) IG3: 0 CG: N (9) This was the only AE occurring in ≥10% of patients in any single treatment group</p> <p>Sedation IG1: 0 IG2: 3 (2.75) IG3: 0 CG: 0</p> <p>Upper abdominal pain IG1: 0 IG2: 6 (5.5) IG3: 0 CG: 2 (1.79)</p> <p>Diarrhea IG1: 2 (1.87) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p> <p>Influenza IG1: 0 IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				Insomnia IG1: 5 (4.67) IG2: 3 (2.75) IG3: 0 CG: 1 (0.89)  Sinusitis IG1: 0 IG2: 4 (3.67) IG3: 0 CG: 2 (1.79)  Vomiting IG1: 4 (3.74) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, observed case analysis (n=359) 12 weeks, adjusted mean (SD) IG1: 10.9 (0.3) IG2: 13.7 (0.2) IG3: 11.3 (0.3) CG: 14.5 (0.6) No between-group differences: p=NS  Comparison of change in SIQ-Jr total score from baseline to 12 weeks, observed case analysis (n=359) IG1>IG2: p=0.004 IG1>IG3: p=0.04 IG1>CG: p=0.02  Emergence or worsening of suicidal ideation (change from baseline SIQ-Jr <31 to SIQ-Jr ≥31 at 6 or 12 weeks), observed case analysis (n=374) 12 weeks, n (%) IG1: 2/93 (2.2) IG2: 7/96 (7.3) IG3: 2/93 (2.2) CG: 7/92 (7.6) No between-group differences: p=NS  Worsening of suicidality from baseline to 6 or 12 weeks (CDRS-R item 13 worsening by ≥1 point),	NA	Self-reported PSC, observed case analysis (n=364) 12 weeks, mean (SD) IG1: 11.0 (8.2) IG2: 13.0 (10.5) IG3: 18.5 (17.5) CG: 12.3 (8.9)  Statistical comparisons of medication-based arms (IG1; IG2, and CG) with IG3 found that IG3 patients reported significantly higher/worse PSC scores: IG1<IG3: p=0.0036 IG2<IG3: p=0.0328 CG<IG3: p=0.0280 No between-group differences between IG1; IG2, and CG arms (all p's=NS)  Factor-based PSC scores (sleep, upper respiratory, pain, cardiac, panic, elimination, nausea, and skin), observed case analysis (N=364) 12 weeks All treatment arms showed improvement on each of the 8 PSC factors. Pain was the only factor with a significant treatment-by-time	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>observed case analysis (n=374)</p> <p>Calculated n (%)</p> <p>IG1: 2/93 (5.0)</p> <p>IG2: 7/96 (13.4)</p> <p>IG3: 2/93 (15.2)</p> <p>CG: 7/92 (7.2)</p> <p>No between-group differences: p=NS</p> <p>Emergence of suicidality from baseline to 6 or 12 weeks (change from CDRS-R item score=1 or 2 to ≥5), observed case analysis (n=374)</p> <p>Calculated n (%)</p> <p>IG1: 0/93 (0)</p> <p>IG2: 4/96 (3.7)</p> <p>IG3: 1/93 (1.3)</p> <p>CG: 2/92 (2.6)</p> <p>No between-group differences: p=NS</p> <p>Suicide-Related AEs (primary analysis: C-CASA Codes 1, 2, and 6), ITT (n=439)</p> <p>12 weeks, N (%)</p> <p>IG1: 5 (4.7)</p> <p>IG2: 10 (9.2)</p> <p>IG3: 5 (4.5)</p> <p>CG: 3 (2.7)</p> <p>Statistical comparisons of groups, OR (95% CI)</p> <p>IG1=IG3: p=NS</p> <p>IG1=CG: p=NS</p> <p>IG2&gt;CG: 3.7 (1.00 to 13.7), p=0.0402, meaning higher incidence in IG2</p>		<p>interaction (p=NR), based on significantly more improvement compared with IG3 IG1&gt;IG3: p=0.0011</p> <p>IG2&gt;IG3: p=0.0017</p> <p>Treatment-emergent physical AEs (spontaneous), ITT (n=439)</p> <p>12 weeks, N patients [N events], (calculated % patients)</p> <p>IG1: 37 [61] (34.6)</p> <p>IG2: 35 [81] (32.1)</p> <p>IG3: NR [9] (NR)</p> <p>CG: 34 [60] (30.4)</p> <p>No between-group differences in arms receiving pills (IG1; IG2, and CG), but more events reported in IG2 than IG1 or CG (p=NR).</p> <p>Spontaneously reported physical AEs reported in ≥2% of active treatment arms and at rates at least twice that of CG, ITT (n=429)</p> <p>12 weeks</p> <p>Sedation</p> <p>IG1: 1 (0.9)</p> <p>IG2: 3 (2.8)</p> <p>IG3: 0</p> <p>CG: 0</p> <p>IG2 vs. CG ratio: 3.00</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Suicide-Related AEs (sensitivity analysis: C-CASA Codes 1, 2, 3, and 6), ITT (n=439) 12 weeks, N (%) IG1: 6 (5.6) IG2: 10 (9.2) IG3: 5 (4.5) CG: 3 (2.7) Between-group differences NR</p> <p>Suicide attempts (C-CASA Code 1), ITT (n=439) 12 weeks, N (%) IG1: 2 (1.9) IG2: 1 (1.8) IG3: 1 (0.9) CG: 0</p> <p>Preparatory actions toward imminent suicidal behavior (C-CASA Code 2), ITT (n=439) No events at 12 weeks Self-injurious behavior: unknown intent (C-CASA Code 3), ITT (n=439) 12 weeks, N (%) IG1: 1 (0.9) IG2: 0 IG3: 0 CG: 0</p>		<p>Insomnia IG1: 5 (4.7) IG2: 3 (2.8) IG3: 0 CG: 1 (0.9) IG1 vs. CG ratio: 5.23 IG2 vs. CG ratio: 3.08</p> <p>Vomiting IG1: 4 (3.7) IG2: 2 (1.8) IG3: 1 (0.9) CG: 1 (0.9) IG1 vs. CG ratio: 4.19</p> <p>Upper abdominal pain IG1: 1 (0.9) IG2: 6 (5.5) IG3: 0 CG: 2 (1.8) IG2 vs. CG ratio: 3.08</p> <p>Headache: only spontaneously reported physical AE occurring in &gt;5% of patients, ITT (N=429) 12 weeks, calculated n (%) IG1: 7 (6.8) IG2: 13 (11.9) IG3: NA CG: 12 (10.7) No between-group differences (p=NS)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Suicidal ideation (C-CASA Code 6), ITT (n=439) 12 weeks, N (%) IG1: 3 (2.8) IG2: 8 (7.3) IG3: 4 (3.6) CG: 3 (2.7)</p> <p>Timing of suicide-related events, ITT (n=439) 12 weeks, mean days (SD) IG1: 52.0 (20.8) IG2: 38.0 (21.7) IG3: 45.4 (26.7) CG: 32.0 (15.0) No between-group differences: p=NS</p>		<p>Emergence or worsening of physical symptoms (change from baseline PSC severity of 0 [not at all] or 1 [just a little] to 2 [pretty much] or 3 [very much] at 6 or 12 weeks), observed case analysis (N=374) 12 weeks, n (%) (NOTE: patients with multiple reports of same event were counted only once) Sleep disturbance: Trouble sleeping IG1: 12 (3.3) IG2: 14 (15.2) IG3: 11 (12.5) CG: 14 (15.1)</p> <p>Sleep disturbance: Feeling drowsy or too sleepy IG1: 17 (18.9) IG2: 15 (16.3) IG3: 12 (13.5) CG: 16 (17.2)</p> <p>Sleep disturbance: Sleeplessness IG1: 12 (13.3) IG2: 17 (18.5) IG3: 16 (18.2) CG: 9 (9.7)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Sleep disturbance: Nightmares or very strange dreams IG1: 11 (12.2) IG2: 17 (18.5) IG3: 7 (8.0) CG: 13 (14.0)</p> <p>Sleep disturbance: Restless or uncomfortable urge to move IG1: 2 (2.2) IG2: 9 (9.8) IG3: 5 (5.7) CG: 10 (10.8)</p> <p>Upper respiratory: Head cold or sniffles IG1: 15 (16.7) IG2: 16 (17.4) IG3: 13 (14.6) CG: 16 (17.2)</p> <p>Upper respiratory: Allergies IG1: 10 (11.1) IG2: 13 (14.1) IG3: 13 (14.6) CG: 8 (8.6)</p> <p>Upper respiratory: Sore throat IG1: 8 (8.9) IG2: 6 (6.5) IG3: 9 (10.1) CG: 14 (15.1)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Upper respiratory: Dry mouth IG1: 9 (10.0) IG2: 8 (8.7) IG3: 8 (9.0) CG: 7 (7.5)</p> <p>Upper respiratory: Coughing or wheezing IG1: 6 (6.7) IG2: 5 (5.4) IG3: 6 (6.8) CG: 8 (8.6)</p> <p>Upper respiratory: Fever IG1: 6 (6.7) IG2: 4 (4.4) IG3: 6 (6.7) CG: 4 (4.3)</p> <p>Pain: Stomach pain or ache IG1: 6 (6.7) IG2: 10 (10.9) IG3: 9 (10.1) CG: 13 (14.0)</p> <p>Pain: Muscle aches or cramps IG1: 9 (10.0) IG2: 5 (5.4) IG3: 12 (13.6) CG: 12 (12.9)</p> <p>Pain: Joint pain IG1: 3 (3.3) IG2: 2 (2.2) IG3: 8 (8.9) CG: 9 (9.7)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Pain: Numbness or tingling in arms or legs IG1: 3 (3.3) IG2: 3 (3.3) IG3: 5 (5.7) CG: 5 (5.4)  Cardiac: Chest pain IG1: 4 (4.4) IG2: 5 (5.4) IG3: 4 (4.6) CG: 6 (6.5)  Cardiac: Racing or pounding heart IG1: 2 (2.2) IG2: 2 (2.2) IG3: 5 (5.7) CG: 6 (6.5)  Cardiac: Heart skips beats IG1: 1 (1.1) IG2: 2 (2.2) IG3: 3 (3.4) CG: 1 (1.1)  Panic: Excessive sweating IG1: 3 (3.3) IG2: 6 (6.5) IG3: 2 (2.3) CG: 9 (9.7)  Panic: Difficulty breathing IG1: 4 (4.4) IG2: 3 (3.3) IG3: 2 (2.3) CG: 6 (6.5)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Panic: Can't hear well IG1: 3 (3.3) IG2: 2 (2.2) IG3: 4 (4.6) CG: 2 (2.2)  Elimination: Frequent urination IG1: 6 (6.7) IG2: 4 (4.4) IG3: 11 (12.5) CG: 6 (6.5)  Elimination: Feeling bloated or gassy IG1: 2 (2.2) IG2: 6 (6.5) IG3: 6 (6.8) CG: 7 (7.5)  Elimination: Pain with urination IG1: 2 (2.2) IG2: 1 (1.1) IG3: 3 (3.4) CG: 0  Elimination: Constipation IG1: 1 (1.1) IG2: 0) IG3: 4 (4.6) CG: 3 (3.2)  Diarrhea IG1: 4 (4.4) IG2: 5 (5.4) IG3: 6 (6.7) CG: 7 (7.5)	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Nausea or vomiting IG1: 8 (8.9) IG2: 3 (3.3) IG3: 10 (11.2) CG: 5 (5.4)</p> <p>Skin: Skin rash IG1: 6 (6.7) IG2: 4 (4.4) IG3: 9 (10.1) CG: 4 (4.3)</p> <p>Skin: Hives IG1: 0 IG2: 2 (2.2) IG3: 1 (1.1) CG: 2 (2.2)</p> <p>Other: Headache IG1: 12 (13.3) IG2: 18 (19.6) IG3: 14 (15.7) CG: 16 (17.2)</p> <p>Treatment with FLX (i.e.; IG1 or IG2) did not lead to significantly higher rates of symptom worsening or emergence on any physical symptoms (p=NR).</p> <p>Furthermore, the double-blind treatment arms (IG2 and CG) did not differ significantly on symptom worsening or emergence on any physical symptoms (p=NR).</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Worsening of Psychiatric Symptoms (CGI-I <math>\geq 5-7</math> [slightly worse, much worse, or very much worse] at 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 3 (2.8) IG3: 10 (9.0) CG: 7 (6.3) Between-group differences : IG1 and IG2 (FLX arms) had significantly lower rates of worsening than IG3 and CG (non-FLX arms) (<math>p=0.01</math>). Ns of individual arms too small to allow statistical comparison.</p> <p>Worsening of Psychiatric Symptoms (CGI-S <math>\geq 1</math> point from baseline to 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 2 (1.8) IG3: 5 (4.5) CG: 9 (8.0) Between-group differences NR</p> <p>Treatment-emergent psychiatric AEs (spontaneously reported), ITT (N=429)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>12 weeks, n (%) (NOTE: Patients may be represented in more than one arm due to patient-initiated crossover)</p> <p>Any treatment-emergent psychiatric AE            IG1: 6 (5.6)            IG2: 12 (11.0)            IG3: 1 (0.91)            CG: 5 (4.5)            Between-group comparisons:            IG1 and IG2 (FLX arms) experienced more psychiatric AEs than IG3 or CG (non-FLX arms).            IG2 experienced more psychiatric AEs than CG, but Ns too small to detect statistical significance.</p> <p>Mania spectrum (mania, hypomania, elevated mood)            IG1: 1 (0.93)            IG2: 4 (3.67)            IG3: 0            CG: 1 (0.89)</p> <p>Irritability spectrum (hypersensitivity, irritability, anger, worsening depression, crying)            IG1: 2 (1.86)            IG2: 4 (3.67)            IG3: 0            CG: 1 (0.89)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Agitation spectrum (agitation, akathisia, nervousness, restlessness, hyperactivity) IG1: 1 (0.93) IG2: 2 (1.84) IG3: 2 (1.78) CG: 0</p> <p>Anxiety (anxiety, panic attacks) IG1: 0 IG2: 2 (1.84) IG3: 1 (0.91) CG: 0</p> <p>Other (tremor, "abnormal behavior", "feeling spacy") IG1: 2 (1.84) IG2: 2 (1.84) IG3: 0 CG: 1 (0.89)</p> <p>ADS Mania subscale severity scores (clinician-reported), ITT (N=429) 12 weeks, mean (SD) IG1: 0.5 (0.8) IG2: 1.1 (1.0) IG3: 1.0 (1.2) CG: 1.1 (0.1)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Between-group comparisons:  IG1&lt;IG2: p=0.013  IG1&lt;CG: p=0.003  IG1&lt;IG3: p=0.012  IG2=IG3: p=NR</p> <p>ADS Mania change from baseline of <math>\geq 3</math> points, modified ITT (n=424 with <math>\geq 2</math> mania total scores) 12 weeks, n (%)  IG1: 21 (20)  IG2: 15 (14.2)  IG3: 13 (12.3)  CG: 16 (15.0)</p> <p>Between-group differences  NR  Incidence of mania or hypomania: ADS Mania scale, ITT (N=429) 12 weeks, n (calculated %)  IG1: 3 (2.8)  IG2: 1 (0.9)  IG3: 0  CG: 1 (0.9)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Wagner, 2004 <sup>52</sup> Index article Companion article: Forest, 2001 <sup>53</sup>	G1: Citalopram G2: Placebo	NR	Withdrawn due to Adverse Events, n(%) G1: 5 (5.6) G2: 5 (5.9)	Subject with at least one TEAE G1: 75 (84.3) G2: 59 (69.4)	NR
			Withdrawn due to Lack of Efficacy, n(%) G1: 2 (2.2) G2: 1 (1.2)	Headache G1: 17 (19.1) G2: 17 (20.0)	
			Withdrawn for other reasons, n(%) G1: 11 (12.4) G2: 12 (14.1)	Rhinitis G1: 12 (13.5) G2: 5 (5.9)	
				Nausea G1: 12 (13.5) G2: 3 (3.5)	
				Abdominal Pain G1: 10 (11.2) G2: 6 (7.1)	
				Menstrual Cramps (female only: N(G1)=47 N(G2)=46) G1: 3 (6.4) G2: 4 (8.7)	
				Pharyngitis G1: 6 (6.7) G2: 7 (8.2)	
				Fever G1: 5 (5.6) G2: 5 (5.9)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Wagner, 2004 <sup>52</sup> Index article Companion article: Forest, 2001 <sup>53</sup> (continued)				Upper Respiratory Tract Infection G1: 4 (4.5)  Coughing G1: 4 (4.5) G2: 6 (7.1)  Influenza-like symptoms G1: 6 (6.7) G2: 0  Fever G1: 5 (5.6) G2: 5 (5.9)  Vomiting G1: 5 (5.6) G2: 5 (5.9)  Back Pain G1: 5 (5.6) G2: 3 (3.5)  Fatigue G1: 5 (5.6) G2: 1 (1.2)  Diarrhea G1: 5 (5.6) G2: 1 (1.2)  Dizziness G1: 1 (1.1) G2: 4 (4.7)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Wagner, 2004 <sup>52</sup> Index article Companion article: Forest, 2001 <sup>53</sup> (continued)				<p>Inflicted injury G1: 3 (3.4) G2: 4 (4.7)</p> <p>No fatal SAEs were reported. A non-fatal SAE was reported in the control group (G2) and one case of impulsive behavior was reported in the same group.</p>	
Weihls, 2018 <sup>55</sup>	IG1: Desvenlafaxine (25, 35, or 50 mg/d) IG2: Fluoxetine (20 mg/d) CG: Placebo	<p>Treatment-emergent suicidal ideation or behavior at any post-baseline assessment: n (%) Overall IG1: 9/115 (7.8) IG2: 12/110 (10.9) CG: 8/112 (7.1)</p> <p>New-onset IG1: 8/102 (7.8) IG2: 10/97 (10.3) CG: 7/104 (6.7)</p> <p>Worsening IG1: 1/13 (7.7) IG2: 2/13 (15.4) CG: 1/8 (12.5)</p> <p>Treatment-emergent suicidal ideation at any post-baseline assessment: n (%) Overall IG1: 9/115 (7.8) IG2: 12/110 (10.9) CG: 8/112 (7.1)</p>	<p>Discontinued study treatment: n (%) IG1: 16 (13.9, calculated) IG2: 13 (11.5, calculated) CG: 13 (11.6, calculated)</p> <p>Discontinued due to AE: n (%) IG1: 2 (1.7, calculated) IG2: 1 (0.9, calculated) CG: 2 (1.8, calculated)</p> <p>Discontinued due to lack of efficacy: n (%) IG1: 1 (0.9, calculated) IG2: 0 (0.0, calculated) CG: 3 (2.7, calculated)</p> <p>Discontinued due to lost to followup: n (%) IG1: 6 (5.2, calculated) IG2: 5 (4.4, calculated) CG: 4 (3.6, calculated)</p>	<p>Any treatment-emergent AEs: % IG1: 69/115 (60.0) IG2: 72/112 (64.3) CG: 79 /112 (70.5)</p> <p>Severe AEs (not defined) considered unrelated to study medication: % IG1: 3.5% IG2: 5.4% CG: 3.6%</p> <p>Severe AEs (not defined) considered related to study medication: n (%) IG1: 3 (2.6, calculated) IG2: 0 (0.0%) CG: 2 (1.8, calculated)</p> <p>Serious AEs: n (%) IG1: 3 (2.6, calculated) IG2: 2 (1.8, calculated) CG: 0 (0.0)</p> <p>Deaths: none</p>	NA



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Weihs, 2018 <sup>55</sup> (continued)		<p>New-onset IG1: 8/102 (7.8) IG2: 10/97 (10.3) CG: 7/104 (6.7)</p> <p>Worsening IG1: 1/13 (7.7) IG2: 2/13 (15.4) CG: 1/8 (12.5)</p> <p>Treatment-emergent suicidal behavior at any post-baseline assessment: n (%) Overall IG1: 0/115 (0.0) IG2: 1/110 (0.9) CG: 0/112 (0.0)</p> <p>New-onset IG1: 0/115 (0.0) IG2: 1/110 (0.9) CG: 0/112 (0.0)</p> <p>Worsening IG1: 0 (0.0) IG2: 0 (0.0) CG: 0 (0.0)</p>	<p>Discontinued due to protocol violation: n (%) IG1: 3 (2.6, calculated) IG2: 0 (0.0, calculated) CG: 1 (0.9, calculated)</p> <p>Discontinued due to no longer willing to participate: n (%) IG1: 2 (1.7, calculated) IG2: 7 (6.2, calculated) CG: 2 (1.8, calculated)</p> <p>Discontinued due to other: n (%) IG1: 2 (1.7, calculated) IG2: 0 (0.0, calculated) CG: 1 (0.9, calculated)</p>		

ADS = anxiety and depression scale; AE = adverse event; C-CASA = Columbia Classification Algorithm of Suicide Assessment; CG = control group; CRF = Corticotropin-releasing factor; CSR = clinical study report; C-SSRS = Columbia-suicide severity rating scale; FLX = fluoxetine; IG = intervention group; ITT = intent to treat; KQ = Key Question; MCSSRS = Modified Columbia Suicide Severity Rating Scale; NR = not reported; NS = not significant; OR = odds ratio; PSC = physical symptom severity; RIAT = restoring invisible and abandoned trials; SAE = significant adverse event; SD = standard deviation; SIQ-JR = Suicide Ideation Questionnaire-Junior High School; SKB = SmithKline Beecham; TAE = treatment adverse event; TEAE = treatment-emergent adverse event.

**Table F-11. KQ 2a: Harms of fluoxetine for relapse prevention versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup>	IG: Continued treatment with fluoxetine at current dose (20-60 mg/day) CG: Switch to placebo	Suicidal ideation, ITT (IG=20; CG=20) 19 to 51 weeks, n (calculated %) IG: 0 CG: 1 (5) Between-group difference NR	Overall withdrawal, ITT (IG=20; CG=20) 19 to 51 weeks, n (calculated %) IG: 10 (50) CG: 12 (60) Between-group difference NR  Withdrawal due to AEs, ITT (IG=20; CG=20) 19 to 51 weeks, n (calculated %) IG: 1 (5) CG: 0 (0) Between-group difference NR  Withdrawal due to relapse (CDRS-R score of >40 with a 2-week history of worsening symptoms or relapse in the opinion of the physician), ITT (IG=20; CG=20) 19 to 51 weeks, n (calculated %) IG: 6 (30) CG: 0 (0) Between-group difference NR	"Nonsolicited" treatment-emergent AEs, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 14 (70.0) CG: 12 (60.0) No between-group difference (p=0.741)  Patients reporting any AEs, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 14 (70) CG: 12 (60) No between-group difference: p=0.741  Accidental injury, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 3 (15) CG: 1 (5) No between-group difference: p=0.605  Bronchitis, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 3 (15) CG: 0 No between-group difference: p=0.231  Flu syndrome, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 3 (15) CG: 1 (5)	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup> (continued)				<p>No between-group difference: p=0.605 Infection, ITT (IG=20; CG=20)</p> <p>19 to 51 weeks, n (%) IG: 3 (15) CG: 0 No between-group difference: p=0.231</p> <p>Rhinitis, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 3 (15) CG: 2 (10) No between-group difference: p=1.00</p> <p>Vomiting, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 3 (15) CG: 2 (10) No between-group difference: p=1.00</p> <p>Abdominal pain, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 2 (10) CG: 0 No between-group difference: p=0.487</p> <p>Cough increased, ITT (IG=20; CG=20)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup> (continued)				<p>19 to 51 weeks, n (%) IG: 2 (10) CG: 0 No between-group difference: p=0.487</p> <p>Ecchymosis, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 2 (10) CG: 1 (5) No between-group difference: p=1.00</p> <p>Fever, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 2 (10) CG: 1 (5) No between-group difference: p=1.00</p> <p>Pain, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 2 (10) CG: 0 No between-group difference: p=0.487</p> <p>Pharyngitis, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 2 (10) CG: 0 No between-group difference: p=0.487</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup> (continued)				<p>Sinusitis, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 2 (10) CG: 1 (5) No between-group difference: p=1.00</p> <p>Headache, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 1 (5) CG: 3 (15) No between-group difference: p=0.605</p> <p>Depression, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 0 CG: 2 (10) No between-group difference: p=0.487</p> <p>Diarrhea, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 0 CG: 2 (10) No between-group difference: p=0.487</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup> (continued)				Dizziness, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 0 CG: 2 (10) No between-group difference: p=0.487  Myalgia, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 0 CG: 2 (10) No between-group difference: p=0.487  Nervousness, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 0 CG: 2 (10) No between-group difference: p=0.487  Weight gain, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 0 CG: 2 (10) No between-group difference: p=0.487  "Solicited" treatment-emergent AEs, ITT (IG=20; CG=20) 19 to 51 weeks	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup> (continued)				<p>No significant between-group differences in n's of patients reporting any specific AEs (p=NS)</p> <p>Laboratory values: mean change from baseline, ITT (IG=20; CG=20) 19 to 51 weeks No between-group differences in mean change of lab values or incidence of treatment-emergent abnormal lab values (p=NS)</p> <p>Systolic BP, mean change from baseline, ITT (IG=20; CG=20) 19 to 51 weeks, mean in mm (unadjusted for baseline BP at week 19) IG: 3.6 CG: 2.5 Significantly greater decrease in IG arm than CG arm, but difference not considered clinically meaningful and possibly affected by significant baseline difference in systolic BP: p=0.048 Systolic BP (adjusted for baseline BP at week 19) No between-group difference: p=NS</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup> (continued)				<p>Abnormally high systolic BP, ITT (IG=20; CG=20) 19 to 51 weeks, n (%) IG: 1 (6) CG: 4 (20) No between-group difference: p=0.344</p> <p>Change in height from 19 to 51 weeks, ITT (IG=20; CG=20) Mean (SD) in cm (unadjusted for baseline height) IG: 1.1 (2.1) CG: 2.4 (2.4) No between-group difference: p=0.092 Least-squares mean (SD) in cm (adjusted for baseline height) IG: 1.3 (NR) CG: 2.3 (NR) No between-group difference: p=0.107</p> <p>Change in height from baseline (0 weeks) to 51 weeks, ITT (IG=20; CG=20) Mean (SD) in cm (unadjusted for baseline height) IG: 2.9 (NR) CG: 3.1 (NR) No between-group difference: p=NR</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Emslie, 2004 <sup>56</sup> (continued)				<p>Least-squares mean (SD) in cm (adjusted for baseline height) IG: 3.5 (NR) CG: NR Between-group difference NR</p> <p>Change in weight from 19 to 51 weeks, ITT (IG=20; CG=20) Mean (SD) in kg (unadjusted for baseline height) IG: 3.4 (4.2) CG: 3.3 (3.9) No between-group difference: p=0.986</p> <p>Change in QTc interval using Fridericia's correction from 19 to 51 weeks, ITT (IG=20; CG=20) Mean (unadjusted for baseline QTc) IG: -1.67 CG: -4.90 No between-group difference: p=0.564</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2008 <sup>57</sup> Index article	IG1: Fluoxetine continuation CG: Placebo	NR	Continuation phase Adverse event IG1: 1 CG: 0 Withdrew consent (various reasons) IG1: 8 CG: 6  Lost to followup IG1: 1 CG: 0  Nonadherent IG1: 2 CG: 1	SAEs IG1: 1 suicide attempt (week 16) CG: 2 hospitalizations (preexisting condition)	NR

AE = adverse event; BP = blood pressure; CG = control group; IG = intervention group; ITT = intent to treat; KQ = Key Question; NA = not applicable; NR = not reported; NS = not significant; QTc = QT interval prolongation extended corrected; SD = standard deviation.

**Table F-12. KQ 2a: Harms of SNRIs versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson, 2018 <sup>59</sup>	IG1: Low-dose Desvenlafaxine IG2: High-dose Desvenlafaxine CG: Placebo	SIB, n/N (%) Treatment-emergent IG1: 9/120 (7.5) IG2: 14/121 (11.6) CG: 16/119 (13.4)  New onset, n/N (%) IG1: 9/113 (8.0) IG2: 13/108 (12.0) CG: 14/107 (13.1)  Worsening, n/N (%) IG1: 0/113 (0) IG2: 1/13 (7.7) CG: 2/12 (16.7) SI, n/N (%)  SB, n/N (%) Treatment-emergent IG1: 1/120 (0.8) IG2: 0/121 (0) CG: 1/119 (0.8)  New onset IG1: 1/120 (0.8) IG2: 0/121 (0) CG: 1/119 (0.8)  Suicide attempt, N IG1: 1 IG2: 0 CG: 1  Worsening IG1: 0 IG2: 0 CG: 0	Discontinued due to AE, N IG1: 8 IG2: 3 CG: 8  Discontinued due to lack of efficacy, N IG1: 2 IG2: 0 CG: 2  Lost to followup, N IG1: 3 IG2: 1 CG: 5  Protocol violation, N IG1: 1 IG2: 2 CG: 3  No longer willing to participate, N IG1: 4 IG2: 9 CG: 3  Other, N IG1: 1 IG2: 2 CG: 2	Overall TAEs with Incidence ≥5% in any group, N (%) Any TAE IG1: 81 (66.4) IG2: 81 (66.9) CG: 73 (60.8)  Abdominal pain, upper, n (%) IG1: 7 (5.7) IG2: 11 (9.1) CG: 9 (7.5)  Accidental overdose, n (%) IG1: 0 IG2: 3 (2.5) CG: 1 (0.8)  Aggression, n (%) IG1: 2 (1.6) IG2: 0 CG: 0  Blood triglycerides increased, n (%) IG1: 2 (1.6) IG2: 0 CG: 0  Cough, n (%) IG1: 2 (1.6) IG2: 3 (2.5) CG: 5 (4.2)  Decreased appetite, n (%) IG1: 6 (4.9) IG2: 6 (5.0) CG: 6 (5.0)	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson, 2018 <sup>59</sup> (continued)				Diarrhea, n (%) IG1: 3 (2.5) IG2: 3 (2.5) CG: 2 (1.7)  Dizziness, n (%) IG1: 5 (4.1) IG2: 6 (5.0) CG: 3 (2.5)  Dysmenorrhea, n (%) IG1: 1 (1.4) IG2: 4 (5.3) CG: 1 (1.7)  Fatigue, n (%) IG1: 4 (3.3) IG2: 9 (7.4) CG: 2 (1.7)  Feeling jittery, n (%) IG1: 1 (0.8) IG2: 4 (3.3) CG: 0  Viral gastroenteritis, n (%) IG1: 2 (1.6) IG2: 3 (2.5) CG: 2 (1.7)  Headache, n (%) IG1: 22 (18.0) IG2: 25 (20.7) CG: 15 (12.5)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson, 2018 <sup>59</sup> (continued)				Insomnia, n (%) IG1: 7 (5.7) IG2: 4 (3.3) CG: 1 (0.8)  Nausea, n (%) IG1: 12 (9.8) IG2: 14 (11.6) CG: 7 (5.8)  Nasopharyngitis, n (%) IG1: 8 (6.6) IG2: 7 (5.8) CG: 2 (1.7)  Psychomotor hyperactivity, n (%) IG1: 1 (0.8) IG2: 4 (3.3) CG: 0  Pyrexia, n (%) IG1: 3 (2.5) IG2: 2 (1.7) CG: 0  Skin abrasion, n (%) IG1: 0 IG2: 2 (1.7) CG: 0  Upper respiratory tract infection, n (%) IG1: 4 (3.3) IG2: 6 (J5) CG: 3 (2.5)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson, 2018 <sup>59</sup> (continued)				Vomiting, n (%) IG1: 1 (0.8) IG2: 9 (7.4) CG: 4 (3.3)	
Emslie 2014 <sup>46</sup>	IG1: duloxetine 60 mg QD IG2: duloxetine 30 mg QD IG3: fluoxetine 20 mg QD CG: placebo	No statistically significant differences between any treatment groups for any outcome on the C-SSRS during acute treatment.  Any Occurrence of Suicidal Ideation at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 17 (16.2%) IG2: 11 (9.6%) IG3: 13 (11.6%) CG: 15 (12.8%)  Any Occurrence of Suicidal Behaviors at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)  Any Occurrence of Suicidal Acts at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)	Discontinuation in Acute Phase (IG1:108; IG2: 116; IG3: 117 CG: 122) IG1: 33 (30.6%) IG2: 35 (30.2%) IG3: 33 (28.2%) CG: 37 (30.3%)  Discontinuation in Extension Phase (IG1: 73; IG2: 81; IG3: 84; CG: 82) IG1: 30 (41.1%) IG2: 31 (38.3%) IG3: 35 (41.7%) CG: 38 (46.3%)  Discontinuation due to AE in Acute Phase (IG1:108; IG2: 116; IG3: 117 CG: 122) IG1: 12 (11.1%) IG2: 7 (6.0%) IG3: 6 (5.1%) CG: 4 (3.3%)  Discontinuation due to AE in Extension Phase (IG1: 73; IG2: 81; IG3: 84; CG: 82) IG1: 4 (5.5%) IG2: 6 (7.4%) IG3: 3 (3.6%) CG: 7 (8.5%)	Patients with Serious Adverse Events (all resulted in hospitalization, 9 suicide related) IG1+IG2: 14 IG3: 6 CG: 2  At least one treatment-emergent adverse event (TEAE) at 10 weeks IG1: 73.1% IG2: 57.8% IG3: 61.5% CG: 58.2%  Significantly more IG1 patients experiencing at least one TEAE compared with CG ( p=0.02) and IG2 ( p=0.02).  At least one TEAE at 36 weeks IG1: 68.5% IG2: 56.8% IG3: 53.6% CG: 67.1% (transitioned to duloxetine) Greater among IG1 and CG than IG2 and IG3	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie 2014 <sup>46</sup> (continued)	Any Occurrence of Nonsuicidal self-injurious behavior at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 116) IG1: 3 (2.9%) IG2: 6 (5.2%) IG3: 2 (1.8%) CG: 5 (4.3%)	<p>Treatment-emergent Suicidal Ideation at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 7 (6.7%) IG2: 6 (5.2%) IG3: 9 (8.0%) CG: 11 (9.4%)</p> <p>Treatment-emergent Suicidal Behaviors at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)</p> <p>Treatment-emergent Nonsuicidal self-injurious behavior at 10 weeks (IG1:104; IG2: 112; IG3: 112; CG: 115) IG1: 3 (2.9%) IG2: 3 (2.7%) IG3: 2 (1.8%) CG: 5 (4.3%)</p>			

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Weihls, 2018 <sup>55</sup>	IG1: Desvenlafaxine (25, 35, or 50 mg/d) IG2: Fluoxetine (20 mg/d) CG: Placebo	<p>Treatment-emergent suicidal ideation or behavior at any post-baseline assessment: n (%)</p> <p>Overall IG1: 9/115 (7.8) IG2: 12/110 (10.9) CG: 8/112 (7.1)</p> <p>New-onset IG1: 8/102 (7.8) IG2: 10/97 (10.3) CG: 7/104 (6.7)</p> <p>Worsening IG1: 1/13 (7.7) IG2: 2/13 (15.4) CG: 1/8 (12.5)</p> <p>Treatment-emergent suicidal ideation at any post-baseline assessment: n (%)</p> <p>Overall IG1: 9/115 (7.8) IG2: 12/110 (10.9) CG: 8/112 (7.1)</p> <p>New-onset IG1: 8/102 (7.8) IG2: 10/97 (10.3) CG: 7/104 (6.7)</p> <p>Worsening IG1: 1/13 (7.7) IG2: 2/13 (15.4) CG: 1/8 (12.5)</p>	<p>Discontinued study treatment: n (%)</p> <p>IG1: 16 (13.9, calculated) IG2: 13 (11.5, calculated) CG: 13 (11.6, calculated)</p> <p>Discontinued due to AE: n (%)</p> <p>IG1: 2 (1.7, calculated) IG2: 1 (.9, calculated) CG: 2 (1.8, calculated)</p> <p>Discontinued due to lack of efficacy: n (%)</p> <p>IG1: 1 (0.9, calculated) IG2: 0 (0.0, calculated) CG: 3 (2.7, calculated)</p> <p>Discontinued due to lost to followup: n (%)</p> <p>IG1: 6 (5.2, calculated) IG2: 5 (4.4, calculated) CG: 4 (3.6, calculated)</p> <p>Discontinued due to protocol violation: n (%)</p> <p>IG1: 3 (2.6, calculated) IG2: 0 (0.0, calculated) CG: 1 (0.9, calculated)</p> <p>Discontinued due to no longer willing to participate: n (%)</p> <p>IG1: 2 (1.7, calculated) IG2: 7 (6.2, calculated) CG: 2 (1.8, calculated)</p>	<p>Any treatment-emergent AEs: %</p> <p>IG1: 69/115 (60.0) IG2: 72/112 (64.3) CG: 79 /112 (70.5)</p> <p>Severe AEs [<i>not defined</i>] considered unrelated to study medication: %</p> <p>IG1: 3.5% IG2: 5.4% CG: 3.6%</p> <p>Severe AEs [not defined]considered related to study medication: n (%)</p> <p>IG1: 3 (2.6, calculated) IG2: 0 (0.0%) CG: 2 (1.8, calculated)</p> <p>Serious AEs: N (%)</p> <p>IG1: 3 (2.6, calculated) IG2: 2 (1.8, calculated) CG: 0 (0.0)</p> <p>Deaths - none</p>	NA



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Weihs, 2018 <sup>55</sup> (continued)		Treatment-emergent suicidal behavior at any post-baseline assessment: n (%) Overall IG1: 0/115 (0.0) IG2: 1/110 (0.9) CG: 0/112 (0.0)  New-onset IG1: 0/115 (0.0) IG2: 1/110 (0.9) CG: 0/112 (0.0)  Worsening IG1: 0 (0.0) IG2: 0 (0.0) CG: 0 (0.0)	Discontinued due to other: n (%) IG1: 2 (1.7, calculated) IG2: 0 (0.0, calculated) CG: 1 (0.9, calculated)		

AE = adverse event; CG = control group; IG = intervention group; KQ = Key Question; n/N = number; NA = not applicable; QD = every day; SIB = suicidal ideation and behavior; TAE = treatment adverse event; TEAE = treatment-emergent adverse event.

**Table F-13. KQ 2a: Harms of TCAs versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Geller, 1989 <sup>61</sup>	IG: Nortriptyline CG: Placebo	NA	Overall withdrawal Randomized sample (n=60; original Ns of patients in IG and CG=NR) 8 weeks, N Overall: 10 IG: NR CG: NR Withdrawal due to suicidal behavior Randomized sample (n=60; original Ns of patients in IG and CG=NR) 8 weeks, N Overall: 1 IG: NR CG: NR	Modified Asberg Side Effects Scale: % change from baseline Completers analysis (n=50; IG: 26 and CG: 24)  8 weeks, mean (SD) IG: -57.00 (37.2) CG: -47.70 (47.7)  Between-group difference: t-test, Bonferroni correction: -0.77; p=0.45  Heart rate (beats/minute): % change from baseline  Completers analysis (n=50; IG: 26 and CG: 24) 8 weeks, mean (SD) IG: 20.40 (10.3) CG: -0.80 (6.8)  Between-group difference: t-test, Bonferroni correction: 8.65; p=0.0001  P-R interval (seconds): % change from baseline  Completers analysis (n=50; IG: 26 and CG: 24) 8 weeks, mean (SD) IG: 4.00 (7.7) CG: 0.80 (6.6)	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Geller, 1989 <sup>61</sup> (continued)				<p>Between-group difference: t-test, Bonferroni correction: 1.57; p=0.12</p> <p>QRS interval (seconds): % change from baseline Completers analysis (n=50; IG: 26 and CG: 24) 8 weeks, mean (SD) IG: 4.80 (10.5) CG: 0.00 (10.2)</p> <p>Between-group difference: t-test, Bonferroni correction: 1.63; p=0.11 Blood pressure: NR</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Geller, 1992 <sup>62</sup>	IG: Nortriptyline CG: Placebo	NR	72 entered, 12 responded during the placebo wash-out phase; 50 completed double-blind, placebo-controlled phase, and 10 discontinued during the double-blind, placebo-controlled phase, no break down by group	Weight Mean Percentage of Change IG Week 1: 2.5 (2.9) CG Week 10: 4.7 (3.1) t=-2.59, p=0.013  Comparisons of the Modified Asberg Side Effects Scales Percentages Weeks 1-2 Tired IG: 23.1 CG:12.5  Sleep IG:19.2 CG:12.5  Headache IG:7.7 CG:8.3  Vertigo IG:3.9 CG:0	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Geller, 1992 <sup>62</sup> (continued)				<p>Weeks 6-9</p> <p>Tired IG: 23.1 CG:29.2</p> <p>Sleep IG:23.1 CG:29.2</p> <p>Headache IG:3.9 CG:12.5</p> <p>Vertigo IG:3.9 CG:0</p> <p>Perspiration IG:0 CG:4.2</p>	
GlaxoSmithKline, 1998 <sup>48</sup> Index article	IG1: paroxetine IG2: imipramine CG: placebo		<p>Treatment-emergent adverse experiences, regardless of attribution, leading to withdrawal (IG1: 93; IG2: 95; CG: 87)</p> <p>Body as a whole IG1: 2 (2.2%) IG2: 7 (7.4%) CG: 1 (1.1%)</p> <p>Cardiovascular System IG1: 1 (1.1%) IG2: 13 (13.7%) CG: 2 (2.3%)</p>	<p>Adverse experiences requiring corrective treatment (IG1: 93; IG2: 95; CG: 87)</p> <p>Headache IG1: 20 (21.5%) IG2: 20 (21.1%) CG: 23 (26.4%)</p> <p>Respiratory Disorder IG1: 8 (8.6%) IG2: 5 (5.3%) CG: 27 (8.0%)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article (continued)			Urogenital System IG1: 0 (0.0%) IG2: 3 (3.2%) CG: 0 (0.0%)	Rhinitis IG1: 6 (6.5%) IG2: 3 (3.2%) CG: 23 (3.4%)	
			Digestive System IG1: 2 (2.2%) IG2: 8 (8.4%) CG: 1 (1.1%)	Pharyngitis IG1: 4 (4.3%) IG2: 9 (9.5%) CG: 25 (5.7%)	
			Musculoskeletal System IG1: 1 (1.1%) IG2: 1 (1.1%) CG: 0 (0.0%)	Infection IG1: 4 (4.3%) IG2: 2 (2.1%) CG: 27 (8.0%) I think this is a typo, should be 7 not 27	
			Nervous System IG1: 8 (8.6%) IG2: 7 (7.4%) CG: 2 (2.3%)	Sinusitis IG1: 4 (4.3%) IG2: 1 (1.1%) CG: 26 (6.9%) I think a typo again, should be 6?	
			Respiratory System IG1: 0 (0.0%) IG2: 2 (2.1%) CG: 0 (0.0%)	Back Pain IG1: 4 (4.3%) IG2: 1 (1.1%) CG: 25 (5.7%)should be 5, not 25?	
			Skin and Appendages IG1: 0 (0.0%) IG2: 4 (4.2%) CG: 1 (1.1%)	Severe Adverse Events IG1: 18 IG2: 11 CG: 2	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup>	IG1: paroxetine IG2: imipramine CG: placebo	Emotional lability (e.g. suicidal ideation/gestures) IG1: 2 IG2: 1 CG: 1	Premature Withdrawal for AE IG1: 9 (9.7%) IG2: 30 (31.6%) CG: 6 (6.9%)	Serious Adverse Effects (resulted in hospitalization, associated with suicidal gestures, or described as serious by treating physician) IG1: 11 IG2: 5 CG: 2  Adverse Effects in ≥5% of Subjects ITT (IG1=90; IG2=94; CG=87) n (%)  Cardiovascular Tachycardia IG1: 2 (2%) IG2: 18 (19%) CG: 1 (1%)  Postural Hypotension IG1: 1 (1%) IG2: 13 (14%) CG: 1 (1%)  Vasodilatation IG1: 0 (0%) IG2: 6 (6%) CG: 2 (2%)	No

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup> (continued)				<p>Chest Pain IG1: 2 (25) IG2: 5 (5%) CG: 2 (2%)</p> <p>Digestive System Dry Mouth IG1: 19 (20%) IG2: 43 (45%) CG: 12 (14%)</p> <p>Nausea IG1: 22 (23.7%) IG2: 23 (24.2%) CG: 17 (19.5%)</p> <p>Constipation IG1: 5 (5.4%) IG2: 9 (9.5%) CG: 4 (4.6%)</p> <p>Decreased Appetite IG1: 7 (7.5%) IG2: 2 (2.1%) CG: 4 (4.6%)</p> <p>Diarrhea IG1: 7 (7.5%) IG2: 3 (3.2%) CG: 7 (8.0%)</p> <p>Dyspepsia IG1: 6 (6.5%) IG2: 9 (9.5%) CG: 4 (4.6%)</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup> (continued)				<p>Tooth Disorder IG1: 5 (5.4%) IG2: 2 (2.1%) CG: 2 (2.3%)</p> <p>Vomiting IG1: 3 (3.2%) IG2: 8 (8.4%) CG: 6 (6.9%)</p> <p>Abdominal Pain IG1: 10 (10.8) IG2: 7 (7.4) CG: 10 (11.5)</p> <p>Nervous System Dizziness IG1: 22 (23.7%) IG2: 45 (47.4%) CG: 16 (18.4%)</p> <p>Emotional Lability IG1: 6 (6.5%) IG2: 3 (3.2%) CG: 1 (1.1%)</p> <p>Hostility IG1: 7 (7.5%) IG2: 3 (3.2%) CG: 0 (0.0%)</p> <p>Insomnia IG1: 14 (15.1%) IG2: 13 (13.7%) CG: 4 (4.6%)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup> (continued)				<p>Nervousness IG1: 8 (8.6%) IG2: 6 (6.3%) CG: 5 (5.7%)</p> <p>Somnolence IG1: 16 (17.2%) IG2: 13 (13.7%) CG: 3 (3.4%)</p> <p>Tremor IG1: 10 (10.8%) IG2: 14 (14.7%) CG: 2 (2.3%)</p> <p>Headache IG1: 32 (34.4) IG2: 38 (40.0) CG: 34 (39.1)</p> <p>Respiratory system Cough Increased IG1: 5 (5.4%) IG2: 3 (3.2%) CG: 6 (6.9%)</p> <p>Pharyngitis IG1: 5 (5.4%) IG2: 12 (12.6%) CG: 8 (9.2%)</p> <p>Respiratory Disorder IG1: 10 (10.8%) IG2: 7 (7.4%) CG: 11 (12.6%)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Keller, 2001 <sup>50</sup> (continued)				Rhinitis IG1: 7 (7.5%) IG2: 3 (3.2%) CG: 5 (5.7%)  Sinusitis IG1: 6 (6.5%) IG2: 2 (2.1%) CG: 7 (8.0%)  Other Sweating IG1: 1 (1.1%) IG2: 6 (6.3%) CG: 1 (1.1%)  Abnormal Vision IG1: 1 (1.1%) IG2: 7 (7.4%) CG: 2 (2.3%) Asthenia IG1: 10 (10.8%) IG2: 7 (7.4%) CG: 10 (11.5%)  Back Pain IG1: 4 (4.3%) IG2: 2 (2.1%) CG: 10 (11.5%)  Infection IG1: 10 (10.8%) IG2: 5 (5.3%) CG: 9 (10.3%)  Trauma IG1: 2 (2.2%) IG2: 3 (3.2%) CG: 6 (6.9%)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup>	IG1: paroxetine IG2: imipramine CG: placebo	Suicidal or self injurious behaviors (IG1: 93; IG2: 95; CG: 87) CSR, Keller, RIAT IG1: 5, 7, 11 IG2: 3, 3, 4 (3 definite, 1 possible) CG: 1, 1, 2 (1 definite, 1 possible)	Withdrawal for adverse events among 86 patients (IG1: 93; IG2: 95; CG: 87) N (%) CSR IG1: 11 (11.8%) IG2: 30 (31.5%) CG: 6 (6.9%)  RIAT IG1: 14 (15.0%) IG2: 31 (32.6%) CG: 6 (6.9%)  Withdrawal for protocol violations CSR IG1: 3 (3.2%) IG2: 5 (5.3%) CG: 7 (8.0%)  RIAT IG1: 1 (1.1%) IG2: 5 (5.3%) CG: 9 (10.3%)  Total dropout rate CSR IG1: 26 (28%) IG2: 38 (40%) CG: 21 (24%)  RIAT IG1: 27 (29%) IG2: 38 (40%) CG: 21 (24%)	Adverse events found in CRFs (IG1: 31; IG2: 40; CG: 22) IG1: 159 IG2: 257 CG: 77  Adverse events appendix of original trial (IG1: 31; IG2: 40; CG: 22) IG1: 136 IG2: 240 CG: 67  % underestimate in relying only on adverse event appendix (IG1: 31; IG2: 40; CG: 22) IG1: 14% IG2: 7% CG: 13%  Adverse events in SKB CSR, Keller 2001, RIAT reanalysis (IG1: 93; IG2: 95; CG: 87) CSR, Keller, RIAT  Cardiovascular IG1: 7, 5, 44 IG2: 60, 42, 130 CG: 12, 6, 32	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)				Gastrointestinal/digestive IG1: 80, 84, 112 IG2: 108, 106, 147 CG: 59, 61, 79  Psychiatric IG1: NR, NR, 103 IG2: NR, NR, 63 CG: NR, NR, 24  Respiratory IG1: 39, 33, 42 IG2: 32, 27, 22 CG: 43, 37, 39  Neurological/ nervous system IG1: 106, 115, 101 IG2: 117, 135, 114 CG: 42, 65, 77  Other IG1: 121, 28, 79 IG2: 51, 30, 76 CG: 30, 38, 79  Body as whole IG1: 106, NR, NR IG2: 125, NR, NR CG: 121, NR, NR  Total IG1: 338, 265, 481 IG2: 493, 340, 552 CG: 277, 207, 330	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)				<p>Adverse events in original study and reorganized by RIAT analysis (IG1: 93; IG2: 95; CG: 87)</p> <p>Cardiovascular IG1: 1 IG2: 3 CG: 0</p> <p>Gastrointestinal IG1: 25 IG2: 20 CG: 4</p> <p>Psychiatric IG1: 32 IG2: 4 CG: 6</p> <p>Respiratory IG1: 2 IG2: 1 CG: 4</p> <p>Neurological IG1: 7 IG2: 14 CG: 7</p> <p>Other IG1: 3 IG2: 8 CG: 5</p> <p>Total IG1: 70 IG2: 50 CG: 26</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup>	IG1: paroxetine IG2: imipramine CG: placebo	RIAT Suicidality and suicide-related events (IG1: 23; IG2: 9; CG: 5)  Total Suspected Suicide-Related AEs, N IG1: 23 IG2: 11 CG: 5  Acute Phase, N IG1: 12 IG2: 6 CG: 2  Continuation Phase, N IG1: 6 IG2: 5 CG: 3 (includes one case that could be classed as trauma)  Taper Phase, N IG1: 5 IG2: 0 CG: 0  Total Confirmed Suicidality and Suicide-Related Episodes, N IG1: 20 IG2: 9 CG: 5  Acute Phase, N IG1: 9 IG2: 4 CG: 2	Continuation Phase Dropouts (as reported in Table 1) SKB, N ITT: IG1=93; IG2=95; CG=87 IG1: 34 IG2: 27 CG: 20  RIAT, N IG1: 31 <sup>a</sup> IG2: 27 CG: 18  Continuation Phase Dropouts (as reported in Table 3), N ITT: IG1=93; IG2=95; CG=87 IG1: 12 IG2: 14 CG: 11  Acute Phase Dropouts (as reported in Table 3), N ITT: IG1=93; IG2=95; CG=87 IG1: 6 IG2: 5 CG: 3	Acute Phase Lack of Efficacy, N ITT: IG1=93; IG2=95; CG=87 IG1: 29 IG2: 36 IG3: 38  Continuation Phase Lack of Efficacy, N ITT: IG1=93; IG2=95; CG=87 IG1: 3 IG2: 2 CG: 2  Total AEs (Severe AEs) by phase and type  Cardiac and vascular disorders Acute Patients Only, N total (N severe) (IG1=44; IG2=56; CG=53) IG1: 14 (1) IG2: 91 (3) CG: 22  Continuation Patients Only, N (IG1=49; IG2=39; CG=31) IG1: 26 IG2: 22 IG3=10	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup> (continued)		Continuation Phase, N IG1: 6 IG2: 5 CG: 3  Taper Phase, N IG1: 5 IG2: 0 CG: 0	Reasons for Withdrawal among Continuation Phase Dropouts (IG1=31; IG2=27; CG=18) Adverse Events, N SKB, RIAT IG1: 2, 5 IG2: 8, 9 CG: 4, 4  Lack of Efficacy N SKB, RIAT IG1: 7, 1 IG2: 8, 9 CG: 6, 2  Relapse SKB, RIAT IG1: 0, 4 IG2: 0, 3 CG: 0, 4  Protocol violation non-compliance SKB, RIAT IG1: 11, 9 IG2: 6, 6 CG: 4, 3  Protocol violation - by investigator SKB, RIAT IG1: 0, 1 IG2: 0, 2 CG: 2, 3	Gastrointestinal disorders Acute Patients Only, N total (N severe) (IG1=44; IG2=56; CG=53) IG1: 45 (5) IG2: 74 (9) CG: 45 (2)  Continuation Patients Only, N total (N severe) (IG1=49; IG2=39; CG=31) IG1: 62 (16) IG2: 59 (7) CG: 32 (2)  Psychiatric Disorders Acute Patients Only, N total (N severe) (IG1=44; IG2=56; CG=53) IG1: 58 (18) IG2: 39 (4) CG: 20 (4)  Continuation Patients Only, N total (N severe) (IG1=49; IG2=39; CG=31) IG1: 42 (6) IG2: 24 IG3: 7 (1)  Nervous system disorders Acute Patients Only, N total (N severe) (IG1=44; IG2=56; CG=53) IG1: 31 (1) IG2: 73 (9) CG: 55 (3)	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup> (continued)			<p>Lost to followup SKB, RIAT IG1: 2,2 IG2: 1,1 CG: 2,3</p> <p>Other ("Feeling well") SKB, RIAT IG1: 1, 0 IG2: 0,0 CG: 0,0</p>	<p>Continuation Patients Only, N total (N severe) (IG1=49; IG2=39; CG=31) IG1: 63 (5) IG2: 34 (3) IG3: 22 (4)</p> <p>Respiratory and thoracic disorders Acute Patients Only, N total (N severe) (IG1=44; IG2=56; CG=53) IG1: 18 (1) IG2: 15 (1) CG: 27 (2)</p> <p>Continuation Patients Only, N total (N severe) (IG1=49; IG2=39; CG=31) IG1: 21 (1) IG2: 7 IG3: 13 (2)</p> <p>Respiratory and thoracic disorders Acute Patients Only, N total (N severe) (IG1=44; IG2=56; CG=53) IG1: 18 (1) IG2: 15 (1) CG: 27 (2)</p> <p>Continuation Patients Only, N total (N severe) (IG1=49; IG2=39; CG=31) IG1: 21 (1) IG2: 7 IG3: 13 (2)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup> (continued)				<p>All other SOC's</p> <p>Acute Patients Only, N total (N severe) (IG1=44; IG2=56; CG=53) IG1: 24 IG2: 44 (4) CG: 51 (1)</p> <p>Continuation Patients Only, N total (N severe) (IG1=49; IG2=39; CG=31) IG1: 53 (3) IG2: 24 (1) IG3: 26 (4)</p> <p>Total AEs</p> <p>Acute Patients Only, N total (N severe) (IG1=44; IG2=56; CG=53) IG1: 190 (26) IG2: 336 (30) CG: 220 (12)</p> <p>Continuation Patients Only, N total (N severe) (IG1=49; IG2=39; CG=31) IG1: 267 (31) IG2: 184 (11) IG3: 110 (13)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Klein, 1998 <sup>63</sup>	IG: Desipramine CG: Placebo	NR	<p>Withdrawals IG:5 (developed unrelated to DMI, rash, improved completely and terminated treatment, inadequate compliance-2) CG:4 (moved away, rash, Stomachaches, drug use)</p> <p>Withdrawals due to AE IG: 1 (rash) CG: 2 (rash and Stomachache)</p>	Any Side Effects IG: 52% CG: 18% p=0.02	NR
Kye, 1996 <sup>64</sup>	IG: AMI CG: Placebo	Suicidality IG: 0 CG: 1/13	<p>Noncompleters IG:12 CG 10 p=NS</p> <p>Noncompleters due to Noncompliance IG: 2 CG: 0</p> <p>Suicidality IG: 0 CG: 1</p> <p>Side effects IG: 1 CG: 1</p> <p>First-degree heart block IG: 1 CG: 0</p>	Side Effects Scale IG associated with poor appetite, p <0.04 IG associated with blurry vision, p <0.01	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Kye, 1996 <sup>64</sup> (continued)			Hypomania IG: 2 CG: 1		

AE = adverse event; AMI = amitriptyline; CG = control group; CRF = corticotropin-releasing factor; CSR = clinical study report; FET = Functional Ensemble of Temperament; IG = intervention group; KQ = Key Question; n/N = number; NA = not applicable; NR = not reported; QRS = QRS complex of graphical deflections seen on a electrocardiogram; RIAT = restoring invisible and abandoned trials; SKB = SmithKline Beecham; SOC = system organ class.

**Table F-14. KQ 2a: Harms of MAOIs versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
DeBello, 2014 <sup>65</sup>	IG: STS CG: Placebo	Suicidal ideation IG: 4/152 CG: 4/156	Withdrawals IG: 51/152 CG: 42/156  Withdrawals due to AEs IG: 10/152 CG: 5/156  Withdrawals due to suicidal ideation IG: 1 CG: 1  Withdrawals due to medication-induced agitation, agitation, and uncontrolled screaming IG: 3 CG: 0	Any AE IG: 95 (62.5%) CG: 90 (57.7%)  Serious AEs: 14 events (10 patients [3.2%] discontinued from the study)  Most common AEs Patch Application reactions: 71 (23.1%) Headache: 52 (16.9%) Nausea: 23 (7.5%)  More frequently in STS-treated subjects (generally reported as mild to moderate in intensity) Decreased appetite IG: 3.3% CG: 1.3%  Agitation IG: 2.6% CG: 1.9%  Anxiety IG: 2.6% CG: 1.3%  Insomnia IG: 5.9% CG: 2.6%	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
DeBello, 2014 <sup>65</sup> (continued)				<p>Somnolence IG: 4.6% CG: 2.6%</p> <p>Upper respiratory tract infection IG: 7.2% CG: 2.6%</p> <p>Vomiting IG: 4.6% CG: 2.6%</p> <p>Other AEs GI disorders IG: 31 (20.4) CG: 31 (19.9)</p> <p>Abdominal pain IG: 3 (2.0) CG: 4 (2.6)</p> <p>Abdominal pain upper IG: 4 (2.6) CG: 7 (4.5)</p> <p>Diarrhea IG: 5 (3.3) CG: 7 (4.5)</p> <p>Nausea IG: 11 (7.2) CG: 12 (7.7)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
DeBello, 2014 <sup>65</sup> (continued)				<p>General disorders and administration site conditions IG: 42 (27.6) CG: 42 (26.9)</p> <p>Application site reaction IG: 37 (24.3) CG: 34 (21.8)</p> <p>Fatigue IG: 4 (2.6) CG: 4 (2.6)</p> <p>Infections and infestations IG: 18 (11.8) CG: 18 (11.5)</p> <p>Nasopharyngitis IG: 6 (3.9) CG: 7 (4.5)</p> <p>Metabolism and nutrition disorders IG: 6 (3.9) CG: 4 (2.6)</p> <p>Musculoskeletal and connective tissue disorders IG: 13 (8.6) CG: 9 (5.8)</p> <p>Back pain IG: 4 (2.6) CG: 4 (2.6)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
DeIbello, 2014 <sup>65</sup> (continued)				Nervous system disorders IG: 41 (27.0) CG: 38 (24.4)  Dizziness IG: 8 (5.3) CG: 7 (4.5)  Headache IG: 26 (17.1) CG: 26 (16.7)  Psychiatric disorders IG: 24 (15.8) CG: 17 (10.9)  Irritability IG: 2 (1.3) CG: 4 (2.6)  Respiratory, thoracic & mediastinal disorders IG: 25 (16.4) CG: 12 (7.7)  Pharyngolaryngeal pain IG: 4 (2.6) CG: 3 (1.9)	

AE = adverse event; CG = control group; IG = intervention group; KQ = Key Question; NR = not reported; STS = Selegiline Transdermal system.



**Table F-15. KQ 2a: Harms of venlafaxine plus active control versus placebo plus active control**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Mandoki 1997 <sup>66</sup>	IG: venlafaxine and therapy CG: placebo and therapy	NR	Failed to come to clinic by second week for unknown reasons IG: 3 CG: 3  Manic episode resulting in hospitalization IG: 1 CG: 0	Nausea (2nd week) All patients at 2nd week IG: 43.75% CG: 6.75% p=0.37	NR

CG = control group; IG = intervention group; KQ = Key Question; NR = not reported.

**Table F-16. KQ 3a: Harms of fluoxetine plus CBT versus placebo**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, observed case analysis (n=359) 12 weeks, adjusted mean (SD) IG1: 10.9 (0.3) IG2: 13.7 (0.2) IG3: 11.3 (0.3) CG: 14.5 (0.6) No between-group differences: p=NS  Comparison of change in SIQ-Jr total score from baseline to 12 weeks, observed case analysis (n=359) IG1>IG2: p=0.004 IG1>IG3: p=0.04 IG1>CG: p=0.02  Emergence or worsening of suicidal ideation (change from baseline SIQ-Jr <31 to SIQ-Jr ≥31 at 6 or 12 weeks), observed case analysis (n=374) 12 weeks, n (%) IG1: 2/93 (2.2) IG2: 7/96 (7.3) IG3: 2/93 (2.2) CG: 7/92 (7.6) No between-group differences: p=NS	NA	Self-reported PSC, observed case analysis (n=364) 12 weeks, mean (SD) IG1: 11.0 (8.2) IG2: 13.0 (10.5) IG3: 18.5 (17.5) CG: 12.3 (8.9)  Statistical comparisons of medication-based arms (IG1; IG2, and CG) with IG3 found that IG3 patients reported significantly higher/worse PSC scores: IG1<IG3: p=0.0036 IG2<IG3: p=0.0328 CG<IG3: p=0.0280 No between-group differences between IG1; IG2, and CG arms (all p's=NS)  Factor-based PSC scores (sleep, upper respiratory, pain, cardiac, panic, elimination, nausea, and skin), observed case analysis (N=364) 12 weeks	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Worsening of suicidality from baseline to 6 or 12 weeks (CDRS-R item 13 worsening by <math>\geq 1</math> point), observed case analysis (n=374) Calculated n (%) IG1: 2/93 (5.0) IG2: 7/96 (13.4) IG3: 2/93 (15.2) CG: 7/92 (7.2) No between-group differences: p=NS</p> <p>Emergence of suicidality from baseline to 6 or 12 weeks (change from CDRS-R item score=1 or 2 to <math>\geq 5</math>), observed case analysis (n=374) Calculated n (%) IG1: 0/93 (0) IG2: 4/96 (3.7) IG3: 1/93 (1.3) CG: 2/92 (2.6) No between-group differences: p=NS</p> <p>Suicide-Related AEs (primary analysis: C-CASA Codes 1, 2, and 6), ITT (n=439) 12 weeks, N (%) IG1: 5 (4.7) IG2: 10 (9.2) IG3: 5 (4.5) CG: 3 (2.7) Statistical comparisons of groups, OR (95% CI) IG1=IG3: p=NS IG1=CG: p=NS IG2&gt;CG: 3.7 (1.00 to 13.7), p=0.0402, meaning higher incidence in IG2</p>		<p>All treatment arms showed improvement on each of the 8 PSC factors. Pain was the only factor with a significant treatment-by-time interaction (p=NR), based on significantly more improvement compared with IG3 IG1&gt;IG3: p=0.0011 IG2&gt;IG3: p=0.0017</p> <p>Treatment-emergent physical AEs (spontaneous), ITT (n=439) 12 weeks, N patients [N events], (calculated % patients) IG1: 37 [61] (34.6) IG2: 35 [81] (32.1) IG3: NR [9] (NR) CG: 34 [60] (30.4) No between-group differences in arms receiving pills (IG1; IG2, and CG), but more events reported in IG2 than IG1 or CG (p=NR).</p> <p>Spontaneously reported physical AEs reported in <math>\geq 2\%</math> of active treatment arms and at rates at least twice that of CG, ITT (n=429) 12 weeks Sedation IG1: 1 (0.9) IG2: 3 (2.8) IG3: 0 CG: 0 IG2 vs. CG ratio: 3.00</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Suicide-Related AEs (sensitivity analysis: C-CASA Codes 1, 2, 3, and 6), ITT (n=439) 12 weeks, N (%) IG1: 6 (5.6) IG2: 10 (9.2) IG3: 5 (4.5) CG: 3 (2.7) Between-group differences NR</p> <p>Suicide attempts (C-CASA Code 1), ITT (n=439) 12 weeks, N (%) IG1: 2 (1.9) IG2: 1 (1.8) IG3: 1 (0.9) CG: 0</p> <p>Preparatory actions toward imminent suicidal behavior (C-CASA Code 2), ITT (n=439) No events at 12 weeks Self-injurious behavior: unknown intent (C-CASA Code 3), ITT (n=439) 12 weeks, N (%) IG1: 1 (0.9) IG2: 0 IG3: 0 CG: 0</p>		<p>Insomnia IG1: 5 (4.7) IG2: 3 (2.8) IG3: 0 CG: 1 (0.9) IG1 vs. CG ratio: 5.23 IG2 vs. CG ratio: 3.08</p> <p>Vomiting IG1: 4 (3.7) IG2: 2 (1.8) IG3: 1 (0.9) CG: 1 (0.9) IG1 vs. CG ratio: 4.19</p> <p>Upper abdominal pain IG1: 1 (0.9) IG2: 6 (5.5) IG3: 0 CG: 2 (1.8) IG2 vs. CG ratio: 3.08</p> <p>Headache: only spontaneously reported physical AE occurring in &gt;5% of patients, ITT (N=429) 12 weeks, calculated n (%) IG1: 7 (6.8) IG2: 13 (11.9) IG3: NA CG: 12 (10.7) No between-group differences (p=NS)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Suicidal ideation (C-CASA Code 6), ITT (n=439) 12 weeks, N (%) IG1: 3 (2.8) IG2: 8 (7.3) IG3: 4 (3.6) CG: 3 (2.7)</p> <p>Timing of suicide-related events, ITT (n=439) 12 weeks, mean days (SD) IG1: 52.0 (20.8) IG2: 38.0 (21.7) IG3: 45.4 (26.7) CG: 32.0 (15.0) No between-group differences: p=NS</p>		<p>Emergence or worsening of physical symptoms (change from baseline PSC severity of 0 [not at all] or 1 [just a little] to 2 [pretty much] or 3 [very much] at 6 or 12 weeks), observed case analysis (N=374) 12 weeks, n (%) (NOTE: patients with multiple reports of same event were counted only once)</p> <p>Sleep disturbance: Trouble sleeping IG1: 12 (3.3) IG2: 14 (15.2) IG3: 11 (12.5) CG: 14 (15.1)</p> <p>Sleep disturbance: Feeling drowsy or too sleepy IG1: 17 (18.9) IG2: 15 (16.3) IG3: 12 (13.5) CG: 16 (17.2)</p> <p>Sleep disturbance: Sleeplessness IG1: 12 (13.3) IG2: 17 (18.5) IG3: 16 (18.2) CG: 9 (9.7)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Sleep disturbance: Nightmares or very strange dreams IG1: 11 (12.2) IG2: 17 (18.5) IG3: 7 (8.0) CG: 13 (14.0)</p> <p>Sleep disturbance: Restless or uncomfortable urge to move IG1: 2 (2.2) IG2: 9 (9.8) IG3: 5 (5.7) CG: 10 (10.8)</p> <p>Upper respiratory: Head cold or sniffles IG1: 15 (16.7) IG2: 16 (17.4) IG3: 13 (14.6) CG: 16 (17.2)</p> <p>Upper respiratory: Allergies IG1: 10 (11.1) IG2: 13 (14.1) IG3: 13 (14.6) CG: 8 (8.6)</p> <p>Upper respiratory: Sore throat IG1: 8 (8.9) IG2: 6 (6.5) IG3: 9 (10.1) CG: 14 (15.1)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Upper respiratory: Dry mouth IG1: 9 (10.0) IG2: 8 (8.7) IG3: 8 (9.0) CG: 7 (7.5)  Upper respiratory: Coughing or wheezing IG1: 6 (6.7) IG2: 5 (5.4) IG3: 6 (6.8) CG: 8 (8.6)  Upper respiratory: Fever IG1: 6 (6.7) IG2: 4 (4.4) IG3: 6 (6.7) CG: 4 (4.3)  Pain: Stomach pain or ache IG1: 6 (6.7) IG2: 10 (10.9) IG3: 9 (10.1) CG: 13 (14.0)  Pain: Muscle aches or cramps IG1: 9 (10.0) IG2: 5 (5.4) IG3: 12 (13.6) CG: 12 (12.9)  Pain: Joint pain IG1: 3 (3.3) IG2: 2 (2.2) IG3: 8 (8.9) CG: 9 (9.7)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Pain: Numbness or tingling in arms or legs IG1: 3 (3.3) IG2: 3 (3.3) IG3: 5 (5.7) CG: 5 (5.4)  Cardiac: Chest pain IG1: 4 (4.4) IG2: 5 (5.4) IG3: 4 (4.6) CG: 6 (6.5)  Cardiac: Racing or pounding heart IG1: 2 (2.2) IG2: 2 (2.2) IG3: 5 (5.7) CG: 6 (6.5)  Cardiac: Heart skips beats IG1: 1 (1.1) IG2: 2 (2.2) IG3: 3 (3.4) CG: 1 (1.1)  Panic: Excessive sweating IG1: 3 (3.3) IG2: 6 (6.5) IG3: 2 (2.3) CG: 9 (9.7)  Panic: Difficulty breathing IG1: 4 (4.4) IG2: 3 (3.3) IG3: 2 (2.3) CG: 6 (6.5)	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Panic: Can't hear well IG1: 3 (3.3) IG2: 2 (2.2) IG3: 4 (4.6) CG: 2 (2.2)  Elimination: Frequent urination IG1: 6 (6.7) IG2: 4 (4.4) IG3: 11 (12.5) CG: 6 (6.5)  Elimination: Feeling bloated or gassy IG1: 2 (2.2) IG2: 6 (6.5) IG3: 6 (6.8) CG: 7 (7.5)  Elimination: Pain with urination IG1: 2 (2.2) IG2: 1 (1.1) IG3: 3 (3.4) CG: 0  Elimination: Constipation IG1: 1 (1.1) IG2: 0) IG3: 4 (4.6) CG: 3 (3.2)  Diarrhea IG1: 4 (4.4) IG2: 5 (5.4) IG3: 6 (6.7) CG: 7 (7.5)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Nausea or vomiting IG1: 8 (8.9) IG2: 3 (3.3) IG3: 10 (11.2) CG: 5 (5.4)</p> <p>Skin: Skin rash IG1: 6 (6.7) IG2: 4 (4.4) IG3: 9 (10.1) CG: 4 (4.3)</p> <p>Skin: Hives IG1: 0 IG2: 2 (2.2) IG3: 1 (1.1) CG: 2 (2.2)</p> <p>Other: Headache IG1: 12 (13.3) IG2: 18 (19.6) IG3: 14 (15.7) CG: 16 (17.2)</p> <p>Treatment with FLX (i.e.; IG1 or IG2) did not lead to significantly higher rates of symptom worsening or emergence on any physical symptoms (p=NR).</p> <p>Furthermore, the double-blind treatment arms (IG2 and CG) did not differ significantly on symptom worsening or emergence on any physical symptoms (p=NR).</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Worsening of Psychiatric Symptoms (CGI-I <math>\geq 5-7</math> [slightly worse, much worse, or very much worse] at 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 3 (2.8) IG3: 10 (9.0) CG: 7 (6.3) Between-group differences : IG1 and IG2 (FLX arms) had significantly lower rates of worsening than IG3 and CG (non-FLX arms) (<math>p=0.01</math>). Ns of individual arms too small to allow statistical comparison.</p> <p>Worsening of Psychiatric Symptoms (CGI-S <math>\geq 1</math> point from baseline to 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 2 (1.8) IG3: 5 (4.5) CG: 9 (8.0) Between-group differences NR</p> <p>Treatment-emergent psychiatric AEs (spontaneously reported), ITT (N=429) 12 weeks, n (%) (NOTE: Patients may be represented in more than one arm due to patient-initiated crossover)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Any treatment-emergent psychiatric AE  IG1: 6 (5.6)  IG2: 12 (11.0)  IG3: 1 (0.91)  CG: 5 (4.5)</p> <p>Between-group comparisons:  IG1 and IG2 (FLX arms) experienced more psychiatric AEs than IG3 or CG (non-FLX arms).  IG2 experienced more psychiatric AEs than CG, but Ns too small to detect statistical significance.</p> <p>Mania spectrum (mania, hypomania, elevated mood)  IG1: 1 (0.93)  IG2: 4 (3.67)  IG3: 0  CG: 1 (0.89)</p> <p>Irritability spectrum (hypersensitivity, irritability, anger, worsening depression, crying)  IG1: 2 (1.86)  IG2: 4 (3.67)  IG3: 0  CG: 1 (0.89)</p> <p>Agitation spectrum (agitation, akathisia, nervousness, restlessness, hyperactivity)  IG1: 1 (0.93)  IG2: 2 (1.84)  IG3: 2 (1.78)  CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Anxiety (anxiety, panic attacks) IG1: 0 IG2: 2 (1.84) IG3: 1 (0.91) CG: 0</p> <p>Other (tremor, "abnormal behavior", "feeling spacy") IG1: 2 (1.84) IG2: 2 (1.84) IG3: 0 CG: 1 (0.89)</p> <p>ADS Mania subscale severity scores (clinician-reported), ITT (N=429) 12 weeks, mean (SD) IG1: 0.5 (0.8) IG2: 1.1 (1.0) IG3: 1.0 (1.2) CG: 1.1 (0.1)</p> <p>Between-group comparisons: IG1&lt;IG2: p=0.013 IG1&lt;CG: p=0.003 IG1&lt;IG3: p=0.012 IG2=IG3: p=NR</p> <p>ADS Mania change from baseline of ≥3 points, modified ITT (n=424 with ≥2 mania total scores) 12 weeks, n (%) IG1: 21 (20) IG2: 15 (14.2) IG3: 13 (12.3) CG: 16 (15.0)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Between-group differences NR Incidence of mania or hypomania: ADS Mania scale, ITT (N=429) 12 weeks, n (calculated %) IG1: 3 (2.8) IG2: 1 (0.9) IG3: 0 CG: 1 (0.9)	

AE = adverse event; CBT = cognitive behavioral therapy; C-CASA = Columbia Classification Algorithm of Suicide Assessment; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CI = confidence interval; FLX = fluoxetine; IG = intervention group; ITT = intent to treat; KQ = Key Question; NA = not applicable; NS = not significant; OR = odds ratio; PSC = physical symptom severity; SD = standard deviation; SIQ-JR = Suicide Ideation Questionnaire-Junior High School; TADS = Treatment among Adolescents with Depression.

**Table F-17. KQ 5a: Harms of CBT versus other psychotherapy**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Index article	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	Adverse event scores; Mean (SD); Median (range) Baseline IG1 (n=154): 5.1 (1.0); 5 (2–6) IG2 (n=156): 5.0 (1.1); 5 (2–6) CG (n=155): 5.0 (1.1); 5 (1–6)  6 weeks IG1 (n=104): 4.6 (1.3); 5 (2–6) IG2 (n=107): 4.4 (1.5); 5 (0–6) CG (n=99): 4.4 (1.5); 5 (0–6)  12 weeks IG1 (n=106): 4.0 (1.5); 4 (0–6) IG2 (n=108): 4.2 (1.6); 4 (0–6) CG (n=112): 4.2 (1.6); 4 (0–6)  36 weeks IG1 (n=104): 3.6 (1.6); 4 (0–6) IG2 (n=109): 3.6 (1.7); 4 (0–6) CG (n=105): 4.1 (1.6); 4 (0–6)  52 weeks IG1 (n=111): 3.5 (1.9); 4 (0–6) IG2 (n=110): 3.2 (1.9); 3 (0–6) CG (n=105): 3.5 (1.8); 3.5 (0–6)  86 weeks IG1 (n=123): 3.4 (1.9); 4 (0–6) IG2 (n=114): 3.2 (1.8); 3 (0–6) CG (n=116): 3.3 (1.8); 3.5 (0–6)	NR	Recent nonsuicidal self-injury is defined as within 2 weeks, so the time frame for recent suicide attempt is likely similar	
Goodyer, 2017 <sup>16</sup> Index article Companion article: Goodyer, 2017 <sup>17</sup>	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	See Goodyer, 2017 <sup>16</sup> Index article (in this study, data can be found in Table 1)	See Goodyer, 2017 <sup>16</sup> Index article (information in this study can be found in "Figure: Trial Profile")	See Goodyer, 2017 <sup>16</sup> Index article (data reported in this study in Table 4)	CBT and short-term psychoanalytic psychotherapy vs. brief psychosocial intervention

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out	Other Harms	Subgroup(s) Examined
Goodyer, 2017 <sup>16</sup> Companion: O'Keeffe, 2018 <sup>19</sup>	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention		IG1: 32% IG2: 43% CG: 36% No evidence of difference in chi-square test ( $\chi^2(4, N=453)=9.07, p=0.059$ )		

CG = control group; IG = intervention group; KQ = Key Question; NR = not reported; SD = standard deviation.



**Table F-18. KQ 5a: Harms of psychotherapy versus pharmacotherapy**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Iftene, 2015 <sup>78</sup>	IG1: Sertraline IG2: Group Rational Emotive Behavior Therapy/CBT IG3: Sertraline plus Group Rational Emotive Behavior Therapy/CBT	0 Suicide Attempts During Trial  Suicide Ideation, report decrease across groups, $F(4, 72)=25.37$ , $p<0.001$ , but no differences across groups, $F(2,72)=0.042$ , $p<0.05$	Withdrawals IG1: 5 IG2: 5 IG3: 4	None of the participants reported major side effects.  Headaches IG1: 2 IG2: 1 IG3: 3  Insomnia IG1: 1 IG2: 1 IG3: 0  Sleepiness IG1: 1 IG2: 0 IG3: 1  Low appetite IG1: 2 IG2: 0 IG3: 1  Weight Gain IG1: 1 IG2: 0 IG3: 0  Fatigue IG1: 1 IG2: 0 IG3: 0	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Iftene, 2015 <sup>78</sup> (continued)				Dizziness IG1: 0 IG2: 0 IG3: 1  Sweats IG1: 0 IG2: 0 IG3: 1	
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, ITT (n=439) 6 weeks, adjusted mean (SD) IG1: 14.31 (12.58) IG2: 16.20 (12.42) IG3: 13.18 (11.34) CG: 16.85 (11.70)  12 weeks, adjusted mean (SD) IG1: 11.79 (11.69) IG2: 14.44 (11.13) IG3: 11.40 (10.44) CG: 15.01 (11.05)  None of the post-hoc supportive contrasts at 12 weeks comparing improvement following active treatments vs. placebo were statistically significant  Across all 12 weeks: Time-by-treatment interaction based on SIQ-Jr random regression slope coefficients: p=0.01;	Early termination at 12 weeks Patient-initiated withdrawal, N (calculated %) IG1: 7 (6.54) IG2: 5 (4.59) IG3: 16 (14.41) CG: 10 (8.93) Between-group difference: p=0.18  Patient Removal due to out-of-protocol treatment in place of or in addition to study treatment, N (calculated %) IG1: 8 (7.48) IG2: 13 (11.93) IG3: 8 (7.21) CG: 13 (11.61) Between-group difference: p=0.50	Serious AEs, N (%) IG1: 9 (8.41) IG2: 13 (11.93) IG3: 5 (4.50) CG: 6 (5.36)  Serious AEs, OR (95% CI) vs. CG: IG1: 1.62 (0.56 to 4.72) IG2: 2.39 (0.87 to 6.54) IG3: 0.83 (0.25 to 2.81) CG: NA Between-groups p=0.15 NOTE: ORs ≤2 reflect little or no increased risk  Serious Psychiatric-Related AEs, ITT (n=439) N patients [N events], (calculated %) IG1: 0 IG2: 1 [1] (0.92) (worsening depression, also captured below) IG3: 0 CG: 1 [1] (0.89) (mania, also captured below)	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Statistically comparing improvement: IG1&gt;CG (p=0.02); IG1&gt;IG2 (p=0.002); IG1&gt;IG3 (p=0.05); IG2=IG3 (p=0.22); IG2=CG (p=0.36); IG3=CG (p=0.76)</p> <p>Hedge g effect sizes relative to placebo (CG) IG1: 0.28 IG2: 0.05 IG3: 0.33</p> <p>NOTE: Above means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model</p> <p>Suicide-Related AEs, N (%) IG1: 6 (5.61) IG2: 9 (8.26) IG3: 5 (4.50) CG: 4 (3.57)</p>		<p>Any Psychiatric-Related AEs, ITT (n=439) N patients [N events], (%) IG1: 12 [16] (15) IG2: 20 [23] (21) IG3: 1 [1] (1) CG: 9 [11] (9.8) These events more frequent in fluoxetine arms (IG1 and IG2) than CBT (IG3) or placebo (CG), but p=NR</p> <p>Mania, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)</p> <p>Hypomania, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p> <p>Elevated mood, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Hypersensitivity, ITT (n=439) N events (%) IG1: 0 IG2: 2 (1.83) IG3: 0 CG: 0</p> <p>Irritability, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Anger, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Worsening of depression, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		Suicide-Related AEs, OR (95% CI) vs. CG: IG1: 1.60 (0.44 to 5.85) IG2: 2.43 (0.73 to 8.14) IG3: 1.27 (0.33 to 4.87) CG: NA Suicide attempts, N (calculated %) IG1: 4 (3.74%) IG2: 2 (1.83%) IG3: 1 (0.90%) CG: 0 N of events too small to allow statistical comparison of suicide events		Crying, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0  Agitation, ITT (n=439) N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)  Akathisia, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0  Nervousness, ITT (n=439) N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)  Restlessness, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Hyperactivity, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Panic attacks, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 1 (0.91) CG: 0</p> <p>Anxiety, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Somnolence, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Insomnia, ITT (n=439) N events (%) IG1: 5 (4.67) IG2: 3 (2.75) IG3: 0 CG: 1 (0.89)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Nightmares, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0</p> <p>Night sweats, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Sedation, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 3 (2.75) IG3: 0 CG: 0</p> <p>Fatigue, ITT (n=439) N events (%) IG1: 2 (1.87) IG2: 1 (0.92) IG3: 0 CG: 2 (1.79)</p> <p>Tremors, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 2 (1.83) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Abnormal behavior N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Feeling abnormal N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0 p=NR</p> <p>Nonpsychiatric AEs, ITT (n=439) Generally more frequent in fluoxetine-treated arms (IG1 and IG2) than CBT (IG3) or placebo (CG)</p> <p>Headache, ITT (n=439) N patients (%) IG1: N (5.6) IG2: N (12) IG3: 0 CG: N (9) This was the only AE occurring in ≥10% of patients in any single treatment group</p> <p>Sedation IG1: 0 IG2: 3 (2.75) IG3: 0 CG: 0</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				Upper abdominal pain IG1: 0 IG2: 6 (5.5) IG3: 0 CG: 2 (1.79)  Diarrhea IG1: 2 (1.87) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)  Influenza IG1: 0 IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)  Insomnia IG1: 5 (4.67) IG2: 3 (2.75) IG3: 0 CG: 1 (0.89)  Sinusitis IG1: 0 IG2: 4 (3.67) IG3: 0 CG: 2 (1.79)  Vomiting IG1: 4 (3.74) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, observed case analysis (n=359) 12 weeks, adjusted mean (SD) IG1: 10.9 (0.3) IG2: 13.7 (0.2) IG3: 11.3 (0.3) CG: 14.5 (0.6) No between-group differences: p=NS  Comparison of change in SIQ-Jr total score from baseline to 12 weeks, observed case analysis (n=359) IG1>IG2: p=0.004 IG1>IG3: p=0.04 IG1>CG: p=0.02  Emergence or worsening of suicidal ideation (change from baseline SIQ-Jr <31 to SIQ-Jr ≥31 at 6 or 12 weeks), observed case analysis (n=374) 12 weeks, n (%) IG1: 2/93 (2.2) IG2: 7/96 (7.3) IG3: 2/93 (2.2) CG: 7/92 (7.6) No between-group differences: p=NS	NA	Self-reported PSC, observed case analysis (n=364) 12 weeks, mean (SD) IG1: 11.0 (8.2) IG2: 13.0 (10.5) IG3: 18.5 (17.5) CG: 12.3 (8.9)  Statistical comparisons of medication-based arms (IG1; IG2, and CG) with IG3 found that IG3 patients reported significantly higher/worse PSC scores: IG1<IG3: p=0.0036 IG2<IG3: p=0.0328 CG<IG3: p=0.0280 No between-group differences between IG1; IG2, and CG arms (all p's=NS)  Factor-based PSC scores (sleep, upper respiratory, pain, cardiac, panic, elimination, nausea, and skin), observed case analysis (N=364) 12 weeks	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Worsening of suicidality from baseline to 6 or 12 weeks (CDRS-R item 13 worsening by <math>\geq 1</math> point), observed case analysis (n=374) Calculated n (%) IG1: 2/93 (5.0)</p> <p>IG2: 7/96 (13.4) IG3: 2/93 (15.2) CG: 7/92 (7.2) No between-group differences: p=NS</p> <p>Emergence of suicidality from baseline to 6 or 12 weeks (change from CDRS-R item score=1 or 2 to <math>\geq 5</math>), observed case analysis (n=374) Calculated n (%) IG1: 0/93 (0) IG2: 4/96 (3.7) IG3: 1/93 (1.3) CG: 2/92 (2.6) No between-group differences: p=NS</p> <p>Suicide-Related AEs (primary analysis: C-CASA Codes 1, 2, and 6), ITT (n=439) 12 weeks, N (%) IG1: 5 (4.7) IG2: 10 (9.2) IG3: 5 (4.5) CG: 3 (2.7)</p>		<p>All treatment arms showed improvement on each of the 8 PSC factors. Pain was the only factor with a significant treatment-by-time interaction (p=NR), based on significantly more improvement compared with IG3 IG1&gt;IG3: p=0.0011 IG2&gt;IG3: p=0.0017</p> <p>Treatment-emergent physical AEs (spontaneous), ITT (n=439) 12 weeks, N patients [N events], (calculated % patients) IG1: 37 [61] (34.6) IG2: 35 [81] (32.1) IG3: NR [9] (NR) CG: 34 [60] (30.4) No between-group differences in arms receiving pills (IG1; IG2, and CG), but more events reported in IG2 than IG1 or CG (p=NR).</p> <p>Spontaneously reported physical AEs reported in <math>\geq 2\%</math> of active treatment arms and at rates at least twice that of CG, ITT (n=429) 12 weeks Sedation IG1: 1 (0.9) IG2: 3 (2.8) IG3: 0 CG: 0 IG2 vs. CG ratio: 3.00</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Statistical comparisons of groups, OR (95% CI) IG1=IG3: p=NS IG1=CG: p=NS IG2&gt;CG: 3.7 (1.00 to 13.7), p=0.0402, meaning higher incidence in IG2</p> <p>Suicide-Related AEs (sensitivity analysis: C-CASA Codes 1, 2, 3, and 6), ITT (n=439) 12 weeks, N (%) IG1: 6 (5.6) IG2: 10 (9.2) IG3: 5 (4.5) CG: 3 (2.7) Between-group differences NR</p> <p>Suicide attempts (C-CASA Code 1), ITT (n=439) 12 weeks, N (%) IG1: 2 (1.9) IG2: 1 (1.8) IG3: 1 (0.9) CG: 0</p> <p>Preparatory actions toward imminent suicidal behavior (C-CASA Code 2), ITT (n=439) No events at 12 weeks Self-injurious behavior: unknown intent (C-CASA Code 3), ITT (n=439) 12 weeks, N (%) IG1: 1 (0.9) IG2: 0 IG3: 0 CG: 0</p>		<p>Insomnia IG1: 5 (4.7) IG2: 3 (2.8) IG3: 0 CG: 1 (0.9) IG1 vs. CG ratio: 5.23 IG2 vs. CG ratio: 3.08</p> <p>Vomiting IG1: 4 (3.7) IG2: 2 (1.8) IG3: 1 (0.9) CG: 1 (0.9) IG1 vs. CG ratio: 4.19</p> <p>Upper abdominal pain IG1: 1 (0.9) IG2: 6 (5.5) IG3: 0 CG: 2 (1.8) IG2 vs. CG ratio: 3.08</p> <p>Headache: only spontaneously reported physical AE occurring in &gt;5% of patients, ITT (N=429) 12 weeks, calculated n (%) IG1: 7 (6.8) IG2: 13 (11.9) IG3: NA CG: 12 (10.7) No between-group differences (p=NS)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Suicidal ideation (C-CASA Code 6), ITT (n=439) 12 weeks, N (%) IG1: 3 (2.8) IG2: 8 (7.3) IG3: 4 (3.6) CG: 3 (2.7)</p> <p>Timing of suicide-related events, ITT (n=439) 12 weeks, mean days (SD) IG1: 52.0 (20.8) IG2: 38.0 (21.7) IG3: 45.4 (26.7) CG: 32.0 (15.0) No between-group differences: p=NS</p>		<p>Emergence or worsening of physical symptoms (change from baseline PSC severity of 0 [not at all] or 1 [just a little] to 2 [pretty much] or 3 [very much] at 6 or 12 weeks), observed case analysis (N=374) 12 weeks, n (%) (NOTE: patients with multiple reports of same event were counted only once)</p> <p>Sleep disturbance: Trouble sleeping IG1: 12 (3.3) IG2: 14 (15.2) IG3: 11 (12.5) CG: 14 (15.1)</p> <p>Sleep disturbance: Feeling drowsy or too sleepy IG1: 17 (18.9) IG2: 15 (16.3) IG3: 12 (13.5) CG: 16 (17.2)</p> <p>Sleep disturbance: Sleeplessness IG1: 12 (13.3) IG2: 17 (18.5) IG3: 16 (18.2) CG: 9 (9.7)</p> <p>Sleep disturbance: Nightmares or very strange dreams IG1: 11 (12.2) IG2: 17 (18.5) IG3: 7 (8.0) CG: 13 (14.0)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Sleep disturbance: Restless or uncomfortable urge to move IG1: 2 (2.2) IG2: 9 (9.8) IG3: 5 (5.7) CG: 10 (10.8)</p> <p>Upper respiratory: Head cold or sniffles IG1: 15 (16.7) IG2: 16 (17.4) IG3: 13 (14.6) CG: 16 (17.2)</p> <p>Upper respiratory: Allergies IG1: 10 (11.1) IG2: 13 (14.1) IG3: 13 (14.6) CG: 8 (8.6)</p> <p>Upper respiratory: Sore throat IG1: 8 (8.9) IG2: 6 (6.5) IG3: 9 (10.1) CG: 14 (15.1)</p> <p>Upper respiratory: Dry mouth IG1: 9 (10.0) IG2: 8 (8.7) IG3: 8 (9.0) CG: 7 (7.5)</p> <p>Upper respiratory: Coughing or wheezing IG1: 6 (6.7) IG2: 5 (5.4) IG3: 6 (6.8) CG: 8 (8.6)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Upper respiratory: Fever IG1: 6 (6.7) IG2: 4 (4.4) IG3: 6 (6.7) CG: 4 (4.3)  Pain: Stomach pain or ache IG1: 6 (6.7) IG2: 10 (10.9) IG3: 9 (10.1) CG: 13 (14.0)  Pain: Muscle aches or cramps IG1: 9 (10.0) IG2: 5 (5.4) IG3: 12 (13.6) CG: 12 (12.9)  Pain: Joint pain IG1: 3 (3.3) IG2: 2 (2.2) IG3: 8 (8.9) CG: 9 (9.7)  Pain: Numbness or tingling in arms or legs IG1: 3 (3.3) IG2: 3 (3.3) IG3: 5 (5.7) CG: 5 (5.4)  Cardiac: Chest pain IG1: 4 (4.4) IG2: 5 (5.4) IG3: 4 (4.6) CG: 6 (6.5)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Cardiac: Racing or pounding heart IG1: 2 (2.2) IG2: 2 (2.2) IG3: 5 (5.7) CG: 6 (6.5)</p> <p>Cardiac: Heart skips beats IG1: 1 (1.1) IG2: 2 (2.2) IG3: 3 (3.4) CG: 1 (1.1)</p> <p>Panic: Excessive sweating IG1: 3 (3.3) IG2: 6 (6.5) IG3: 2 (2.3) CG: 9 (9.7)</p> <p>Panic: Difficulty breathing IG1: 4 (4.4) IG2: 3 (3.3) IG3: 2 (2.3) CG: 6 (6.5)</p> <p>Panic: Can't hear well IG1: 3 (3.3) IG2: 2 (2.2) IG3: 4 (4.6) CG: 2 (2.2)</p> <p>Elimination: Frequent urination IG1: 6 (6.7) IG2: 4 (4.4) IG3: 11 (12.5) CG: 6 (6.5)</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Elimination: Feeling bloated or gassy IG1: 2 (2.2) IG2: 6 (6.5) IG3: 6 (6.8) CG: 7 (7.5)</p> <p>Elimination: Pain with urination IG1: 2 (2.2) IG2: 1 (1.1) IG3: 3 (3.4) CG: 0</p> <p>Elimination: Constipation IG1: 1 (1.1) IG2: 0 IG3: 4 (4.6) CG: 3 (3.2)</p> <p>Diarrhea IG1: 4 (4.4) IG2: 5 (5.4) IG3: 6 (6.7) CG: 7 (7.5)</p> <p>Nausea or vomiting IG1: 8 (8.9) IG2: 3 (3.3) IG3: 10 (11.2) CG: 5 (5.4)</p> <p>Skin: Skin rash IG1: 6 (6.7) IG2: 4 (4.4) IG3: 9 (10.1) CG: 4 (4.3)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Skin: Hives IG1: 0 IG2: 2 (2.2) IG3: 1 (1.1) CG: 2 (2.2)</p> <p>Other: Headache IG1: 12 (13.3) IG2: 18 (19.6) IG3: 14 (15.7) CG: 16 (17.2)</p> <p>Treatment with FLX (i.e., IG1 or IG2) did not lead to significantly higher rates of symptom worsening or emergence on any physical symptoms (p=NR).</p> <p>Furthermore, the double-blind treatment arms (IG2 and CG) did not differ significantly on symptom worsening or emergence on any physical symptoms (p=NR).</p> <p>Worsening of Psychiatric Symptoms (CGI-I <math>\geq</math>5-7 [slightly worse, much worse, or very much worse] at 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 3 (2.8) IG3: 10 (9.0) CG: 7 (6.3)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Between-group differences : IG1 and IG2 (FLX arms) had significantly lower rates of worsening than IG3 and CG (non-FLX arms) (p=0.01). Ns of individual arms too small to allow statistical comparison.</p> <p>Worsening of Psychiatric Symptoms (CGI-S <math>\geq</math>1 point from baseline to 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 2 (1.8) IG3: 5 (4.5) CG: 9 (8.0) Between-group differences NR</p> <p>Treatment-emergent psychiatric AEs (spontaneously reported), ITT (N=429) 12 weeks, n (%) (NOTE: Patients may be represented in more than one arm due to patient-initiated crossover)</p> <p>Any treatment-emergent psychiatric AE IG1: 6 (5.6) IG2: 12 (11.0) IG3: 1 (0.91) CG: 5 (4.5)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Between-group comparisons: IG1 and IG2 (FLX arms) experienced more psychiatric AEs than IG3 or CG (non-FLX arms). IG2 experienced more psychiatric AEs than CG, but Ns too small to detect statistical significance.</p> <p>Mania spectrum (mania, hypomania, elevated mood) IG1: 1 (0.93) IG2: 4 (3.67) IG3: 0 CG: 1 (0.89)</p> <p>Irritability spectrum (hypersensitivity, irritability, anger, worsening depression, crying) IG1: 2 (1.86) IG2: 4 (3.67) IG3: 0 CG: 1 (0.89)</p> <p>Agitation spectrum (agitation, akathisia, nervousness, restlessness, hyperactivity) IG1: 1 (0.93) IG2: 2 (1.84) IG3: 2 (1.78) CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Anxiety (anxiety, panic attacks) IG1: 0 IG2: 2 (1.84) IG3: 1 (0.91) CG: 0</p> <p>Other (tremor, "abnormal behavior", "feeling spacy") IG1: 2 (1.84) IG2: 2 (1.84) IG3: 0 CG: 1 (0.89)</p> <p>ADS Mania subscale severity scores (clinician-reported), ITT (N=429) 12 weeks, mean (SD) IG1: 0.5 (0.8) IG2: 1.1 (1.0) IG3: 1.0 (1.2) CG: 1.1 (0.1)</p> <p>Between-group comparisons: IG1&lt;IG2: p=0.013 IG1&lt;CG: p=0.003 IG1&lt;IG3: p=0.012 IG2=IG3: p=NR</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>ADS Mania change from baseline of <math>\geq 3</math> points, modified ITT (n=424 with <math>\geq 2</math> mania total scores) 12 weeks, n (%) IG1: 21 (20) IG2: 15 (14.2) IG3: 13 (12.3) CG: 16 (15.0)</p> <p>Between-group differences NR Incidence of mania or hypomania: ADS Mania scale, ITT (N=429) 12 weeks, n (calculated %) IG1: 3 (2.8) IG2: 1 (0.9) IG3: 0 CG: 1 (0.9)</p>	
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2006 <sup>68</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA

ADS = anxiety and depression scale; AE = adverse event; CBT = cognitive behavioral therapy; C-CASA = Columbia Classification Algorithm of Suicide Assessment; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-I = Clinical Global Impressions Scale-Improvement Scale; CI = confidence interval; FLX = fluoxetine; IG = intervention group; ITT = intent to treat; KQ = Key Question; n/N = number; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; PSC = physical symptom severity; SD = standard deviation; SIQ-JR = Suicide Ideation Questionnaire-Junior High School; TADS = Treatment among Adolescents with Depression.

**Table F-19. KQ 5a: Harms of psychotherapy plus pharmacotherapy versus psychotherapy**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Bernstein, 2000 <sup>80</sup> Index article	IG: Imipramine+CBT CG: Placebo+CBT	NR	NR	NR	Side Effects Completers: 0.33 (0.46) Noncompleters: 0.36 (0.40) t=0.21, df=58, NS
Bernstein, 2000 <sup>80</sup> Index article Companion article: Bernstein, 2000 <sup>81</sup>	IG: Imipramine+CBT CG: Placebo+CBT	NR	Dropouts IG: 7 CG: 9	Reasons for dropping out: missed 22 doses of medication (n=1), missed 2 therapy appointments (n=1), developed manic symptoms on the study medication (n=1), required hospitalization for psychiatric symptoms (n=1), and declined further participation in the study (n=12)	NR
Iftene, 2015 <sup>78</sup>	IG1: Sertraline IG2: Group Rational Emotive Behavior Therapy/CBT IG3: Sertraline plus Group Rational Emotive Behavior Therapy/CBT	0 Suicide Attempts During Trial  Suicide Ideation, report decrease across groups, F(4, 72)=25.37, p<0.001, but no differences across groups, F(2,72)=0.042, p<0.05	Withdrawals IG1: 5 IG2: 5 IG3: 4	None of the participants reported major side effects.  Headaches IG1: 2 IG2: 1 IG3: 3  Insomnia IG1: 1 IG2: 1 IG3: 0	NR



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Iftene, 2015 <sup>78</sup> (continued)				<p>Sleepiness IG1: 1 IG2: 0 IG3: 1</p> <p>Low appetite IG1: 2 IG2: 0 IG3: 1</p> <p>Weight Gain IG1: 1 IG2: 0 IG3: 0</p> <p>Fatigue IG1: 1 IG2: 0 IG3: 0</p> <p>Dizziness IG1: 0 IG2: 0 IG3: 1</p> <p>Sweats IG1: 0 IG2: 0 IG3: 1</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, ITT (n=439) 6 weeks, adjusted mean (SD) IG1: 14.31 (12.58) IG2: 16.20 (12.42) IG3: 13.18 (11.34) CG: 16.85 (11.70)  12 weeks, adjusted mean (SD) IG1: 11.79 (11.69) IG2: 14.44 (11.13) IG3: 11.40 (10.44) CG: 15.01 (11.05)  None of the post-hoc supportive contrasts at 12 weeks comparing improvement following active treatments vs. placebo were statistically significant  Across all 12 weeks: Time-by-treatment interaction based on SIQ-Jr random regression slope coefficients: p=0.01; Statistically comparing improvement : IG1>CG (p=0.02); IG1>IG2 (p=0.002); IG1>IG3 (p=0.05); IG2=IG3 (p=0.22); IG2=CG (p=0.36); IG3=CG (p=0.76)	Early termination at 12 weeks Patient-initiated withdrawal, N (calculated %) IG1: 7 (6.54) IG2: 5 (4.59) IG3: 16 (14.41) CG: 10 (8.93) Between-group difference: p=0.18  Patient Removal due to out-of-protocol treatment in place of or in addition to study treatment, N (calculated %) IG1: 8 (7.48) IG2: 13 (11.93) IG3: 8 (7.21) CG: 13 (11.61) Between-group difference: p=0.50	Serious AEs, N (%) IG1: 9 (8.41) IG2: 13 (11.93) IG3: 5 (4.50) CG: 6 (5.36)  Serious AEs, OR (95% CI) vs. CG: IG1: 1.62 (0.56 to 4.72) IG2: 2.39 (0.87 to 6.54) IG3: 0.83 (0.25 to 2.81) CG: NA  Between-groups p=0.15 NOTE: ORs ≤2 reflect little or no increased risk  Serious Psychiatric-Related AEs, ITT (n=439) N patients [N events], (calculated %) IG1: 0 IG2: 1 [1] (0.92) (worsening depression, also captured below) IG3: 0 CG: 1 [1] (0.89) (mania, also captured below)  Any Psychiatric-Related AEs, ITT (n=439) N patients [N events], (%) IG1: 12 [16] (15) IG2: 20 [23] (21) IG3: 1 [1] (1) CG: 9 [11] (9.8) These events more frequent in fluoxetine arms (IG1 and IG2) than CBT (IG3) or placebo (CG), but p=NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Hedge g effect sizes relative to placebo (CG) IG1: 0.28 IG2: 0.05 IG3: 0.33</p> <p>NOTE: Above means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model</p> <p>Suicide-Related AEs, N (%) IG1: 6 (5.61) IG2: 9 (8.26) IG3: 5 (4.50) CG: 4 (3.57)</p> <p>Suicide-Related AEs, OR (95% CI) vs. CG: IG1: 1.60 (0.44 to 5.85) IG2: 2.43 (0.73 to 8.14) IG3: 1.27 (0.33 to 4.87) CG: NA</p>		<p>Mania, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)</p> <p>Hypomania, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p> <p>Elevated mood, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Hypersensitivity, ITT (n=439) N events (%) IG1: 0 IG2: 2 (1.83) IG3: 0 CG: 0</p> <p>Irritability, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 1 (0.92) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		Suicide attempts, N (calculated %) IG1: 4 (3.74%) IG2: 2 (1.83%) IG3: 1 (0.90%) CG: 0 N of events too small to allow statistical comparison of suicide events		Anger, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0  Worsening of depression, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)  Crying, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0  Agitation, ITT (n=439) N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)  Akathisia, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Nervousness, ITT (n=439) N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Restlessness, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)</p> <p>Hyperactivity, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Panic attacks, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 1 (0.91) CG: 0</p> <p>Anxiety, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Somnolence, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Insomnia, ITT (n=439) N events (%) IG1: 5 (4.67) IG2: 3 (2.75) IG3: 0 CG: 1 (0.89)</p> <p>Nightmares, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0</p> <p>Night sweats, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Sedation, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 3 (2.75) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Fatigue, ITT (n=439) N events (%) IG1: 2 (1.87) IG2: 1 (0.92) IG3: 0 CG: 2 (1.79)</p> <p>Tremors, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 2 (1.83) IG3: 0 CG: 0</p> <p>Abnormal behavior N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Feeling abnormal N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0 p=NR</p> <p>Nonpsychiatric AEs, ITT (n=439) Generally more frequent in fluoxetine-treated arms (IG1 and IG2) than CBT (IG3) or placebo (CG)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Headache, ITT (n=439) N patients (%) IG1: N (5.6) IG2: N (12) IG3: 0 CG: N (9) This was the only AE occurring in ≥10% of patients in any single treatment group</p> <p>Sedation IG1: 0 IG2: 3 (2.75) IG3: 0 CG: 0</p> <p>Upper abdominal pain IG1: 0 IG2: 6 (5.5) IG3: 0 CG: 2 (1.79)</p> <p>Diarrhea IG1: 2 (1.87) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p> <p>Influenza IG1: 0 IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				Insomnia IG1: 5 (4.67) IG2: 3 (2.75) IG3: 0 CG: 1 (0.89)  Sinusitis IG1: 0 IG2: 4 (3.67) IG3: 0 CG: 2 (1.79)  Vomiting IG1: 4 (3.74) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)	
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, observed case analysis (n=359) 12 weeks, adjusted mean (SD) IG1: 10.9 (0.3) IG2: 13.7 (0.2) IG3: 11.3 (0.3) CG: 14.5 (0.6) No between-group differences: p=NS  Comparison of change in SIQ-Jr total score from baseline to 12 weeks, observed case analysis (n=359) IG1>IG2: p=0.004 IG1>IG3: p=0.04 IG1>CG: p=0.02  Emergence or worsening of suicidal ideation (change from baseline SIQ-Jr <31 to SIQ-Jr ≥31 at 6 or 12 weeks), observed case analysis (n=374) 12 weeks, n (%) IG1: 2/93 (2.2) IG2: 7/96 (7.3) IG3: 2/93 (2.2) CG: 7/92 (7.6) No between-group differences: p=NS  Worsening of suicidality from baseline to 6 or 12 weeks (CDRS-R item 13 worsening by ≥1 point), observed case analysis (n=374)	NA	Self-reported PSC, observed case analysis (n=364) 12 weeks, mean (SD) IG1: 11.0 (8.2) IG2: 13.0 (10.5) IG3: 18.5 (17.5) CG: 12.3 (8.9)  Statistical comparisons of medication-based arms (IG1; IG2, and CG) with IG3 found that IG3 patients reported significantly higher/worse PSC scores: IG1<IG3: p=0.0036 IG2<IG3: p=0.0328 CG<IG3: p=0.0280 No between-group differences between IG1; IG2, and CG arms (all p's=NS)  Factor-based PSC scores (sleep, upper respiratory, pain, cardiac, panic, elimination, nausea, and skin), observed case analysis (N=364) 12 weeks All treatment arms showed improvement on each of the 8 PSC factors. Pain was the only factor with a significant treatment-by-time interaction (p=NR), based on significantly more improvement compared with IG3 IG1>IG3: p=0.0011 IG2>IG3: p=0.0017	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Calculated n (%)</p> <p>IG1: 2/93 (5.0)</p> <p>IG2: 7/96 (13.4)</p> <p>IG3: 2/93 (15.2)</p> <p>CG: 7/92 (7.2)</p> <p>No between-group differences: p=NS</p> <p>Emergence of suicidality from baseline to 6 or 12 weeks (change from CDRS-R item score=1 or 2 to ≥5), observed case analysis (n=374)</p> <p>Calculated n (%)</p> <p>IG1: 0/93 (0)</p> <p>IG2: 4/96 (3.7)</p> <p>IG3: 1/93 (1.3)</p> <p>CG: 2/92 (2.6)</p> <p>No between-group differences: p=NS</p> <p>Suicide-Related AEs (primary analysis: C-CASA Codes 1, 2, and 6), ITT (n=439)</p> <p>12 weeks, N (%)</p> <p>IG1: 5 (4.7)</p> <p>IG2: 10 (9.2)</p> <p>IG3: 5 (4.5)</p> <p>CG: 3 (2.7)</p> <p>Statistical comparisons of groups, OR (95% CI)</p> <p>IG1=IG3: p=NS</p> <p>IG1=CG: p=NS</p> <p>IG2&gt;CG: 3.7 (1.00 to 13.7), p=0.0402, meaning higher incidence in IG2</p>		<p>Treatment-emergent physical AEs (spontaneous), ITT (n=439)</p> <p>12 weeks, N patients [N events], (calculated % patients)</p> <p>IG1: 37 [61] (34.6)</p> <p>IG2: 35 [81] (32.1)</p> <p>IG3: NR [9] (NR)</p> <p>CG: 34 [60] (30.4)</p> <p>No between-group differences in arms receiving pills (IG1; IG2, and CG), but more events reported in IG2 than IG1 or CG (p=NR).</p> <p>Spontaneously reported physical AEs reported in ≥2% of active treatment arms and at rates at least twice that of CG, ITT (n=429)</p> <p>12 weeks</p> <p>Sedation</p> <p>IG1: 1 (0.9)</p> <p>IG2: 3 (2.8)</p> <p>IG3: 0</p> <p>CG: 0</p> <p>IG2 vs. CG ratio: 3.00</p> <p>Insomnia</p> <p>IG1: 5 (4.7)</p> <p>IG2: 3 (2.8)</p> <p>IG3: 0</p> <p>CG: 1 (0.9)</p> <p>IG1 vs. CG ratio: 5.23</p> <p>IG2 vs. CG ratio: 3.08</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Suicide-Related AEs (sensitivity analysis: C-CASA Codes 1, 2, 3, and 6), ITT (n=439) 12 weeks, N (%) IG1: 6 (5.6) IG2: 10 (9.2) IG3: 5 (4.5) CG: 3 (2.7) Between-group differences NR</p> <p>Suicide attempts (C-CASA Code 1), ITT (n=439) 12 weeks, N (%) IG1: 2 (1.9) IG2: 1 (1.8) IG3: 1 (0.9) CG: 0</p> <p>Preparatory actions toward imminent suicidal behavior (C-CASA Code 2), ITT (n=439) No events at 12 weeks Self-injurious behavior: unknown intent (C-CASA Code 3), ITT (n=439) 12 weeks, N (%) IG1: 1 (0.9) IG2: 0 IG3: 0 CG: 0</p> <p>Suicidal ideation (C-CASA Code 6), ITT (n=439) 12 weeks, N (%) IG1: 3 (2.8) IG2: 8 (7.3) IG3: 4 (3.6) CG: 3 (2.7)</p>		<p>Vomiting IG1: 4 (3.7) IG2: 2 (1.8) IG3: 1 (0.9) CG: 1 (0.9) IG1 vs. CG ratio: 4.19</p> <p>Upper abdominal pain IG1: 1 (0.9) IG2: 6 (5.5) IG3: 0 CG: 2 (1.8) IG2 vs. CG ratio: 3.08</p> <p>Headache: only spontaneously reported physical AE occurring in &gt;5% of patients, ITT (N=429) 12 weeks, calculated n (%) IG1: 7 (6.8) IG2: 13 (11.9) IG3: NA CG: 12 (10.7) No between-group differences (p=NS)</p> <p>Emergence or worsening of physical symptoms (change from baseline PSC severity of 0 [not at all] or 1 [just a little] to 2 [pretty much] or 3 [very much] at 6 or 12 weeks), observed case analysis (N=374) 12 weeks, n (%) (NOTE: patients with multiple reports of same event were counted only once)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		Timing of suicide-related events, ITT (n=439) 12 weeks, mean days (SD) IG1: 52.0 (20.8) IG2: 38.0 (21.7) IG3: 45.4 (26.7) CG: 32.0 (15.0) No between-group differences: p=NS		Sleep disturbance: Trouble sleeping IG1: 12 (3.3) IG2: 14 (15.2) IG3: 11 (12.5) CG: 14 (15.1)  Sleep disturbance: Feeling drowsy or too sleepy IG1: 17 (18.9) IG2: 15 (16.3) IG3: 12 (13.5) CG: 16 (17.2)  Sleep disturbance: Sleeplessness IG1: 12 (13.3) IG2: 17 (18.5) IG3: 16 (18.2) CG: 9 (9.7)  Sleep disturbance: Nightmares or very strange dreams IG1: 11 (12.2) IG2: 17 (18.5) IG3: 7 (8.0) CG: 13 (14.0)  Sleep disturbance: Restless or uncomfortable urge to move IG1: 2 (2.2) IG2: 9 (9.8) IG3: 5 (5.7) CG: 10 (10.8)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Upper respiratory: Head cold or sniffles IG1: 15 (16.7) IG2: 16 (17.4) IG3: 13 (14.6) CG: 16 (17.2)  Upper respiratory: Allergies IG1: 10 (11.1) IG2: 13 (14.1) IG3: 13 (14.6) CG: 8 (8.6)  Upper respiratory: Sore throat IG1: 8 (8.9) IG2: 6 (6.5) IG3: 9 (10.1) CG: 14 (15.1)  Upper respiratory: Dry mouth IG1: 9 (10.0) IG2: 8 (8.7) IG3: 8 (9.0) CG: 7 (7.5)  Upper respiratory: Coughing or wheezing IG1: 6 (6.7) IG2: 5 (5.4) IG3: 6 (6.8) CG: 8 (8.6)  Upper respiratory: Fever IG1: 6 (6.7) IG2: 4 (4.4) IG3: 6 (6.7) CG: 4 (4.3)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Pain: Stomach pain or ache IG1: 6 (6.7) IG2: 10 (10.9) IG3: 9 (10.1) CG: 13 (14.0)  Pain: Muscle aches or cramps IG1: 9 (10.0) IG2: 5 (5.4) IG3: 12 (13.6) CG: 12 (12.9)  Pain: Joint pain IG1: 3 (3.3) IG2: 2 (2.2) IG3: 8 (8.9) CG: 9 (9.7)  Pain: Numbness or tingling in arms or legs IG1: 3 (3.3) IG2: 3 (3.3) IG3: 5 (5.7) CG: 5 (5.4)  Cardiac: Chest pain IG1: 4 (4.4) IG2: 5 (5.4) IG3: 4 (4.6) CG: 6 (6.5)  Cardiac: Racing or pounding heart IG1: 2 (2.2) IG2: 2 (2.2) IG3: 5 (5.7) CG: 6 (6.5)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Cardiac: Heart skips beats IG1: 1 (1.1) IG2: 2 (2.2) IG3: 3 (3.4) CG: 1 (1.1)  Panic: Excessive sweating IG1: 3 (3.3) IG2: 6 (6.5) IG3: 2 (2.3) CG: 9 (9.7)  Panic: Difficulty breathing IG1: 4 (4.4) IG2: 3 (3.3) IG3: 2 (2.3) CG: 6 (6.5)  Panic: Can't hear well IG1: 3 (3.3) IG2: 2 (2.2) IG3: 4 (4.6) CG: 2 (2.2)  Elimination: Frequent urination IG1: 6 (6.7) IG2: 4 (4.4) IG3: 11 (12.5) CG: 6 (6.5)  Elimination: Feeling bloated or gassy IG1: 2 (2.2) IG2: 6 (6.5) IG3: 6 (6.8) CG: 7 (7.5)	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Elimination: Pain with urination IG1: 2 (2.2) IG2: 1 (1.1) IG3: 3 (3.4) CG: 0</p> <p>Elimination: Constipation IG1: 1 (1.1) IG2: 0) IG3: 4 (4.6) CG: 3 (3.2)</p> <p>Diarrhea IG1: 4 (4.4) IG2: 5 (5.4) IG3: 6 (6.7) CG: 7 (7.5)</p> <p>Nausea or vomiting IG1: 8 (8.9) IG2: 3 (3.3) IG3: 10 (11.2) CG: 5 (5.4)</p> <p>Skin: Skin rash IG1: 6 (6.7) IG2: 4 (4.4) IG3: 9 (10.1) CG: 4 (4.3)</p> <p>Skin: Hives IG1: 0 IG2: 2 (2.2) IG3: 1 (1.1) CG: 2 (2.2)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Other: Headache IG1: 12 (13.3) IG2: 18 (19.6) IG3: 14 (15.7) CG: 16 (17.2)</p> <p>Treatment with FLX (i.e.; IG1 or IG2) did not lead to significantly higher rates of symptom worsening or emergence on any physical symptoms (p=NR).</p> <p>Furthermore, the double-blind treatment arms (IG2 and CG) did not differ significantly on symptom worsening or emergence on any physical symptoms (p=NR).</p> <p>Worsening of Psychiatric Symptoms (CGI-I <math>\geq</math>5-7 [slightly worse, much worse, or very much worse] at 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 3 (2.8) IG3: 10 (9.0) CG: 7 (6.3) Between-group differences : IG1 and IG2 (FLX arms) had significantly lower rates of worsening than IG3 and CG (non-FLX arms) (p=0.01). Ns of individual arms too small to allow statistical comparison.</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Worsening of Psychiatric Symptoms (CGI-S <math>\geq 1</math> point from baseline to 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 2 (1.8) IG3: 5 (4.5) CG: 9 (8.0) Between-group differences NR</p> <p>Treatment-emergent psychiatric AEs (spontaneously reported), ITT (N=429) 12 weeks, n (%) (NOTE: Patients may be represented in more than one arm due to patient-initiated crossover)</p> <p>Any treatment-emergent psychiatric AE IG1: 6 (5.6) IG2: 12 (11.0) IG3: 1 (0.91) CG: 5 (4.5) Between-group comparisons: IG1 and IG2 (FLX arms) experienced more psychiatric AEs than IG3 or CG (non-FLX arms). IG2 experienced more psychiatric AEs than CG, but Ns too small to detect statistical significance.</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Mania spectrum (mania, hypomania, elevated mood) IG1: 1 (0.93) IG2: 4 (3.67) IG3: 0 CG: 1 (0.89)</p> <p>Irritability spectrum (hypersensitivity, irritability, anger, worsening depression, crying) IG1: 2 (1.86) IG2: 4 (3.67) IG3: 0 CG: 1 (0.89)</p> <p>Agitation spectrum (agitation, akathisia, nervousness, restlessness, hyperactivity) IG1: 1 (0.93) IG2: 2 (1.84) IG3: 2 (1.78) CG: 0</p> <p>Anxiety (anxiety, panic attacks) IG1: 0 IG2: 2 (1.84) IG3: 1 (0.91) CG: 0</p> <p>Other (tremor, "abnormal behavior", "feeling spacy") IG1: 2 (1.84) IG2: 2 (1.84) IG3: 0 CG: 1 (0.89)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>ADS Mania subscale severity scores (clinician-reported), ITT (N=429) 12 weeks, mean (SD) IG1: 0.5 (0.8) IG2: 1.1 (1.0) IG3: 1.0 (1.2) CG: 1.1 (0.1)</p> <p>Between-group comparisons: IG1&lt;IG2: p=0.013 IG1&lt;CG: p=0.003 IG1&lt;IG3: p=0.012 IG2=IG3: p=NR</p> <p>ADS Mania change from baseline of ≥3 points, modified ITT (n=424 with ≥2 mania total scores) 12 weeks, n (%) IG1: 21 (20) IG2: 15 (14.2) IG3: 13 (12.3) CG: 16 (15.0)</p> <p>Between-group differences NR Incidence of mania or hypomania: ADS Mania scale, ITT (N=429) 12 weeks, n (calculated %) IG1: 3 (2.8) IG2: 1 (0.9) IG3: 0 CG: 1 (0.9)</p>	
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2006 <sup>68</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	
Melvin, 2006 <sup>79</sup>	G1: CBT G2: Sertraline G3: Combined	Mean (SD) G1: 19.41 (19.64) G2: 24.23 (26.90) G3: 23.20 (20.24)  Suicidal ideation adverse events and other adverse events not reported by group	NR	NR	NR

ADS = anxiety and depression scale; AE = adverse event; CBT = cognitive behavioral therapy; C-CASA = Columbia Classification Algorithm of Suicide Assessment; CDRS-R = Children's Depression Rating Scale-Revised; CG = control group; CGI-I = Clinical Global Impressions Scale-Improvement Scale; CI = confidence interval; FLX = fluoxetine; IG = intervention group; ITT = intent to treat; KQ = Key Question; n/N = number; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; PSC = physical symptom severity; SD = standard deviation; SIQ-JR = Suicide Ideation Questionnaire-Junior High School; TADS = Treatment among Adolescents with Depression.

**Table F-20. KQ 5a: Harms of psychotherapy plus pharmacotherapy versus pharmacotherapy**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Iftene, 2015 <sup>78</sup>	IG1: Sertraline IG2: Group Rational Emotive Behavior Therapy/CBT IG3: Sertraline plus Group Rational Emotive Behavior Therapy/CBT	0 Suicide Attempts During Trial  Suicide Ideation, report decrease across groups, $F(4, 72)=25.37$ , $p<0.001$ , but no differences across groups, $F(2,72)=0.042$ , $p<0.05$	Withdrawals IG1: 5 IG2: 5 IG3: 4	None of the participants reported major side effects.  Headaches IG1: 2 IG2: 1 IG3: 3  Insomnia IG1: 1 IG2: 1 IG3: 0  Sleepiness IG1: 1 IG2: 0 IG3: 1  Low appetite IG1: 2 IG2: 0 IG3: 1  Weight Gain IG1: 1 IG2: 0 IG3: 0  Fatigue IG1: 1 IG2: 0 IG3: 0	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Iftene, 2015 <sup>78</sup> (continued)				Dizziness IG1: 0 IG2: 0 IG3: 1  Sweats IG1: 0 IG2: 0 IG3: 1	
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, ITT (n=439) 6 weeks, adjusted mean (SD) IG1: 14.31 (12.58) IG2: 16.20 (12.42) IG3: 13.18 (11.34) CG: 16.85 (11.70)  12 weeks, adjusted mean (SD) IG1: 11.79 (11.69) IG2: 14.44 (11.13) IG3: 11.40 (10.44) CG: 15.01 (11.05)  None of the post-hoc supportive contrasts at 12 weeks comparing improvement following active treatments vs. placebo were statistically significant  Across all 12 weeks: Time-by-treatment interaction based on SIQ-Jr random regression slope coefficients: p=0.01;	Early termination at 12 weeks Patient-initiated withdrawal, N (calculated %) IG1: 7 (6.54) IG2: 5 (4.59) IG3: 16 (14.41) CG: 10 (8.93) Between-group difference: p=0.18  Patient Removal due to out-of-protocol treatment in place of or in addition to study treatment, N (calculated %) IG1: 8 (7.48) IG2: 13 (11.93) IG3: 8 (7.21) CG: 13 (11.61) Between-group difference: p=0.50	Serious AEs, N (%) IG1: 9 (8.41) IG2: 13 (11.93) IG3: 5 (4.50) CG: 6 (5.36)  Serious AEs, OR (95% CI) vs. CG: IG1: 1.62 (0.56 to 4.72) IG2: 2.39 (0.87 to 6.54) IG3: 0.83 (0.25 to 2.81) CG: NA Between-groups p=0.15 NOTE: ORs ≤2 reflect little or no increased risk  Serious Psychiatric-Related AEs, ITT (n=439) N patients [N events], (calculated %) IG1: 0 IG2: 1 [1] (0.92) (worsening depression, also captured below) IG3: 0 CG: 1 [1] (0.89) (mania, also captured below)	NR



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		<p>Statistically comparing improvement :</p> <p>IG1&gt;CG (p=0.02); IG1&gt;IG2 (p=0.002); IG1&gt;IG3 (p=0.05); IG2=IG3 (p=0.22); IG2=CG (p=0.36); IG3=CG (p=0.76)</p> <p>Hedge g effect sizes relative to placebo (CG) IG1: 0.28 IG2: 0.05 IG3: 0.33</p> <p>NOTE: Above means adjusted for both fixed (treatment and time) and random (participant and site) effects derived from linear random coefficient model</p> <p>Suicide-Related AEs, N (%) IG1: 6 (5.61) IG2: 9 (8.26) IG3: 5 (4.50) CG: 4 (3.57) Suicide-Related AEs, OR (95% CI) vs. CG: IG1: 1.60 (0.44 to 5.85) IG2: 2.43 (0.73 to 8.14) IG3: 1.27 (0.33 to 4.87) CG: NA</p>		<p>Any Psychiatric-Related AEs, ITT (n=439) N patients [N events] (%) IG1: 12 [16] (15) IG2: 20 [23] (21) IG3: 1 [1] (1) CG: 9 [11] (9.8) These events more frequent in fluoxetine arms (IG1 and IG2) than CBT (IG3) or placebo (CG), but p=NR</p> <p>Mania, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)</p> <p>Hypomania, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p> <p>Elevated mood, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Hypersensitivity, ITT (n=439) N events (%) IG1: 0 IG2: 2 (1.83) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)		Suicide attempts, N (calculated %) IG1: 4 (3.74%) IG2: 2 (1.83%) IG3: 1 (0.90%) CG: 0 N of events too small to allow statistical comparison of suicide events		Irritability, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 1 (0.92) IG3: 0 CG: 0  Anger, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0  Worsening of depression, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)  Crying, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0  Agitation, ITT (n=439) N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Akathisia, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0</p> <p>Nervousness, ITT (n=439) N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Restlessness, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 1 (0.89)</p> <p>Hyperactivity, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Panic attacks, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 1 (0.91) CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Anxiety, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p> <p>Somnolence, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Insomnia, ITT (n=439) N events (%) IG1: 5 (4.67) IG2: 3 (2.75) IG3: 0 CG: 1 (0.89)</p> <p>Nightmares, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0</p> <p>Night sweats, ITT (n=439) N events (%) IG1: 0 IG2: 1 (0.92) IG3: 0 CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Sedation, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 3 (2.75) IG3: 0 CG: 0</p> <p>Fatigue, ITT (n=439) N events (%) IG1: 2 (1.87) IG2: 1 (0.92) IG3: 0 CG: 2 (1.79)</p> <p>Tremors, ITT (n=439) N events (%) IG1: 1 (0.93) IG2: 2 (1.83) IG3: 0 CG: 0</p> <p>Abnormal behavior N events (%) IG1: 0 IG2: 0 IG3: 0 CG: 1 (0.89)</p> <p>Feeling abnormal N events (%) IG1: 1 (0.93) IG2: 0 IG3: 0 CG: 0 p=NR</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				<p>Nonpsychiatric AEs, ITT (n=439) Generally more frequent in fluoxetine-treated arms (IG1 and IG2) than CBT (IG3) or placebo (CG)</p> <p>Headache, ITT (n=439) N patients (%) IG1: N (5.6) IG2: N (12) IG3: 0 CG: N (9) This was the only AE occurring in ≥10% of patients in any single treatment group</p> <p>Sedation IG1: 0 IG2: 3 (2.75) IG3: 0 CG: 0</p> <p>Upper abdominal pain IG1: 0 IG2: 6 (5.5) IG3: 0 CG: 2 (1.79)</p> <p>Diarrhea IG1: 2 (1.87) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article TADS (continued)				Influenza IG1: 0 IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)  Insomnia IG1: 5 (4.67) IG2: 3 (2.75) IG3: 0 CG: 1 (0.89)  Sinusitis IG1: 0 IG2: 4 (3.67) IG3: 0 CG: 2 (1.79)  Vomiting IG1: 4 (3.74) IG2: 2 (1.83) IG3: 0 CG: 1 (0.89)	
March, 2004 <sup>3</sup> Index article Companion article: Curry, 2006 <sup>4</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	Adjusted SIQ-Jr total score, observed case analysis (n=359) 12 weeks, adjusted mean (SD) IG1: 10.9 (0.3) IG2: 13.7 (0.2) IG3: 11.3 (0.3) CG: 14.5 (0.6) No between-group differences: p=NS  Comparison of change in SIQ-Jr total score from baseline to 12 weeks, observed case analysis (n=359) IG1>IG2: p=0.004 IG1>IG3: p=0.04 IG1>CG: p=0.02  Emergence or worsening of suicidal ideation (change from baseline SIQ-Jr <31 to SIQ-Jr ≥31 at 6 or 12 weeks), observed case analysis (n=374) 12 weeks, n (%) IG1: 2/93 (2.2) IG2: 7/96 (7.3) IG3: 2/93 (2.2) CG: 7/92 (7.6) No between-group differences: p=NS	NA	Self-reported physical symptom severity (PSC), observed case analysis (n=364) 12 weeks, mean (SD) IG1: 11.0 (8.2) IG2: 13.0 (10.5) IG3: 18.5 (17.5) CG: 12.3 (8.9)  Statistical comparisons of medication-based arms (IG1; IG2, and CG) with IG3 found that IG3 patients reported significantly higher/worse PSC scores: IG1<IG3: p=0.0036 IG2<IG3: p=0.0328 CG<IG3: p=0.0280 No between-group differences between IG1; IG2, and CG arms (all p's=NS)  Factor-based PSC scores (sleep, upper respiratory, pain, cardiac, panic, elimination, nausea, and skin), observed case analysis (N=364) 12 weeks	NA



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Worsening of suicidality from baseline to 6 or 12 weeks (CDRS-R item 13 worsening by <math>\geq 1</math> point), observed case analysis (n=374) Calculated n (%) IG1: 2/93 (5.0) IG2: 7/96 (13.4) IG3: 2/93 (15.2) CG: 7/92 (7.2) No between-group differences: p=NS</p> <p>Emergence of suicidality from baseline to 6 or 12 weeks (change from CDRS-R item score=1 or 2 to <math>\geq 5</math>), observed case analysis (n=374) Calculated n (%) IG1: 0/93 (0) IG2: 4/96 (3.7) IG3: 1/93 (1.3) CG: 2/92 (2.6) No between-group differences: p=NS</p> <p>Suicide-Related AEs (primary analysis: C-CASA Codes 1, 2, and 6), ITT (n=439) 12 weeks, N (%) IG1: 5 (4.7) IG2: 10 (9.2) IG3: 5 (4.5) CG: 3 (2.7)</p>		<p>All treatment arms showed improvement on each of the 8 PSC factors. Pain was the only factor with a significant treatment-by-time interaction (p=NR), based on significantly more improvement compared with IG3 IG1&gt;IG3: p=0.0011 IG2&gt;IG3: p=0.0017</p> <p>Treatment-emergent physical AEs (spontaneous), ITT (n=439) 12 weeks, N patients [N events], (calculated % patients) IG1: 37 [61] (34.6) IG2: 35 [81] (32.1) IG3: NR [9] (NR) CG: 34 [60] (30.4) No between-group differences in arms receiving pills (IG1; IG2, and CG), but more events reported in IG2 than IG1 or CG (p=NR).</p> <p>Spontaneously reported physical AEs reported in <math>\geq 2\%</math> of active treatment arms and at rates at least twice that of CG, ITT (n=429)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>Statistical comparisons of groups, OR (95% CI)  IG1=IG3: p=NS  IG1=CG: p=NS  IG2&gt;CG: 3.7 (1.00 to 13.7), p=0.0402, meaning higher incidence in IG2</p> <p>Suicide-Related AEs (sensitivity analysis: C-CASA Codes 1, 2, 3, and 6), ITT (n=439)  12 weeks, N (%)  IG1: 6 (5.6)  IG2: 10 (9.2)  IG3: 5 (4.5)  CG: 3 (2.7)  Between-group differences NR</p> <p>Suicide attempts (C-CASA Code 1), ITT (n=439)  12 weeks, N (%)  IG1: 2 (1.9)  IG2: 1 (1.8)  IG3: 1 (0.9)  CG: 0</p> <p>Preparatory actions toward imminent suicidal behavior (C-CASA Code 2), ITT (n=439)  No events at 12 weeks  Self-injurious behavior: unknown intent (C-CASA Code 3), ITT (n=439)</p>		<p>12 weeks  Sedation  IG1: 1 (0.9)  IG2: 3 (2.8)  IG3: 0  CG: 0  IG2 vs. CG ratio: 3.00</p> <p>Insomnia  IG1: 5 (4.7)  IG2: 3 (2.8)  IG3: 0  CG: 1 (0.9)  IG1 vs. CG ratio: 5.23  IG2 vs. CG ratio: 3.08</p> <p>Vomiting  IG1: 4 (3.7)  IG2: 2 (1.8)  IG3: 1 (0.9)  CG: 1 (0.9)  IG1 vs. CG ratio: 4.19</p> <p>Upper abdominal pain  IG1: 1 (0.9)  IG2: 6 (5.5)  IG3: 0  CG: 2 (1.8)  IG2 vs. CG ratio: 3.08</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)		<p>12 weeks, N (%)</p> <p>IG1: 1 (0.9)</p> <p>IG2: 0</p> <p>IG3: 0</p> <p>CG: 0</p> <p>Suicidal ideation (C-CASA Code 6), ITT (n=439)</p> <p>12 weeks, N (%)</p> <p>IG1: 3 (2.8)</p> <p>IG2: 8 (7.3)</p> <p>IG3: 4 (3.6)</p> <p>CG: 3 (2.7)</p> <p>Timing of suicide-related events, ITT (n=439)</p> <p>12 weeks, mean days (SD)</p> <p>IG1: 52.0 (20.8)</p> <p>IG2: 38.0 (21.7)</p> <p>IG3: 45.4 (26.7)</p> <p>CG: 32.0 (15.0)</p> <p>No between-group differences: p=NS</p>		<p>Headache: only spontaneously reported physical AE occurring in &gt;5% of patients, ITT (N=429)</p> <p>12 weeks, calculated n (%)</p> <p>IG1: 7 (6.8)</p> <p>IG2: 13 (11.9)</p> <p>IG3: NA</p> <p>CG: 12 (10.7)</p> <p>No between-group differences (p=NS)</p> <p>Emergence or worsening of physical symptoms (change from baseline PSC severity of 0 [not at all] or 1 [just a little] to 2 [pretty much] or 3 [very much] at 6 or 12 weeks), observed case analysis (N=374)</p> <p>12 weeks, n (%) (NOTE: patients with multiple reports of same event were counted only once)</p> <p>Sleep disturbance: Trouble sleeping</p> <p>IG1: 12 (3.3)</p> <p>IG2: 14 (15.2)</p> <p>IG3: 11 (12.5)</p> <p>CG: 14 (15.1)</p> <p>Sleep disturbance: Feeling drowsy or too sleepy</p> <p>IG1: 17 (18.9)</p> <p>IG2: 15 (16.3)</p> <p>IG3: 12 (13.5)</p> <p>CG: 16 (17.2)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Sleep disturbance: Sleeplessness IG1: 12 (13.3) IG2: 17 (18.5) IG3: 16 (18.2) CG: 9 (9.7)</p> <p>Sleep disturbance: Nightmares or very strange dreams IG1: 11 (12.2) IG2: 17 (18.5) IG3: 7 (8.0) CG: 13 (14.0)</p> <p>Sleep disturbance: Restless or uncomfortable urge to move IG1: 2 (2.2) IG2: 9 (9.8) IG3: 5 (5.7) CG: 10 (10.8)</p> <p>Upper respiratory: Head cold or sniffles IG1: 15 (16.7) IG2: 16 (17.4) IG3: 13 (14.6) CG: 16 (17.2)</p> <p>Upper respiratory: Allergies IG1: 10 (11.1) IG2: 13 (14.1) IG3: 13 (14.6) CG: 8 (8.6)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Upper respiratory: Sore throat IG1: 8 (8.9) IG2: 6 (6.5) IG3: 9 (10.1) CG: 14 (15.1)  Upper respiratory: Dry mouth IG1: 9 (10.0) IG2: 8 (8.7) IG3: 8 (9.0) CG: 7 (7.5)  Upper respiratory: Coughing or wheezing IG1: 6 (6.7) IG2: 5 (5.4) IG3: 6 (6.8) CG: 8 (8.6)  Upper respiratory: Fever IG1: 6 (6.7) IG2: 4 (4.4) IG3: 6 (6.7) CG: 4 (4.3)  Pain: Stomach pain or ache IG1: 6 (6.7) IG2: 10 (10.9) IG3: 9 (10.1) CG: 13 (14.0)  Pain: Muscle aches or cramps IG1: 9 (10.0) IG2: 5 (5.4) IG3: 12 (13.6) CG: 12 (12.9)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Pain: Joint pain IG1: 3 (3.3) IG2: 2 (2.2) IG3: 8 (8.9) CG: 9 (9.7)  Pain: Numbness or tingling in arms or legs IG1: 3 (3.3) IG2: 3 (3.3) IG3: 5 (5.7) CG: 5 (5.4)  Cardiac: Chest pain IG1: 4 (4.4) IG2: 5 (5.4) IG3: 4 (4.6) CG: 6 (6.5)  Cardiac: Racing or pounding heart IG1: 2 (2.2) IG2: 2 (2.2) IG3: 5 (5.7) CG: 6 (6.5)  Cardiac: Heart skips beats IG1: 1 (1.1) IG2: 2 (2.2) IG3: 3 (3.4) CG: 1 (1.1)  Panic: Excessive sweating IG1: 3 (3.3) IG2: 6 (6.5) IG3: 2 (2.3) CG: 9 (9.7)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Panic: Difficulty breathing IG1: 4 (4.4) IG2: 3 (3.3) IG3: 2 (2.3) CG: 6 (6.5)  Panic: Can't hear well IG1: 3 (3.3) IG2: 2 (2.2) IG3: 4 (4.6) CG: 2 (2.2)  Elimination: Frequent urination IG1: 6 (6.7) IG2: 4 (4.4) IG3: 11 (12.5) CG: 6 (6.5)  Elimination: Feeling bloated or gassy IG1: 2 (2.2) IG2: 6 (6.5) IG3: 6 (6.8) CG: 7 (7.5)  Elimination: Pain with urination IG1: 2 (2.2) IG2: 1 (1.1) IG3: 3 (3.4) CG: 0  Elimination: Constipation IG1: 1 (1.1) IG2: 0) IG3: 4 (4.6) CG: 3 (3.2)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				Diarrhea IG1: 4 (4.4) IG2: 5 (5.4) IG3: 6 (6.7) CG: 7 (7.5)  Nausea or vomiting IG1: 8 (8.9) IG2: 3 (3.3) IG3: 10 (11.2) CG: 5 (5.4)  Skin: Skin rash IG1: 6 (6.7) IG2: 4 (4.4) IG3: 9 (10.1) CG: 4 (4.3)  Skin: Hives IG1: 0 IG2: 2 (2.2) IG3: 1 (1.1) CG: 2 (2.2)  Other: Headache IG1: 12 (13.3) IG2: 18 (19.6) IG3: 14 (15.7) CG: 16 (17.2)  Treatment with FLX (i.e.; IG1 or IG2) did not lead to significantly higher rates of symptom worsening or emergence on any physical symptoms (p=NR).	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Furthermore, the double-blind treatment arms (IG2 and CG) did not differ significantly on symptom worsening or emergence on any physical symptoms (p=NR).</p> <p>Worsening of Psychiatric Symptoms (CGI-I <math>\geq 5-7</math> [slightly worse, much worse, or very much worse] at 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 3 (2.8) IG3: 10 (9.0) CG: 7 (6.3) Between-group differences : IG1 and IG2 (FLX arms) had significantly lower rates of worsening than IG3 and CG (non-FLX arms) (p=0.01). Ns of individual arms too small to allow statistical comparison.</p> <p>Worsening of Psychiatric Symptoms (CGI-S <math>\geq 1</math> point from baseline to 6 or 12 weeks), ITT (N=429) n (%) IG1: 2 (1.9) IG2: 2 (1.8) IG3: 5 (4.5) CG: 9 (8.0) Between-group differences NR</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Treatment-emergent psychiatric AEs (spontaneously reported), ITT (N=429) 12 weeks, n (%) (NOTE: Patients may be represented in more than one arm due to patient-initiated crossover)</p> <p>Any treatment-emergent psychiatric AE IG1: 6 (5.6) IG2: 12 (11.0) IG3: 1 (0.91) CG: 5 (4.5) Between-group comparisons: IG1 and IG2 (FLX arms) experienced more psychiatric AEs than IG3 or CG (non-FLX arms). IG2 experienced more psychiatric AEs than CG, but Ns too small to detect statistical significance.</p> <p>Mania spectrum (mania, hypomania, elevated mood) IG1: 1 (0.93) IG2: 4 (3.67) IG3: 0 CG: 1 (0.89)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Irritability spectrum (hypersensitivity, irritability, anger, worsening depression, crying) IG1: 2 (1.86) IG2: 4 (3.67) IG3: 0 CG: 1 (0.89)</p> <p>Agitation spectrum (agitation, akathisia, nervousness, restlessness, hyperactivity) IG1: 1 (0.93) IG2: 2 (1.84) IG3: 2 (1.78) CG: 0</p> <p>Anxiety (anxiety, panic attacks) IG1: 0 IG2: 2 (1.84) IG3: 1 (0.91) CG: 0</p> <p>Other (tremor, "abnormal behavior", "feeling spacy") IG1: 2 (1.84) IG2: 2 (1.84) IG3: 0 CG: 1 (0.89)</p> <p>ADS Mania subscale severity scores (clinician-reported), ITT (N=429) 12 weeks, mean (SD) IG1: 0.5 (0.8) IG2: 1.1 (1.0) IG3: 1.0 (1.2) CG: 1.1 (0.1)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Emslie, 2006 <sup>5</sup> TADS (continued)				<p>Between-group comparisons:  IG1&lt;IG2: p=0.013  IG1&lt;CG: p=0.003  IG1&lt;IG3: p=0.012  IG2=IG3: p=NR</p> <p>ADS Mania change from baseline of <math>\geq 3</math> points, modified ITT (n=424 with <math>\geq 2</math> mania total scores)  12 weeks, n (%)  IG1: 21 (20)  IG2: 15 (14.2)  IG3: 13 (12.3)  CG: 16 (15.0)</p> <p>Between-group differences NR  Incidence of mania or hypomania: ADS Mania scale, ITT (N=429)  12 weeks, n (calculated %)  IG1: 3 (2.8)  IG2: 1 (0.9)  IG3: 0  CG: 1 (0.9)</p>	
March, 2004 <sup>3</sup> Index article Companion article: Kennard, 2006 <sup>6</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2006 <sup>68</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA
March, 2004 <sup>3</sup> Index article Companion article: Vitiello, 2006 <sup>7</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA
March, 2004 <sup>3</sup> Index article Companion article: Kratochvil, 2009 <sup>8</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	
March, 2004 <sup>3</sup> Index article TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	NA	NA	NA	NA
Melvin, 2006 <sup>79</sup>	G1: CBT G2: Sertraline G3: Combined	Mean (SD) G1: 19.41 (19.64) G2: 24.23 (26.90) G3: 23.20 (20.24)  Suicidal ideation adverse events and other adverse events not reported by group	NR	NR	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Wilkinson, 2011 <sup>87</sup>	IG: SSRI CG:SSRI plus CBT	<p>Treatment group not associated with higher risk of suicide Presence of Event (Absence of Event) IG1: 24 (55) IG2: 26 (59) OR,1.01; X2, .00; p=1.0</p> <p>Treatment group not associated with self-injury during followup Presence of Event (Absence of Event) IG1: 25 (53) IG2: 35 (50) OR, 1.48; X2, 1.5; p=0.2</p>	NR	NR	NR

ADS = anxiety and depression scale; AE = adverse event; CBT = cognitive behavioral therapy; C-CASA = Columbia Classification Algorithm of Suicide Assessment; CG = control group; FLX = fluoxetine; IG = intervention group; ITT = intent to treat; KQ = Key Question; n/N = number; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; SD = standard deviation; SIQ-JR = Suicide Ideation Questionnaire-Junior High School; SSRI = selective serotonin reuptake inhibitors; TADS = Treatment among Adolescents with Depression; vs. = versus.

**Table F-21. KQ 5a: Harms of SSRIs versus SNRIs**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson 2014 <sup>38</sup>	IG1: duloxetine IG2: fluoxetine CG: placebo	<p>No statistically significant differences between any treatment groups for any outcome on the C-SSRS during acute treatment.</p> <p>Any Occurrence of Suicidal Ideation at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 16 (14.2%) IG2: 16 (14.2%) CG: 15 (14.6%)</p> <p>Any Occurrence of Suicidal Behaviors at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 0 IG2: 1 (0.9%) CG: 0</p> <p>Any Occurrence of Suicidal Acts at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 0 IG2: 1 (0.9%) CG: 0</p> <p>Any Occurrence of Nonsuicidal self-injurious behavior at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 4 (3.5%) IG2: 6 (5.3%) CG: 2 (1.9%)</p>	<p>Discontinuation in Acute Phase (IG1: 117; IG2: 117; CG: 103) IG1: 30 (25.6%) IG2: 26 (22.2%) CG: 16 (5.5%)</p> <p>Discontinuation in Extension Phase (IG1: 83; IG2: 92; CG: 86) IG1: 27 (32.5%) IG2: 27 (29.3%) CG: 17 (19.8%)</p> <p>Discontinuation due to AE in Acute Phase (IG1: 117; IG2: 117; CG: 103) IG1: 9 (7.7%) IG2: 1 (0.9%) CG: 3 (2.9%)</p> <p>Significantly more IG1 than IG2, p=0.019</p> <p>Discontinuation due to AE in Extension Phase (IG1: 83; IG2: 92; CG: 86) IG1: 2 (2.4%) IG2: 8 (8.7%) CG: 4 (4.7%)</p>	<p>Patients with Serious Adverse Events (all resulted in hospitalization, 3 suicide related) IG1: 7 IG2: 6 CG: 1 (major depression)</p> <p>At least one TEAE at 10 weeks IG1: 59.8% IG2: 62.4% CG: 66.0% No significant difference</p> <p>At least one TEAE at 36 weeks IG1: 63.9% IG2: 62.0% CG: 72.1% (transitioned to either duloxetine or fluoxetine) No significant difference</p>	NR

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson 2014 <sup>38</sup> (continued)		<p>Treatment-emergent Suicidal Ideation at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 8 (7.1%) IG2: 9 (8.0%) CG: 7 (6.8%)</p> <p>Treatment-emergent Suicidal Behaviors at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 0 IG2: 1 (0.9%) CG: 0</p> <p>Treatment-emergent Nonsuicidal self-injurious behavior at 10 weeks (IG1: 113; IG2: 113; CG: 103) IG1: 4 (3.5%) IG2: 6 (5.3%) CG: 1 (1.0%)</p>			



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie 2014 <sup>46</sup>	IG1: duloxetine 60 mg QD IG2: duloxetine 30 mg QD IG3: fluoxetine 20 mg QD CG: placebo	No statistically significant differences between any treatment groups for any outcome on the C-SSRS during acute treatment.  Any Occurrence of Suicidal Ideation at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 17 (16.2%) IG2: 11 (9.6%) IG3: 13 (11.6%) CG: 15 (12.8%)  Any Occurrence of Suicidal Behaviors at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)  Any Occurrence of Suicidal Acts at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)	Discontinuation in Acute Phase (IG1:108; IG2: 116; IG3: 117 CG: 122) IG1: 33 (30.6%) IG2: 35 (30.2%) IG3: 33 (28.2%) CG: 37 (30.3%)  Discontinuation in Extension Phase (IG1: 73; IG2: 81; IG3: 84; CG: 82) IG1: 30 (41.1%) IG2: 31 (38.3%) IG3: 35 (41.7%) CG: 38 (46.3%)  Discontinuation due to AE in Acute Phase (IG1:108; IG2: 116; IG3: 117 CG: 122) IG1: 12 (11.1%) IG2: 7 (6.0%) IG3: 6 (5.1%) CG: 4 (3.3%)  Discontinuation due to AE in Extension Phase (IG1: 73; IG2: 81; IG3: 84; CG: 82) IG1: 4 (5.5%) IG2: 6 (7.4%) IG3: 3 (3.6%) CG: 7 (8.5%)	Patients with Serious Adverse Events (all resulted in hospitalization, 9 suicide related) IG1+IG2: 14 IG3: 6 CG: 2  At least one TEAE at 10 weeks IG1: 73.1% IG2: 57.8% IG3: 61.5% CG: 58.2%  Significantly more IG1 patients experiencing at least one TEAE compared with CG ( p=0.02) and IG2 ( p=0.02).  At least one treatment-emergent adverse event (TEAE) at 36 weeks IG1: 68.5% IG2: 56.8% IG3: 53.6% CG: 67.1% (transitioned to duloxetine) Greater among IG1 and CG than IG2 and IG3	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie 2014 <sup>46</sup> (continued)		<p>Any Occurrence of Nonsuicidal self-injurious behavior at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 116)</p> <p>IG1: 3 (2.9%) IG2: 6 (5.2%) IG3: 2 (1.8%) CG: 5 (4.3%)</p> <p>Treatment-emergent Suicidal Ideation at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117)</p> <p>IG1: 7 (6.7%) IG2: 6 (5.2%) IG3: 9 (8.0%) CG: 11 (9.4%)</p> <p>Treatment-emergent Suicidal Behaviors at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117)</p> <p>IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)</p> <p>Treatment-emergent Nonsuicidal self-injurious behavior at 10 weeks (IG1:104; IG2: 112; IG3: 112; CG: 115)</p> <p>IG1: 3 (2.9%) IG2: 3 (2.7%) IG3: 2 (1.8%) CG: 5 (4.3%)</p>			

AE = adverse event; CG = control group; C-SSRS = Columbia-suicide severity rating scale; IG = intervention group; KQ = Key Question; NR = not reported; QD = every day; TEAE = treatment-emergent adverse event.

**Table F-22. KQ 5a: Harms of SSRIs versus TCAs**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article	IG1: paroxetine IG2: imipramine CG: placebo		<p>Treatment-emergent adverse experiences, regardless of attribution, leading to withdrawal (IG1: 93; IG2: 95; CG: 87)</p> <p>Body as a whole IG1: 2 (2.2%) IG2: 7 (7.4%) CG: 1 (1.1%)</p> <p>Cardiovascular System IG1: 1 (1.1%) IG2: 13 (13.7%) CG: 2 (2.3%)</p> <p>Urogenital System IG1: 0 (0.0%) IG2: 3 (3.2%) CG: 0 (0.0%)</p> <p>Digestive System IG1: 2 (2.2%) IG2: 8 (8.4%) CG: 1 (1.1%)</p> <p>Musculoskeletal System IG1: 1 (1.1%) IG2: 1 (1.1%) CG: 0 (0.0%)</p> <p>Nervous System IG1: 8 (8.6%) IG2: 7 (7.4%) CG: 2 (2.3%)</p>	<p>Adverse experiences requiring corrective treatment (IG1: 93; IG2: 95; CG: 87)</p> <p>Headache IG1: 20 (21.5%) IG2: 20 (21.1%) CG: 23 (26.4%)</p> <p>Respiratory Disorder IG1: 8 (8.6%) IG2: 5 (5.3%) CG: 27 (8.0%)</p> <p>Rhinitis IG1: 6 (6.5%) IG2: 3 (3.2%) CG: 23 (3.4%)</p> <p>Pharyngitis IG1: 4 (4.3%) IG2: 9 (9.5%) CG: 25 (5.7%)</p> <p>Infection IG1: 4 (4.3%) IG2: 2 (2.1%) CG: 7 (8.0%)</p> <p>Sinusitis IG1: 4 (4.3%) IG2: 1 (1.1%) CG: 6 (6.9%)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article (continued)			Respiratory System IG1: 0 (0.0%) IG2: 2 (2.1%) CG: 0 (0.0%)  Skin and Appendages IG1: 0 (0.0%) IG2: 4 (4.2%) CG: 1 (1.1%)	Back Pain IG1: 4 (4.3%) IG2: 1 (1.1%) CG: 5 (5.7%)  Severe Adverse Events IG1: 18 IG2: 11 CG: 2	
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup>	IG1: paroxetine IG2: imipramine CG: placebo	Suicidal or self-injurious behaviors (IG1: 93; IG2: 95; CG: 87) CSR, Keller, RIAT IG1: 5, 7, 11 IG2: 3, 3, 4 (3 definite, 1 possible) CG: 1, 1, 2 (1 definite, 1 possible)	Withdrawal for adverse events among 86 patients (IG1: 93; IG2: 95; CG: 87) N (%) CSR IG1: 11 (11.8%) IG2: 30 (31.5%) CG: 6 (6.9%)  RIAT IG1: 14 (15.0%) IG2: 31 (32.6%) CG: 6 (6.9%)  Withdrawal for protocol violations CSR IG1: 3 (3.2%) IG2: 5 (5.3%) CG: 7 (8.0%)	Adverse events found in CRFs NR (IG1: 31; IG2: 40; CG: 22) IG1: 159 IG2: 257 CG: 77  Adverse events appendix of original trial (IG1: 31; IG2: 40; CG: 22) IG1: 136 IG2: 240 CG: 67  % underestimate in relying only on adverse event appendix (IG1: 31; IG2: 40; CG: 22) IG1: 14% IG2: 7% CG: 13%	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)			RIAT IG1: 1 (1.1%) IG2: 5 (5.3%) CG: 9 (10.3%)  Total dropout rate CSR IG1: 26 (28%) IG2: 38 (40%) CG: 21 (24%)  RIAT IG1: 27 (29%) IG2: 38 (40%) CG: 21 (24%)	Adverse events in SKB CSR, Keller 2001, RIAT reanalysis (IG1: 93; IG2: 95; CG: 87) CSR, Keller, RIAT  Cardiovascular IG1: 7, 5, 44 IG2: 60, 42, 130 CG: 12, 6, 32  Gastrointestinal/digestive IG1: 80, 84, 112 IG2: 108, 106, 147 CG: 59, 61, 79  Psychiatric IG1: NR, NR, 103 IG2: NR, NR, 63 CG: NR, NR, 24  Respiratory IG1: 39, 33, 42 IG2: 32, 27, 22 CG: 43, 37, 39  Neurological/ nervous system IG1: 106, 115, 101 IG2: 117, 135, 114 CG: 42, 65, 77  Other IG1: 121, 28, 79 IG2: 51, 30, 76 CG: 30, 38, 79	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)				<p>Body as whole IG1: 106, NR, NR IG2: 125, NR, NR CG: 121, NR, NR</p> <p>Total IG1: 338, 265, 481 IG2: 493, 340, 552 CG: 277, 207, 330</p> <p>Adverse events in original study and reorganized by RIAT analysis (IG1: 93; IG2: 95; CG: 87) Cardiovascular IG1: 1 IG2: 3 CG: 0</p> <p>Gastrointestinal IG1: 25 IG2: 20 CG: 4</p> <p>Psychiatric IG1: 32 IG2: 4 CG: 6</p> <p>Respiratory IG1: 2 IG2: 1 CG: 4</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury, 2015 <sup>49</sup> (continued)				Neurological IG1: 7 IG2: 14 CG: 7  Other IG1: 3 IG2: 8 CG: 5  Total IG1: 70 IG2: 50 CG: 26	
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup>	IG1: paroxetine IG2: imipramine CG: placebo	RIAT Suicidality and suicide-related events (IG1: 23; IG2: 9; CG: 5)  Total Suicide-Related AEs IG1: 23 IG2: 11 CG: 5  Acute Phase IG1: 12 IG2: 6 CG: 2  Continuation Phase IG1: 6 IG2: 5 CG: 3 (includes one class that could be classed as trauma)	Continuation Phase Dropouts (as reported in Table 1) SKB ITT: IG1=93; IG2=95; CG=87 IG1: 34 IG2: 27 CG: 20  RIAT IG1: 31* IG2: 27 CG: 18  *reported as 30 in text and 31 in table 1. N of 31 includes on patients who was discontinued during taper phase for AE suicidal overdose	Acute Phase Lack of Efficacy ITT: IG1=93; IG2=95; CG=87 IG1: 29 IG2: 36 IG3: 38  Continuation Phase Lack of Efficacy ITT: IG1=93; IG2=95; CG=87 IG1: 3 IG2: 2 CG: 2  Total AEs (Severe AEs) by Phase and type	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup> (continued)		Taper Phase IG1: 5 IG2: 0 CG: 0	Continuation Phase Dropouts (as reported in Table 3) ITT: IG1=93; IG2=95; CG=87 IG1: 12 IG2: 14 CG: 11	Cardiac and vascular disorders Acute Patients Only (IG1=44; IG2=56; CG=53) IG1: 14 (1) IG2: 91 (3) CG: 22	
		Total Suicidality and suicide-related Episodes IG1: 20 IG2: 9 CG: 5		Continuation Patients Only (IG1=49; IG2=39; CG=31) IG1: 26 IG2: 22 IG3=10	
		Acute Phase IG1: 9 IG2: 4 CG: 2	Acute Phase Dropouts (as reported in Table 3) ITT: IG1=93; IG2=95; CG=87 IG1: 6 IG2: 5 CG: 3	Gastrointestinal disorders Acute Patients Only (IG1=44; IG2=56; CG=53)	
		Continuation Phase IG1: 6 IG2: 5 CG: 3	Reasons for Withdrawal among Continuation Phase Dropouts (IG1=31; IG2=27; CG=18)	IG1: 45 (5) IG2: 74 (9) CG: 45 (2)	
		Taper Phase IG1: 5 IG2: 0	Adverse Events SKB, RIAT IG1: 2, 5 IG2: 8, 9 CG: 4, 4	Continuation Patients Only (IG1=49; IG2=39; CG=31) IG1: 62 (16) IG2: 59 (7) CG: 32 (2)	
			Lack of Efficacy SKB, RIAT IG1: 7, 1 IG2: 8, 9 CG: 6, 2	Psychiatric Disorders Acute Patients Only (IG1=44; IG2=56; CG=53) IG1: 58 (18) IG2: 39 (4) CG: 20 (4)	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup> (continued)			Relapse SKB, RIAT IG1: 0, 4 IG2: 0, 3 CG: 0, 4	Continuation Patients Only (IG1=49; IG2=39; CG=31) IG1: 42 (6) IG2: 24 IG3: 7 (1)	
			Protocol violation non-compliance SKB, RIAT IG1: 11, 9 IG2: 6, 6 CG: 4, 3	Nervous system disorders Acute Patients Only (IG1=44; IG2=56; CG=53) IG1: 31 (1) IG2: 73 (9) CG: 55 (3)	
			Protocol violation - by investigator SKB, RIAT IG1: 0, 1 IG2: 0, 2 CG: 2, 3	Continuation Patients Only (IG1=49; IG2=39; CG=31) IG1: 63 (5) IG2: 34 (3) IG3: 22 (4)	
			Lost to followup SKB, RIAT IG1: 2,2 IG2: 1,1 CG: 2,3	Respiratory and thoracic disorders Acute Patients Only (IG1=44; IG2=56; CG=53) IG1: 18 (1) IG2: 15 (1) CG: 27 (2)	
			Other ("Feeling well") SKB, RIAT IG1: 1, 0 IG2: 0,0 CG: 0,0	Continuation Patients Only (IG1=49; IG2=39; CG=31) IG1: 21 (1) IG2: 7 IG3: 13 (2)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
GlaxoSmithKline, 1998 <sup>48</sup> Index article Companion article: Le Noury 2016 <sup>51</sup> (continued)				Respiratory and thoracic disorders Acute Patients Only (IG1=44; IG2=56; CG=53) IG1: 18 (1) IG2: 15 (1) CG: 27 (2)  Continuation Patients Only (IG1=49; IG2=39; CG=31) IG1: 21 (1) IG2: 7 IG3: 13 (2)  All other SOCs Acute Patients Only (IG1=44; IG2=56; CG=53) IG1: 24 IG2: 44 (4) CG: 51 (1)  Continuation Patients Only (IG1=49; IG2=39; CG=31) IG1: 53 (3) IG2: 24 (1) IG3: 26 (4)  Total AEs Acute Patients Only (IG1=44; IG2=56; CG=53) IG1: 190 (26) IG2: 336 (30) CG: 220 (12)  Continuation Patients Only (IG1=49; IG2=39; CG=31) IG1: 267 (31) IG2: 184 (11) IG3: 110 (13)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Weihls, 2018 <sup>55</sup>	IG1: Desvenlafaxine (25, 35, or 50 mg/d) IG2: Fluoxetine (20 mg/d) CG: Placebo	<p>Treatment-emergent suicidal ideation or behavior at any post-baseline assessment: n (%)</p> <p>Overall IG1: 9/115 (7.8) IG2: 12/110 (10.9) CG: 8/112 (7.1)</p> <p>New-onset IG1: 8/102 (7.8) IG2: 10/97 (10.3) CG: 7/104 (6.7)</p> <p>Worsening IG1: 1/13 (7.7) IG2: 2/13 (15.4) CG: 1/8 (12.5)</p> <p>Treatment-emergent suicidal ideation at any post-baseline assessment: n (%)</p> <p>Overall IG1: 9/115 (7.8) IG2: 12/110 (10.9) CG: 8/112 (7.1)</p> <p>New-onset IG1: 8/102 (7.8) IG2: 10/97 (10.3) CG: 7/104 (6.7)</p>	<p>Discontinued study treatment: n (%)</p> <p>IG1: 16 (13.9, calculated) IG2: 13 (11.5, calculated) CG: 13 (11.6, calculated)</p> <p>Discontinued due to AE: n (%)</p> <p>IG1: 2 (1.7, calculated) IG2: 1 (.9, calculated) CG: 2 (1.8, calculated)</p> <p>Discontinued due to lack of efficacy: n (%)</p> <p>IG1: 1 (0.9, calculated) IG2: 0 (0.0, calculated) CG: 3 (2.7, calculated)</p> <p>Discontinued due to lost to followup: n (%)</p> <p>IG1: 6 (5.2, calculated) IG2: 5 (4.4, calculated) CG: 4 (3.6, calculated)</p> <p>Discontinued due to protocol violation: n (%)</p> <p>IG1: 3 (2.6, calculated) IG2: 0 (0.0, calculated) CG: 1 (0.9, calculated)</p>	<p>Any treatment-emergent AEs: %</p> <p>IG1: 69/115 (60.0) IG2: 72/112 (64.3) CG: 79 /112 (70.5)</p> <p>Severe AEs [not defined] considered unrelated to study medication: %</p> <p>IG1: 3.5% IG2: 5.4% CG: 3.6%</p> <p>Severe AEs [not defined] considered related to study medication: n (%)</p> <p>IG1: 3 (2.6, calculated) IG2: 0 (0.0%) CG: 2 (1.8, calculated)</p> <p>Serious AEs: N (%)</p> <p>IG1: 3 (2.6, calculated) IG2: 2 (1.8, calculated) CG: 0 (0.0)</p> <p>Deaths: none</p>	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Weihs, 2018 <sup>55</sup> (continued)		<p>Worsening IG1: 1/13 (7.7) IG2: 2/13 (15.4) CG: 1/8 (12.5)</p> <p>Treatment-emergent suicidal behavior at any post-baseline assessment: n (%) Overall IG1: 0/115 (0.0) IG2: 1/110 (0.9) CG: 0/112 (0.0)</p> <p>New-onset IG1: 0/115 (0.0) IG2: 1/110 (0.9) CG: 0/112 (0.0)</p> <p>Worsening IG1: 0 (0.0) IG2: 0 (0.0) CG: 0 (0.0)</p>	<p>Discontinued due to no longer willing to participate: n (%) IG1: 2 (1.7, calculated) IG2: 7 (6.2, calculated) CG: 2 (1.8, calculated)</p> <p>Discontinued due to other: n (%) IG1: 2 (1.7, calculated) IG2: 0 (0.0, calculated) CG: 1 (0.9, calculated)</p>		

AE = adverse event; CG = control group; CRF = Corticotropin-releasing factor; CSR = clinical study report; IG = intervention group; ITT = intent to treat; KQ = Key Question; n/N = number; NA = not applicable; NR = not reported; RIAT = restoring invisible and abandoned trials; SKB = SmithKline Beecham; SOC = system organ class.

**Table F-23. KQ 5a: Harms of pharmacotherapy dose comparisons**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson, 2018 <sup>59</sup>	IG1: Low-dose Desvenlafaxine IG2: High-dose Desvenlafaxine CG: Placebo	SIB, n/N (%) Treatment-emergent IG1: 9/120 (7.5) IG2: 14/121 (11.6) CG: 16/119 (13.4)  New onset IG1: 9/113 (8.0) IG2: 13/108 (12.0) CG: 14/107 (13.1)  Worsening IG1: 0/113 (0) IG2: 1/13 (7.7) CG: 2/12 (16.7) SI, n/N (%)  Treatment-emergent IG1: 9/120 (7.5) IG2: 14/121 (11.6) CG: 16/119 (13.4)  New onset IG1: 9/113 (8.0) IG2: 13/108 (12.0) CG: 14/107 (13.1)  Worsening IG1: 0 IG2: 1/13 (7.7) CG: 2/12 (16.7) SB, n/N (%)  Treatment-emergent IG1: 1/120 (0.8) IG2: 0/121 (0) CG: 1/119 (0.8)	Discontinued due to AE (N): IG1: 8 IG2: 3 CG: 8  Discontinued due to lack of efficacy (N): IG1: 2 IG2: 0 CG: 2  Lost to followup (N): IG1: 3 IG2: 1 CG: 5  Protocol violation (N): IG1: 1 IG2: 2 CG: 3  No longer willing to participate (N): IG1: 4 IG2: 9 CG: 3  Other (N): IG1: 1 IG2: 2 CG: 2	Overall TAEs with Incidence ≥5% in any group, N (%) <sup>*</sup> Any TAE IG1: 81 (66.4) IG2: 81 (66.9) CG: 73 (60.8)  Abdominal pain, upper: IG1: 7 (5.7) IG2: 11 (9.1) CG: 9 (7.5)  Accidental overdose: IG1: 0 IG2: 3 (2.5) CG: 1 (0.8)  Aggression: IG1: 2 (1.6) IG2: 0 CG: 0  Blood triglycerides increased: IG1: 2 (1.6) IG2: 0 CG: 0  Cough: IG1: 2 (1.6) IG2: 3 (2.5) CG: 5 (4.2)  Decreased appetite: IG1: 6 (4.9) IG2: 6 (5.0) CG: 6 (5.0)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson, 2018 <sup>59</sup> (continued)		New-onset IG1: 1/120 (0.8) IG2: 0/121 (0) CG: 1/119 (0.8)		Diarrhea: IG1: 3 (2.5) IG2: 3 (2.5) CG: 2 (1.7)	
		Suicide attempt, N IG1: 1 IG2: 0 CG: 1		Dizziness: IG1: 5 (4.1) IG2: 6 (5.0) CG: 3 (2.5)	
		Worsening IG1: 0 IG2: 0 CG: 0		Dysmenorrhea: IG1: 1 (1.4) IG2: 4 (5.3) CG: 1 (1.7)	
				Fatigue: IG1: 4 (3.3) IG2: 9 (7.4) CG: 2 (1.7)	
				Feeling jittery: IG1: 1 (0.8) IG2: 4 (3.3) CG: 0	
				Viral gastroenteritis: IG1: 2 (1.6) IG2: 3 (2.5) CG: 2 (1.7)	
				Headache: IG1: 22 (18.0) IG2: 25 (20.7) CG: 15 (12.5)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson, 2018 <sup>59</sup> (continued)				Insomnia: IG1: 7 (5.7) IG2: 4 (3.3) CG: 1 (0.8)  Nausea: IG1: 12 (9.8) IG2: 14 (11.6) CG: 7 (5.8)  Nasopharyngitis: IG1: 8 (6.6) IG2: 7 (5.8) CG: 2 (1.7)  Psychomotor hyperactivity: IG1: 1 (0.8) IG2: 4 (3.3) CG: 0  Pyrexia IG1: 3 (2.5) IG2: 2 (1.7) CG: 0  Skin abrasion IG1: 0 IG2: 2 (1.7) CG: 0  Upper respiratory tract infection IG1: 4 (3.3) IG2: 6 (J5) CG: 3 (2.5)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Atkinson, 2018 <sup>59</sup> (continued)				Vomiting IG1: 1 (0.8) IG2: 9 (7.4) CG: 4 (3.3)  * TAEs presented by age-specific subgroups as well	
Durgam, 2018 <sup>40</sup>	IG1: Vilazodone 15 mg/d IG2: Vilazodone 30 mg/d CG: Placebo	Incidence of suicidal ideation based on C-SSRS (%) IG1: 36.0 IG2: 31.1 CG: 33.3  Incidence of suicidal behavior based on C-SSRS (%) IG1: 1.1 IG2: 1.1 CG: 1.8	Total premature discontinuation after randomization, N IG1: 26 IG2: 19 CG: 32  Discontinuation prior to entering safety pop. Lost to followup, N IG1: 0 IG2: 0 CG: 1	Any TAE, N (%) IG1: 122 (69.7) IG2: 135 (75.0) CG: 105 (61.4)  Any SAE, N (%) IG1: 2 (1.1) IG2: 3 (1.7) CG: 1 (0.6)  Discontinuation due to AEs, N (%) IG1: 9 (5.1) IG2: 8 (4.4) CG: 4 (2.3)	NR



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup> (continued)		Suicide attempt, patient reported on C-SSRS, N IG1: 1 IG2: 1 CG: 2	<p>Withdrew consent, N IG1: 0 IG2: 0 CG: 1</p> <p>Protocol violation, N IG1: 0 IG2: 0 CG: 1</p> <p>Discontinuation prior to entering ITT pop. Withdrew consent, N IG1: 1 IG2: 0 CG: 1</p> <p>Discontinuation prior to completed treatment Adverse event IG1: 9 IG2: 8 CG: 4</p> <p>Withdrew consent, N IG1: 6 IG2: 8 CG: 8</p> <p>Lost to followup, N IG1: 3 IG2: 1 CG: 6</p> <p>Protocol violation, N IG1: 4 IG2: 2 CG: 3</p>	<p>Nausea, N (%) IG1: 51 (29.1) IG2: 49 (27.2) CG: 14 (8.2)</p> <p>Headache, N (%) IG1: 22 (12.6) IG2: 29 (16.1) CG: 27 (15.8)</p> <p>Upper abdominal pain, N (%) IG1: 7 (4.0) IG2: 28 (15.6) CG: 11 (6.4)</p> <p>Vomiting, N (%) IG1: 11 (6.3) IG2: 21 (11.7) CG: 6 (3.5)</p> <p>Diarrhea, N (%) IG1: 15 (8.6) IG2: 16 (8.9) CG: 8 (4.7)</p> <p>Dizziness, N (%) IG1: 8 (4.6) IG2: 13 (7.2) CG: 5 (2.9)</p> <p>Nasopharyngitis, N (%) IG1: 6 (3.4) IG2: 11 (6.1) CG: 6 (3.5)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Durgam, 2018 <sup>40</sup> (continued)			Insufficient therapeutic response, N IG1: 3 IG2: 0 CG: 5  Other, N IG1: 0 IG2: 0 CG: 2	Abdominal discomfort, N (%) IG1: 7 (4.0) IG2: 8 (4.4) CG: 2 (1.2)  Upper respiratory tract infection, N (%) IG1: 7 (4.0) IG2: 7 (3.9) CG: 4 (2.3)  Insomnia, N (%) IG1: 5 (2.9) IG2: 7 (3.9) CG: 5 (2.9)  Fatigue, N (%) IG1: 4 (2.3) IG2: 7 (3.9) CG: 7 (4.1)  Decreased appetite, N (%) IG1: 7 (4.0) IG2: 6 (3.3) CG: 1 (0.6)  Somnolence, N (%) IG1: 8 (4.6) IG2: 4 (2.2) CG: 1 (0.6)	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie 2014 <sup>46</sup>	IG1: duloxetine 60 mg QD IG2: duloxetine 30 mg QD IG3: fluoxetine 20 mg QD CG: placebo	No statistically significant differences between any treatment groups for any outcome on the C-SSRS during acute treatment.  Any Occurrence of Suicidal Ideation at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 17 (16.2%) IG2: 11 (9.6%) IG3: 13 (11.6%) CG: 15 (12.8%)  Any Occurrence of Suicidal Behaviors at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117) IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)	Discontinuation in Acute Phase (IG1:108; IG2: 116; IG3: 117 CG: 122) IG1: 33 (30.6%) IG2: 35 (30.2%) IG3: 33 (28.2%) CG: 37 (30.3%)  Discontinuation in Extension Phase (IG1: 73; IG2: 81; IG3: 84; CG: 82) IG1: 30 (41.1%) IG2: 31 (38.3%) IG3: 35 (41.7%) CG: 38 (46.3%)  Discontinuation due to AE in Acute Phase (IG1:108; IG2: 116; IG3: 117 CG: 122) IG1: 12 (11.1%) IG2: 7 (6.0%) IG3: 6 (5.1%) CG: 4 (3.3%)	Patients with Serious Adverse Events (all resulted in hospitalization, 9 suicide related) IG1+IG2: 14 IG3: 6 CG: 2  At least one treatment-emergent adverse event (TEAE) at 10 weeks IG1: 73.1% IG2: 57.8% IG3: 61.5% CG: 58.2%  Significantly more IG1 patients experiencing at least one TEAE compared with CG ( p=0.02) and IG2 ( p=0.02).	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie 2014 <sup>46</sup> (continued)		<p>Any Occurrence of Suicidal Acts at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117)</p> <p>IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)</p> <p>Any Occurrence of Nonsuicidal self-injurious behavior at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 116)</p> <p>IG1: 3 (2.9%) IG2: 6 (5.2%) IG3: 2 (1.8%) CG: 5 (4.3%)</p> <p>Treatment-emergent Suicidal Ideation at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117)</p> <p>IG1: 7 (6.7%) IG2: 6 (5.2%) IG3: 9 (8.0%) CG: 11 (9.4%)</p> <p>Treatment-emergent Suicidal Behaviors at 10 weeks (IG1:105; IG2: 115; IG3: 112; CG: 117)</p> <p>IG1: 0 IG2: 0 IG3: 1 (0.9%) CG: 1 (0.9%)</p>	<p>Discontinuation due to AE in Extension Phase (IG1: 73; IG2: 81; IG3: 84; CG: 82)</p> <p>IG1: 4 (5.5%) IG2: 6 (7.4%) IG3: 3 (3.6%) CG: 7 (8.5%)</p>	<p>At least one TEAE at 36 weeks</p> <p>IG1: 68.5% IG2: 56.8% IG3: 53.6% CG: 67.1% (transitioned to duloxetine)</p> <p>Greater among IG1 and CG than IG2 and IG3</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie 2014 <sup>46</sup> (continued)		Treatment-emergent Nonsuicidal self-injurious behavior at 10 weeks (IG1:104; IG2: 112; IG3: 112; CG: 115) IG1: 3 (2.9%) IG2: 3 (2.7%) IG3: 2 (1.8%) CG: 5 (4.3%)			

AE = adverse event; CG = control group; C-SSRS = Columbia-suicide severity rating scale; IG = intervention group; ITT = intent to treat; KQ = Key Question; N/A = not applicable; n/N = number; QD = every day; SAE = significant adverse event; SIB = Suicidal ideation and behavior; TAE = treatment adverse event; TEAE = treatment-emergent adverse event.

**Table F-24. KQ 5a: Harms of treatment-resistant depression interventions**

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Brent, 2008 <sup>88</sup> Index article TORDIA	IG1: Switch to a second, different SSRI (citalopram, or fluoxetine, 20-40 mg) IG2: Switch to a different SSRI plus CBT IG3: Switch to venlafaxine (150-225 mg) IG4: Switch to venlafaxine plus CBT	Harm related AEs, N (%) IG1+IG2: 31 (18.5) IG3+IG4: 37 (22.3) IG1+IG3: 32 (19.0) IG2+IG4: 36 (21.7)  Suicide attempts, N (%) IG1+IG2: 6 (3.6) IG3+IG4: 11 (6.6) IG1+IG3: 7 (4.2) IG2+IG4: 10 (6.0)  SIQ score, mean (SD) [95% CI] 6 weeks G1+IG2: 33.3 (20.7) [30.0 to 36.6] IG3+IG4: 35.1 (21.5) [31.5 to 38.7] IG1+IG3: 34.3 (20.5) [31.0 to 37.7] IG2+IG4: 33.9 (21.7) [30.4 to 37.5]  12 weeks G1+IG2: 31.6 (17.9) [28.6 to 34.6] IG3+IG4: 31.5 (19.7) [28.2 to 34.7] IG1+IG3: 31.4 (17.5) [28.5 to 34.2] IG2+IG4: 31.7 (20.2) [28.3 to 35.1]	Withdrew due to serious AEs, N IG1: 5 IG2: 10 IG3: 6 IG4: 8  Withdrew due to AEs, N IG1: 4 IG2: 3 IG3: 3 IG4: 2  Withdrew due to nonadherence, N IG1: 4 IG2: 1 IG3: 4 IG4: 4  Withdrew consent, N IG1: 2 IG2: 2 IG3: 2 IG4: 6  Lost to followup, N IG1: 2 IG2: 0 IG3: 2 IG4: 2	≥1 Serious AE, N (%) IG1+IG2: 18 (10.7) IG3+IG4: 19 (11.4) IG1+IG3: 14 (8.3) IG2+IG4: 23 (13.9)  ≥1 AE, N (%) IG1+IG2: 86 (51.2) IG3+IG4: 78 (47.0) IG1+IG3: 84 (50.0) IG2+IG4: 80 (48.2)  Breakdown of AE by type (except for suicidality related AEs), N (%) Sleep IG1+IG2: 5 (3.0) IG3+IG4: 12 (7.2) IG1+IG3: 7 (4.2) IG2+IG4: 10 (6.0)  Irritability IG1+IG2: 8 (4.8) IG3+IG4: 8 (4.8) IG1+IG3: 6 (3.6) IG2+IG4: 10 (6.0)  Flu-like IG1+IG2: 31 (18.5) IG3+IG4: 21 (12.7) IG1+IG3: 26 (15.5) IG2+IG4: 26 (15.7)	See subgroup response in benefits tab

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Brent, 2008 <sup>88</sup> Index article TORDIA (continued)			Worsening depression, N IG1: 3 IG2: 2 IG3: 3 IG4: 4	Aches IG1+IG2: 24 (14.3) IG3+IG4: 23 (13.9) IG1+IG3: 23 (13.7) IG2+IG4: 24 (14.5)	
			Ancillary treatment–comorbidity, N IG1: 3 IG2: 1 IG3: 1 IG4: 3	Accident/injury IG1+IG2: 12 (7.1) IG3+IG4: 7 (4.2) IG1+IG3: 10 (6.0) IG2+IG4: 9 (5.4)	
			Received paroxetine, N IG1: 0 IG2: 3 IG3: 0 IG4: 0	Gastrointestinal IG1+IG2: 9 (5.4) IG3+IG4: 7 (4.2) IG1+IG3: 7 (4.2) IG2+IG4: 9 (5.4)	
			Received psychotropic medication, N IG1: 0 IG2: 1 IG3: 0 IG4: 1	Skin IG1+IG2: 3 (1.8) IG3+IG4: 13 (7.8) IG1+IG3: 7 (4.2) IG2+IG4: 9 (5.4)	
			Pregnancy, N IG1: 1 IG2: 0 IG3: 0 IG4: 0	By medication: X2/1=6.69; p=0.01 Musculoskeletal IG1+IG2: 6 (3.6) IG3+IG4: 10 (6.0) IG1+IG3: 5 (3.0) IG2+IG4: 11 (6.6)	
			Psychosis, N IG1: 0 IG2: 1 IG3: 0 IG4: 0		

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Brent, 2008 <sup>88</sup> Index article TORDIA (continued)			Substance abuse, N IG1: 1 IG2: 1 IG3: 0 IG4: 0  Hypomania, N IG1: 0 IG2: 0 IG3: 1 IG4: 0		
Brent, 2008 <sup>88</sup> Index article Companion article: Asarnow, 2009 <sup>89</sup> TORDIA	See Brent 2008 index article (#3010)	NR	NR	NR	NR
Brent, 2008 <sup>88</sup> Index article Companion article: Brent, 2009 <sup>90</sup> TORDIA	See Brent, 2008 <sup>88</sup> Index article TORDIA	Effect of treatment on hazard of a suicidal event in figures	NR	Effect of treatment on nonsuicidal self-injury in figures  Rates of NSSI and suicidal AEs were estimated using software from Figure 2.  Rate of adverse events by treatment group Nonsuicidal self-injury events, % IG1: 8.4 IG2: 9.6 IG3: 4.7 IG4: 14.5  Suicidal events, % IG1: 18.1 IG2: 14.5 IG3: 10.6 IG4: 14.5	Only one baseline predictor variable was found to moderate treatment effects with respect to onset or time to either suicidal or nonsuicidal event adverse events; significant interaction between medication and suicidal ideation (z=3.10, p=0.002) with respect to occurrence of any self-harm adverse event. Participants with baseline SIQ score $\geq 35$ were more likely to experience a self-harm event if they were treated with Venlafaxine (IG3/IG4) than with an SSRI: (37.2% versus 23.3%, $\chi^2=3.83$ , df=1, p=0.05).



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup>	IG: Dose-titration of fluoxetine dose from 20 mg/day to 40-60 mg/day CG: Continued treatment with fluoxetine at fixed dose of 20 mg/day	Self-mutilatory behavior of mild severity, ITT (IG=14; CG=15) 19 weeks, n (calculated %) IG: 1 (7.1) CG: 0 Between-group difference NR	Overall withdrawal, ITT (IG=14; CG=15) NR from 10 to 19 weeks Withdrawal due to AEs, ITT (IG=14; CG=15) 19 weeks, n (calculated %) IG: 0 CG: 3 (20) Between-group difference NR Withdrawal due to lack of efficacy, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7.1) (same patient who presented with self-mutilatory behavior of mild severity) CG: 0 Between-group difference NR	"Nonsolicited" treatment-emergent AEs: no significant between-group differences for any specific AEs (p=NS) Patients reporting any AEs, ITT (IG=14; CG=15)  19 weeks, n (%) IG: 9 (64) CG: 7 (47) No between-group difference: p=0.462 Personality disorder, ITT (IG=14; CG=15)  19 weeks, n (%) IG: 0 CG: 3 (20) No between-group difference: p=0.224  Cough increased, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 2 (13) No between-group difference: p=1.00	NA

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>Hostility, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 0 CG: 2 (13) No between-group difference: p=0.483</p> <p>Rhinitis, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 2 (13) No between-group difference: p=1.00</p> <p>Fever, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 1 (7) No between-group difference: p=1.00</p> <p>Somnolence, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 1 (7) No between-group difference: p=1.00</p> <p>Diarrhea, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 0 CG: 1 (7)</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>No between-group difference: p=1.00</p> <p>Ear pain, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 0 CG: 1 (7) No between-group difference: p=1.00</p> <p>Euphoria, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 0 CG: 1 (7) No between-group difference: p=1.00</p> <p>Insomnia, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 0 CG: 1 (7) No between-group difference: p=1.00</p> <p>Lymphadenopathy, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 0 CG: 1 (7) No between-group difference: p=1.00</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				Speech disorder, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 0 CG: 1 (7) No between-group difference: p=1.00  Thinking abnormal, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 0 CG: 1 (7) No between-group difference: p=1.00  Accidental injury, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 3 (21) CG: 0 No between-group difference: p=0.100  Abdominal pain, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>Dry mouth, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224</p> <p>Infection, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224</p> <p>Neck rigidity, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224</p> <p>Pain, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224</p> <p>Pharyngitis, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>Amblyopia, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Back pain, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Bronchitis, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Contact dermatitis, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Dizziness, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>No between-group difference: p=0.483</p> <p>Increased salivation, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Intentional injury, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Nervousness, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Pruritus, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>Rash, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Sinus bradycardia, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Sinusitis, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Ulcerative stomatitis, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Vomiting, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p>	



First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>"Solicited" treatment-emergent AEs: no significant between-group differences for any specific AEs (p=NS) Patients reporting any AEs, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 11 (79) CG: 8 (53) No between-group difference: p=0.245</p> <p>Stomachaches, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 3 (21) CG: 2 (13) No between-group difference: p=0.651</p> <p>Cold or sniffles, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 3 (21) CG: 2 (13) No between-group difference: p=0.651</p> <p>Feeling sleepy, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 2 (13) No between-group difference: p=1.00</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>Sleeping, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 2 (13) No between-group difference: p=1.00</p> <p>Crying, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 2 (13) No between-group difference: p=1.00</p> <p>Paying attention, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 4 (29) CG: 1 (7) No between-group difference: p=0.169</p> <p>Muscle cramps, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 3 (21) CG: 1 (7) No between-group difference: p=0.330</p> <p>Headache, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 3 (21) CG: 1 (7) No between-group difference: p=0.330</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>Tiredness, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 1 (7) No between-group difference: p=0.598</p> <p>Getting mad, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 1 (7) No between-group difference: p=0.598</p> <p>Eating, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 1 (7) No between-group difference: p=1.00</p> <p>Being sick to your stomach, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 1 (7) No between-group difference: p=1.00</p> <p>Shakiness, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 1 (7) No between-group difference: p=1.00</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>Bad dreams, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 1 (7) No between-group difference: p=1.00</p> <p>Diarrhea, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 0 CG: 1 (7) No between-group difference: p=1.00</p> <p>Dizziness, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 3 (21) CG: 0 No between-group difference: p=0.100</p> <p>Dry mouth and lips, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224</p> <p>Itchy or scratchy skin, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>No between-group difference: p=0.224</p> <p>Sitting still, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224</p> <p>Getting along with parents, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224</p> <p>Getting along with kids, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224</p> <p>Not being happy, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 2 (14) CG: 0 No between-group difference: p=0.224</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				<p>Drinking, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Wetness in mouth, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Pronouncing words, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p> <p>Doing things with your hand, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483</p>	

First Author's Last Name; Year; Trial Name	Treatment Interventions and Comparators	Suicidality	Withdrawal From Intervention/Drop Out From Study	Other Harms	Subgroup(s) Examined
Emslie, 2002 <sup>42</sup> Index article Companion article: Heiligenstein, 2006 <sup>91</sup> (continued)				Being sad, ITT (IG=14; CG=15) 19 weeks, n (%) IG: 1 (7) CG: 0 No between-group difference: p=0.483	
AE = adverse event; CG = control group; IG = intervention group; ITT = intent to treat; KQ = Key Question; N = number; NA = not applicable; NR = not reported; NS = not significant; SIQ = Suicidal Ideation Questionnaire; SSRI = selective serotonin reuptake inhibitors; TORDIA = Treatment of SSRI-Resistant Depression in Adolescents trial.					

## Appendix G. Subpopulation Tables

Table G-1. KQ 1b: Subgroup analysis for CBT versus pill placebo .....	G-2
Table G-2. KQ 1b: Subgroup analysis for CBT versus active control .....	G-3
Table G-3. KQ 1b: Subgroup analysis for family therapy versus pill placebo.....	G-3
Table G-4. KQ 1b: Subgroup analysis for family therapy versus active control.....	G-4
Table G-5. KQ 1b: Subgroup analysis for omega-3 versus pill placebo .....	G-4
Table G-6. KQ 2b: Subgroup analysis for SSRIs versus placebo.....	G-5
Table G-7. KQ 2b: Subgroup analysis for fluoxetine for relapse prevention versus placebo ....	G-8
Table G-8. KQ 2b: Subgroup analysis for TCAs versus placebo .....	G-8
Table G-9. KQ 3b: Subgroup analysis for fluoxetine plus CBT versus placebo.....	G-9
Table G-10. KQ 3b: Subgroup analysis for omega-3 plus family therapy versus pill placebo	G-10
Table G-11. KQ 5b: Subgroup analysis for psychotherapy within-type comparisons of delivery methods or approaches .....	G-10
Table G-12. KQ 5b: Subgroup analysis for psychotherapy versus pharmacotherapy .....	G-11
Table G-13. KQ 5b: Subgroup analysis for psychotherapy plus pharmacotherapy versus psychotherapy.....	G-12
Table G-14. KQ 5b: Subgroup analysis for psychotherapy plus pharmacotherapy versus pharmacotherapy .....	G-13
Table G-15. KQ 5b: Subgroup analysis for SSRIs versus TCAs .....	G-14
Table G-16. KQ 5b: Subgroup analysis for pharmacotherapy dose comparisons.....	G-14
Table G-17. KQ 5b: Subgroup analysis for treatment-resistant depression: within-type comparisons of interventions.....	G-15



**Table G-1. KQ 1b: Subgroup analysis for CBT versus pill placebo**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Family Income	CBT vs. pill placebo	Functional Impairment, clinician report	<div>&lt;\$75,000/year</div> <div>&gt;\$75,000/year</div>	In the lower income group, CBT=placebo (no significant differences in functional impairment) but in the higher income group, those in CBT did better than placebo adolescents (effect size=0.72) <sup>4</sup>
Depressive Symptom Severity	CBT vs. Pill Placebo	Functional Impairment, Clinician Report	<div>Mild/Moderate</div> <div>Marked/Severe</div>	No significant differences between CBT and pill placebo groups in functional impairment across depressive symptom severity subgroups. <sup>4</sup>
ADHD	CBT vs. Pill Placebo	Depressive Symptoms, Clinician report	<div>ADHD</div> <div>No ADHD</div>	Adolescents with ADHD in the CBT group had significantly greater improvements in depressive symptoms than those with ADHD in the placebo group; those without ADHD did not have any differences in depressive symptoms between CBT and placebo groups at end of treatment. <sup>8</sup>

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; CSA = childhood sexual abuse; KQ = Key Question.

**Table G-2. KQ 1b: Subgroup analysis for CBT versus active control**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Suicidality	CBT vs. active control, SBFT vs. active control	Remission	Lifetime suicidal Lifetime nonsuicidal	For adolescents receiving CBT or SBFT, lifetime suicidality did not moderate treatment response, but for adolescents in the active control group, the response of participants with suicidal history was less favorable than for nonsuicidal participants (64% vs. 23%, $p=0.04$ ). <sup>36</sup>
Race	CBT vs. Active Control	Time to Recovery	White Non-White	Adolescents in CBT group recovered faster than those in the LS group among Whites but no differences across treatment groups found among non-White adolescents. <sup>37</sup>
Number of MDD Episodes	CBT vs. Active Control	Time to Recovery	Recurrent MDD First Onset MDD	Adolescents in the CBT group recovered faster than those in the LS group among those with prior MDD episodes but no differences across treatment groups found among those with first-episode MDD. <sup>37</sup>
Coping Skills	CBT vs. Active Control	Time to Recovery	High Positive Coping Skills Poor Positive Coping Skills	Adolescents in the CBT group recovered faster than those in the LS group among those with high levels of positive coping skills but no differences across treatment groups found among those with poor levels of positive coping skills. <sup>37</sup>

CBT = cognitive behavioral therapy; KQ = Key Question; MDD = major depressive disorder; SBFT = Systemic behavior family therapy.

**Table G-3. KQ 1b: Subgroup analysis for family therapy versus pill placebo**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Psychological stress	Family therapy vs. pill placebo	Depression severity	Number of psychological stressors	When families reported fewer psychosocial stressors, the intervention arm had a significant decline in depression severity and little impact in the placebo arm. <sup>27</sup>
Maternal depression	Family therapy vs. pill placebo	Depression severity	No maternal depression Maternal depression	No moderating effects associated with a history of maternal depression. <sup>27</sup>

KQ = Key Question.

**Table G-4. KQ 1b: Subgroup analysis for family therapy versus active control**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Demographic variables	Family therapy vs. active control	Treatment response	Demographic variables	Age group, gender, race, family composition, family income had no moderating effects <sup>30</sup>
Clinical variables	Family therapy vs. active control	Treatment response	Clinical variables	Syndromal versus subsyndromal depression, baseline CDRS score, comorbid anxiety disorder, comorbid disruptive behavior disorder, chronicity, or current antidepressant medication had no moderating effects <sup>30</sup>

CDRS = Children's Depression Rating Scale; KQ = Key Question.

**Table G-5. KQ 1b: Subgroup analysis for omega-3 versus pill placebo**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Psychological stress	Omega-3 vs. pill placebo	Depression severity	Number of psychological stressors	When families reported fewer psychosocial stressors, the intervention arm had a significant decline in depression severity and little impact in the placebo arm <sup>27</sup>
Maternal depression	Omega-3 vs. pill placebo	Depression severity	No maternal depression	No moderating effects associated with a history of maternal depression <sup>27</sup>
			Maternal depression	

KQ = Key Question.

**Table G-6. KQ 2b: Subgroup analysis for SSRIs versus placebo**

<b>Subgroup</b>	<b>Comparison</b>	<b>Outcome</b>	<b>Subgroup Variable</b>	<b>Conclusion</b>
Family Income	Fluoxetine vs. Placebo	Functional Impairment, Clinician Report	<\$75,000/year >\$75,000/year	In the lower income group, fluoxetine was more effective than placebo, but in the higher income group, the effectiveness of fluoxetine did not significantly differ from that of placebo <sup>4</sup>
Depressive Symptom Severity	Fluoxetine vs. Pill Placebo	Functional Impairment, Clinician Report	Mild/Moderate Marked/Severe	Fluoxetine was more effective than placebo, independent of functional impairment level. <sup>4</sup>
Comorbid Condition: ADHD	Fluoxetine vs. Placebo	Depressive Symptoms, Clinician report	ADHD No ADHD	Adolescents with ADHD in the fluoxetine group had significantly greater improvements in depressive symptoms than those with ADHD in the placebo group; those without ADHD did not have significant differences in depressive symptoms between fluoxetine and placebo groups at end of treatment. <sup>8</sup>
Age Group	Fluoxetine vs. Placebo	Depressive Symptoms, Clinician report	Children 8-12 years old Adolescents aged 13-17	Two studies found the effect of fluoxetine versus placebo on change in depressive symptoms did not significantly differ by age group. <sup>41, 42</sup>
Sex	Fluoxetine vs. Placebo	Depressive Symptoms, Clinician report	Males Females	Two studies found the effect of fluoxetine versus placebo on change in depressive symptoms did not significantly differ by sex. <sup>41, 42</sup>
Family History of Depression	Fluoxetine vs. Placebo	Depressive Symptoms, Clinician report	Family history of depression No family history of depression	The effect of fluoxetine versus placebo on change in depressive symptoms did not significantly differ by family history of depression. <sup>42</sup>
Age Group	Fluoxetine vs. Placebo	Response	Children 8-12 years old Adolescents aged 13-17	The effect of fluoxetine versus placebo on change in response did not significantly differ by age group. <sup>42</sup>
Sex	Fluoxetine vs. Placebo	Response	Males Females	The effect of fluoxetine versus placebo on change in response did not significantly differ by sex <sup>42</sup>
Family History of Depression	Fluoxetine vs. Placebo	Response	Family history of depression No family history of depression	The effect of fluoxetine versus placebo on change in response did not significantly differ by family history of depression. <sup>42</sup>
Depression Chronicity	Fluoxetine vs. Placebo	Depressive Symptoms, Clinician report	Chronic (episode lasting 9 months or more) Transient (episode lasting less than 9 months)	In a sample with co-morbid depression and substance use disorder, those with chronic (as compared with transient) depression showed significantly decreases in depressive symptoms in the fluoxetine versus placebo groups <sup>67</sup>
Level of Alcohol Consumption	Fluoxetine vs. Placebo	Depressive Symptoms, Clinician report	Heavy use No use, single use, or moderate use No use, single use, or moderate use	In a sample with co-morbid depression and substance use disorder, those with moderate use of alcohol or less (as compared with heavy use) showed significantly greater decreases in depressive symptoms in the fluoxetine versus placebo groups. <sup>67</sup>

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Depression Chronicity	Fluoxetine vs. Placebo	Response	Chronic (episode lasting 9 months or more) Transient (episode lasting less than 9 months)	In a sample with co-morbid depression and substance use disorder, those with chronic (as compared with transient) depression showed significantly greater response to fluoxetine than placebo. <sup>67</sup>
Level of Alcohol Consumption	Fluoxetine vs. Placebo	Response	Heavy use No use, single use, or moderate use	In a sample with co-morbid depression and substance use disorder, those with moderate use of alcohol or less (as compared with heavy use) showed significantly greater response to fluoxetine than placebo. <sup>67</sup>
Level of Marijuana Consumption	Fluoxetine vs. Placebo	Response	Heavy use No use, single use, or moderate use	In a sample with co-morbid depression and substance use disorder, the effect of fluoxetine versus placebo on response did not significantly differ by level of marijuana consumption. <sup>67</sup>
Sex	Fluoxetine vs. Placebo	Relapse	Male Female	Females who remained on fluoxetine after the end of treatment (12 months) were almost 9 times more likely to relapse than males who remained on fluoxetine. <sup>58</sup>
Baseline Depression Severity	Fluoxetine vs. Placebo	Relapse	Continuous CDRS-R score (baseline)	Those with higher depression severity levels who remained on fluoxetine after end of treatment (12 weeks) were more likely to relapse than those with lower levels. <sup>58</sup>
End of Acute Phase Treatment Depression Severity	Fluoxetine vs. Placebo	Relapse	Continuous CDRS-R score at 12 weeks (end of treatment)	Those with higher depression severity levels who remained on fluoxetine after end of treatment (12 weeks) were more likely to relapse than those with lower levels. <sup>58</sup>
Age	Fluoxetine vs. Placebo	Relapse	Children Adolescents	Age did not moderate the effect of fluoxetine versus placebo on relapse. <sup>58</sup>
Race	Fluoxetine vs. Placebo	Relapse	Caucasian Non-Caucasian	Race did not moderate the effect of fluoxetine versus placebo on relapse. <sup>58</sup>
Recurrent Depression	Fluoxetine vs. Placebo	Relapse	Yes No	Number of prior depressive episodes did not moderate the effect of fluoxetine versus placebo on relapse. <sup>58</sup>
Comorbid Dysthymia or Anxiety Disorder	Fluoxetine vs. Placebo	Relapse	Yes No	Comorbid dysthymia or anxiety did not moderate the effect of fluoxetine versus placebo on relapse. <sup>58</sup>
Parent Characteristics	Fluoxetine vs. Placebo	Relapse		Age did not moderate the effect of fluoxetine versus placebo on relapse. <sup>58</sup>
Age Group	Paroxetine vs. Placebo	Depressive Symptoms, Clinician report	Children aged 7-11 years Adolescents aged 12-17 years	Among children, those in the placebo group had greater decreases in depressive symptoms than children receiving paroxetine, whereas there were no significant differences in depressive symptoms at end of treatment among adolescents. <sup>43</sup>

<b>Subgroup</b>	<b>Comparison</b>	<b>Outcome</b>	<b>Subgroup Variable</b>	<b>Conclusion</b>
Age Group	Paroxetine vs. Placebo	Symptoms and response	Adolescents aged 13-15 Adolescents aged 16-18	Older adolescents showed greater improvement than younger adolescents on the sadness item from MADRS and on response <sup>39</sup>
Features of Depression	Paroxetine vs. Placebo	Response	<u>Atypical depression</u> Not atypical depression	The effect of paroxetine versus placebo on response did not significantly differ by the presence of atypical depression features. <sup>48</sup>
Features of Depression	Paroxetine vs. Placebo	Response	<u>Melancholic features</u> No melancholic features	The effect of paroxetine versus placebo on response did not significantly differ by the presence of melancholic features. <sup>48</sup>
Comorbid Condition: Anxiety Disorder	Paroxetine vs. Placebo	Response	<u>Anxiety disorder</u> No anxiety disorder	The effect of paroxetine versus placebo on response did not significantly differ by the presence of anxiety disorder. <sup>48</sup>
Comorbid Condition: Comorbid Disorder	Paroxetine vs. Placebo	Response	<u>Any comorbid Disorder</u> No comorbid disorder	The effect of paroxetine versus placebo on response did not significantly differ by the presence of any comorbid disorder. <sup>48</sup>
Depression Age of Onset	Paroxetine vs. Placebo	Response	<u>11 years or younger onset of depression</u> 12 years or older onset of depression	The effect of paroxetine versus placebo on response did not significantly differ by age of onset of depression. <sup>48</sup>
Number of Depression Episodes	Paroxetine vs. Placebo	Response	1 episode	The effect of paroxetine versus placebo on response did not significantly differ by number of depression episodes. <sup>48</sup>
Age group	Paroxetine vs. Placebo	Adverse events	Adolescents aged 13-15 Adolescents aged 16-18	The magnitude of the difference between paroxetine and placebo arms was greater among older adolescents <sup>39</sup>

ADHD = Attention-Deficit/Hyperactivity Disorder; CDRS-R = Children's Depression Rating Scale-Revised; KQ = Key Question  
MADRS = Montgomery-Asberg Depression Rating Scale; vs. = versus.

**Table G-7. KQ 2b: Subgroup analysis for fluoxetine for relapse prevention versus placebo**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Residual symptoms	Relapse prevention with fluoxetine versus placebo	Relapse	Residual symptoms	Odds of relapse in the placebo arm was 6.3 (95% CI, 1.8 to 22.9) compared with the odds of relapse with residual symptoms (2.1; 95% CI, 0.7 to 6.6 <sup>57</sup>
			No residual symptoms	

CI = confidence interval; KQ = Key Question.

**Table G-8. KQ 2b: Subgroup analysis for TCAs versus placebo**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Features of Depression	Imipramine vs. Placebo	Response	Atypical depression Not atypical depression	The effect of imipramine versus placebo on response did not significantly differ by the presence of atypical depression features. <sup>48</sup>
Features of Depression	Imipramine vs. Placebo	Response	Melancholic features No melancholic features	The effect of imipramine versus placebo on response did not significantly differ by the presence of melancholic features. <sup>48</sup>
Comorbid Condition: Anxiety Disorder	Imipramine vs. Placebo	Response	Anxiety disorder No anxiety disorder	The effect of imipramine versus placebo on response did not significantly differ by the presence of anxiety disorder. <sup>48</sup>
Comorbid Condition: Comorbid Disorder	Imipramine vs. Placebo	Response	Any comorbid Disorder No comorbid disorder	The effect of imipramine versus placebo on response did not significantly differ by the presence of any comorbid disorder. <sup>48</sup>
Depression Age of Onset	Imipramine vs. Placebo	Response	11 years or younger onset of depression 12 years or older onset of depression	The effect of imipramine versus placebo on response did not significantly differ by age of onset of depression. <sup>48</sup>
Number of Depression Episodes	Imipramine vs. Placebo	Response	1 episode 2 or more episodes	The effect of imipramine versus placebo on response did not significantly differ by number of depression episodes. <sup>48</sup>

ADHD = Attention-Deficit/Hyperactivity Disorder; CDRS-R = Children's Depression Rating Scale-Revised; KQ = Key Question; vs. = versus.

**Table G-9. KQ 3b: Subgroup analysis for fluoxetine plus CBT versus placebo**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Family Income	Fluoxetine plus CBT vs. Pill Placebo	Depressive Symptoms, Clinician report	<\$75,000/year >\$75,000/year	In the lower income group, those in the Fluoxetine plus CBT arm did better than those in the placebo arm. In the higher income group, those in the fluoxetine plus CBT did better than placebo adolescents <sup>4</sup>
Depressive Symptom Severity	Fluoxetine plus CBT vs. Pill Placebo	Depressive Symptoms, Clinician report	Mild/Moderate Marked/Severe	In the mild/moderate group, those in the fluoxetine plus CBT did better than those in the placebo group. In the marked/severe group, those in the fluoxetine plus CBT group did better than those in the placebo group but the study reported that in “the acute stage of treatment there is no immediate symptomatic benefit of adding CBT to [fluoxetine] for these teens.” <sup>4</sup>
ADHD	Fluoxetine plus CBT vs. Pill Placebo	Depressive Symptoms, Clinician report	ADHD	Adolescents with ADHD in the fluoxetine plus CBT group had significantly greater improvements in depressive symptoms than those with ADHD in the placebo group. Adolescents without ADHD in the fluoxetine plus CBT group had significantly greater improvements in depressive symptoms than those without ADHD in the placebo group. <sup>8</sup>

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; KQ = Key Question.



**Table G-10. KQ 3b: Subgroup analysis for omega-3 plus family therapy versus pill placebo**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Psychosocial stressors	Omega-3 plus family therapy vs. pill placebo	Functional Impairment, Clinician Report	Psychosocial stressors	When families reported fewer psychosocial stressors, the intervention arm had a significant decline in depression severity and little impact in the placebo arm. <sup>27</sup>
History of maternal depression	Fluoxetine plus CBT vs. Pill Placebo	Functional Impairment, Clinician Report	History of maternal depression	When families had a history of maternal depression, the intervention arm had significant declines in the combined arm and no change in the placebo arm. <sup>27</sup>

CBT = cognitive behavioral therapy; KQ = Key Question; vs. = versus.

**Table G-11. KQ 5b: Subgroup analysis for psychotherapy within-type comparisons of delivery methods or approaches**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Severity of MDD	CBT group therapy for adolescents and parents vs. CBT group therapy for adolescents	Depression scores (BDI, CES-D, HDRS)	High baseline severity of MDD	No difference in outcomes <sup>74</sup>
			Low baseline severity of MDD	

BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CES-D = Center for Epidemiologic Studies Depression Scale; HDRS = Hamilton Depression Rating Scale; KQ = Key Question; MDD = major depressive disorder.

**Table G-12. KQ 5b: Subgroup analysis for psychotherapy versus pharmacotherapy**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Family income	CBT vs. fluoxetine	Functional impairment, clinician report	<\$75,000/year >\$75,000/year	In the lower income group, CBT was inferior to fluoxetine, but in the higher income group, the study reported no difference between active treatments <sup>4</sup>
Depressive symptom severity	CBT vs. fluoxetine	Functional impairment, clinician report	Mild/moderate Marked/severe	In the mild/moderate functional impairment group, the study reported no difference between active treatments, but in the marked/severe group, CBT was inferior to fluoxetine <sup>4, 93</sup>
ADHD	CBT vs. fluoxetine	Depressive symptoms, clinician report	ADHD No ADHD	CBT was inferior to fluoxetine in the ADHD group but not in the non-ADHD group <sup>8</sup>
Demographic variables not listed above	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Age, race, gender	No moderating effect <sup>92</sup>
Study features	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Study site, referral source	No moderating effect <sup>92</sup>
Patient clinical characteristics not listed above	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Current episode duration, functional impairment, suicidal ideation, childhood trauma, melancholic features, number comorbid diagnoses, hopelessness, cognitive distortions, dysthymia, anxiety disorder	No moderating effect <sup>92</sup>
Patient nonclinical characteristics not listed above	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Verbal intelligence, treatment expectations, conflict with caregiver	No moderating effect <sup>92</sup>
Caregiver characteristics	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Caregiver depression, parent treatment expectations	No moderating effect <sup>92</sup>

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; KQ = Key Question; vs. = versus.

**Table G-13. KQ 5b: Subgroup analysis for psychotherapy plus pharmacotherapy versus psychotherapy**

<b>Subgroup</b>	<b>Comparison</b>	<b>Outcome</b>	<b>Subgroup Variable</b>	<b>Conclusion</b>
Family income	CBT plus fluoxetine vs. CBT	Functional impairment, clinician report	<\$75,000/year \$75,000/year	In the lower income group, CBT plus fluoxetine was superior to CBT alone, but in the higher income group, the study reported no difference between active treatments <sup>4</sup>
Depressive symptom severity	CBT plus fluoxetine vs. CBT	Functional impairment, clinician report	Mild/moderate Marked/severe	CBT plus fluoxetine was superior to CBT alone in both subgroups <sup>4</sup>
ADHD	CBT plus fluoxetine vs. CBT	Depressive symptoms, clinician report	ADHD No ADHD	Fluoxetine plus CBT was superior to CBT in the ADHD group but not in the non-ADHD group <sup>8</sup>

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; KQ = Key Question; vs. = versus.

**Table G-14. KQ 5b: Subgroup analysis for psychotherapy plus pharmacotherapy versus pharmacotherapy**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Family income	CBT plus fluoxetine vs. fluoxetine	Functional impairment, clinician report	<\$75,000/year >\$75,000/year	No difference between subgroups in effect of active treatments <sup>4</sup>
Depressive symptom severity	CBT plus fluoxetine vs. fluoxetine	Functional impairment, clinician report	Mild/moderate Marked/severe	CBT plus fluoxetine was superior to fluoxetine alone in mild/moderate subgroup but not in the marked/severe subgroups <sup>4</sup>
ADHD	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	ADHD No ADHD	CBT plus fluoxetine plus was superior to fluoxetine alone in the ADHD group but not in the non-ADHD group <sup>8</sup>
Childhood trauma	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Childhood trauma No childhood trauma	The superiority of CBT plus fluoxetine over fluoxetine was reduced among patients with childhood trauma. <sup>93</sup>
Treatment expectations	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Higher treatment expectations Lower treatment expectations	CBT plus fluoxetine outperformed fluoxetine in patients with higher treatment expectations. <sup>93</sup>
Demographic variables not listed above	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Age, race, gender	No moderating effect <sup>92</sup>
Study features	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Study site, referral source	No moderating effect <sup>92</sup>
Patient clinical characteristics not listed above	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Current episode duration, functional impairment, suicidal ideation, melancholic features, number comorbid diagnoses, hopelessness, cognitive distortions, dysthymia, anxiety disorder	No moderating effect <sup>92</sup>
Patient nonclinical characteristics not listed above	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Verbal intelligence, conflict with caregiver	No moderating effect <sup>92</sup>
Caregiver characteristics	CBT plus fluoxetine vs. fluoxetine	Depressive symptoms, clinician report	Caregiver depression, parent treatment expectations	No moderating effect <sup>92</sup>

ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive behavioral therapy; KQ = Key Question; vs. = versus.

**Table G-15. KQ 5b: Subgroup analysis for SSRIs versus TCAs**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Features of atypical depression	Paroxetine vs. Imipramine	Responders (defined by 50% reduction or score of 8 or less in the total HAM-D).	Features of atypical depression No features of atypical depression	No difference in calculated outcomes for pair-wise comparison <sup>48</sup>
Melancholic feature	Paroxetine vs. Imipramine	Responders (defined by 50% reduction or score of 8 or less in the total HAM-D).	Melancholic features No melancholic features	No difference in calculated outcomes for pair-wise comparison <sup>48</sup>
Anxiety disorder	Paroxetine vs. Imipramine	Responders (defined by 50% reduction or score of 8 or less in the total HAM-D).	Anxiety disorder No anxiety disorder	No reported difference in outcomes <sup>48</sup>
Any comorbid disorder	Paroxetine vs. Imipramine	Responders (defined by 50% reduction or score of 8 or less in the total HAM-D).	Comorbid disorder No comorbid disorder	No reported difference in outcomes <sup>48</sup>
Family history of depression	Paroxetine vs. Imipramine	Responders (defined by 50% reduction or score of 8 or less in the total HAM-D).	Family history of depression No family history or depression	No reported difference in outcomes <sup>48</sup>
Age at onset	Paroxetine vs. Imipramine	Responders (defined by 50% reduction or score of 8 or less in the total HAM-D).	<12 ≥12	No reported difference in outcomes <sup>48</sup>
Number of depressive episodes	Paroxetine vs. Imipramine	Responders (defined by 50% reduction or score of 8 or less in the total HAM-D).	≤1 >1	No difference calculated outcomes for pair-wise comparison <sup>48</sup>

HAM-D = Hamilton Depression Rating Scale; KQ = Key Question; vs. = versus.

**Table G-16. KQ 5b: Subgroup analysis for pharmacotherapy dose comparisons**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Age	Low-dose vs. high-dose desvenlafaxine	Depression (clinician-report, CDRS-R)	Adolescents (12-17 years)	No difference between subgroups in by age <sup>59</sup>

CDRS-R = Children's Depression Rating Scale—Revised; KQ = Key Question; vs. = versus.

**Table G-17. KQ 5b: Subgroup analysis for treatment-resistant depression: within-type comparisons of interventions**

Subgroup	Comparison	Outcome	Subgroup Variable	Conclusion
Abuse history	Switch to CBT (with switch to new SSRI or to venlafaxine) vs. no CBT (with switch to new SSRI or to venlafaxine)	Response (CGI-I score $\leq 2$ and CDRS-R decline $\geq 50\%$ from baseline at week 12)	Abuse history No abuse history	Significantly greater efficacy in CBT+medication group than in no-CBT+medication group among those with no abuse history P-value for difference between the no-CBT+medication group and the CBT-medication group among those with a abuse history 0.06 <sup>88-90</sup>
Comorbid disorders			1 or more comorbid disorders No comorbid disorders	Significantly greater efficacy in CBT+medication group than in no-CBT+medication group among those at least 1 comorbid disorder; no difference in efficacy between groups among those with no comorbid disorders <sup>88-90</sup>
Hopelessness			High hopelessness Low hopelessness	Significantly greater efficacy in CBT+medication group than in no-CBT+medication group among those with low levels of hopelessness, but no differences in response rates among those in the CBT-medication and no-CBT+medication groups among those with a high levels of hopelessness <sup>88-90</sup>

CBT = cognitive behavioral therapy; CDRS-R = Children's Depression Rating Scale—Revised; CGI-I = Clinical Global Impressions Scale; KQ = Key Question; SSRI = selective serotonin reuptake inhibitors.

## Appendix H. Risk of Bias of Randomized Controlled Trials

Table H-1. Randomized controlled trials, part 1.....	H-2
Table H-2. Randomized controlled trials, part 2.....	H-11
Table H-3. Randomized controlled trials, part 3.....	H-19
Table H-4. Randomized controlled trials, part 4.....	H-28
Table H-5. Randomized controlled trials, part 5.....	H-32
Table H-6. Randomized controlled trials, part 6.....	H-36
Table H-7. Randomized controlled trials, part 7.....	H-44

**Table H-1. Randomized controlled trials, part 1**

First Author's Last Name, Year	Describe Groups (Treatment Interventions and Comparators)	Study Design	1. Was method of randomization adequate?	2. Was allocation concealment adequate?	3. Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Atkinson, 2014 <sup>38</sup>	IG1: Duloxetine IG2: Fluoxetine CG: Placebo	RCT, parallel	Probably yes	Probably yes	Probably no	Low	
Atkinson, 2018 <sup>59</sup>	IG1: Low-dose Desvenlafaxine IG2: High-dose Desvenlafaxine CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	No	Some concerns	Randomization procedure and allocation concealment process not described
Berard, 2006 <sup>39</sup>	IG: Paroxetine CG: Placebo	RCT, parallel	Yes	Yes	Probably no	Low	
Bernstein, 2000 <sup>80</sup> Companion: Bernstein, 2000 <sup>81</sup>	IG: Imipramine+CBT CG: Placebo+CBT	RCT, parallel	Yes	No	Probably no	Low	
Brent, 1997 <sup>12</sup> Companions: Brent, 1998 <sup>13</sup> Barbe, 2004 <sup>36</sup> Barbe, 2004 <sup>69</sup> Dietz, 2014 <sup>70</sup>	IG1: Individual CBT IG2: Systemic behavior family therapy (SBFT) CG: Nondirective supportive therapy (NST)	RCT, parallel	No	Uncertain because no information	No	Some concerns	Modified coin toss used for randomization, unknown allocation concealment
Brent, 2008 <sup>88</sup> Companions: Brent, 2009 <sup>90</sup> Asarnow, 2009 <sup>89</sup> TORDIA	IG1: Switch to a second, different SSRI (citalopram, or fluoxetine, 20-40 mg) IG2: Switch to a different SSRI plus CBT IG3: Switch to venlafaxine (150-225 mg) IG4: Switch to venlafaxine plus CBT	RCT, parallel	Probably yes	Yes	Probably no	Low	Some baseline imbalance on BDI and PTSD at baseline, but could be chance
Clarke, 2016 <sup>94</sup>	IG: Treatment as usual (TAU)+cognitive behavioral therapy (CBT) CG: Self-selected TAU	RCT, parallel	Uncertain because no information	Yes	Uncertain because no information	Uncertain	



First Author's Last Name, Year	Describe Groups (Treatment Interventions and Comparators)	Study Design	1. Was method of randomization adequate?	2. Was allocation concealment adequate?	3. Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Clarke, 1999 <sup>9</sup>	IG1: Child CBT IG2: Child CBT with separate parent sessions CG: Wait-list control	RCT, parallel	Uncertain because no information	Uncertain because no information	Probably no	Some concerns	Uncertain randomization and allocation concealment
Clarke, 2002 <sup>11</sup>	IG: Group CBT (Adolescent Coping With Depression Course)+Usual care CG: Usual care	RCT, parallel	Uncertain because no information	Uncertain because no information	No	Some concerns	Information not provided
Clarke, 2005 <sup>84</sup>	IG: Collaborative care - brief individual CBT+TAU SSRIs CG: TAU SSRIs	RCT, parallel	Uncertain because no information	Uncertain because no information	No	Some concerns	Information not provided
Deas, 2000 <sup>82</sup>	IG: Sertraline plus group CBT CG: Placebo plus group CBT	RCT, parallel	Yes	Yes	Probably no	Low	
DelBello, 2014 <sup>65</sup>	IG: Selegiline Transdermal system (STS) CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	Probably no	Some concerns	Information not provided
Diamond, 2002 <sup>25</sup> Companion: Diamond, 2003 <sup>95</sup>	IG: Attachment-based family therapy (ABFT) CG: Wait-list control	RCT, parallel	Uncertain because no information	Uncertain because no information	No	Some concerns	Uncertain randomization method and concealment.
Dietz, 2015 <sup>24</sup>	IG: Family Based Interpersonal psychotherapy (FB-IPT) CG: Child-centered therapy (CCT)	RCT, parallel	Probably yes	Uncertain because no information	Uncertain because no information	Some concerns	No info on allocation concealment and groups differed on SSRI augmentation at baseline
Durgam, 2018 <sup>40</sup>	IG1: Vilazodone 15 mg/d IG2: Vilazodone 30 mg/d CG: Placebo	RCT, parallel	Yes	Uncertain because no information	No	Low	
Emslie, 1997 <sup>41</sup>	IG: Fluoxetine 20 mg/d CG: Placebo	RCT, parallel	Probably yes	Probably yes	Yes	Some concerns	Baseline comorbidity differences

First Author's Last Name, Year	Describe Groups (Treatment Interventions and Comparators)	Study Design	1. Was method of randomization adequate?	2. Was allocation concealment adequate?	3. Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Emslie, 2002 <sup>42</sup> Companions: Emslie, 2004 <sup>56</sup> Heiligenstein, 2006 <sup>91</sup>	IG: Fluoxetine 10-20 mg/day CG: Placebo	RCT, parallel	Probably yes	Probably yes	No	Some concerns	Groups differed on some characteristics at baseline
Emslie, 2004 <sup>56</sup>	IG: Continued treatment with fluoxetine at current dose (20-60 mg/day) CG: Switch to placebo	RCT, parallel	Probably yes	Probably yes	No	Some concerns	Groups differed on some characteristics at baseline
Emslie, 2006 <sup>43</sup>	IG: Paroxetine CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	Probably no	Some concerns	Information not provided
Emslie, 2007 <sup>60</sup> Study 1	IG: venlafaxine ER (112.5 mg, 150 mg, or 22mg based on weight) CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	Uncertain because no information	Uncertain	Two studies pooled, no information on randomization, allocation concealment of study level differences
Emslie, 2007 <sup>60</sup> Study 2	IG: venlafaxine ER (112.5 mg, 150 mg, or 22mg based on weight) CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	Uncertain because no information	Uncertain	Two studies pooled, no information on randomization, allocation concealment of study level differences
Emslie, 2008 <sup>57</sup> Companion: Kennard, 2018 <sup>58</sup>	IG1: Fluoxetine continuation CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	No	Uncertain	
Emslie, 2009 <sup>44</sup> Companion: Findling, 2013 <sup>45</sup>	IG: Escitalopram CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	Probably no	Some concerns	Uncertain randomization and allocation concealment
Emslie, 2014 <sup>46</sup>	IG1: Duloxetine 60 mg QD IG2: Duloxetine 30 mg QD IG3: Fluoxetine 20 mg QD CG: Placebo	RCT, parallel	Probably yes	Probably yes	Probably no	Low	

First Author's Last Name, Year	Describe Groups (Treatment Interventions and Comparators)	Study Design	1. Was method of randomization adequate?	2. Was allocation concealment adequate?	3. Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Findling, 2009 <sup>47</sup> Companion: Hirschtritt, 2012 <sup>67</sup>	IG: Fluoxetine CG: Placebo	RCT, parallel	Probably yes	Uncertain because no information	Probably no	Some concerns	Unknown allocation concealment
Fristad, 2009 <sup>27</sup>	IG1: PEP (Family therapy)+Omega 3 IG2: Omega-3 IG3: PEP+placebo CG: Placebo	RCT, parallel	Yes	Yes	No	Low	
Geller, 1989 <sup>61</sup>	IG: Nortriptyline CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	No	Some concerns	Information not provided
Geller, 1992 <sup>62</sup>	IG: Nortriptyline CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	No	Some concerns	No discussion of randomization or concealment at all other than in abstract "A random assignment"
Glaxo, 1998 <sup>48</sup> Companions: Keller 2001 <sup>50</sup> Le Noury, 2016 <sup>51</sup> Le Noury, 2015 <sup>49</sup>	IG1: Paroxetine IG2: Imipramine CG: Placebo	RCT, parallel	Yes	Yes	Yes	Low	
Goodyer, 2017 <sup>17</sup> Companion: Goodyer, 2017 <sup>16</sup> O'Keeffe, 2018 <sup>18</sup> O'Keeffe, 2019 <sup>19</sup>	IG1: CBT IG2: Short-term psychoanalytical therapy CG: Brief psychosocial intervention	RCT, parallel	Yes	No	No	Some concerns	No allocation concealment
Gunlicks-Stoessel, 2016 <sup>71</sup>	IG: Adaptation interpersonal psychotherapy (IPT-AP) CG: Adaptation interpersonal psychotherapy (IPT-A)	RCT, parallel	Uncertain because no information	Uncertain because no information	Probably no	Uncertain	

First Author's Last Name, Year	Describe Groups (Treatment Interventions and Comparators)	Study Design	1. Was method of randomization adequate?	2. Was allocation concealment adequate?	3. Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Heiligenstein, 2006 <sup>91</sup>	IG: Dose-titration of fluoxetine dose from 20 mg/day to 40-60 mg/day CG: Continued treatment with fluoxetine at fixed dose of 20 mg/day	RCT, parallel	Probably yes	Probably yes	No	Some concerns	Imbalance at baseline
Hughes, 2013 <sup>33</sup>	IG: Aerobic exercise CG: Nonstrenuous exercise group	RCT, parallel	Yes	Uncertain because no information	Probably no	Low	
Iftene, 2015 <sup>78</sup>	IG1: Sertraline IG2: Group Rational Emotive Behavior Therapy/CBT IG3: Sertraline plus Group Rational Emotive Behavior Therapy/CBT	RCT, parallel	Uncertain because no information	Uncertain because no information	No		
Israel, 2013 <sup>26</sup>	IG: Attachment Based Family Therapy (ABFT) CG: Treatment as Usual (TAU)	RCT, parallel	Yes	Yes	No	Low	
Jelalian, 2016 <sup>72</sup>	IG: CBT plus Healthy Lifestyle Enhancement CG: CBT	RCT, parallel	Yes	Yes	No	Low	
Kennard, 2008 <sup>20</sup>	IG: Relapse prevention CBT plus continued antidepressant medication management CG: Continued antidepressant medication management	RCT, parallel	Uncertain because no information	Uncertain because no information	Probably no	Uncertain	
Kennard, 2014 <sup>21</sup> Companion: Emslie, 2015 <sup>22</sup>	IG: Relapse prevention CBT plus continued antidepressant medication management CG: Continued antidepressant medication management	RCT, parallel	Probably yes	Probably yes	No	Low	

First Author's Last Name, Year	Describe Groups (Treatment Interventions and Comparators)	Study Design	1. Was method of randomization adequate?	2. Was allocation concealment adequate?	3. Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Kim, 2012 <sup>85</sup>	IG: CBT plus bupropion CG: Bupropion	RCT, parallel	Uncertain because no information	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Klein, 1998 <sup>63</sup>	IG: Desipramine CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	Uncertain because no information	Uncertain because no information	No discussion of randomization method or concealment
Kye, 1996 <sup>64</sup>	IG: Amitriptyline (AMI) CG: Placebo	RCT, parallel	No	Uncertain because no information	No	Some concerns	Variation of a coin toss used for randomization, no reports of allocation concealment
Luby, 2012 <sup>32</sup>	IG: Parent Child Interaction Therapy CG: Psycho-education	RCT, parallel	Yes	Uncertain because no information	Probably no	Some concerns	Unknown allocation concealment
Mandoki, 1997 <sup>66</sup>	IG: Venlafaxine and therapy CG: Placebo and therapy	RCT, parallel	Uncertain because no information	Uncertain because no information	Probably no	Uncertain	
March, 2004 <sup>3</sup> Companions: Kennard, 2006 <sup>6</sup> Vitiello, 2006 <sup>7</sup> Curry, 2006 <sup>4</sup> Emslie, 2006 <sup>5</sup> Kratochvil, 2006 <sup>68</sup> Kratochvil, 2009 <sup>8</sup> Foster, 2018 <sup>92</sup> Foster, 2019 <sup>93</sup> TADS	IG1: Fluoxetine+CBT IG2: Fluoxetine IG3: CBT CG: Placebo	RCT, parallel	Yes	Uncertain because no information	Probably no	Some concerns	Not sure about allocation concealment
Melvin, 2006 <sup>79</sup>	G1: CBT G2: Sertraline G3: Combined	RCT, parallel	Yes	Yes	No	Low	
Mufson, 1999 <sup>23</sup>	IG: Interpersonal Psychotherapy for Depressed Adolescents (IPT-A) CG: Clinical Monitoring	RCT, parallel	Probably yes	Unclear	Probably no	Some concerns	Allocation concealment not reported

First Author's Last Name, Year	Describe Groups (Treatment Interventions and Comparators)	Study Design	1. Was method of randomization adequate?	2. Was allocation concealment adequate?	3. Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Nelson, 2004 <sup>73</sup>	IG1: CBT over ITV IG2: CBT Face to face	RCT, parallel	Probably yes	No	Uncertain because no information	High	Coin toss used for randomization, no allocation concealment.
Nemets, 2006 <sup>35</sup>	G1: Omega-3 fatty acids G2: Placebo	RCT, parallel	Probably no	Probably no	Yes	High	Method of randomization and allocation concealment not described. Patients in placebo were more likely to have comorbid mental health disorders than those in the omega group.
Poole, 2018 <sup>28, 29</sup>	IG: BEST MOOD family systems therapy CG: PAST family group therapy	RCT, parallel	Yes	Yes	No	Low	
Rickhi, 2015 <sup>34</sup>	IG: LEAP online nonfaith-based spirituality program CG: Wait-list	RCT, parallel	Yes	Yes	Probably no	Low	
Rohde, 1994 <sup>74</sup>	IG: CBT group for adolescents IG2: CBT group for adolescents with a separate group for parents CG: Waiting-list	RCT, parallel	Uncertain because no information	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Rohde, 2004 <sup>15</sup> Companion: Rohde, 2006 <sup>37</sup>	G1: Adolescent Coping with Depression course (CWD-A) G2: Life skills/tutoring (LS) condition	RCT, cluster	Yes	No	No	Some concerns	Difference in sex, but accounted for it in the analysis; no allocation concealment
Rohde, 2006 <sup>37</sup>	G1: CWD-A G2: LS	RCT, parallel	Yes	No	Uncertain because no information	Some concerns	No allocation concealment

First Author's Last Name, Year	Describe Groups (Treatment Interventions and Comparators)	Study Design	1. Was method of randomization adequate?	2. Was allocation concealment adequate?	3. Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Rosello, 1999 <sup>10</sup>	IG1: IPT IG2: CBT CG: Wait list control	RCT, parallel	Uncertain because no information	Uncertain because no information	Probably no	Uncertain because no information	Randomization method and concealment (allocation) not reported, only baseline comparisons were for outcomes, so no idea if sociodemographic or other differences between groups were there.
Shirk, 2014 <sup>14</sup>	IG: m-CBT CG: Usual care	RCT, parallel	Uncertain because no information	Uncertain because no information	Probably no	Uncertain	
Spirito, 2015 <sup>75</sup>	IG: Parent-Adolescent-CBT CG: Adolescent Only-CBT	RCT, parallel	Probably no	Uncertain because no information	yes	High	Randomization was unsuccessful in this small sample, as adolescents in the experimental condition had significantly higher levels of preexisting suicidality and psychopathology
Tompson, 2017 <sup>30</sup> Companion: Asarnow, 2018 <sup>31</sup>	IG: FFT-CD CG: Individual supportive psychotherapy (IP)	RCT, parallel	Yes	Yes	No	Low	
Trowell, 2007 <sup>76</sup> Companion: Garoff, 2012 <sup>77</sup>	IG1: Individual Therapy (FIPP) IG2: Family Therapy (SIFT)	RCT, parallel	Uncertain because no information	Uncertain because no information	Probably no	Uncertain	
Wagner, 2004 <sup>52</sup> Companion: Forest, 2001 <sup>53</sup>	G1: Citalopram G2: Placebo	RCT, parallel	Probably yes	Uncertain because no information	Probably no	Some concerns	Unknown allocation concealment
Wagner, 2006 <sup>54</sup>	G1: Escitalopram G2: Placebo	RCT, parallel	Not applicable	Uncertain because no information	Probably no	Uncertain because no information	

First Author's Last Name, Year	Describe Groups (Treatment Interventions and Comparators)	Study Design	1. Was method of randomization adequate?	2. Was allocation concealment adequate?	3. Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Weihls, 2018 <sup>55</sup>	IG1: Desvenlafaxine (25, 35, or 50 mg/d) IG2: Fluoxetine (20 mg/d) CG: Placebo	RCT, parallel	Uncertain because no information	Uncertain because no information	No	Uncertain	
Wilkinson, 2008 <sup>86</sup>	IG: SSRI and psychosocial treatment as usual plus CBT CG: SSRI plus psychosocial treatment as usual	RCT, parallel	Yes	Probably yes	Probably no	Low	
Wilkinson, 2011 <sup>87</sup> (ROB based on Goodyer 2007)	IG: SSRI CG: SSRI plus CBT	RCT, parallel	Uncertain because no information	Not applicable	Probably no	Some concerns	Consulted Goodyer 2007 for information and randomization used but no details of how it was done or whether allocation concealment was used.

CBT = cognitive behavioral therapy; CG = control group; CWD-A = Adolescent Coping with Depression course; FIPP = focused individual psychodynamic psychotherapy; FFT-CD = family-focused treatment for childhood depression; G = group; IG = intervention group; IP = interpersonal therapy; IPT = interpersonal psychotherapy; IPT-A = interpersonal psychotherapy for depressed adolescents; LEAP = Listen-Empathize-Agree-Partner; LS = life skills/tutoring condition; m-CBT = modified cognitive behavioral therapy; mg/d = milligram per day; RCT = randomized controlled trial; RoB = risk of bias; SIFT = solution-focused brief therapy; SSRI = selective serotonin reuptake inhibitors.



**Table H-2. Randomized controlled trials, part 2**

First Author's Last Name, Year	4. Were the patients unaware of their intervention status of participants?	5. Were the trial personnel and clinicians unaware of the intervention status of participants?	6. Were there deviations from the intended intervention beyond what would be expected in usual practice?	6a. If yes to 6, Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	7. Were any participants analyzed in a group different from the one to which they were assigned?	7a. If yes to 7, Was there potential for a substantial impact (on the estimated effect of intervention) of analyzing participants in the wrong group?	Bias arising from departures from intended interventions?	Comments
Atkinson, 2014 <sup>38</sup>	Yes	Yes	Probably no	Not applicable	No	Not applicable	Low	
Atkinson, 2018 <sup>59</sup>	Probably yes	Probably yes	No	Not applicable	Probably no	Not applicable	Low	
Berard, 2006 <sup>39</sup>	Yes	Yes	Probably no	Probably no	No	Not applicable	Some concerns	Potential for uncontrolled cointerventions
Bernstein, 2000 <sup>80</sup> Companion: Bernstein, 2000 <sup>81</sup>	Yes	Probably yes	Probably no	Not applicable	Probably no	Not applicable	Low	
Brent, 1997 <sup>12</sup> Companions: Brent, 1998 <sup>13</sup> Barbe, 2004 <sup>36</sup> Barbe, 2004 <sup>69</sup> Dietz, 2014 <sup>70</sup>	No	No	Probably no		No	Not applicable	High	Patients and personnel not blinded (awareness of intervention could influence outcomes) and 10 had previously undetected exclusionary criteria
Brent, 2008 <sup>88</sup> Brent, 2009 <sup>90</sup> Asarnow, 2009 <sup>89</sup> TORDIA	Yes for medication, no for CBT	Yes for medication, no for CBT	Probably no	Not applicable	Probably no	Not applicable	Low for comparisons of medications, some concerns for comparisons of CBT vs. no CBT	Awareness of intervention may influence outcomes
Clarke, 2016 <sup>94</sup>	No	No	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded; Patients, parents, and clinical personnel awareness of treatment could influence outcomes
Clarke, 1999 <sup>9</sup>	No	No	No	Not applicable	Probably no	Not applicable	Some concerns	Patients not blinded, awareness of intervention could influence outcomes

First Author's Last Name, Year	4. Were the patients unaware of their intervention status of participants?	5. Were the trial personnel and clinicians unaware of the intervention status of participants?	6. Were there deviations from the intended intervention beyond what would be expected in usual practice?	6a. If yes to 6, Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	7. Were any participants analyzed in a group different from the one to which they were assigned?	7a. If yes to 7, Was there potential for a substantial impact (on the estimated effect of intervention) of analyzing participants in the wrong group?	Bias arising from departures from intended interventions?	Comments
Clarke, 2002 <sup>11</sup>	No	No	No	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded; awareness of intervention could influence outcomes.
Clarke, 2005 <sup>84</sup>	No	No	No	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded and those in treatment group had fewer days of medication than those in placebo group. Despite efforts by the CBT therapist to maximize medication adherence, youths in the CBT condition received significantly fewer days of antidepressant medication than those in the control condition, approximately 20% less through the 1-year followup. Also awareness of intervention could influence outcomes.
Deas, 2000 <sup>82</sup>	Yes	Yes	No	Not applicable	Probably no	Not applicable	Low	
DelBello, 2014 <sup>65</sup>	Probably yes	Probably yes	Probably no	Probably no	Probably no	Not applicable	low	
Diamond, 2002 <sup>25</sup> Companion: Diamond, 2003 <sup>95</sup>	Probably no	No	No	Not applicable	No	Not applicable	Some concerns	Patients and clinicians not blinded, awareness of intervention could influence outcomes

First Author's Last Name, Year	4. Were the patients unaware of their intervention status of participants?	5. Were the trial personnel and clinicians unaware of the intervention status of participants?	6. Were there deviations from the intended intervention beyond what would be expected in usual practice?	6a. If yes to 6, Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	7. Were any participants analyzed in a group different from the one to which they were assigned?	7a. If yes to 7, Was there potential for a substantial impact (on the estimated effect of intervention) of analyzing participants in the wrong group?	Bias arising from departures from intended interventions?	Comments
Dietz, 2015 <sup>24</sup>	No	No	Uncertain because no information	Not applicable	Probably no	Not applicable	Some concerns	The authors note that the there was no blinding in the fidelity coding, which was done by the developer of the intervention, used a broad criterion, and did not measure contamination; so potential for contamination
Durgam, 2018 <sup>40</sup>	Yes	Yes	No	Not applicable	No	Not applicable	Low	
Emslie, 1997 <sup>41</sup>	Probably yes	Probably yes	Uncertain because no information	Not applicable	No	Not applicable	Low	
Emslie, 2002 <sup>42</sup> Companions: Emslie, 2004 <sup>56</sup> Heiligenstein, 2006 <sup>91</sup>	Yes	Yes	No	Not applicable	Probably no	Not applicable	Low	
Emslie, 2004 <sup>56</sup>	Yes	Yes	No	Not applicable	Probably no	Not applicable	Low	
Emslie, 2006 <sup>43</sup>	Probably yes	Probably yes	Probably no	Probably no	Probably no	Not applicable	Low	
Emslie, 2007 <sup>60</sup> Study 1	Probably yes	Probably yes	Probably no	Not applicable	No	Not applicable	Low	
Emslie, 2007 <sup>60</sup> Study 2	Probably yes	Probably yes	Probably no	Not applicable	No	Not applicable	Low	
Emslie, 2008 <sup>57</sup> Companion: Kennard, 2018 <sup>58</sup>	Yes	Yes	No	Not applicable	Probably no	Not applicable	Low	

First Author's Last Name, Year	4. Were the patients unaware of their intervention status of participants?	5. Were the trial personnel and clinicians unaware of the intervention status of participants?	6. Were there deviations from the intended intervention beyond what would be expected in usual practice?	6a. If yes to 6, Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	7. Were any participants analyzed in a group different from the one to which they were assigned?	7a. If yes to 7, Was there potential for a substantial impact (on the estimated effect of intervention) of analyzing participants in the wrong group?	Bias arising from departures from intended interventions?	Comments
Emslie, 2009 <sup>44</sup> Companion: Findling, 2013 <sup>45</sup>	Yes	Yes	Probably no	Not applicable	Probably no	Not applicable	Low	
Emslie, 2014 <sup>46</sup>	Yes	Yes	Probably no	Not applicable	No	Not applicable	Low	
Fristad, 2018 <sup>27</sup>	Yes	Yes	Probably no	Not applicable	No	Not applicable	Low	Participants and trial personnel aware of the psychotherapy assignment but were blind to the omega-3/placebo assignment
Findling, 2009 <sup>47</sup> Companion: Hirschtritt, 2012 <sup>67</sup>	Yes	Yes	No	Not applicable	No	Not applicable	Low	
Geller, 1989 <sup>61</sup>	Yes	Yes	No	Not applicable	Probably no	Not applicable	Low	
Geller, 1992 <sup>62</sup>	Probably yes	Probably yes	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Blinding not discussed other than in title
Glaxo, 1998 <sup>48</sup> Companions: Keller 2001 <sup>50</sup> Le Noury, 2016 <sup>51</sup> Le Noury, 2015 <sup>49</sup>	Yes	Yes	Yes	Probably no	No	Not applicable	Low	
Goodyer, 2017 <sup>17</sup> Companion: Goodyer, 2017 <sup>16</sup> O'Keeffe 2018 <sup>19</sup> O'Keeffe, 2019 <sup>19</sup>	No	No	No	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded. Awareness of intervention could influence outcomes
Gunlicks-Stoessel, 2016 <sup>71</sup>	Uncertain because no information	Uncertain because no information	Probably no	Not applicable	Probably no	Not applicable	Uncertain	Probably not blinded because children would know if parents were part of intervention?

First Author's Last Name, Year	4. Were the patients unaware of their intervention status of participants?	5. Were the trial personnel and clinicians unaware of the intervention status of participants?	6. Were there deviations from the intended intervention beyond what would be expected in usual practice?	6a. If yes to 6, Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	7. Were any participants analyzed in a group different from the one to which they were assigned?	7a. If yes to 7, Was there potential for a substantial impact (on the estimated effect of intervention) of analyzing participants in the wrong group?	Bias arising from departures from intended interventions?	Comments
Heiligenstein, 2006 <sup>91</sup>	Yes	Yes	No	Not applicable	Probably no	Not applicable	Low	
Hughes, 2013 <sup>33</sup>	No	No	probably no	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded. Awareness of intervention can influence outcomes
Iftene, 2015 <sup>78</sup>	Probably yes	Probably yes	Probably no	Not applicable	Probably no	Not applicable	Some concerns	blinding not discussed
Israel, 2013 <sup>26</sup>	No	No	No	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded. Awareness of intervention can influence outcomes
Jelalian, 2016 <sup>72</sup>	No	No	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Patients and trial personnel not blinded
Kennard, 2008 <sup>20</sup>	No	No	No	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded. Awareness of intervention could influence outcomes
Emslie, 2015 <sup>22</sup> Companion: Kennard, 2014 <sup>21</sup>	No	No	No	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded. Awareness of intervention could influence outcomes
Kim, 2012 <sup>85</sup>	No	No	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded. Awareness of intervention can influence outcomes
Klein, 1998 <sup>63</sup>	Probably yes	Probably yes	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Blinding noted as "double blind" with no other details.
Kye, 1996 <sup>64</sup>	Probably yes	Probably yes	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Blinding not discussed other than in abstract
Luby, 2012 <sup>32</sup>	No	No	No	Not applicable	No	Not applicable	Some concerns	Personnel not blinded

First Author's Last Name, Year	4. Were the patients unaware of their intervention status of participants?	5. Were the trial personnel and clinicians unaware of the intervention status of participants?	6. Were there deviations from the intended intervention beyond what would be expected in usual practice?	6a. If yes to 6, Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	7. Were any participants analyzed in a group different from the one to which they were assigned?	7a. If yes to 7, Was there potential for a substantial impact (on the estimated effect of intervention) of analyzing participants in the wrong group?	Bias arising from departures from intended interventions?	Comments
Mandoki, 1997 <sup>66</sup>	Probably yes	Probably yes	Probably no	Not applicable	Probably no	Not applicable	Low	
March, 2004 <sup>3</sup>	No	No	No	Not applicable	No	Not applicable	Some concerns	Patients in CBT groups knew they were getting treatment.
Companions:								
Kennard, 2006 <sup>6</sup>								
Vitiello, 2006 <sup>7</sup>								
Curry, 2006 <sup>4</sup>								
Emslie, 2006 <sup>5</sup>								
Kratochvil, 2006 <sup>68</sup>								
Kratochvil, 2009 <sup>8</sup>								
Foster, 2018 <sup>92</sup>								
Foster, 2019 <sup>93</sup>								
TADS								
Melvin, 2006 <sup>79</sup>	Probably no	Probably no	No	Not applicable	Probably no	Not applicable	Some concerns	Awareness of intervention could influence outcomes
Mufson, 1999 <sup>23</sup>	No	No	Probably no	Not applicable	Probably no	Not applicable	Some concerns	awareness of intervention could influence outcomes
Nelson, 2004 <sup>73</sup>	No	No	Probably no	Probably no	Probably no	Not applicable	High	No blinding
Nemets, 2006 <sup>35</sup>	Yes	No	No	Not applicable	Probably no	Not applicable	Some concerns	Active and placebo capsules had a slight difference that authors note "could be distinguished only by an experienced observer familiar with both types of capsules and able to compare them simultaneously"
Poole, 2018 <sup>28, 29</sup>	Yes	Yes	Probably no	Not applicable	No	Not applicable	Low	

First Author's Last Name, Year	4. Were the patients unaware of their intervention status of participants?	5. Were the trial personnel and clinicians unaware of the intervention status of participants?	6. Were there deviations from the intended intervention beyond what would be expected in usual practice?	6a. If yes to 6, Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	7. Were any participants analyzed in a group different from the one to which they were assigned?	7a. If yes to 7, Was there potential for a substantial impact (on the estimated effect of intervention) of analyzing participants in the wrong group?	Bias arising from departures from intended interventions?	Comments
Rickhi, 2015 <sup>34</sup>	No	No	No	Not applicable	No	Not applicable	Some concerns	Patient and provider not blinded; awareness of intervention could influence outcomes
Rohde, 1994 <sup>74</sup>	No	No	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded; awareness of intervention can influence outcomes
Rohde, 2004 <sup>15</sup> Companion: Rohde, 2006 <sup>37</sup>	No	No	No	Not applicable	No	Not applicable	Some concerns	Patient and provider not blinded
Rohde, 2006 <sup>37</sup>	No	No	No	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded
Rosello, 1999 <sup>10</sup>	Probably no	No	No	Not applicable	No	Not applicable	Some concerns	Patients and clinicians not blinded; awareness of intervention could influence outcomes
Shirk, 2014 <sup>14</sup>	Probably no	Probably no	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider likely not blinded; awareness of the intervention can influence outcomes
Spirito, 2015 <sup>75</sup>	No	No	probably no	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded; awareness of intervention can influence outcomes
Tompson, 2017 <sup>30</sup> Companion: Asarnow, 2018 <sup>31</sup>	Yes	No	No	Not applicable	Probably no	Not applicable	Some concerns	Awareness of intervention could influence outcomes; providers not blinded

First Author's Last Name, Year	4. Were the patients unaware of their intervention status of participants?	5. Were the trial personnel and clinicians unaware of the intervention status of participants?	6. Were there deviations from the intended intervention beyond what would be expected in usual practice?	6a. If yes to 6, Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	7. Were any participants analyzed in a group different from the one to which they were assigned?	7a. If yes to 7, Was there potential for a substantial impact (on the estimated effect of intervention) of analyzing participants in the wrong group?	Bias arising from departures from intended interventions?	Comments
Trowell, 2007 <sup>76</sup> Companion: Garoff, 2012 <sup>77</sup>	No	No	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded; awareness of intervention can influence outcomes
Wagner, 2004 <sup>52</sup> Companion: Forest, 2001 <sup>53</sup>	Yes	Yes	Probably no	Not applicable	Probably no	Not applicable	low	
Wagner, 2006 <sup>54</sup>	Probably yes	Probably yes	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Blinding not explicitly stated.
Weihs, 2018 <sup>55</sup>	Probably yes	Probably yes	Probably no	Not applicable	Probably no	Not applicable	Low	
Wilkinson, 2008 <sup>86</sup>	No	No	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Patient and provider not blinded; awareness of intervention can influence outcomes
Wilkinson, 2011 <sup>87</sup> (ROB based on Goodyer 2007)	No	No	Probably no	Not applicable	Probably no	Not applicable	Some concerns	Not blinded (patients or personnel)

CBT = cognitive behavioral therapy; ROB = risk of bias; vs. = versus



**Table H-3. Randomized controlled trials, part 3**

First Author's Last Name, Year	8. What was the overall attrition?	9. Were outcome data available for all, or nearly all, participants randomized?	9a. If yes to 9, are the proportion of participants and reasons for missing data similar across interventions?	9b. If yes to 9, is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Atkinson, 2014 <sup>38</sup>	21.4% overall with differential attrition--duloxetine 25.6%, fluoxetine 22.2% and placebo 15.5%.	No	Not applicable	Not applicable	High and differential attrition	Large overall and differential attrition
Atkinson, 2018 <sup>59</sup>	16.2% overall, 19.2% placebo, 15.6% Desvenlafaxine low, 14.0% Desvenlafaxine high at end of treatment	No	Yes	Yes	Some Concerns	Moderately high attrition but not differential and LOCF used; some dropout across arms, but the rates and reasons are not dissimilar (although fewer dropped out for adverse events in the high dose arm)
Berard, 2006 <sup>39</sup>	28.7% overall and differential by group--paroxetine 30.2% and placebo 25.8%. Also differential withdrawal due to AE with paroxetine having higher rates than placebo	Probably no			High	Large overall and differential attrition
Bernstein, 2000 <sup>80</sup> Companion: Bernstein, 2000 <sup>81</sup>	25.4% attrition in completion overall	Probably no	Uncertain because no information	no	Some Concerns	Some loss to followup and no ITT used or information about differences between those lost to followup and those retained. .
Brent, 1997 <sup>12</sup> Companions: Brent, 1998 <sup>13</sup> Barbe, 2004 <sup>36</sup> Barbe, 2004 <sup>69</sup> Dietz, 2014 <sup>70</sup>	27.1% overall; 31.3% in SFBT and NST and 18.9% in CBT (12.4% differential attrition)	No	Uncertain because no information	Not applicable	High	High attrition, unknown differences in attrition across groups
Brent, 2008 <sup>88</sup> Companions: Brent, 2009 <sup>90</sup> Asarnow, 2009 <sup>89</sup> TORDIA	All in analysis but completion rates lower (29.4%, 31.3%, 26.5%, 36.1%)	No	No	Probably no	High	High attrition, some differential causes for attrition, reliance on LOCF

First Author's Last Name, Year	8. What was the overall attrition?	9. Were outcome data available for all, or nearly all, participants randomized?	9a. If yes to 9, are the proportion of participants and reasons for missing data similar across interventions?	9b. If yes to 9, is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Clarke, 2016 <sup>94</sup>	All used in ITT analysis and 6.6% of both groups not used in survival analysis	Probably yes	Not applicable	Not applicable	Low	
Clarke, 1999 <sup>9</sup>	22%. Differential attrition by group not reported but differed across the two study sites.	Probably yes	Uncertain because no information	Not applicable	High	Substantial attrition, unknown differential attrition, but ITT analyses done
Clarke, 2002 <sup>11</sup>	14.7% overall, group attrition not reported.	No	Uncertain because no information	Probably yes	Some Concerns	Although study reports no difference in results between completers and full sample, no details provided on how outcomes were recorded for those lost to followup; moderate attrition but no info on differential attrition nor how drop-outs were handled in analysis.
Clarke, 2005 <sup>84</sup>	17.3% treatment and 12.7% control at 52 week followup	No	Uncertain because no information	Probably yes	Some Concerns	Although study reports no difference in results between completers and full sample, no details provided on how outcomes were recorded for those lost to followup
Deas, 2000 <sup>82</sup>	All retained for outcomes but attrition 40% in intervention and 0% in control group.	Probably yes	Not applicable	Not applicable	Low	
DelBello, 2014 <sup>65</sup>	26% did not complete intervention but almost all completed at least one followup	Yes	Not applicable	Not applicable	Some Concerns	Relatively high attrition from the intervention, but near complete followup and no differential attrition
Diamond, 2002 <sup>25</sup> Companion: Diamond, 2003 <sup>95</sup>	3%	Probably yes	Uncertain because no information	Not applicable	Low	

First Author's Last Name, Year	8. What was the overall attrition?	9. Were outcome data available for all, or nearly all, participants randomized?	9a. If yes to 9, are the proportion of participants and reasons for missing data similar across interventions?	9b. If yes to 9, is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Dietz, 2015 <sup>24</sup>	9.5% overall, all in treatment condition and none in comparison condition (13.8% vs. 0%)	Yes	Not applicable	Not applicable	Some Concerns	Nearly all the attrition from a single arm
Durgam, 2018 <sup>40</sup>	14.6% overall, 18.4% placebo, 14.9% vilazodone low, 10.6% vilazodone high.	No	No	Uncertain because no information	Some Concerns	Some ITT analysis based on LOCF, reasons for dropout differed across arms; moderate attrition but not differential. Withdrawal ANs different across groups (higher in vilazodone groups)
Emslie, 1997 <sup>41</sup>	29.2% fluoxetine, 45.8% placebo, differential and very large attrition	No	No	Uncertain because no information	High	High (very large) and differential attrition, different reasons for dropout across arms
Emslie, 2002 <sup>42</sup> Companions: Emslie, 2004 <sup>56</sup> Heiligenstein, 2006 <sup>91</sup>	LOCF used for completers but non-completion in IG1:17.4% and CG: 38.2% so differential and high attrition	No	Yes	Uncertain because no information	High	High and differential attrition with LOCF for ITT without investigation of differences in those with versus without completion
Emslie, 2004 <sup>56</sup>	All retained in analysis but IG1: 50% did not complete and CG:60% did not complete	No	Uncertain because no information	Uncertain because no information	High	Very high attrition and no information on ITT
Emslie, 2006 <sup>43</sup>	30% did not complete intervention but almost all completed at least one followup	Yes	Not applicable	Not applicable	Some Concerns	Relatively high attrition from the intervention, but near complete followup and no differential attrition
Emslie, 2007 <sup>60</sup> Study 1	A total of 31/85 [36%] placebo- treated subjects from study 1 and 31/80 [39%] venlafaxine ER treated subjects from study 1 discontinued the study	No	Uncertain because no information	Uncertain because no information	High	High overall attrition, ITT and LOCF analysis conducted but no sensitivity analysis provided
Emslie, 2007 <sup>60</sup> Study 2	A total of 17/94 [18%] placebo- treated subjects from study 1 and 28/102 [27%] venlafaxine ER treated subjects from study 1 discontinued the study	No	Uncertain because no information	Uncertain because no information	High	High differential attrition, ITT and LOCF analysis conducted but no sensitivity analysis provided

First Author's Last Name, Year	8. What was the overall attrition?	9. Were outcome data available for all, or nearly all, participants randomized?	9a. If yes to 9, are the proportion of participants and reasons for missing data similar across interventions?	9b. If yes to 9, is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Emslie, 2008 <sup>57</sup> Companion: Kennard, 2018 <sup>58</sup>	Appears that all were in analysis but 24% in fluoxetine and 13.5% in placebo group did not complete treatment	Uncertain because no information	No	Uncertain because no information	Some Concerns	Differential attrition but full sample used for analysis, no explanation of how data were obtained and robustness of data
Emslie, 2009 <sup>44</sup> Companion: Findling, 2013 <sup>45</sup>	17%; 15.8% vs. 20.2% in the two groups so attrition did not vary by group.	Probably yes	Uncertain because no information	Not applicable	Some concerns	Some attrition
Emslie, 2014 <sup>46</sup>	29.8% overall attrition but no differential attrition.	No	Not applicable	Not applicable	Some concerns	Large overall attrition
Findling, 2009 <sup>47</sup> Companion: Hirschtritt, 2012 <sup>67</sup>	26.5% overall; 33.3% vs. 18.8% across groups	No	Not applicable	Not applicable	High	High attrition and differential attrition. Also, study halted for futility after enrolling 34 patients.
Fristad, 2018 <sup>27</sup>	25.0% overall attrition, IG1: 29.4%, IG2: 15.8%, IG3: 19.9%, CG: 16.7%	Yes	Not applicable	Not applicable	Some concerns	Some differential attrition across arms
Geller, 1989 <sup>61</sup>	16.7% attrition overall but no information provided about group specific attrition or reasons for attrition	No	Uncertain because no information	Uncertain because no information	Some Concerns	No information about group specific drop out or reasons for dropout.
Geller, 1992 <sup>62</sup>	16.7% in both groups.	No	Yes	Yes	Some concerns	Authors did not state how they handled missing data.
Glaxo, 1998 <sup>48</sup> Companions: Keller 2001 <sup>50</sup> Le Noury, 2016 <sup>51</sup> Le Noury, 2015 <sup>49</sup>	IG1: 26/93 (28) IG2: 38/95 (40) CG: 21/87 (24.1) Last observation carried forward for those who did not complete the entire study	No	No	Probably no	High	High and differential attrition
Goodyer, 2017 <sup>17</sup> Companion: Goodyer, 2017 <sup>16</sup> O'Keefe 2018 <sup>19</sup> O'Keefe, 2019 <sup>19</sup>	Differences in lost to followup at various assessment points but ITT used. At 36 week end of treatment, attrition was IG1: 35.5% IG2:29.9% CG: 32.9%	No	Uncertain because no information	Uncertain because no information	Some Concerns	High attrition, reasons for dropout between arms unclear, sensitivity for ITT not reported

First Author's Last Name, Year	8. What was the overall attrition?	9. Were outcome data available for all, or nearly all, participants randomized?	9a. If yes to 9, are the proportion of participants and reasons for missing data similar across interventions?	9b. If yes to 9, is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Gunlicks-Stoessel, 2016 <sup>71</sup>	Intervention 22.2% and control 16.7% attrition but all retained in analyses using multiple imputation	No	Probably yes	Probably yes	Some Concerns	Although the study reports no difference between those dropped and retained, little information on methods of imputation and the degree of certainty of the conclusion of no difference, given the small sample size; moderate attrition
Heiligenstein, 2006 <sup>91</sup>	Nearly all retained other than 1 person in CG group (0% and 6.7%, respectively)	Yes	Not applicable	Uncertain because no information	Low	
Hughes, 2013 <sup>33</sup>	Non-completers 12.5% in IG1 and 14.3% in CG	Probably yes	Not applicable	Not applicable	Low	
Iftene, 2015 <sup>78</sup>	15.9% overall; group attrition ranged from 14.8% to 17.9%	No	Yes	No	Some concerns	ITT
Israel, 2013 <sup>26</sup>	Completion attrition IG1: 18.1% CG:44.4% but ITT using LOCF used	No	Uncertain because no information	No	High	High attrition, differential attrition, ITT uses LOCF
Jelalian, 2016 <sup>72</sup>	24% overall attrition; 29% and 11.1% so a bit differential attrition.	No	No	Uncertain because no information		High attrition, some differential attrition
Kennard, 2008 <sup>20</sup>	13.6% of IG1 and 12.5% of CG were noncompleters but all were retained for followup	Yes	Not applicable	Not applicable	Low	
Kennard, 2014 <sup>21</sup> Companion: Emslie, 2015 <sup>22</sup>	17.3% attrition in IG1 and 24.6% in CG at 30 week assessment but all used in analysis with ITT. Loss to followup then increased over time. At 78 weeks, attrition was 41.3% in IG1 and 44.9% in CG and only completers analyzed	Yes at 30 weeks and no at 78 weeks		Uncertain because no information	Some concerns for short-term outcomes at 30 weeks (no information on how the ITT was done), high for long-term outcomes at 78 weeks	ITT method not clear for 30 week followup and high attrition at 78 week followup
Kim, 2012 <sup>85</sup>	IG1: 8.6%, CG: 10.8%	Probably no	Uncertain because no information	No	Some Concerns	Some loss to followup and no ITT used.

First Author's Last Name, Year	8. What was the overall attrition?	9. Were outcome data available for all, or nearly all, participants randomized?	9a. If yes to 9, are the proportion of participants and reasons for missing data similar across interventions?	9b. If yes to 9, is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Klein, 1998 <sup>63</sup>	20% overall with no differential attrition	No	Yes	Yes	Some concerns	Authors did not state how they handled missing data.
Kye, 1996 <sup>64</sup>	29.0% overall; 33% vs. 23%	No	No	Not applicable	High	High attrition, some more discontinued in treatment group than placebo (2 vs. 0)
Luby, 2012 <sup>32</sup>	53.7% attrition plus differential attrition	No	Not applicable	Not applicable	High	Very high attrition and differential attrition. Used ITT analysis but only for those who had at least one assessment after baseline (20.4% attrition)
Mandoki, 1997 <sup>66</sup>	20% IG1 and 15% CG lost to followup	Probably no	Uncertain because no information	Uncertain because no information	Some Concerns	moderate loss to followup with no ITT
March, 2004 <sup>3</sup> Companions: Kennard, 2006 <sup>6</sup> Vitiello, 2006 <sup>7</sup> Curry, 2006 <sup>4</sup> Emslie, 2006 <sup>5</sup> Kratochvil, 2006 <sup>68</sup> Kratochvil, 2009 <sup>8</sup> Foster, 2018 <sup>92</sup> Foster, 2019 <sup>93</sup> TADS	18%, did not vary (16-22%)	Probably no	Probably no	No	Some concerns	ITT used LOCF, high attrition, some differences in drop outs between groups
Melvin, 2006 <sup>79</sup>	15.1% overall, 4.5% CBT, 19.2% med, 20% combined completed intervention and 9.6% did not complete 6 month followup assessment.	Probably no	Not applicable	Not applicable	Some concerns	15% overall attrition, some differential attrition, no sensitivity analysis for ITT methods
Mufson, 1999 <sup>23</sup>	33%, 88% vs. 46% (control). Very differential attrition	No	Not applicable	Not applicable	High	High attrition, very big differential attrition
Nelson, 2004 <sup>73</sup>	26.3%, by group attrition not reported.	No	Not applicable	Not applicable	High	High attrition, no ITT used

First Author's Last Name, Year	8. What was the overall attrition?	9. Were outcome data available for all, or nearly all, participants randomized?	9a. If yes to 9, are the proportion of participants and reasons for missing data similar across interventions?	9b. If yes to 9, is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Nemets, 2006 <sup>35</sup>	G1: 5/15 (33.3%) G2: 3/13 (23%) 28.6% overall	No	No	Not applicable	High	20/28 had completed at least 1 month of the trial. LOCF was used but only for those who completed at least 1 month.
Poole, 2018 <sup>28, 29</sup>	21.9% overall, 24.2% for control group, and 19.4% for treatment group	Yes	Not applicable	Not applicable	Some concerns	Overall attrition is somewhat high
Rickhi, 2015 <sup>34</sup>	33% of treatment group, 7.7% of control group.	No	No	Yes	Some Concerns	Very differential and large overall attrition but ITT used.
Rohde, 1994 <sup>74</sup>	0%	yes	Not applicable	Not applicable	Low	
Rohde, 2004 <sup>15</sup> Companion: Rohde, 2006 <sup>37</sup>	2.2%, 2.2% and 2.1% for the CWD and LS groups, respectively, at end of treatment (6.5% overall at 1 year, not differential)	Yes	Not applicable	Not applicable	Low	Conducted ITT but used available sample because no difference
Rohde, 2006 <sup>37</sup>	1.8%, 1.8% and 1.6% for the CWD and LS groups, respectively, at end of treatment (6.1% overall at 1 year, not differential)	Yes	Not applicable	Not applicable	Low	
Rosello, 1999 <sup>10</sup>	~17% overall, 12%, 14%, and 22% for IG1, IG2, and CG groups, respectively so no concerning differential attrition	Probably no	Probably no	Probably no	High	No ITT analysis done, high and differential attrition

First Author's Last Name, Year	8. What was the overall attrition?	9. Were outcome data available for all, or nearly all, participants randomized?	9a. If yes to 9, are the proportion of participants and reasons for missing data similar across interventions?	9b. If yes to 9, is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Shirk, 2014 <sup>14</sup>	ITT conducted on sample of 43, full maximum likelihood estimates and/or last observation-carried forward methods, but completers: IG: 15/20 (75%); 25% and 17% did not complete intervention but ITT/LOCF used for analyses CG: 20/23 (87%)	No	Probably no	Probably yes	Some Concerns	Some differential attrition, and number of sessions predicts missing data, however number of completed sessions was not demonstrated to be related to change in depressive symptoms or diagnostic status, those with missing data had lower number of sessions (but not differences in outcomes)
Spirito, 2015 <sup>75</sup>	0%	Yes	Not applicable	Not applicable	Low	
Tompson, 2017 <sup>30</sup> Companion: Asarnow, 2018 <sup>31</sup>	28.5% in intervention group and 23.4% in control group completed intervention. 19.4% and 7.5%, respectively, had at least one postbaseline assessment	No	no	Yes	Some Concerns	High attrition overall and differential for having at least one baseline assessment but ITT and imputation conducted.
Trowell, 2007 <sup>76</sup> Companion: Garoff, 2012 <sup>77</sup>	IG1: 0%, 8.1% CG and ITT used. Authors note, however that 13 families dropped out before 8 individual or 4 sessions were completed and replaced with new families	no	Uncertain because no information	Uncertain because no information	High	13 of the original 72 families replaced with no additional information given
Wagner, 2004 <sup>52</sup> Companion: Forest, 2001 <sup>53</sup>	18%, no differential attrition	No	Not applicable	uncertain because no information	some concerns	4 dropouts before txt completion all in the txt arm, high overall attrition: 18%, LOCF
Wagner, 2006 <sup>54</sup>	21%, both groups about the same so no differential attrition	Probably no	Not applicable	Uncertain because no information	High	Some signal of differences between arms in withdrawal of consent, high attrition with missing information about how missing data was handled



First Author's Last Name, Year	8. What was the overall attrition?	9. Were outcome data available for all, or nearly all, participants randomized?	9a. If yes to 9, are the proportion of participants and reasons for missing data similar across interventions?	9b. If yes to 9, is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Weihs, 2018 <sup>55</sup>	ITT used to include all in analyses (details NR) but rates of not completing ranged from IG1: 13.91% IG2: 11.5% CG: 11.6%	No	Uncertain because no information	Uncertain because no information	Uncertain because no information	Authors don't describe how ITT was done
Wilkinson, 2008 <sup>86</sup>	IG1: 13.3%, CG: 9.1%	No	Uncertain because no information	No	Some Concerns	Some loss to followup and no ITT used
Wilkinson, 2011 <sup>87</sup> (ROB based on Goodyer 2007)	Unclear because only 163 or 164 of the original 192 participants with MDD had suicidal info or self-harm info but group specific information and information about how many completed the protocol is not given.	No	Not applicable	Not applicable	High	Some overall attrition, unclear how ITT was conducted, little information given

AE = adverse event; CBT = cognitive behavioral therapy; CG = control group; CWD = Coping with Depression; IG = intervention group; ITT = intent to treat; LOCF = last observation carried forward; LS = life skills/tutoring condition; NR = not reported; NST = nondirective supportive therapy; ROB = risk of bias; SFBT = systemic behavior family therapy; tx = treatment; vs. = versus.

**Table H-4. Randomized controlled trials, part 4**

First Author's Last Name, Year	10. For benefits, were outcome assessors UNAWARE of the intervention	11. Was measurement of benefit outcomes unlikely to have been influenced by knowledge of the intervention received?	Bias arising from measurement of benefit outcomes?	Comments
Atkinson, 2014 <sup>38</sup>	Probably yes	Probably yes	Low	
Atkinson, 2018 <sup>59</sup>	No	Probably no	Some concerns	Unblinded outcome assessors
Berard, 2006 <sup>39</sup>	Probably yes	Probably yes	Low	
Bernstein, 2000 <sup>80</sup>	Yes	Probably yes	Low	
Companion: Bernstein, 2000 <sup>81</sup>				
Brent, 1997 <sup>12</sup>	Uncertain because no information	No	High	Unknown blinding of outcome assessors
Companions Brent, 1998 <sup>13</sup>				
Barbe, 2004 <sup>36</sup>				
Barbe, 2004 <sup>69</sup>				
Dietz, 2014 <sup>70</sup>				
Brent, 2008 <sup>88</sup>	Yes	No	Low	
Companions: Brent, 2009 <sup>90</sup>				
Asarnow, 2009 <sup>89</sup>				
TORDIA				
Clarke, 2016 <sup>94</sup>	Yes	Probably yes	Low	
Clarke, 1999 <sup>9</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Clarke, 2002 <sup>11</sup>	Yes	Probably yes	Low	
Clarke, 2005 <sup>84</sup>	Yes	Probably yes	Low	
Deas, 2000 <sup>82</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
DelBello, 2014 <sup>65</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Diamond, 2002 <sup>25</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Companion: Diamond, 2003 <sup>95</sup>				
Dietz, 2015 <sup>24</sup>	No	No	High	60% of assessments done by blinded assessor but study therapists administered and coded interviews for remaining 40%.
Durgam, 2018 <sup>40</sup>	Yes	Yes	Low	
Emslie, 1997 <sup>41</sup>	Probably no	Uncertain because no information	Uncertain because no information	

First Author's Last Name, Year	10. For benefits, were outcome assessors UNAWARE of the intervention	11. Was measurement of benefit outcomes unlikely to have been influenced by knowledge of the intervention received?	Bias arising from measurement of benefit outcomes?	Comments
Emslie, 2002 <sup>42</sup> Companions: Emslie, 2004 <sup>56</sup> Heiligenstein, 2006 <sup>91</sup>	Yes	Probably yes	Low	
Emslie, 2004 <sup>56</sup>	Yes	Probably yes	Low	
Emslie, 2006 <sup>43</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Emslie, 2007 <sup>60</sup> Study 1	Probably yes	Probably no	Low	
Emslie, 2007 <sup>60</sup> Study 2	Probably yes	Probably no	Low	
Emslie, 2008 <sup>57</sup> Companion: Kennard, 2018 <sup>58</sup>	Yes	Probably yes	Low	
Emslie, 2009 <sup>44</sup> Companion: Findling, 2013 <sup>45</sup>	Probably yes	Probably yes	Low	
Emslie, 2014 <sup>46</sup>	Probably yes	Probably yes	Low	
Findling, 2009 <sup>47</sup> Companion: Hirschtritt, 2012 <sup>67</sup>	Probably yes	Probably yes	Low	
Fristad, 2009 <sup>27</sup>	Yes	Probably no	Low	
Geller, 1989 <sup>61</sup>	Yes	Probably yes	Low	
Geller, 1992 <sup>62</sup>	Uncertain because no information	Probably no	Some concerns	Unclear masking but stated as double blind
Glaxo, 1998 <sup>48</sup> Companions: Keller 2001 <sup>50</sup> Le Noury, 2016 <sup>51</sup> Le Noury, 2015 <sup>49</sup>	Probably yes	Probably yes	Low	
Goodyer, 2017 <sup>17</sup> Companion: Goodyer, 2017 <sup>16</sup> O'Keeffe 2018 <sup>19</sup> O'Keeffe, 2019 <sup>19</sup>	Yes	Probably yes	Low	
Gunlicks-Stoessel, 2016 <sup>71</sup>	Yes	Probably yes	Low	

First Author's Last Name, Year	10. For benefits, were outcome assessors UNAWARE of the intervention	11. Was measurement of benefit outcomes unlikely to have been influenced by knowledge of the intervention received?	Bias arising from measurement of benefit outcomes?	Comments
Heiligenstein, 2006 <sup>91</sup>	Yes	Probably yes	Low	
Hughes, 2013 <sup>33</sup>	Yes	Probably yes	Low	
Iftene, 2015 <sup>78</sup>	Uncertain because no information	Probably no	Some concerns	Unclear masking but stated as double blind
Israel, 2013 <sup>26</sup>	Yes	Probably yes	Low	
Jelalian, 2016 <sup>72</sup>	Yes	Yes	Low	
Kennard, 2008 <sup>20</sup>	Yes	Yes	Low	
Kennard, 2014 <sup>21</sup>	Yes	Probably yes	Low	
Companion: Emslie, 2015 <sup>22</sup>				
Kim, 2012 <sup>85</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Klein, 1998 <sup>63</sup>	Uncertain because no information	Probably no	Some concerns	Unclear masking but stated as double blind
Kye, 1996 <sup>64</sup>	Uncertain because no information	Probably no	Some concerns	Unclear masking but stated as double blind
Luby, 2012 <sup>32</sup>	Yes	Yes	Low	
Mandoki, 1997 <sup>66</sup>	Probably yes	Probably yes	Low	
March, 2004 <sup>3</sup>	Yes	Probably yes		
Companions: Kennard, 2006 <sup>6</sup> Vitiello, 2006 <sup>7</sup> Curry, 2006 <sup>4</sup> Emslie, 2006 <sup>5</sup> Kratochvil, 2006 <sup>68</sup> Kratochvil, 2009 <sup>8</sup> Foster, 2018 <sup>92</sup> Foster, 2019 <sup>93</sup> TADS				
Melvin, 2006 <sup>79</sup>	No	Probably no	High	Outcome assessors not blinded due to resource constraints
Mufson, 1999 <sup>23</sup>	Probably yes	Probably yes		
Nelson, 2004 <sup>73</sup>	Probably no	Probably no	High	Knowledge of intervention could influence outcomes
Nemets, 2006 <sup>35</sup>	Uncertain because no information	Uncertain because no information	Some concerns	Outcome assessor blinding not reported.
Poole, 2018 <sup>28, 29</sup>	Probably yes	Probably no	Low	
Rickhi, 2015 <sup>34</sup>	Yes	Yes	Low	

<b>First Author's Last Name, Year</b>	<b>10. For benefits, were outcome assessors UNAWARE of the intervention</b>	<b>11. Was measurement of benefit outcomes unlikely to have been influenced by knowledge of the intervention received?</b>	<b>Bias arising from measurement of benefit outcomes?</b>	<b>Comments</b>
Rohde, 1994 <sup>74</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Rohde, 2004 <sup>15</sup> Companion: Rohde, 2006 <sup>37</sup>	Yes	Probably yes	Low	
Rohde, 2006 <sup>37</sup>	Yes	Probably yes	Low	
Rosello, 1999 <sup>10</sup>	Uncertain because no information	Uncertain because no information	high	Blinding not reported, self reported outcomes
Shirk, 2014 <sup>14</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	No information on blinding of outcome assessors
Spirito, 2015 <sup>75</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	Not applicable
Tompson, 2017 <sup>30</sup> Companion: Asarnow, 2018 <sup>31</sup>	Yes	Probably yes	Low	
Trowell, 2007 <sup>76</sup> Companion: Garoff, 2012 <sup>77</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Wagner, 2004 <sup>52</sup> Companion: Forest, 2001 <sup>53</sup>	Uncertain because no information	Probably yes	Uncertain because no information	
Wagner, 2006 <sup>54</sup>	Uncertain because no information	Probably yes	Uncertain because no information	
Weihs, 2018 <sup>55</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	No information on blinding of outcome assessors
Wilkinson, 2008 <sup>86</sup>	Yes	Probably no	Some concerns	Outcome assessors not blinded.
Wilkinson, 2011 <sup>87</sup> (ROB based on Goodyer 2007)	Yes	Yes	Low	

ROB = risk of bias.

**Table H-5. Randomized controlled trials, part 5**

<b>First Author's Last Name, Year</b>	<b>12. For harms, were outcome assessors aware of the intervention received by study participants?</b>	<b>13. Was measurement of harm outcomes unlikely to have been influenced by knowledge of the intervention received?</b>	<b>Bias arising from measurement of harm outcomes?</b>	<b>Comments</b>
Atkinson, 2014 <sup>38</sup>	Probably yes	Probably yes	Low	
Atkinson, 2018 <sup>59</sup>	No	Probably no	Some concerns	Unblinded outcome assessors
Berard, 2006 <sup>39</sup>	Probably yes	Probably yes	Low	
Bernstein, 2000 <sup>80</sup>	Yes	Probably yes	Low	Low
Companion: Bernstein, 2000 <sup>81</sup>				
Brent, 1997 <sup>12</sup>	Uncertain because no information	No	High	Unknown blinding of outcome assessors
Companions Brent, 1998 <sup>13</sup> Barbe, 2004 <sup>36</sup> Barbe, 2004 <sup>69</sup> Dietz, 2014 <sup>70</sup>				
Brent, 2008 <sup>88</sup>	Yes	No	Low	
Companions: Brent, 2009 <sup>90</sup> Asarnow, 2009 <sup>89</sup> TORDIA				
Clarke, 2016 <sup>94</sup>	Not applicable	Not applicable		
Clarke, 1999 <sup>9</sup>	Not applicable	Not applicable	Not applicable	
Clarke, 2002 <sup>11</sup>	Yes	Probably yes	Low	
Clarke, 2005 <sup>84</sup>	Not applicable	Not applicable	Not applicable	
Deas, 2000 <sup>82</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
DeBello, 2014 <sup>65</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Diamond, 2002 <sup>25</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Companion: Diamond, 2003 <sup>95</sup>				
Dietz, 2015 <sup>24</sup>	Not applicable	Not applicable	Not applicable	
Durgam, 2018 <sup>40</sup>	Yes	Yes	Low	
Emslie, 1997 <sup>41</sup>	Probably no	Uncertain because no information	Uncertain because no information	
Emslie, 2002 <sup>42</sup>	Not applicable	Not applicable		

First Author's Last Name, Year	12. For harms, were outcome assessors aware of the intervention received by study participants?	13. Was measurement of harm outcomes unlikely to have been influenced by knowledge of the intervention received?	Bias arising from measurement of harm outcomes?	Comments
Emslie, 2004 <sup>56</sup> Companions: Emslie, 2004 <sup>56</sup> Heiligenstein, 2006 <sup>91</sup>	Not applicable	Not applicable		
Emslie, 2006 <sup>43</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Emslie, 2007 <sup>60</sup> Study 1	Not applicable	Not applicable	Not applicable	
Emslie, 2007 <sup>60</sup> Study 2	Not applicable	Not applicable	Not applicable	
Emslie, 2008 <sup>57</sup> Companion: Kennard, 2018 <sup>58</sup>	Yes	Probably yes	Low	
Emslie, 2009 <sup>44</sup> Companion: Findling, 2013 <sup>45</sup>	No	Yes	Low	
Emslie, 2014 <sup>46</sup>	Probably yes	Probably yes	Low	
Findling, 2009 <sup>47</sup> Companion: Hirschtritt, 2012 <sup>67</sup>	Probably yes	Probably yes	Low	
Fristad, 2009 <sup>27</sup>	Not applicable	Not applicable	Not applicable	
Geller, 1989 <sup>61</sup>	Yes	Probably yes	Low	
Geller, 1992 <sup>62</sup>	Uncertain because no information	Probably no	Some concerns	Unclear masking but stated as double blind
Glaxo, 1998 <sup>48</sup> Companions: Keller 2001 <sup>50</sup> Le Noury, 2016 <sup>51</sup> Le Noury, 2015 <sup>49</sup>	Probably yes	Probably yes	High	Based on LeNoury, coding of harms created issues leading to an underestimation of harms
Goodyer, 2017 <sup>17</sup> Companion: Goodyer, 2017 <sup>16</sup> O'Keeffe 2018 <sup>19</sup> O'Keeffe, 2019 <sup>19</sup>	Yes	Probably yes	Low	
Gunlicks-Stoessel, 2016 <sup>71</sup> Heiligenstein, 2006 <sup>91</sup>	Not applicable	Not applicable	Not applicable	

First Author's Last Name, Year	12. For harms, were outcome assessors aware of the intervention received by study participants?	13. Was measurement of harm outcomes unlikely to have been influenced by knowledge of the intervention received?	Bias arising from measurement of harm outcomes?	Comments
Hughes, 2013 <sup>33</sup>	Yes	Probably yes	Low	
Iftene, 2015 <sup>78</sup>	Uncertain because no information	Probably no	Some concerns	Unclear masking but stated as double blind
Israel, 2013 <sup>26</sup>	Yes	Yes	Low	
Jelalian, 2016 <sup>72</sup>	Not applicable	Not applicable	Not applicable	Not applicable
Kennard, 2008 <sup>20</sup>	No	Yes	Low	
Kennard, 2014 <sup>21</sup>	No	Probably yes	Low	
Companion: Emslie, 2015 <sup>22</sup>				
Kim, 2012 <sup>85</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Klein, 1998 <sup>63</sup>	Uncertain because no information	Probably no	Some concerns	Unclear masking but stated as double blind
Kye, 1996 <sup>64</sup>	Uncertain because no information	Probably no	Some concerns	Unclear masking but stated as double blind
Luby, 2012 <sup>32</sup>	Not applicable	Not applicable		
Mandoki, 1997 <sup>66</sup>	Not applicable	Not applicable		
March, 2004 <sup>3</sup>	Yes	Probably yes	Low	
Companions: Kennard, 2006 <sup>6</sup> Vitiello, 2006 <sup>7</sup> Curry, 2006 <sup>4</sup> Emslie, 2006 <sup>5</sup> Kratochvil, 2006 <sup>68</sup> Kratochvil, 2009 <sup>8</sup> Foster, 2018 <sup>92</sup> Foster, 2019 <sup>93</sup> TADS				
Melvin, 2006 <sup>79</sup>	Yes	Probably no	High	Outcome assessors not blinded due to resource constraints
Mufson, 1999 <sup>23</sup>	Probably yes	Probably yes	Low	
Nelson, 2004 <sup>73</sup>	Not applicable	Not applicable	Not applicable	
Nemets, 2006 <sup>35</sup>	Not applicable	Not applicable	Not applicable	
Poole, 2018 <sup>28, 29</sup>	Not applicable	Not applicable	Not applicable	
Rickhi, 2015 <sup>34</sup>	No	Yes	Low	
Rohde, 1994 <sup>74</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	



First Author's Last Name, Year	12. For harms, were outcome assessors aware of the intervention received by study participants?	13. Was measurement of harm outcomes unlikely to have been influenced by knowledge of the intervention received?	Bias arising from measurement of harm outcomes?	Comments
Rohde, 2004 <sup>15</sup> Companion: Rohde, 2006 <sup>37</sup>	Yes	No	Low	
Rohde, 2006 <sup>37</sup>	Not applicable	Not applicable	Not applicable	
Rosello, 1999 <sup>10</sup>	Not applicable	Not applicable	Uncertain because no information	Outcome assessors not blinded
Shirk, 2014 <sup>14</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	No information on blinding of outcome assessors
Spirito, 2015 <sup>75</sup>	Not applicable	Not applicable		
Tompson, 2017 <sup>30</sup> Companion: Asarnow, 2018 <sup>31</sup>	Not applicable	Not applicable	Not applicable	
Trowell, 2007 <sup>76</sup> Companion: Garoff, 2012 <sup>77</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	
Wagner, 2004 <sup>52</sup> Companion: Forest, 2001 <sup>53</sup>	Probably yes	Probably yes	Uncertain because no information	
Wagner, 2006 <sup>54</sup>	Uncertain because no information	Probably yes	Uncertain because no information	Not applicable
Weihs, 2018 <sup>55</sup>	Uncertain because no information	Uncertain because no information	Uncertain because no information	No information on blinding of outcome assessors
Wilkinson, 2008 <sup>86</sup>	Not applicable	Not applicable	Not applicable	
Wilkinson, 2011 <sup>87</sup> (ROB based on Goodyer 2007)	Yes	Yes	Low	

ROB = risk of bias.

**Table H-6. Randomized controlled trials, part 6**

First Author's Last Name, Year	14. Is the reported effect estimate unlikely to be selected, on the basis of the results, from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments	Study Quality-Benefits	Overall Rating Justification/Comments Benefits
Atkinson, 2014 <sup>38</sup>	Probably yes	Low		High	Relatively high and differential attrition
Atkinson, 2018 <sup>59</sup>	Probably yes	Low		Some concerns	Randomization and allocation concealment processes not described, moderately high attrition; unblinded outcome assessors
Berard, 2006 <sup>39</sup>	Probably yes	low		High	The study used mITT and 11 were lost between randomization and receiving at least 1 dose of study medication (definition used for mITT) and authors do not present differences in these 11 patients vs. those who entered the study or by group. The attrition was high and differential without losing these additional 11 patients. Potential for uncontrolled cointerventions
Bernstein, 2000 <sup>80</sup> Companion: Bernstein, 2000 <sup>81</sup>		Probably yes	Low	Some concerns	Some loss to followup and no ITT used or analyses of those lost vs completed
Brent, 1997 <sup>12</sup> And Companions Brent, 1998 <sup>13</sup> Barbe, 2004 <sup>36</sup> Barbe, 2004 <sup>69</sup> Dietz, 2014 <sup>70</sup>	Probably yes			High	No patient or provider blinding, Unknown outcome assessor blinding, high attrition, several in the study should have been ineligible.
Brent, 2008 <sup>88</sup> Companions: Brent, 2009 <sup>90</sup> Asarnow, 2009 <sup>89</sup> TORDIA	Probably yes	Low		High	High attrition, some differential causes for attrition, reliance on LOCF, some groups not blinded
Clarke, 2016 <sup>94</sup>	Probably yes	Low		Some concerns	Patient and provider not blinded; Patients, parents, and clinical personnel awareness of treatment could influence outcomes

First Author's Last Name, Year	14. Is the reported effect estimate unlikely to be selected, on the basis of the results, from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments	Study Quality-Benefits	Overall Rating Justification/Comments Benefits
Clarke, 1999 <sup>9</sup>	Probably yes	low		Some concerns	Randomization and allocation concealment not reported; patients not blinded, awareness of intervention could influence outcomes; high attrition and unknown differential attrition
Clarke, 2002 <sup>11</sup>	Probably yes	Low		Some concerns	Patients and providers not blinded and no information about how data was handled when missing. Awareness of intervention could influence outcomes. No information on how data on those lost to were obtained
Clarke, 2005 <sup>84</sup>	Probably yes	Low		Some concerns	No allocation concealment and patients and providers not blinded.
Deas, 2000 <sup>82</sup>	Probably yes	Low		Low	
DelBello, 2014 <sup>65</sup>	Probably yes	Low		Some concerns	High attrition and unclear allocation concealment; unclear if outcome assessors were blinded
Diamond, 2002 <sup>25</sup> Companion: Diamond, 2003 <sup>95</sup>	No	High	The WL group only had assessments at 6 weeks (when anyone who had not responded was offered open treatment). The intervention group had a few measured at 6 weeks but most at 12. The 6 week WL group outcomes were compared with the 12 week intervention group outcomes, so inconsistent time periods were compared. Also, clinical significant improvement was defined as BDI>9, which has not been validated.	High	Awareness of intervention could influence outcomes

First Author's Last Name, Year	14. Is the reported effect estimate unlikely to be selected, on the basis of the results, from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments	Study Quality-Benefits	Overall Rating Justification/Comments Benefits
Dietz, 2015 <sup>24</sup>	Probably yes	Low		Some concerns	Possible imbalance in arms, unmeasured contamination; possible differences in attrition and unblinded assessment in 40% of participants
Durgam, 2018 <sup>40</sup>	Probably yes	Low		Some concerns	Unclear allocation concealment and moderate attrition; different reasons for attrition across arms
Emslie, 1997 <sup>41</sup>	Probably no	Low		High	high and differential attrition
Emslie, 2002 <sup>42</sup> Companions: Emslie, 2004 <sup>56</sup> Heiligenstein, 2006 <sup>91</sup>	Probably yes	Low		High	High and differential attrition with LOCF for ITT without further investigation, no sensitivity analysis. Possible imbalance at baseline.
Emslie, 2004 <sup>56</sup>	Probably yes	Low		High	High and differential attrition with LOCF for ITT without further investigation. Possible imbalance at baseline.
Emslie, 2006 <sup>43</sup>	Probably no	Low		Some concerns	High attrition and unclear allocation concealment
Emslie, 2007 <sup>60</sup> Study 1	Probably no	Low		High	High overall attrition
Emslie, 2007 <sup>60</sup> Study 2	Probably no	Low		High	High differential attrition
Emslie, 2008 <sup>57</sup> Companion: Kennard, 2018 <sup>58</sup>	Probably yes	Low		Some concerns	Differential attrition but full sample used for analysis, no explanation of how data were obtained and robustness of data
Emslie, 2009 <sup>44</sup> Companion: Findling, 2013 <sup>45</sup>	Probably yes			Some concerns	Randomization and allocation concealment not reported; high attrition mitigated by ITT; unknown if baseline characteristics differed between groups
Emslie, 2014 <sup>46</sup>	Probably yes	Low		High	High and differential attrition
Findling, 2009 <sup>47</sup> Companion: Hirschtritt, 2012 <sup>67</sup>	Yes	Low		Some concerns	High attrition mitigated by ITT
Fristad, 2009 <sup>27</sup>	No	Low		Some concerns	Potential for differential attrition

First Author's Last Name, Year	14. Is the reported effect estimate unlikely to be selected, on the basis of the results, from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments	Study Quality-Benefits	Overall Rating Justification/Comments Benefits
Geller, 1989 <sup>61</sup>	Probably yes	Low		Some concerns	Patients and providers not blinded and treatment group had lower adherence to medication than controls. No information on how data was recorded for those lost to follow-up; No reasons for or distribution of dropouts specified
Geller, 1992 <sup>62</sup>	Probably no	Low		Some concerns	Moderate attrition, no details on randomization or allocation concealment or blinding.
Glaxo, 1998 <sup>48</sup> Companions: Keller 2001 <sup>50</sup> Le Noury, 2016 <sup>51</sup> Le Noury, 2015 <sup>49</sup>	No	high	Based on LeNoury, four secondary outcomes, not included in the protocol, were included in the CSR and Kellier	High	High and differential attrition, selection bias in reporting results
Goodyer, 2017 <sup>17</sup> Companion: Goodyer, 2017 <sup>16</sup> O'Keeffe 2018 <sup>19</sup> O'Keeffe, 2019 <sup>19</sup>	Probably yes	Low		Some concerns	High attrition, reasons for dropout between arms unclear, sensitivity for ITT not reported, patients and providers not blinded -awareness of intervention could influence outcomes, unclear how ITT was conducted, unclear differences at baseline between groups
Gunlicks-Stoessel, 2016 <sup>71</sup>	Probably yes	Low		Some concerns	Methods used for multiple imputation unclear and moderate attrition
Heiligenstein, 2006 <sup>91</sup>	Probably yes	Low		Some concerns	Possible imbalance at baseline
Hughes, 2013 <sup>33</sup>	Probably yes	Low		Some concerns	Patient and provider not blinded. Awareness of intervention can influence outcomes
Iftene, 2015 <sup>78</sup>	Probably no	Low		Some concerns	Moderate attrition, no details on randomization or allocation concealment or blinding.
Israel, 2013 <sup>26</sup>	Probably yes	Low		High	High attrition, differential attrition, LOCF ITT used, patients and providers not blinded, awareness of intervention could influence outcomes.
Jelalian, 2016 <sup>72</sup>	Probably no	Low		High	Differential attrition

First Author's Last Name, Year	14. Is the reported effect estimate unlikely to be selected, on the basis of the results, from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments	Study Quality-Benefits	Overall Rating Justification/Comments Benefits
Kennard, 2008 <sup>20</sup>	Probably yes	Low		Some concerns	Patient and provider not blinded; awareness of intervention could influence outcomes
Kennard, 2014 <sup>21</sup> Companion: Emslie, 2015 <sup>22</sup>	Probably yes	Low		Some concerns	Patient and provider not blinded; awareness of intervention could influence outcomes
Kim, 2012 <sup>85</sup>	Probably yes	Low		Some concerns	Patients and providers not blinded; awareness of intervention can influence outcomes, unclear outcome assessor blinding, no ITT used and some loss to follow-up.
Klein, 1998 <sup>63</sup>	Probably no	Low		Some concerns	Moderate attrition, no details on randomization or allocation concealment or blinding.
Kye, 1996 <sup>64</sup>	Probably no	low		High	High attrition, no details about allocation concealment or blinding of outcome assessors
Luby, 2012 <sup>32</sup>	Yes	Low		High	Very high and differential attrition, awareness of intervention could influence outcomes
Mandoki, 1997 <sup>66</sup>	Probably yes	Low		Some concerns	Moderate attrition without ITT
March, 2004 <sup>3</sup> Companions: Kennard, 2006 <sup>6</sup> Vitiello, 2006 <sup>7</sup> Curry, 2006 <sup>4</sup> Emslie, 2006 <sup>5</sup> Kratochvil, 2006 <sup>68</sup> Kratochvil, 2009 <sup>8</sup> Foster, 2018 <sup>92</sup> Foster, 2019 <sup>93</sup> TADS	Probably yes	Low		Some concerns	High attrition, unclear allocation status, no patient blinding in some groups

First Author's Last Name, Year	14. Is the reported effect estimate unlikely to be selected, on the basis of the results, from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments	Study Quality-Benefits	Overall Rating Justification/Comments Benefits
Melvin, 2006 <sup>79</sup>	Probably yes	Low		High	Awareness of the intervention could influence outcomes, outcome assessors not blinded (nor were patient and provider). 15% attrition in completing end-of-treatment, differential attrition without sensitivity analysis for ITT.
Mufson, 1999 <sup>23</sup>	Probably yes	Low		High	Not blinded, high attrition, very large differential attrition
Nelson, 2004 <sup>73</sup>	Probably no	Low		High	Unblinded allocation, high attrition, no allocation concealment, coin toss randomization, no ITT analyses used.
Nemets, 2006 <sup>35</sup>	Probably yes	Low		High	High and differential attrition, no attempt to address missing data Unclear methods of randomization and allocation concealment, high attrition, no LOCF for those who completed less than 1 month, no specification of outcome assessor blinding.
Poole, 2018 <sup>28, 29</sup>	Probably low	Low		Some concerns	Potential for attrition bias
Rickhi, 2015 <sup>34</sup>	Probably no	Low		Some concerns	Patient and provider not blinded; ; Awareness of intervention could influence outcomes
Rohde, 1994 <sup>74</sup>	Probably yes	Low		Some concerns	Patient and provider not blinded. Awareness of intervention can influence outcomes
Rohde, 2004 <sup>15</sup> Companion: Rohde, 2006 <sup>37</sup>	Probably yes	Low		Some concerns	Awareness of the intervention could influence outcomes No allocation concealment and patients and providers not blinded.
Rohde, 2006 <sup>37</sup>	Probably yes	Low		Some concerns	Awareness of the intervention could influence outcomes; no allocation concealment and patients and providers not blinded.

First Author's Last Name, Year	14. Is the reported effect estimate unlikely to be selected, on the basis of the results, from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments	Study Quality-Benefits	Overall Rating Justification/Comments Benefits
Rosello, 1999 <sup>10</sup>	Probably no	Some concerns	Unknown	High	No ITT analyses conducted; randomization method not reported; blinding of assessors not reported; no group differences reported at baseline other than for outcomes so do not know how groups may have differed on sociodemographic characteristics, etc., and analyses were not adjusted. High and differential attrition
Shirk, 2014 <sup>14</sup>	Probably yes	Low		Some concerns	Unclear outcome assessor blinding, patients and providers not blinded, some differential attrition with number of visits related to missingness. Awareness of the intervention can influence outcomes, come differential attrition, and number of sessions predicts missing data.
Spirito, 2015 <sup>75</sup>	Probably yes	Low		High	Randomized failed, unclear outcome assessor blinding, no patient and provider blinding – awareness of intervention can influence outcomes .
Tompson, 2017 <sup>30</sup> Companion: Asarnow, 2018 <sup>31</sup>	Probably yes	Low		Some concerns	High attrition and some differential attrition in having at least one completed follow-up assessment (but ITT done with imputation); patients not blinded. Awareness of intervention could influence outcomes, some differential attrition
Trowell, 2007 <sup>76</sup> Companion: Garoff, 2012 <sup>77</sup>	Probably yes	Low		High	13 of 72 families appear to have been replaced after randomization with no indication of the impact of replacement, patients and providers not blinded; awareness of the intervention could influence outcomes
Wagner, 2004 <sup>52</sup> Companion: Forest, 2001 <sup>53</sup>	Yes	Low		Some concerns	High overall attrition



First Author's Last Name, Year	14. Is the reported effect estimate unlikely to be selected, on the basis of the results, from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments	Study Quality-Benefits	Overall Rating Justification/Comments Benefits
Wagner, 2006 <sup>54</sup>	Yes	Low		Some concerns	High attrition but no differential attrition, no specified outcome blinding or patient/intervention provider blinding reported.
Weihs, 2018 <sup>55</sup>	Probably yes	Low		High	Unclear methods of randomization and allocation concealment, how ITT was done, whether outcome assessors were blinded.
Wilkinson, 2008 <sup>86</sup>	Probably yes	Low		High	Patients and providers and outcome assessors not blinded (awareness of intervention can influence outcomes), some loss to followup without ITT used.
Wilkinson, 2011 <sup>87</sup> (ROB based on Goodyer 2007)	Yes	Low		High	Unblinded intervention

BDI = Beck Depression Inventory; ITT = intent to treat; LOCF = last observation carried forward; mITT = modified intention to treat; RoB = risk of bias; WL = wait-list.

**Table H-7. Randomized controlled trials, part 7**

First Author's Last Name, Year	Does ROB Rating of Study Vary by Benefits Outcome?	Study Quality Ratings by Benefits Outcome	Study Quality-Harms	Overall Rating Justification/ Comments Harms	Does Rating of Study Vary by Harm Outcome?	Study Quality Ratings by Harm Outcome
Atkinson, 2014 <sup>38</sup>	No	Not applicable	High	Relatively high and differential attrition	No	Not applicable
Atkinson, 2018 <sup>59</sup>	No	Same	Some concerns	Unblinded outcome assessors	Not applicable	Not applicable
Berard, 2006 <sup>39</sup>	No	Not applicable	High	The study used mITT and 11 were lost between randomization and receiving at least 1 dose of study medication (definition used for mITT) and authors don't present differences in these 11 patients vs. those who entered the study or by group. The attrition was high and differential without losing these additional 11 patients. Potential for uncontrolled cointerventions	No	Not applicable
Bernstein, 2000 <sup>80</sup> Companion: Bernstein, 2000 <sup>81</sup>	No	Same	Some concerns	Some loss to followup and no ITT used or analyses of those lost vs completed	No	Same
Brent, 1997 <sup>12</sup> Companions: Brent, 1998 <sup>13</sup> Barbe, 2004 <sup>36</sup> Barbe, 2004 <sup>69</sup> Dietz, 2014 <sup>70</sup>	No		High	High and possibly differential attrition, unblinded outcome assessors, participants and clinicians not blinded	No	
Brent, 2008 <sup>88</sup> Brent, 2009 <sup>90</sup> Asarnow, 2009 <sup>89</sup> TORDIA	No	Same	High	High attrition, some differential causes for attrition, reliance on LOCF, some groups not blinded	No	Same
Clarke, 2016 <sup>94</sup>	No	Same	Some concerns	Not applicable	Not applicable	Not applicable
Clarke, 1999 <sup>9</sup>	No		Not applicable	Moderate attrition, no details on randomization or allocation concealment or blinding, awareness of intervention could influence outcomes	No	Some concerns
Clarke, 2002 <sup>11</sup>	No	Same	Some concerns	Awareness of intervention could influence outcomes. No information on how data on those lost to were obtained	No	Not applicable
Clarke, 2005 <sup>84</sup>	No	Same	Not applicable	Not applicable	Not applicable	Not applicable

First Author's Last Name, Year	Does ROB Rating of Study Vary by Benefits Outcome?	Study Quality Ratings by Benefits Outcome	Study Quality-Harms	Overall Rating Justification/ Comments Harms	Does Rating of Study Vary by Harm Outcome?	Study Quality Ratings by Harm Outcome
Deas, 2000 <sup>82</sup>	No	Same	Low		No	Same
DelBello, 2014 <sup>65</sup>	No	Same	Some concerns	High attrition and unclear allocation concealment; unclear if outcome assessors were blinded	No	Same
Diamond, 2002 <sup>25</sup> Companion: Diamond, 2003 <sup>95</sup>	Yes	Yes, but it is high or really high so I suppose I would say no. They are all high.	High	Awareness of intervention could influence outcomes	No	
Dietz, 2015 <sup>24</sup>	Possible imbalance in arms, unmeasured contamination, unblinded outcomes evaluation		Not applicable	Not applicable	Not applicable	Not applicable
Durgam, 2018 <sup>40</sup>	No	Same	Some concerns	Unclear allocation concealment and moderate attrition	Not applicable	Not applicable
Emslie, 1997 <sup>41</sup>	No	Same	High	High and differential attrition	No	Same
Emslie, 2002 <sup>42</sup> Companions: Emslie, 2004 <sup>56</sup> Heiligenstein, 2006 <sup>91</sup>	No	Same	High	Not applicable	Not applicable	Not applicable
Emslie, 2004 <sup>56</sup>	No	Same	High	Not applicable	Not applicable	Not applicable
Emslie, 2006 <sup>43</sup>	No	Same	Some concerns	High attrition and unclear allocation concealment	No	Same
Emslie, 2007 <sup>60</sup> Study 1	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Emslie, 2007 <sup>60</sup> Study 2	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Emslie, 2008 <sup>57</sup> Companion: Kennard, 2018 <sup>58</sup>	No	Same	Some concerns	Differential attrition but full sample used for analysis, no explanation of how data were obtained and robustness of data	No	Same
Emslie, 2009 <sup>44</sup> Companion: Findling, 2013 <sup>45</sup>	No	Not applicable	Some concerns	High attrition mitigated by ITT; no details about allocation concealment or blinding of outcome assessors	No	High
Emslie, 2014 <sup>46</sup>	No	Not applicable	High	High and differential attrition	No	

First Author's Last Name, Year	Does ROB Rating of Study Vary by Benefits Outcome?	Study Quality Ratings by Benefits Outcome	Study Quality-Harms	Overall Rating Justification/ Comments Harms	Does Rating of Study Vary by Harm Outcome?	Study Quality Ratings by Harm Outcome
Findling, 2009 <sup>47</sup> Companion: Hirschtritt, 2012 <sup>67</sup>	No	Not applicable	Some concerns	High attrition mitigated by ITT, no details on randomization or allocation concealment or blinding.	No	Some concerns
Fristad, 2009 <sup>27</sup>	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Geller, 1989 <sup>61</sup>	No	Same	Not applicable	Not applicable	Not applicable	Not applicable
Geller, 1992 <sup>62</sup>	No	Some concerns	Some concerns	High attrition, patients and providers not blinded, some differential attrition (but small pilot study)	No	Some concerns
Glaxo, 1998 <sup>48</sup> Companions: Keller 2001 <sup>50</sup> Le Noury, 2016 <sup>51</sup> Le Noury, 2015 <sup>49</sup>	No, original protocol		High	No patient or provider blinding, Unknown outcome assessor blinding, high attrition, several in the study should have been ineligible, selection bias in reporting results, biased measurement of harms outcomes.	No	Not applicable
Goodyer, 2017 <sup>17</sup> Companion: Goodyer, 2017 <sup>16</sup> O'Keeffe 2018 <sup>19</sup> O'Keeffe, 2019 <sup>19</sup>	No	Same	Some concerns	High attrition, reasons for dropout between arms unclear, sensitivity for ITT not reported, patients and providers not blinded -awareness of intervention could influence outcomes, unclear how ITT was conducted, unclear differences at baseline between groups	No	Same
Gunlicks-Stoessel, 2016 <sup>71</sup>	No	Same	Not applicable	Not applicable	Not applicable	Not applicable
Heiligenstein, 2006 <sup>91</sup>	No	Same	Some concerns	Not applicable	Not applicable	Not applicable
Hughes, 2013 <sup>33</sup>	No	Same	Some concerns	Patient and provider not blinded. Awareness of intervention can influence outcomes	No	Same
Iftene, 2015 <sup>78</sup>	No	Some concerns	Some concerns	High attrition	No	
Israel, 2013 <sup>26</sup>	No	Same	Not applicable			
Jelalian, 2016 <sup>72</sup>	No		Not applicable	Not applicable	Not applicable	Not applicable
Kennard, 2008 <sup>20</sup>	No	Some concerns	Some concerns	Patient and provider not blinded. Awareness of intervention could influence outcomes	No	Same

First Author's Last Name, Year	Does ROB Rating of Study Vary by Benefits Outcome?	Study Quality Ratings by Benefits Outcome	Study Quality-Harms	Overall Rating Justification/ Comments Harms	Does Rating of Study Vary by Harm Outcome?	Study Quality Ratings by Harm Outcome
Kennard, 2014 <sup>21</sup> Companion: Emslie, 2015 <sup>22</sup>	Yes, some concerns for outcomes through week 30, high risk of bias (because of attrition) through week 78	Yes, some concerns at 30 weeks and high at 78 week followup	Not applicable	Not applicable	Not applicable	Not applicable
Kim, 2012 <sup>85</sup>	No	Same	Some concerns	Patients and providers not blinded – awareness of intervention can influence outcomes, unclear outcome assessor blinding, no ITT used and some loss to followup.	No	Same
Klein, 1998 <sup>63</sup>	No	Some concerns	Some concerns	Moderate attrition, no details on randomization or allocation concealment or blinding.	No	Some concerns
Kye, 1996 <sup>64</sup>	No	High	High	High attrition	No	Not applicable
Luby, 2012 <sup>32</sup>	No	Not applicable	High	High and differential attrition, awareness of intervention could influence outcomes	No	Not applicable
Mandoki, 1997 <sup>66</sup>	No	Same	Not applicable	Not applicable	Not applicable	Not applicable
March, 2004 <sup>3</sup> Companions: Kennard, 2006 <sup>6</sup> Vitiello, 2006 <sup>7</sup> Curry, 2006 <sup>4</sup> Emslie, 2006 <sup>5</sup> Kratochvil, 2006 <sup>68</sup> Kratochvil, 2009 <sup>8</sup> Foster, 2018 <sup>92</sup> Foster, 2019 <sup>93</sup> TADS	No	NA	Some concerns	High attrition but no differential attrition, no specified outcome blinding or patient/intervention provider blinding reported.	No	Not applicable
Melvin, 2006 <sup>79</sup>	No	Same	High	Awareness of the intervention could influence outcomes, outcome assessors not blinded (nor were patient and provider). 15% attrition in completing end-of-treatment, differential attrition without sensitivity analysis for ITT.	No	Same
Mufson, 1999 <sup>23</sup>	No		High	High and differential attrition, awareness of intervention could influence outcomes	Not applicable	Not applicable

First Author's Last Name, Year	Does ROB Rating of Study Vary by Benefits Outcome?	Study Quality Ratings by Benefits Outcome	Study Quality-Harms	Overall Rating Justification/ Comments Harms	Does Rating of Study Vary by Harm Outcome?	Study Quality Ratings by Harm Outcome
Nelson, 2004 <sup>73</sup>	No	High	Not applicable	Unblinded allocation, unmasked evaluation	No	
Nemets, 2006 <sup>35</sup>	No	Same	Not applicable	High and differential attrition, no attempt to address missing data	Not applicable	Not applicable
Poole, 2018 <sup>28</sup> , #12721	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Rickhi, 2015 <sup>34</sup>	No	Some concerns Same	Some concerns Not applicable	Awareness of intervention could influence outcomes Not applicable	Not applicable	Not applicable
Rohde, 1994 <sup>74</sup>	No	Same	Some concerns	Patient and provider not blinded. Awareness of intervention can influence outcomes	No	Same
Rohde, 2004 <sup>15</sup> Companion: Rohde, 2006 <sup>37</sup>	No	Same	Not applicable	Not applicable	Not applicable	Not applicable
Rohde, 2006 <sup>37</sup>	No	Same	Not applicable	Awareness of the intervention could influence outcomes	Not applicable	Not applicable
Rosello, 1999 <sup>10</sup>	No	Yes, but already high so collectively no. Some outcomes had different N's than others.	Not applicable			
Shirk, 2014 <sup>14</sup>	No	Same	Some concerns	Unclear outcome assessor blinding, patients and providers not blinded, some differential attrition with number of visits related to missingness. Awareness of the intervention can influence outcomes, come differential attrition, and number of sessions predicts missing data.	No	Same
Spirito, 2015 <sup>75</sup>	No	Same	Not applicable	Not applicable	Not applicable	
Tompson, 2017 <sup>30</sup> Companion: Asarnow, 2018 <sup>31</sup>	No	Same	Not applicable	Not applicable	Not applicable	Not applicable

First Author's Last Name, Year	Does ROB Rating of Study Vary by Benefits Outcome?	Study Quality Ratings by Benefits Outcome	Study Quality-Harms	Overall Rating Justification/ Comments Harms	Does Rating of Study Vary by Harm Outcome?	Study Quality Ratings by Harm Outcome
Trowell, 2007 <sup>76</sup> Companion: Garoff, 2012 <sup>77</sup>	No	Same	High	13 of 72 families appear to have been replaced after randomization with no indication of the impact of replacement, patients and providers not blinded - awareness of the intervention could influence outcomes	No	Same
Wagner, 2004 <sup>52</sup> Companion: Forest, 2001 <sup>53</sup>	No	Not applicable	Some concerns	High overall attrition	No	
Wagner, 2006 <sup>54</sup>	No	Not applicable	Some concerns	High overall attrition	No	
Weihs, 2018 <sup>55</sup>	No	Same	Uncertain	Unclear methods of randomization and allocation concealment, how ITT was done, whether outcome assessors were blinded.	No	Same
Wilkinson, 2008 <sup>86</sup>	No	Same	Not applicable	Not applicable	Not applicable	Not applicable
Wilkinson, 2011 <sup>87</sup> (ROB based on Goodyer 2007)	No		High	Unblinded intervention. Very little information reported to allow assessment of quality	No	High

ITT = intent to treat; LOCF = last observation carried forward; mITT = modified intention to treat; RoB = risk of bias.

## Appendix I. Risk of Bias of Nonrandomized Controlled Trials

Table I-1. Nonrandomized tables, part 1 .....	I-2
Table I-2. Nonrandomized tables, part 2 .....	I-3
Table I-3. Nonrandomized tables, part 3 .....	I-3
Table I-4. Nonrandomized tables, part 4 .....	I-4
Table I-5. Nonrandomized tables, part 5 .....	I-4
Table I-6. Nonrandomized tables, part 6 .....	I-4
Table I-7. Nonrandomized tables, part 7 .....	I-5
Table I-8. Nonrandomized tables, part 8 .....	I-5
Table I-9. Nonrandomized tables, part 9 .....	I-5



**Table I-1. Nonrandomized tables, part 1**

First Author's Last Name, Year	Describe groups (treatment interventions and comparators)	Study Design	1. Was selection of participants into the study unrelated to intervention or unrelated to outcome?	1a. Were post intervention variables that influenced selection likely to be associated with the intervention or likely to be influenced by the outcome or a cause of the outcome?	2. Do start of followup and start of intervention coincide for most subjects?	3. Were adjustment techniques used that are likely to correct for the presence of selection biases?	Bias arising from selection?	Comments
Dietz, 2008 <sup>83</sup>	IG: Family Based Interpersonal psychotherapy CG: Family Based Interpersonal psychotherapy plus antidepressant medication	Controlled clinical trials	No	Yes	Yes	Not applicable	High	Parents could opt which intervention their child participated in

CG = control group; IG = intervention group.

**Table I-2. Nonrandomized tables, part 2**

First Author's Last Name, Year	4. Is confounding of the effect of intervention unlikely in this study?	4a. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	4b. Were confounding domains that were controlled for measured validly and reliably by the variables available in the study?	4c. Did the authors avoid adjusting for postintervention variables?	4d. Were participants analyzed according to their initial intervention group throughout followup?	4e. Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome?	Bias arising from confounding?	Comments
Dietz, 2008 <sup>83</sup>	No	No	No	No	No	Not applicable	High	Patients allowed to switch based on symptoms after the intervention started, results were analyzed based on their new treatment

**Table I-3. Nonrandomized tables, part 3**

First Author's Last Name, Year	5. Is intervention status well defined?	6. Was information on intervention status recorded at the time of intervention?	7. Was classification of intervention status unaffected by knowledge of the outcome or risk of the outcome?	Bias arising from measurement of the intervention?	Comments
Dietz, 2008 <sup>83</sup>	Yes	Yes	Yes	Low	

**Table I-4. Nonrandomized tables, part 4**

First Author's Last Name, Year	8. What was the overall attrition? (#not included at followup/#at baseline) What was the attrition by group?	9. Were few or no participants excluded because of missing data on intervention status?	10. Were few or no participants excluded due to missing data on other variables needed for the analysis?	11. Was the proportion of participants and reasons for missing data similar across intervention groups?	12. Were appropriate statistical methods used to account for missing data or assess robustness to presence of missing data?	Bias arising from missing outcome data?	Comments
Dietz, 2008 <sup>83</sup>	Overall attrition 12% and differential attrition not reported.	Yes	Yes	Uncertain because no information	No	Some concerns	Moderate attrition with no report of how data analyzed with respect to missingness

**Table I-5. Nonrandomized tables, part 5**

First Author's Last Name, Year	13. Were there no or minimal deviations from the intended intervention beyond what would be expected in usual practice?	13a. Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	14. Were important cointerventions balanced across intervention groups?	14a. Was the intervention implemented successfully for most participant?	15. Did the study measure adherence with defined intervention?	Bias arising from departures from intended interventions?	Comments
Dietz, 2008 <sup>83</sup>	Uncertain because no information	Not applicable	Uncertain because no information	Probably yes	Yes	Low	

**Table I-6. Nonrandomized tables, part 6**

First Author's Last Name, Year	16. Was measurement of benefit outcomes unlikely to have been influenced by knowledge of the intervention received?	17. Were methods of benefit outcome assessment comparable across groups?	Bias arising from measurement of benefit outcomes?	Comments
Dietz, 2008 <sup>83</sup>	No	Probably yes	Some concerns	Clinician also collected some outcome measures and with very small sample size, this could be an issue.

**Table I-7. Nonrandomized tables, part 7**

First Author's Last Name, Year	18. Was measurement of harms outcomes unlikely to have been influenced by knowledge of the intervention received?	19. Were methods of harm outcome assessment comparable across groups?	Bias arising from measurement of outcomes?	Comments
Dietz, 2008 <sup>83</sup>	Not applicable	Not applicable	Not applicable	Not applicable

**Table I-8. Nonrandomized tables, part 8**

First Author's Last Name, Year	20. Is the reported effect estimate unlikely to be selected, on the basis of the results from multiple outcomes measurements within the domain, multiple analyses, or different subgroups?	Bias arising from selection of reported results?	Comments
Dietz, 2008 <sup>83</sup>	Probably no	Low	

**Table I-9. Nonrandomized tables, part 9**

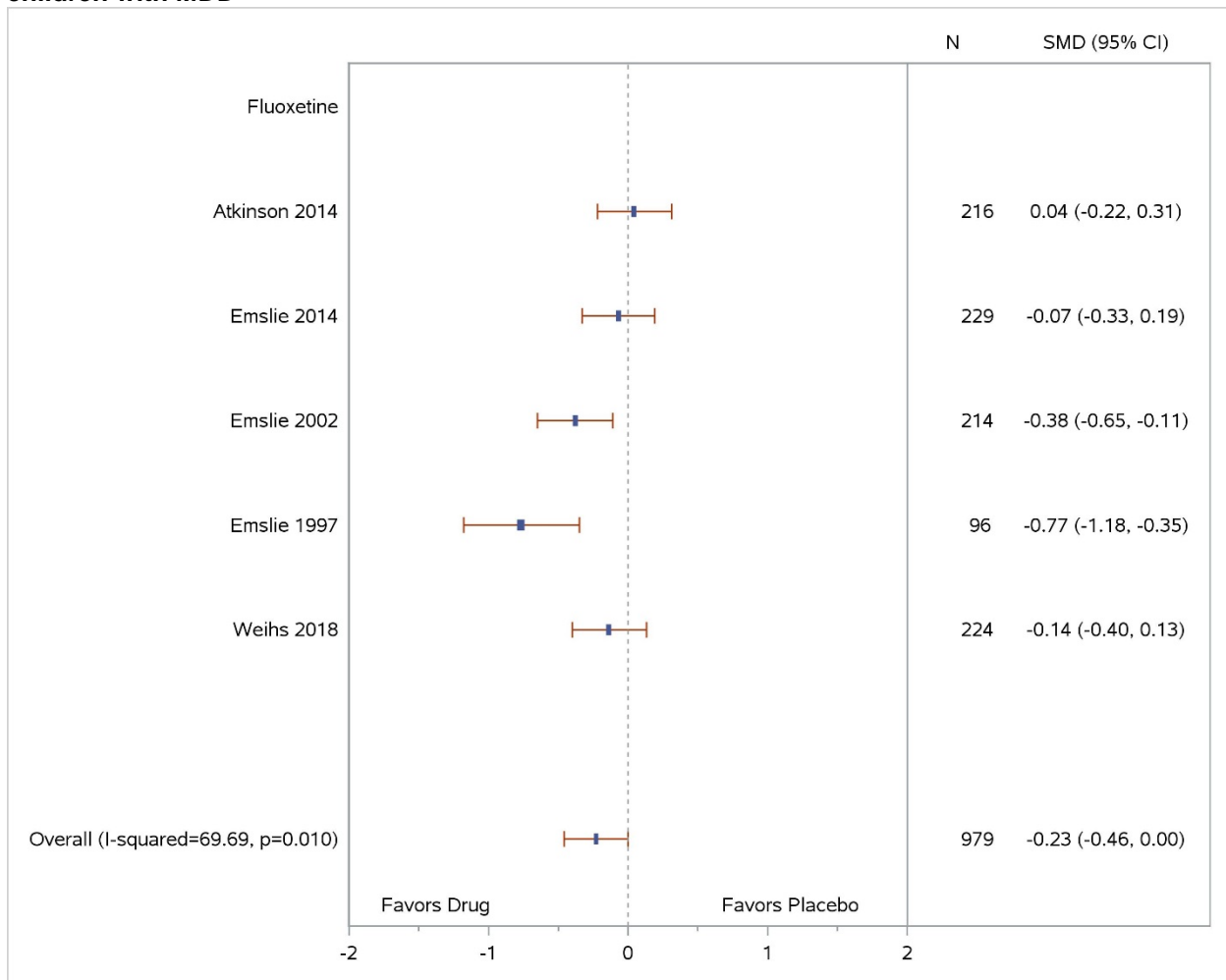
First Author's Last Name, Year	Study Quality-Benefits	Overall Rating Justification/Comments Benefits	Does Rating of Study Vary by Benefits Outcome?	Study Quality Ratings by Benefits Outcome	Study Quality-Harms	Overall Rating Justification/Comments Harms	Does Rating of Study Vary by Harm Outcome?	Study Quality Ratings by Harm Outcome
Dietz, 2008 <sup>83</sup>	High	Because children could choose their own intervention and change throughout the followup period, there is high potential for confounding.	No	High	Not applicable	Not applicable	Not applicable	Not applicable

## Appendix J. Meta-Analysis

Figure J-1. Pooled estimate of effect of fluoxetine on depression symptoms for adolescents and children with MDD .....	J-3
Figure J-2. Pooled estimate of effect of fluoxetine on response for adolescents and children with MDD.....	J-4
Figure J-3. Pooled estimate of effect of fluoxetine on remission for adolescents and children with MDD.....	J-5
Figure J-4. Pooled estimate of effect of SSRIs on clinician-rated depression symptoms for adolescents and children with MDD .....	J-6
Figure J-5. Pooled estimate of effect of SSRIs on clinician-rated depression symptoms for adolescents with MDD .....	J-7
Figure J-6. Pooled estimate of effect of SSRIs on response for adolescents and children with MDD.....	J-8
Figure J-7. Pooled estimate of effect of SSRIs on response for adolescents with MDD .....	J-9
Figure J-8. Pooled estimate of effect of SSRIs on remission for adolescents and children with MDD.....	J-10
Figure J-9. Pooled estimate of effect of SSRIs on remission for adolescents with MDD.....	J-11
Figure J-10. Pooled estimate of effect of SSRIs on functional status for adolescents and children with MDD.....	J-12
Figure J-11. Pooled estimate of effect of fluoxetine on suicidal ideation or behavior for adolescents or children with MDD or other depression diagnoses .....	J-13
Figure J-12. Pooled estimate of effect of fluoxetine on suicidal ideation or behavior for adolescents and children with MDD .....	J-14
Figure J-13. Pooled estimate of effect of fluoxetine on serious adverse events for adolescents or children with MDD .....	J-15
Figure J-14. Pooled estimate of effect of fluoxetine on serious adverse events for adolescents and children with MDD .....	J-16
Figure J-15. Pooled estimate of effect of fluoxetine on withdrawal due to adverse events for adolescents and children with MDD .....	J-17
Figure J-16. Pooled estimate of effect of paroxetine on suicidal ideation for adolescents or children with MDD .....	J-18
Figure J-17. Pooled estimate of effect of paroxetine on withdrawal due to adverse events for adolescents or adolescents and children with MDD .....	J-19
Figure J-18. Pooled estimate of effect of SSRIs on suicidal ideation or behaviors for adolescents or children with MDD or other depression diagnoses.....	J-20
Figure J-19. Pooled estimate of effect of SSRIs on suicidal ideation or behaviors for adolescents and children with MDD.....	J-21
Figure J-20. Pooled estimate of effect of SSRIs on suicidal ideation or behaviors for adolescents with MDD or other depression diagnoses .....	J-22

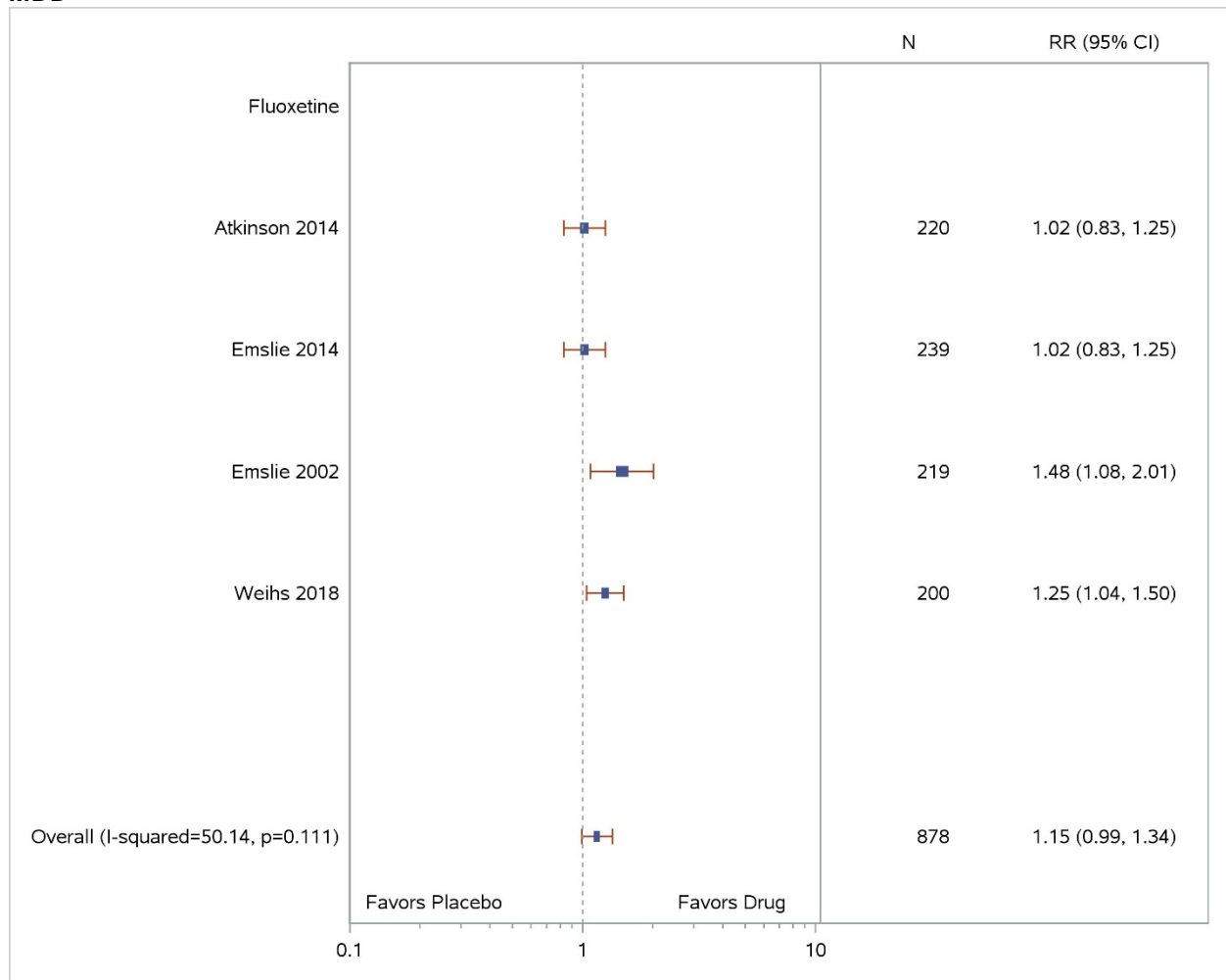
Figure J-21. Pooled estimate of effect of SSRIs on serious adverse events for adolescents or children with MDD .....	J-23
Figure J-22. Pooled estimate of effect of SSRIs on serious adverse events for adolescents and children with MDD .....	J-24
Figure J-23. Pooled estimate of effect of SSRIs on withdrawal due to adverse events for adolescents or children with MDD.....	J-25
Figure J-24. Pooled estimate of effect of SSRIs on withdrawal due to adverse events for adolescents and children with MDD .....	J-26
Figure J-25. Pooled estimate of effect of SSRIs on withdrawal due to adverse events for adolescents with MDD .....	J-27
Figure J-26. Pooled estimate of effect of SNRIs on clinician-rated depression symptoms for adolescents and children with MDD .....	J-28
Figure J-27. Pooled estimate of effect of SNRIs on response for adolescents and children with MDD.....	J-29
Figure J-28. Pooled estimate of effect of SNRIs on suicidal ideation or behaviors for adolescents and children with MDD.....	J-30
Figure J-29. Pooled estimate of effect of SNRIs on withdrawal due to adverse events for adolescents and children with MDD .....	J-31
Figure J-30. Pooled estimate of effect TCAs on self-rated depression symptoms for adolescents with MDD.....	J-32
Figure J-31. Pooled estimate of effect TCAs on withdrawal due to adverse events for adolescents with MDD.....	J-33
Figure J-32. Pooled estimate of effect of psychotherapy plus pharmacotherapy versus pharmacotherapy on self-rated depression symptoms for adolescents with MDD .....	J-34

**Figure J-1. Pooled estimate of effect of fluoxetine on depression symptoms for adolescents and children with MDD**



CI = confidence interval; MDD = major depressive disorder; N = number; SMD = standardized mean difference.

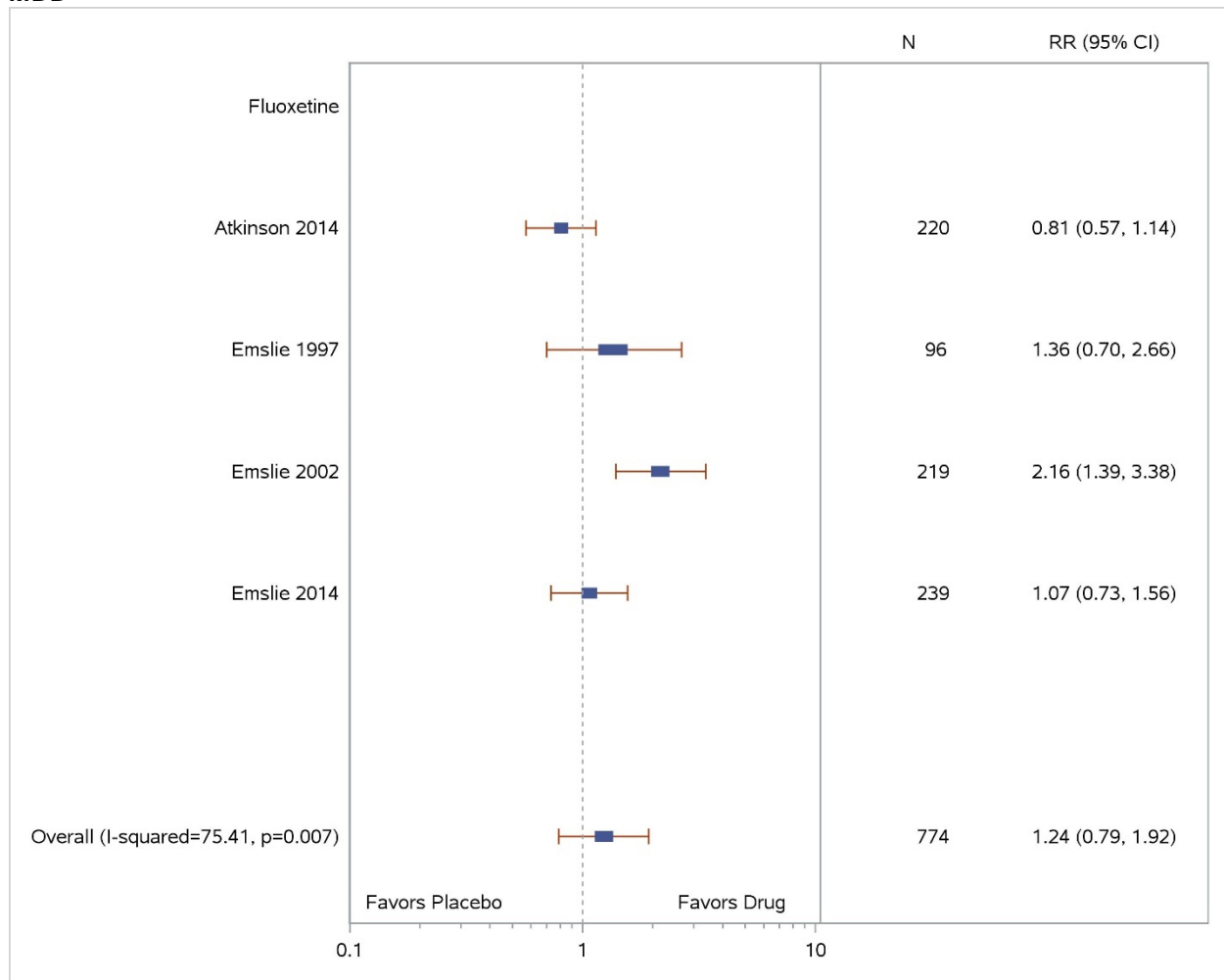
**Figure J-2. Pooled estimate of effect of fluoxetine on response for adolescents and children with MDD**



CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk.

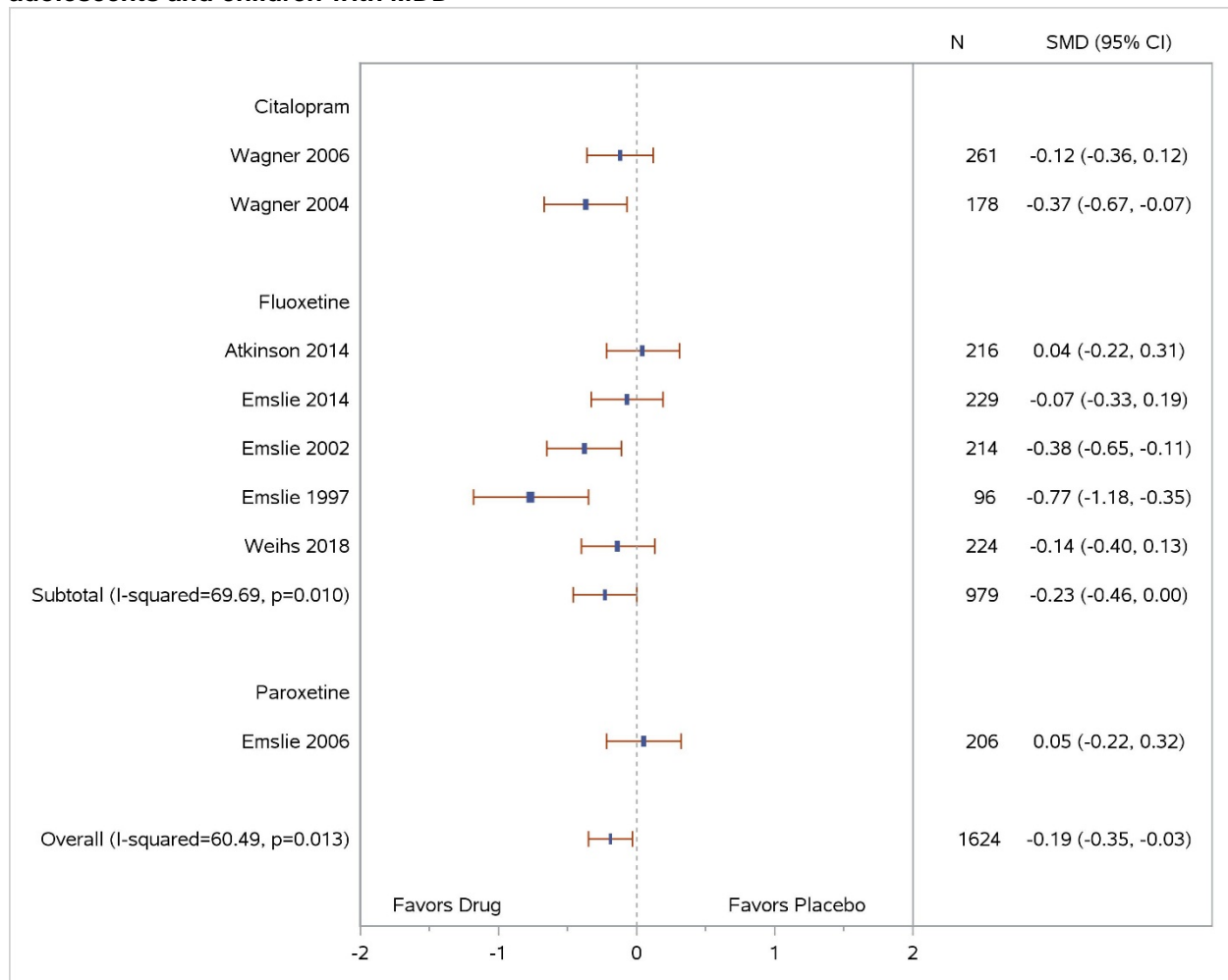


**Figure J-3. Pooled estimate of effect of fluoxetine on remission for adolescents and children with MDD**



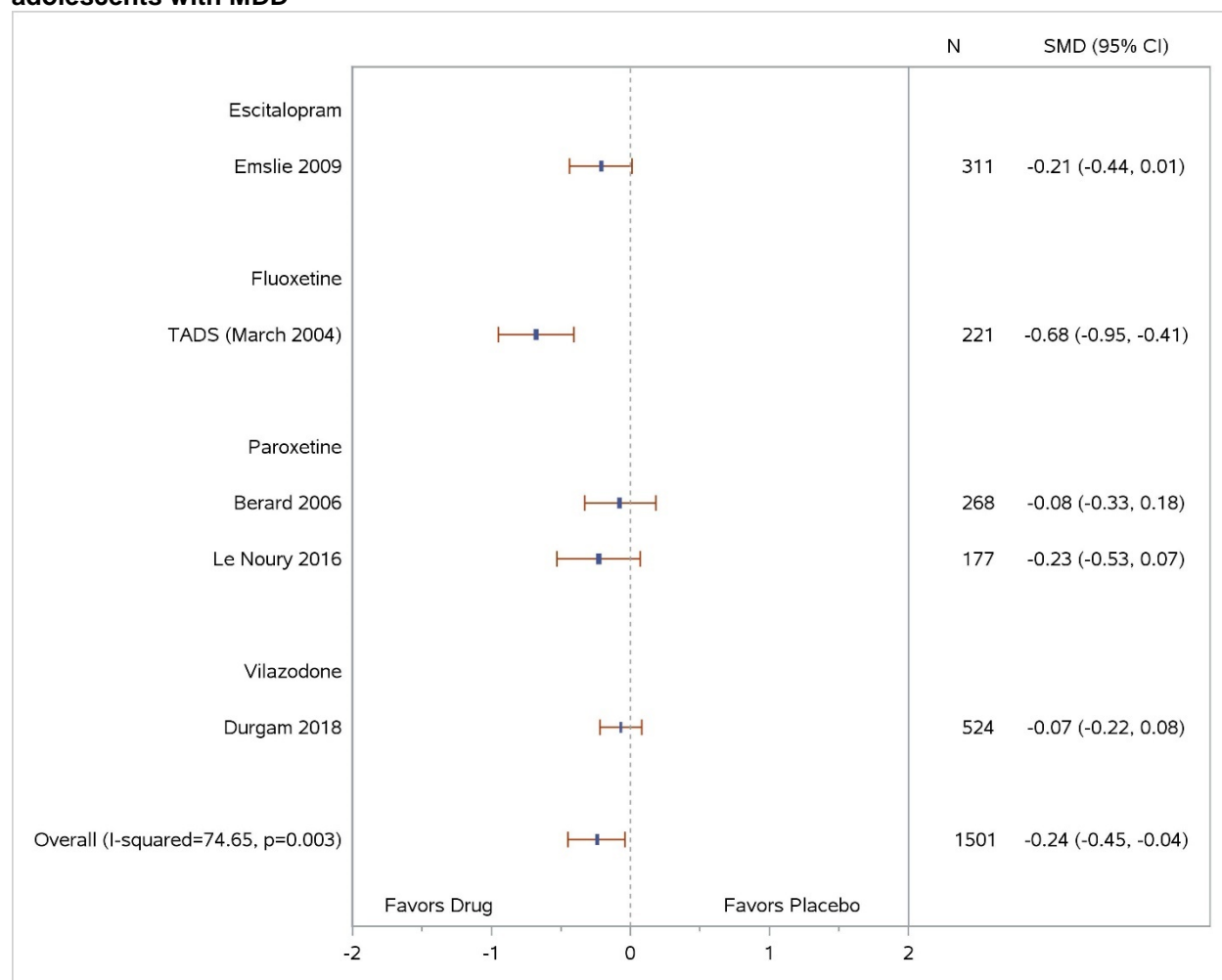
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk.

**Figure J-4. Pooled estimate of effect of SSRIs on clinician-rated depression symptoms for adolescents and children with MDD**



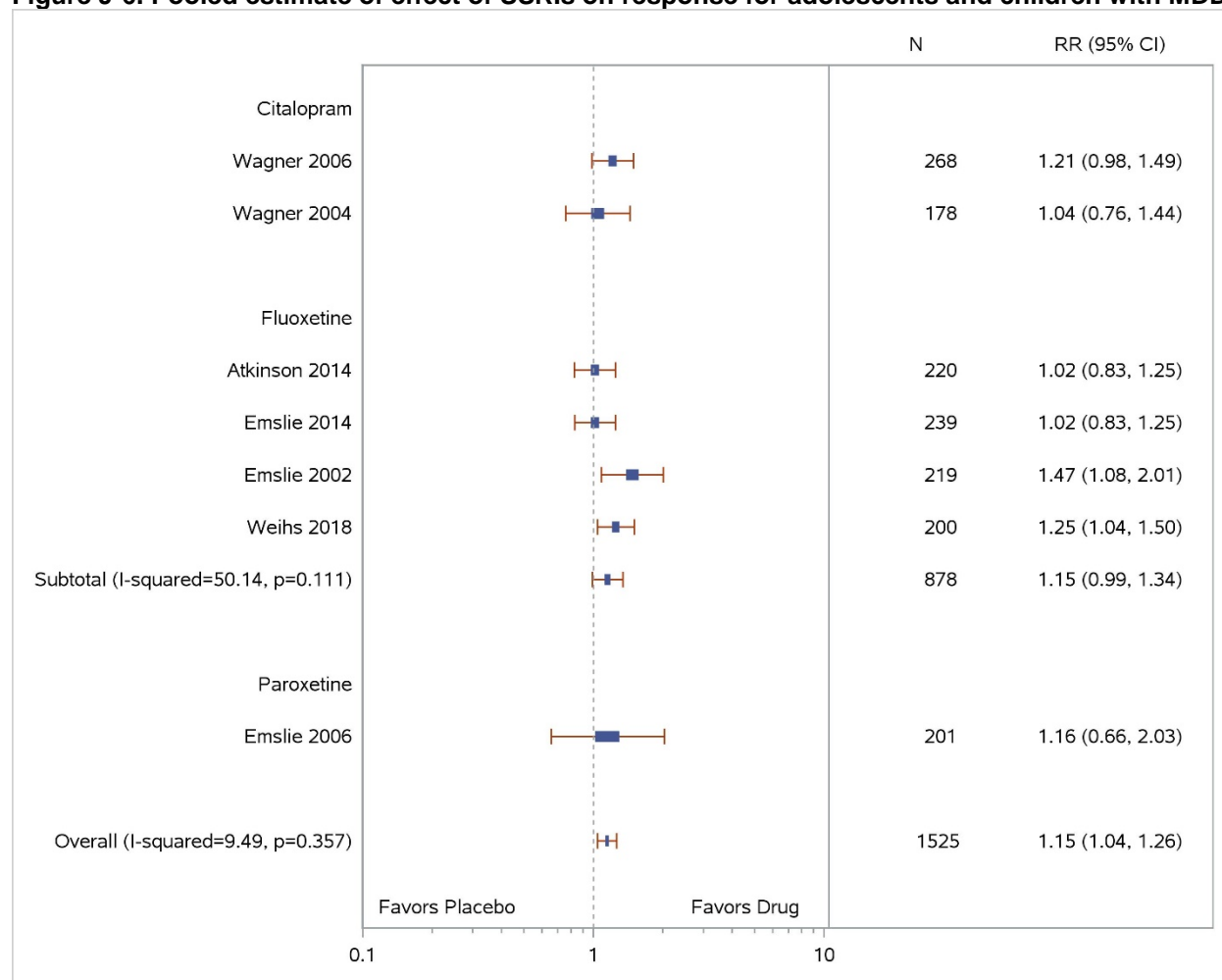
CI = confidence interval; MDD = major depressive disorder; N = number; SMD = standardized mean difference.

**Figure J-5. Pooled estimate of effect of SSRIs on clinician-rated depression symptoms for adolescents with MDD**



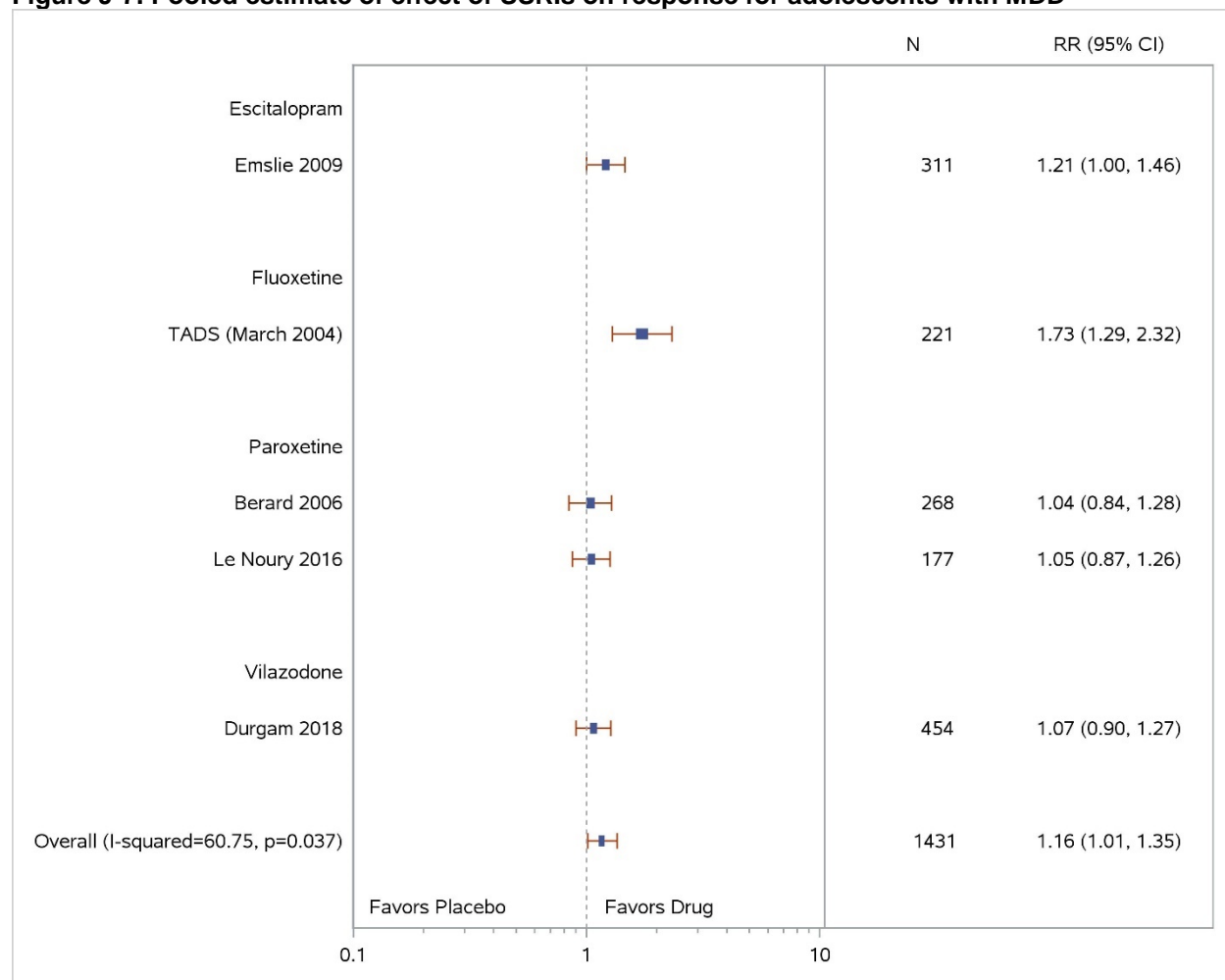
CI = confidence interval; MDD = major depressive disorder; N = number; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitors.

**Figure J-6. Pooled estimate of effect of SSRIs on response for adolescents and children with MDD**



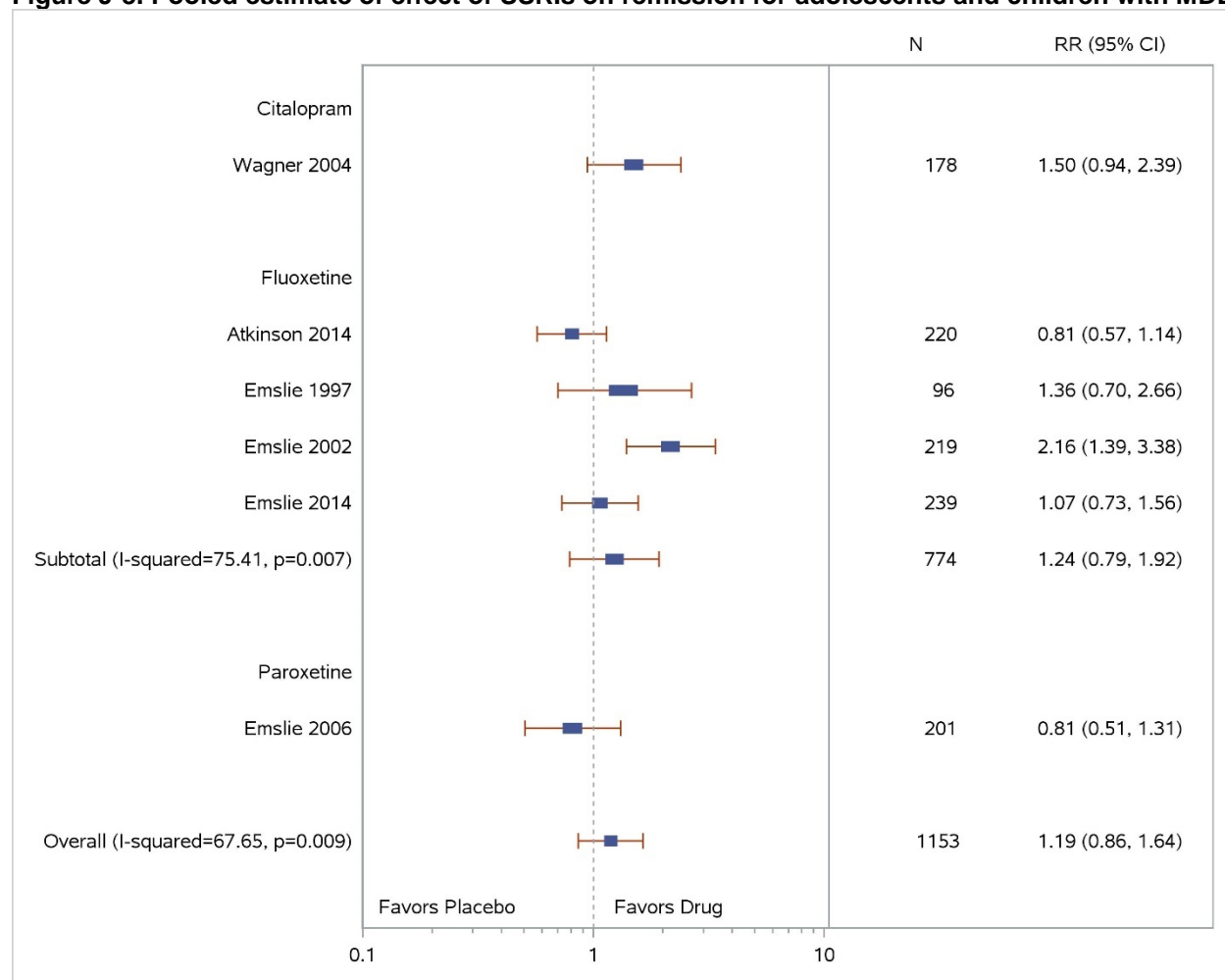
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

**Figure J-7. Pooled estimate of effect of SSRIs on response for adolescents with MDD**



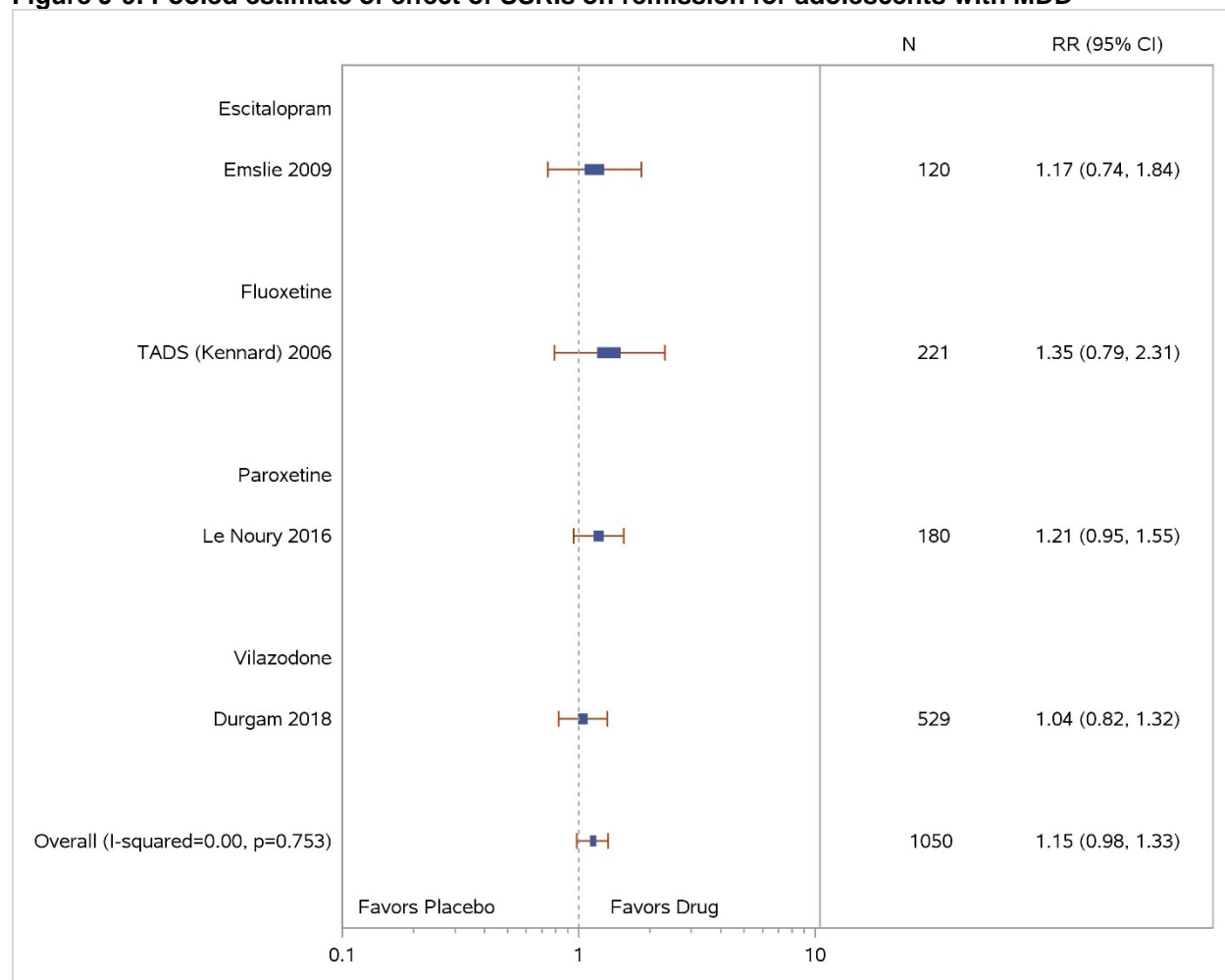
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

**Figure J-8. Pooled estimate of effect of SSRIs on remission for adolescents and children with MDD**



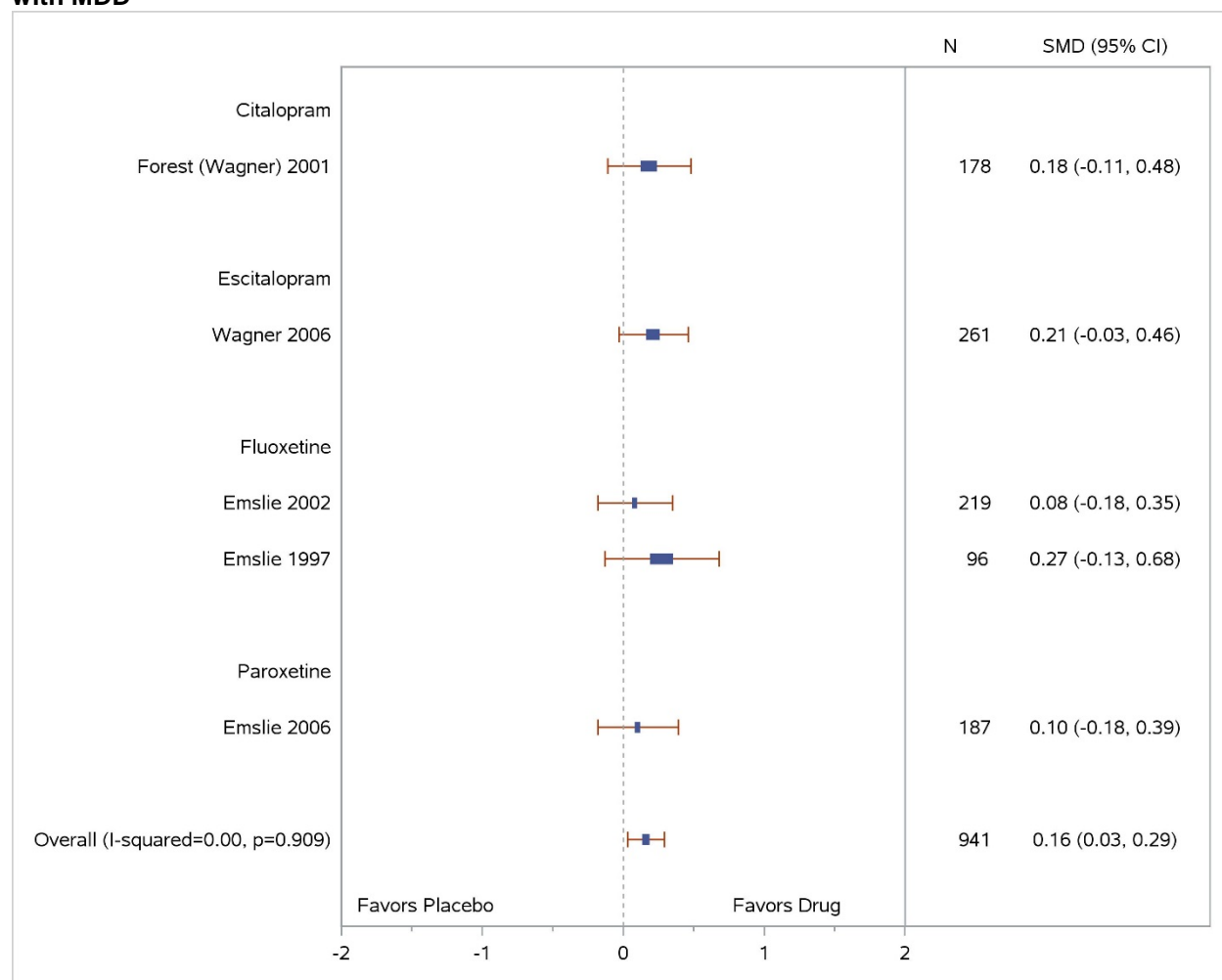
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

**Figure J-9. Pooled estimate of effect of SSRIs on remission for adolescents with MDD**



CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

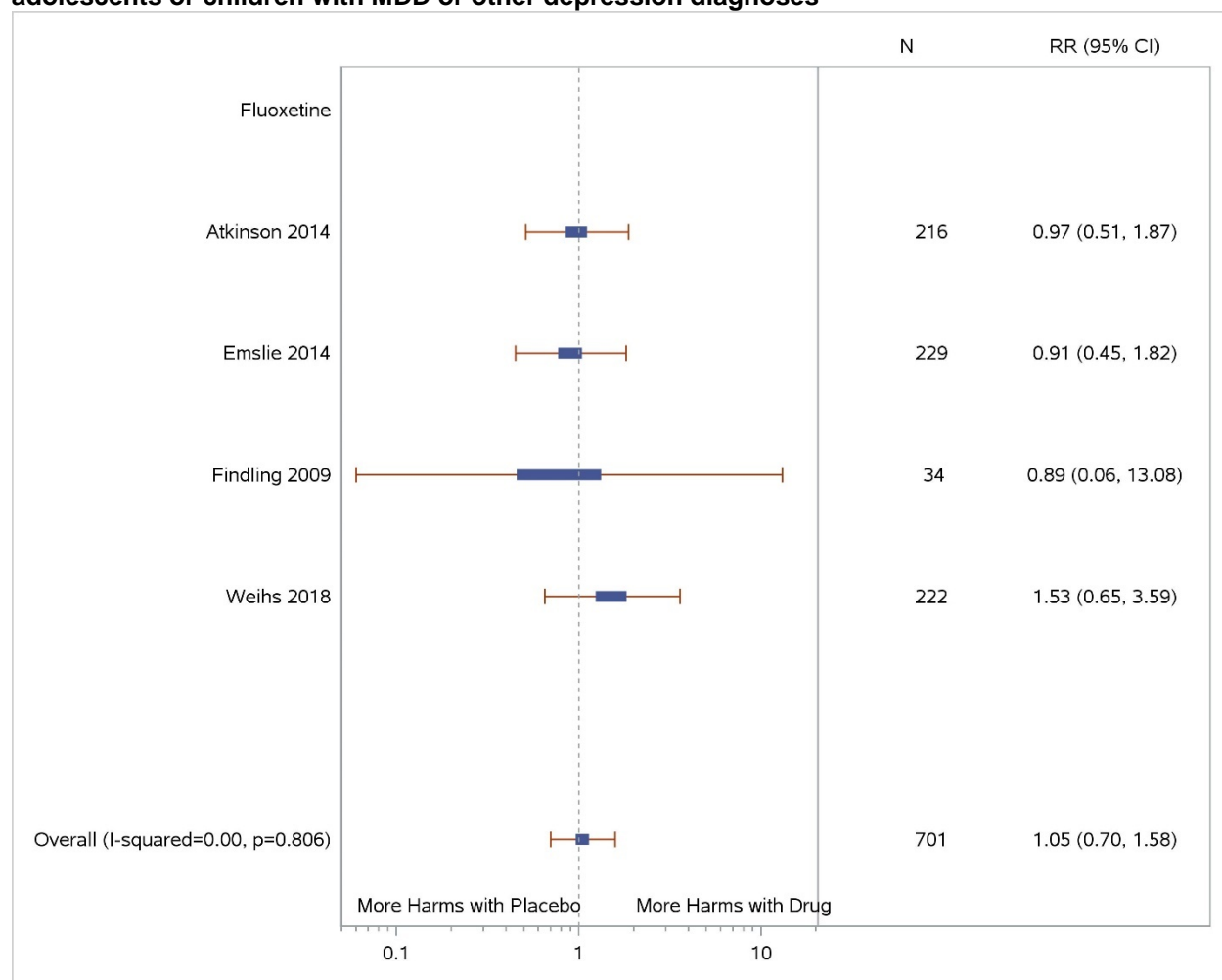
**Figure J-10. Pooled estimate of effect of SSRIs on functional status for adolescents and children with MDD**



CI = confidence interval; MDD = major depressive disorder; N = number; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitors.

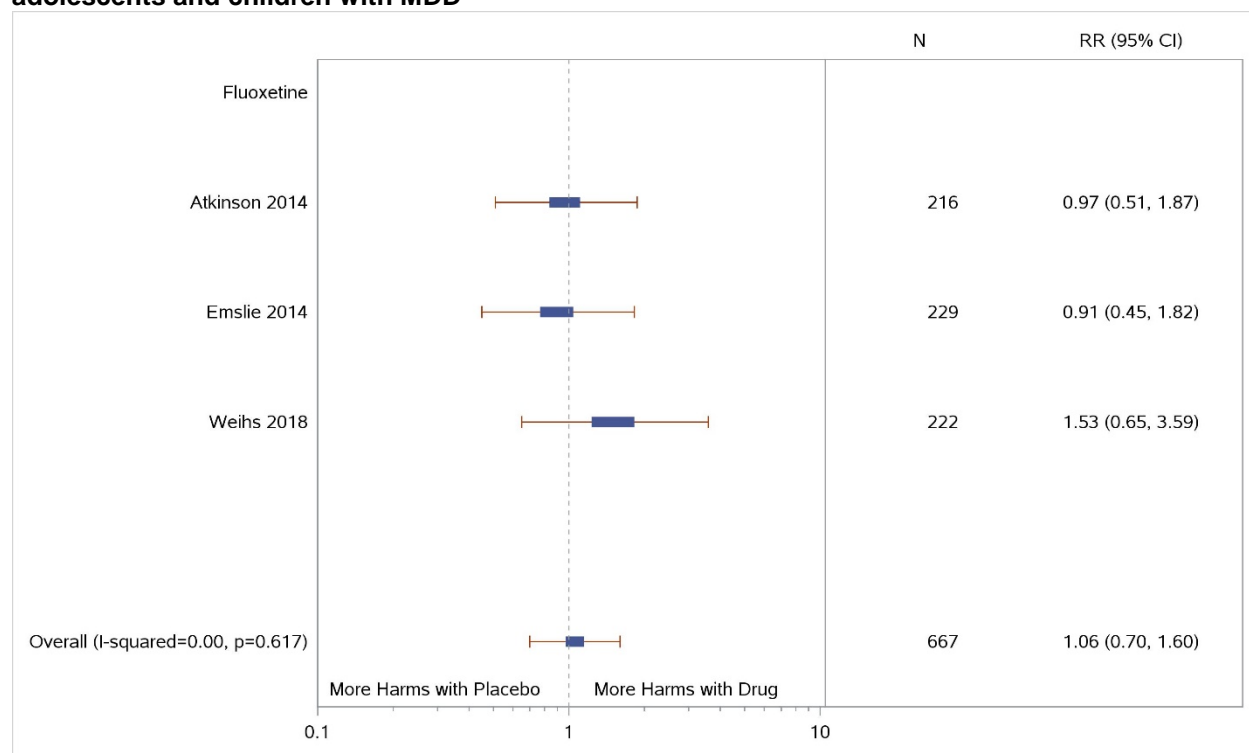


**Figure J-11. Pooled estimate of effect of fluoxetine on suicidal ideation or behavior for adolescents or children with MDD or other depression diagnoses**



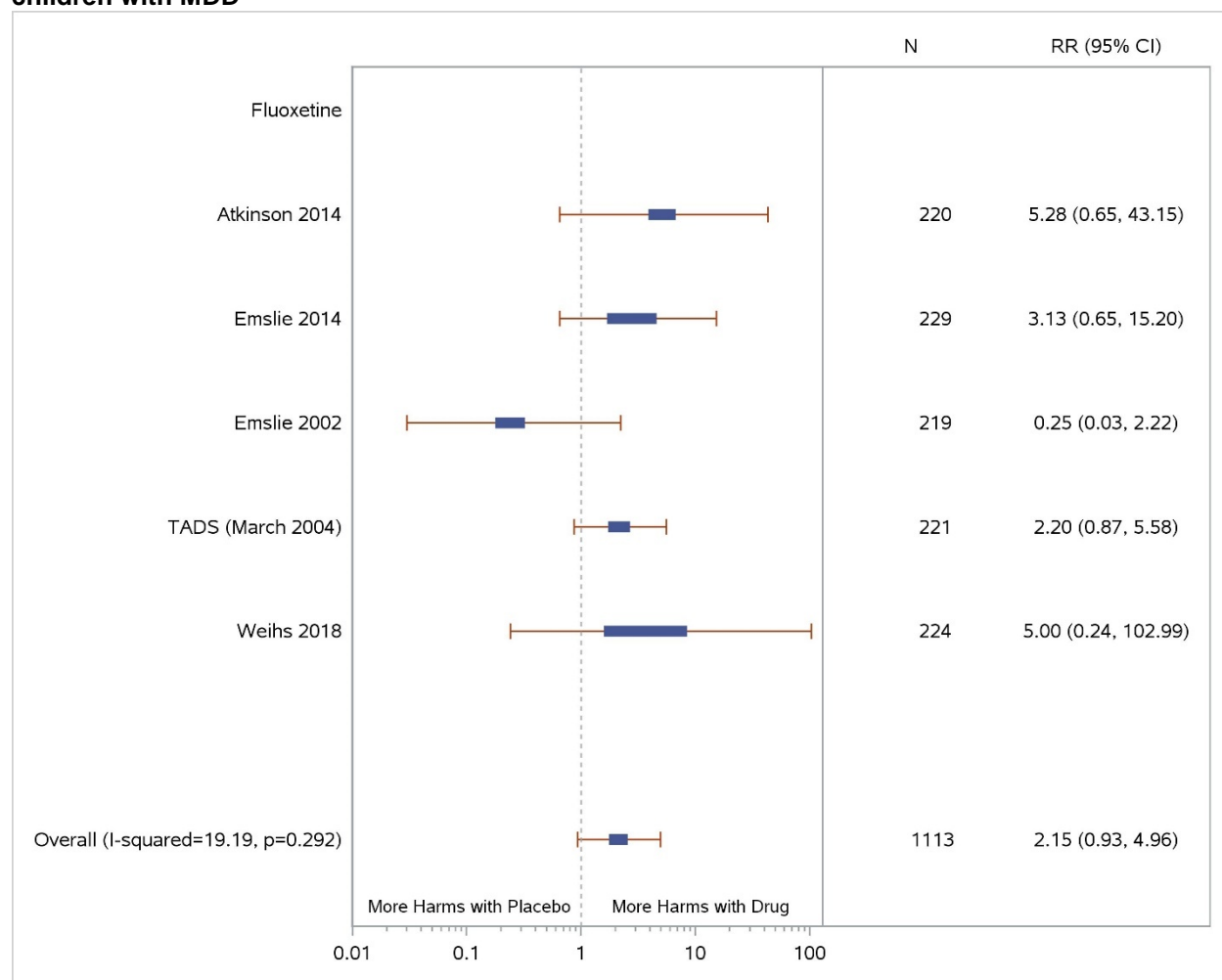
CI = confidence interval; MDD = major depressive disorder; N = number; SMD = standardized mean difference.

**Figure J-12. Pooled estimate of effect of fluoxetine on suicidal ideation or behavior for adolescents and children with MDD**



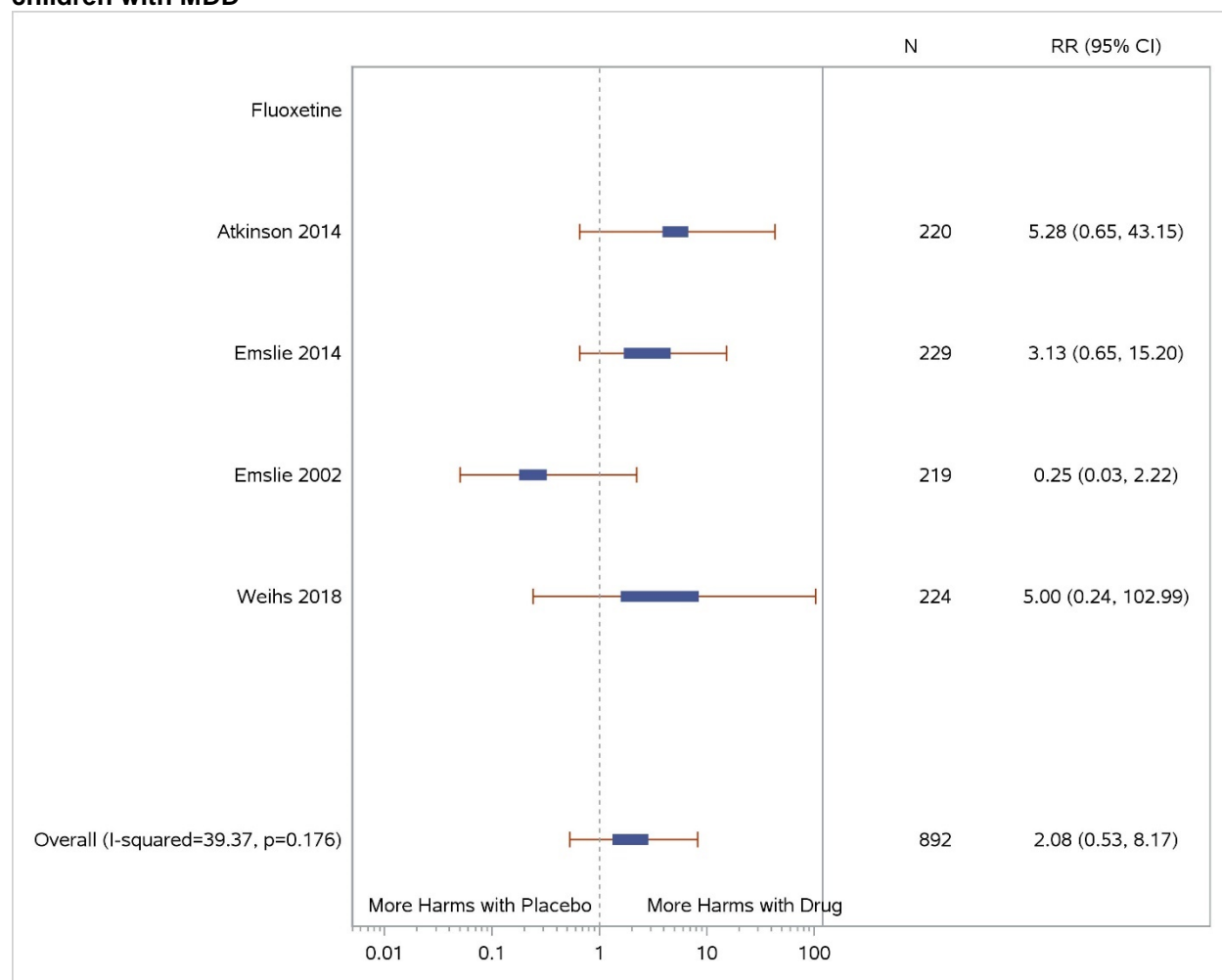
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk.

**Figure J-13. Pooled estimate of effect of fluoxetine on serious adverse events for adolescents or children with MDD**



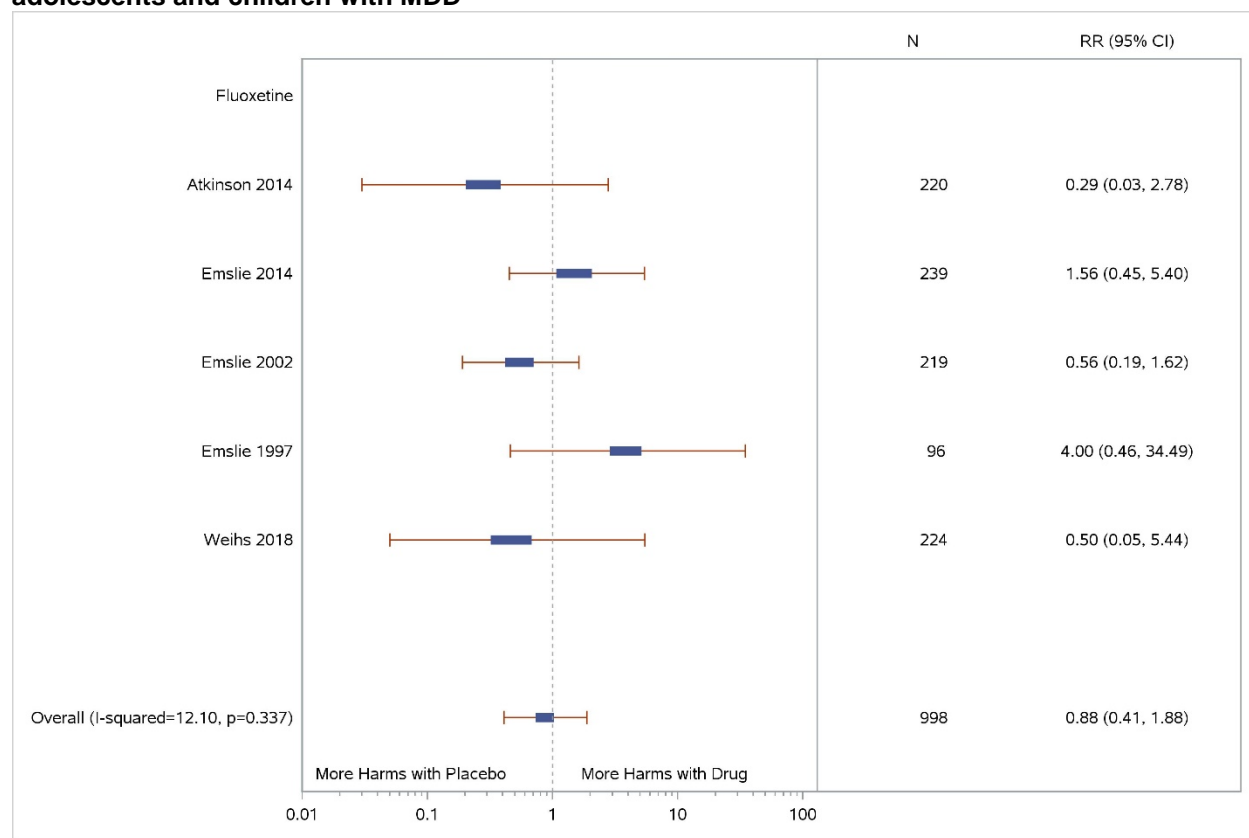
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk.

**Figure J-14. Pooled estimate of effect of fluoxetine on serious adverse events for adolescents and children with MDD**



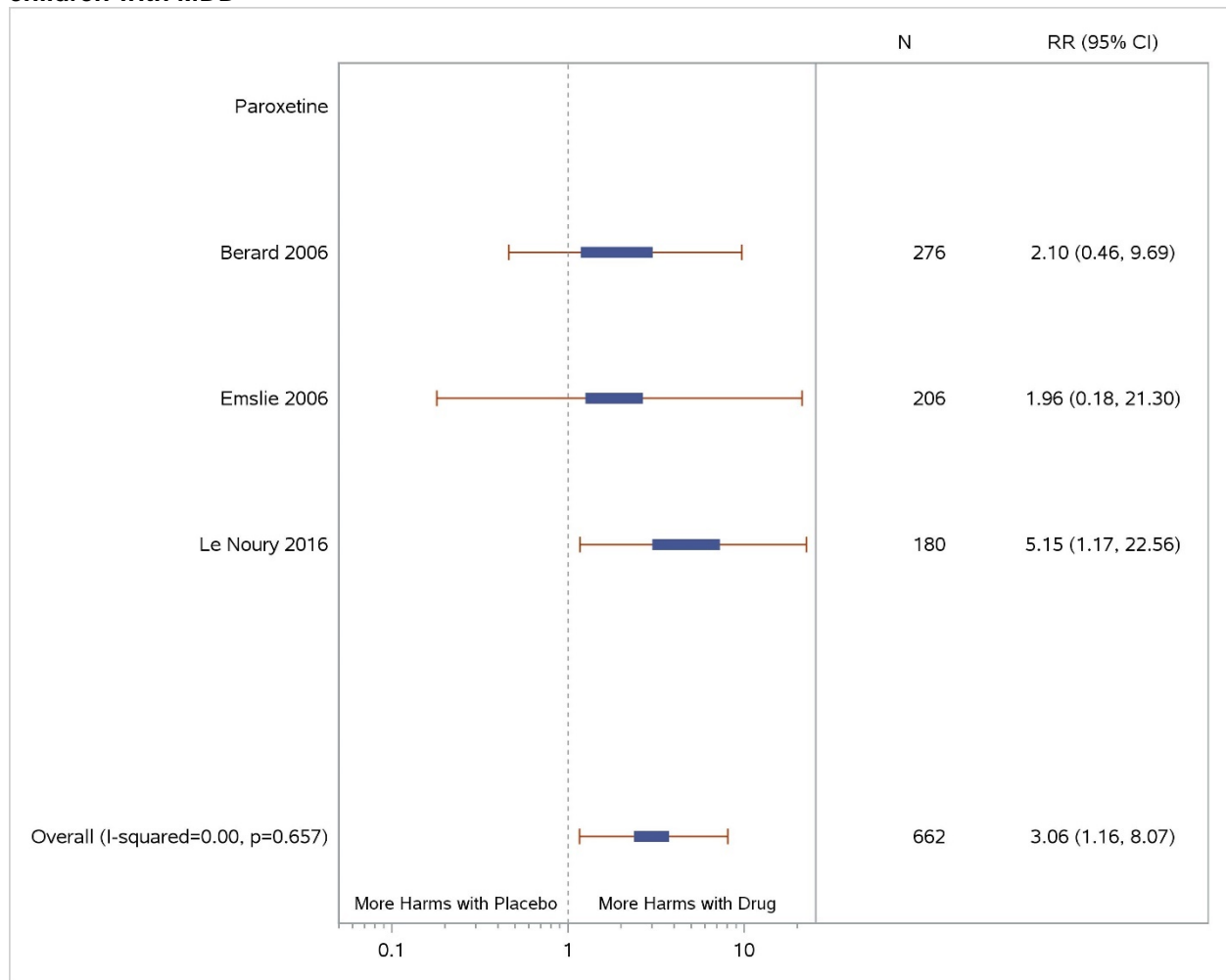
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk.

**Figure J-15. Pooled estimate of effect of fluoxetine on withdrawal due to adverse events for adolescents and children with MDD**

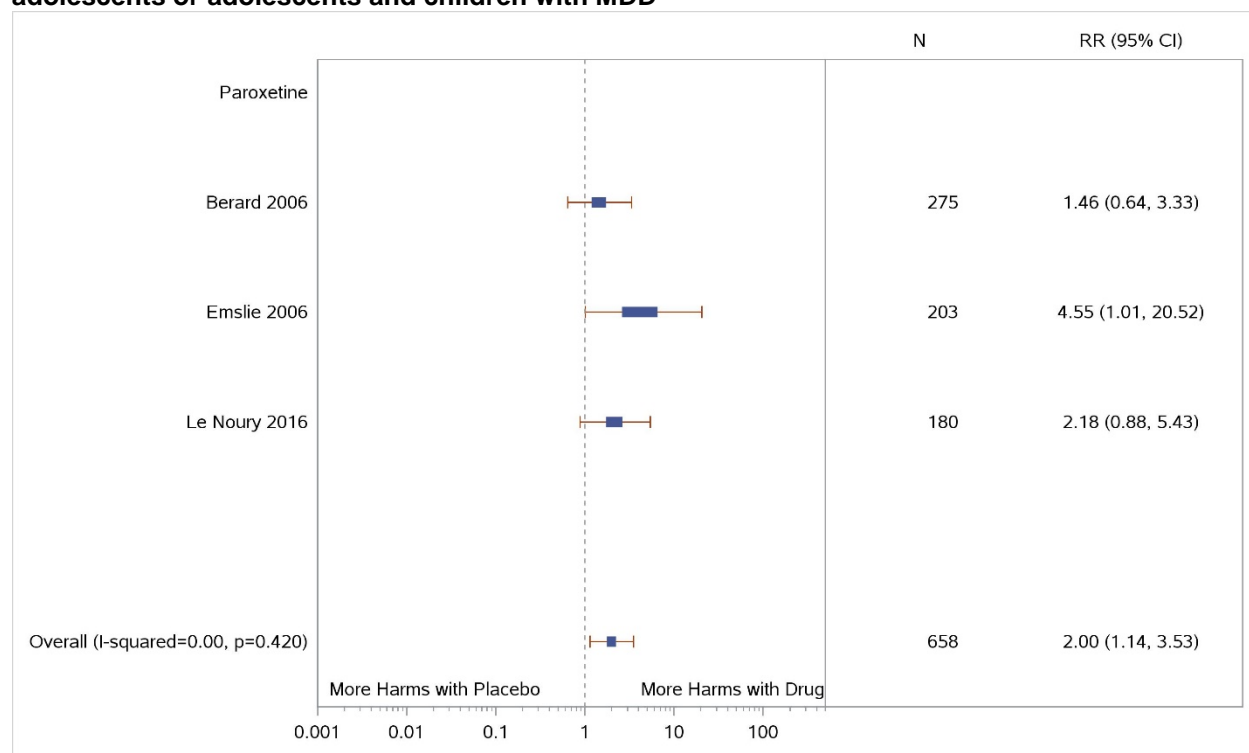


CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk.

**Figure J-16. Pooled estimate of effect of paroxetine on suicidal ideation for adolescents or children with MDD**

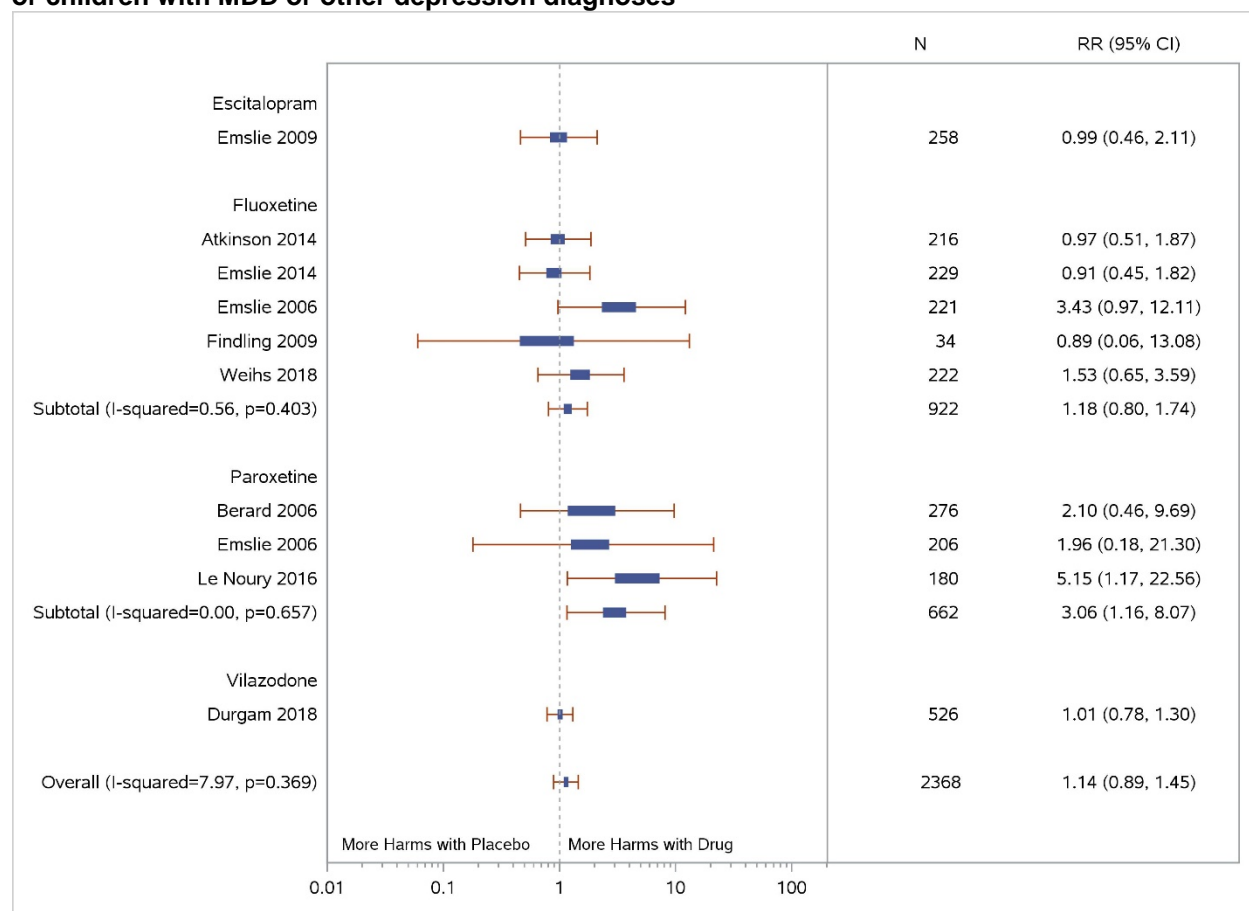


**Figure J-17. Pooled estimate of effect of paroxetine on withdrawal due to adverse events for adolescents or adolescents and children with MDD**



CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk.

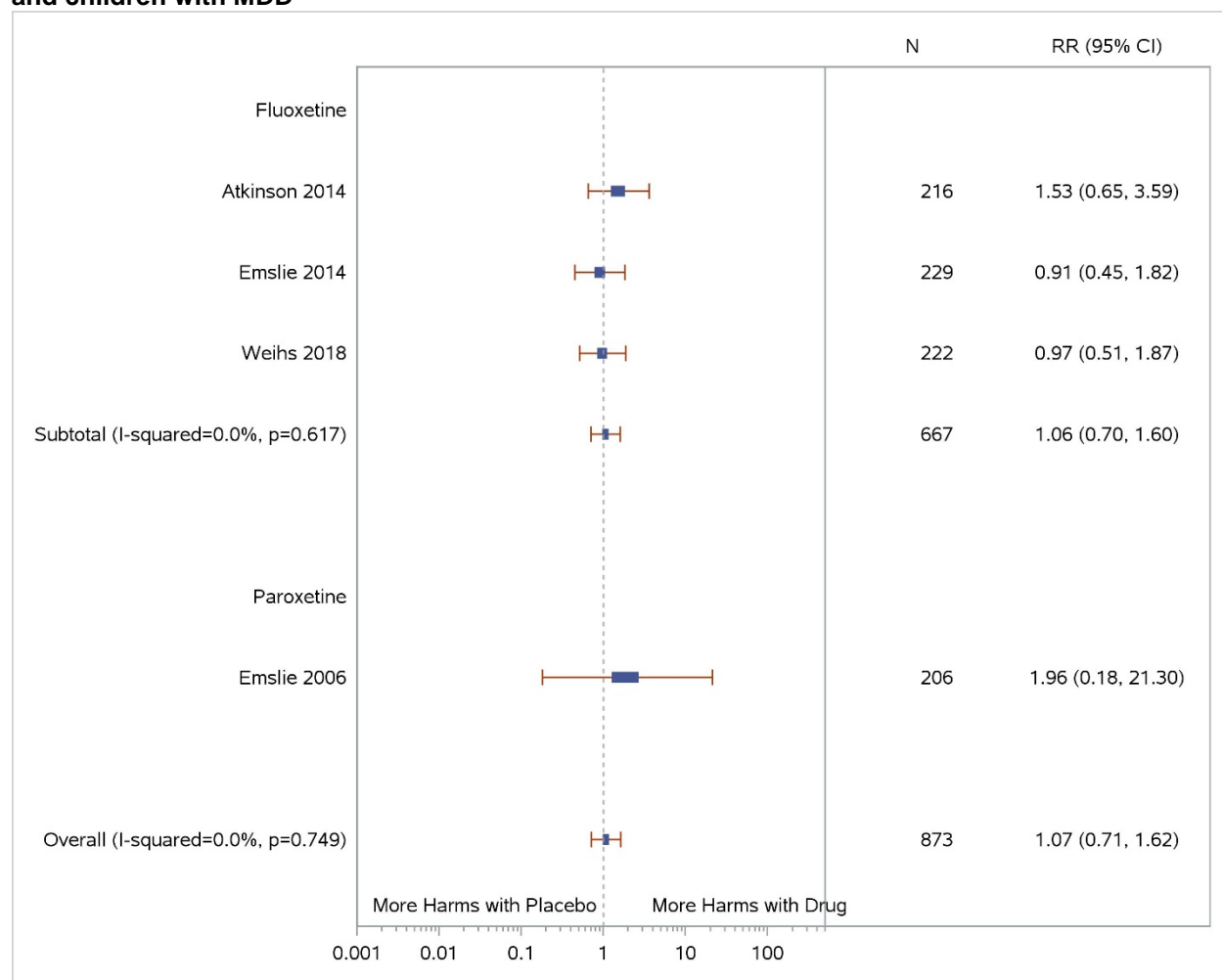
**Figure J-18. Pooled estimate of effect of SSRIs on suicidal ideation or behaviors for adolescents or children with MDD or other depression diagnoses**



CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

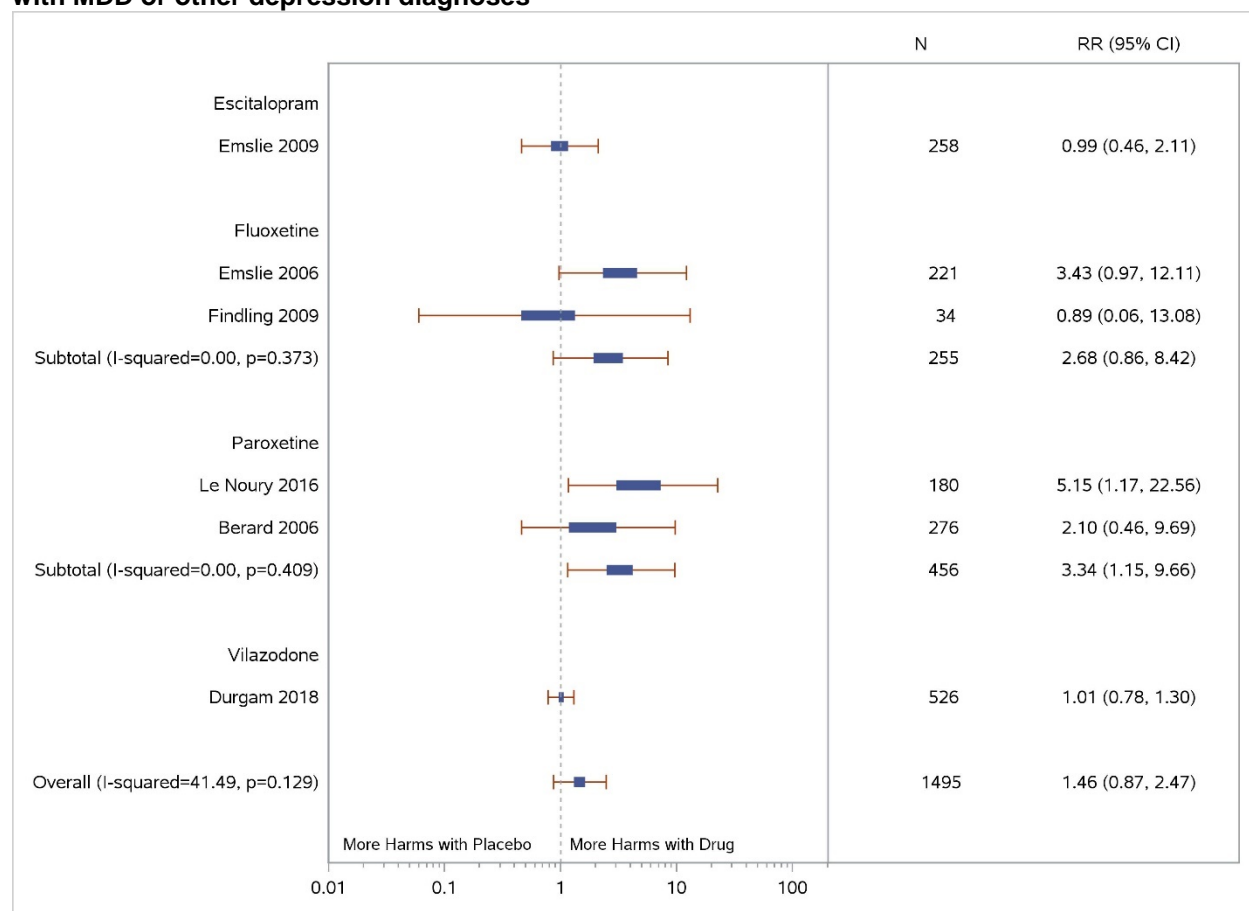


**Figure J-19. Pooled estimate of effect of SSRIs on suicidal ideation or behaviors for adolescents and children with MDD**



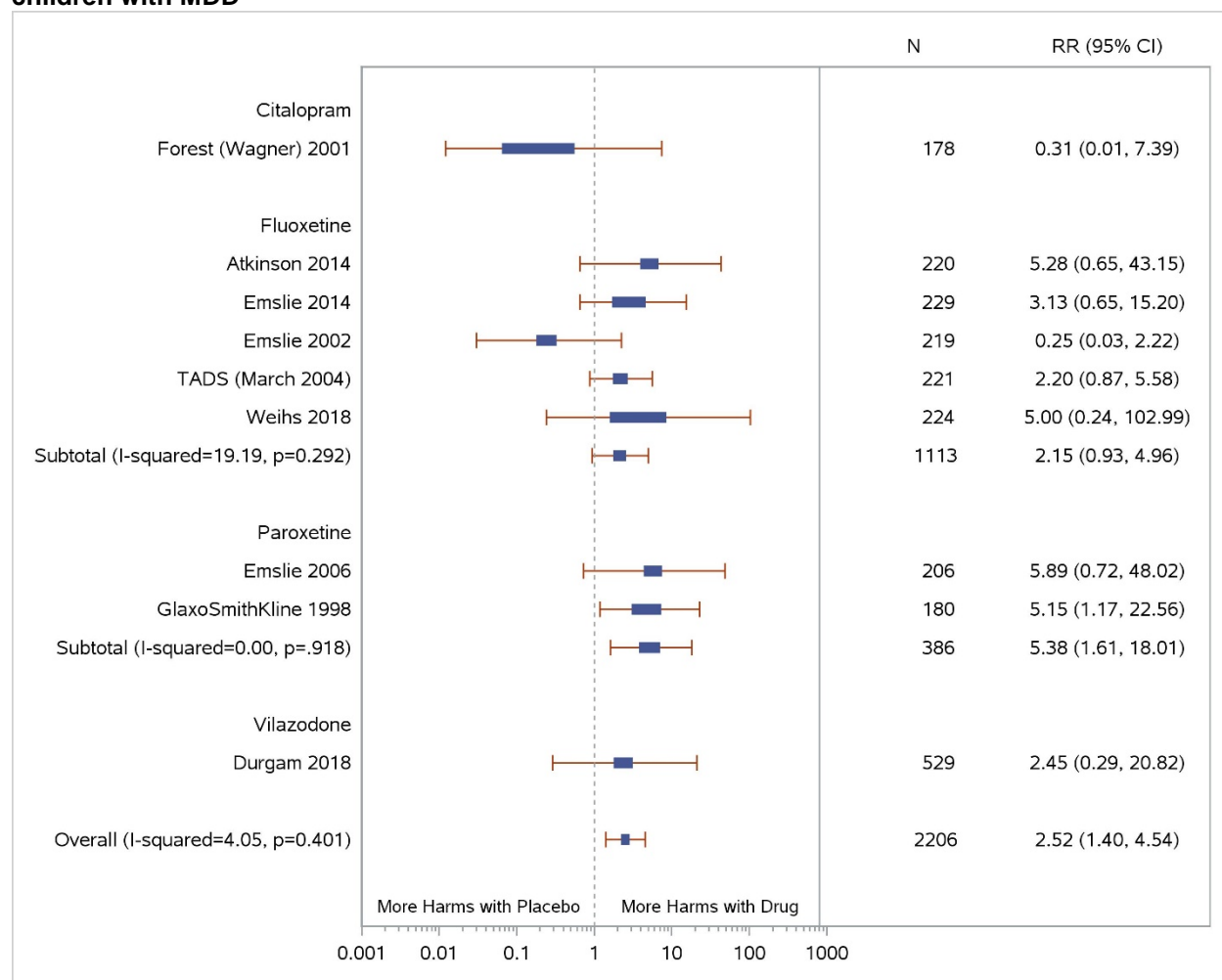
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

**Figure J-20. Pooled estimate of effect of SSRIs on suicidal ideation or behaviors for adolescents with MDD or other depression diagnoses**



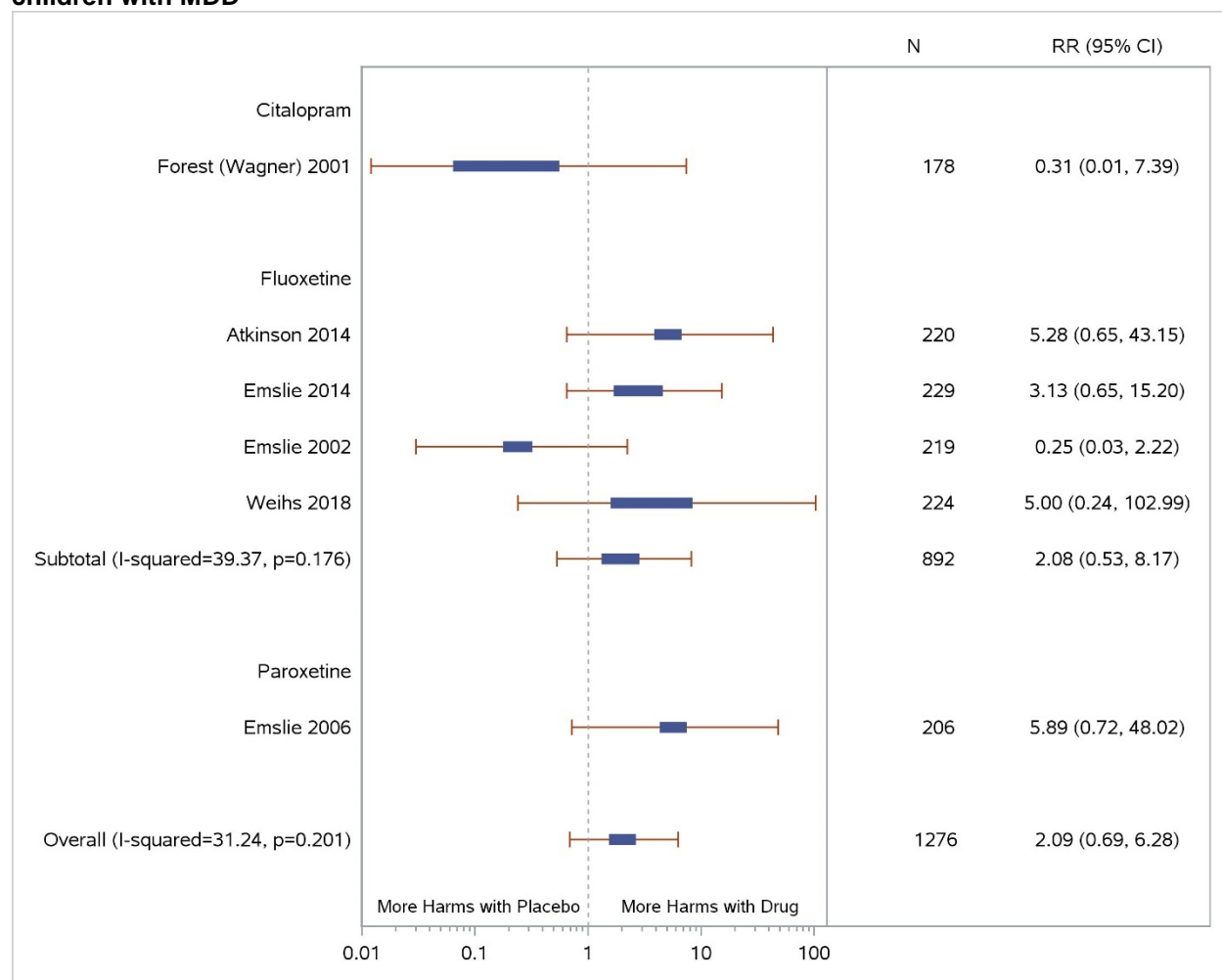
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

**Figure J-21. Pooled estimate of effect of SSRIs on serious adverse events for adolescents or children with MDD**



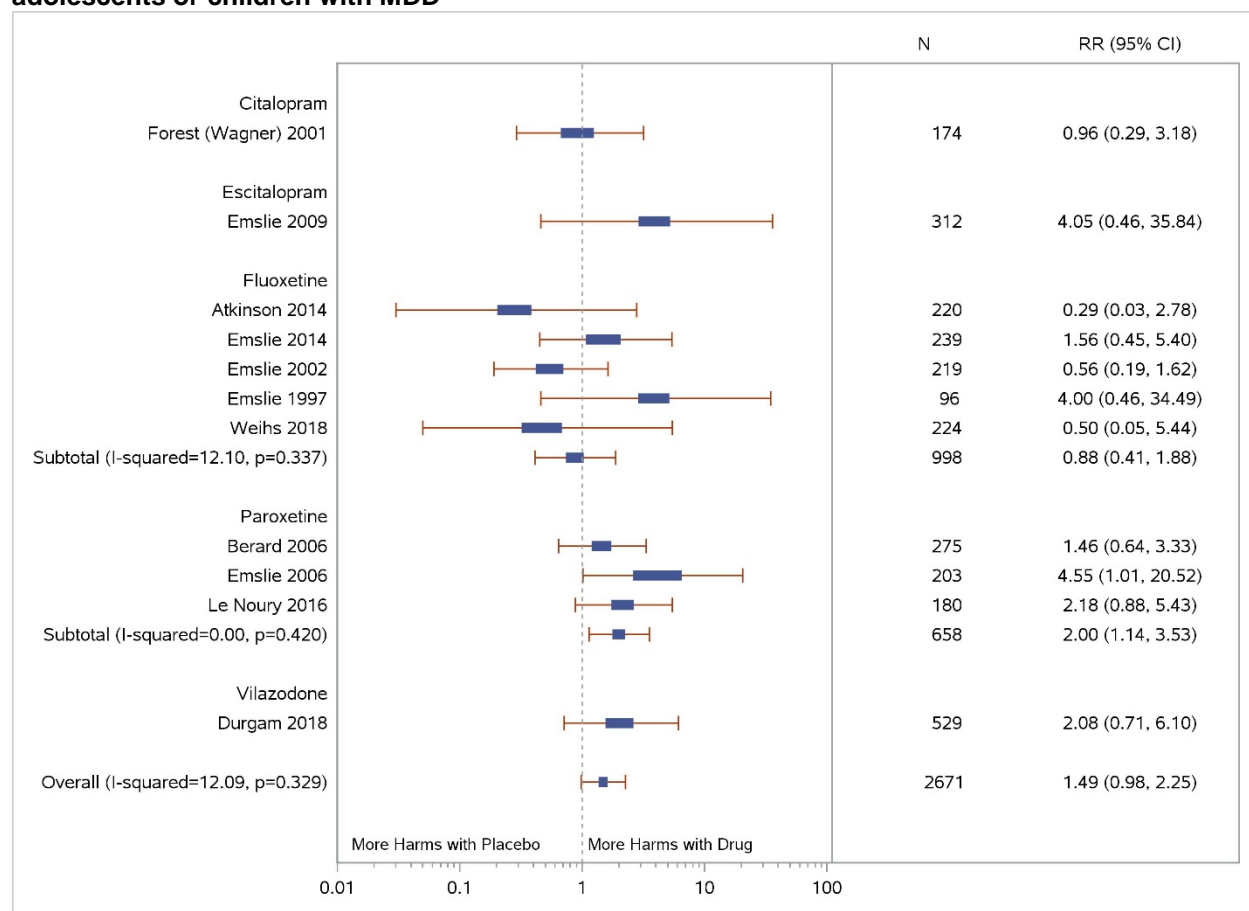
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

**Figure J-22. Pooled estimate of effect of SSRIs on serious adverse events for adolescents and children with MDD**



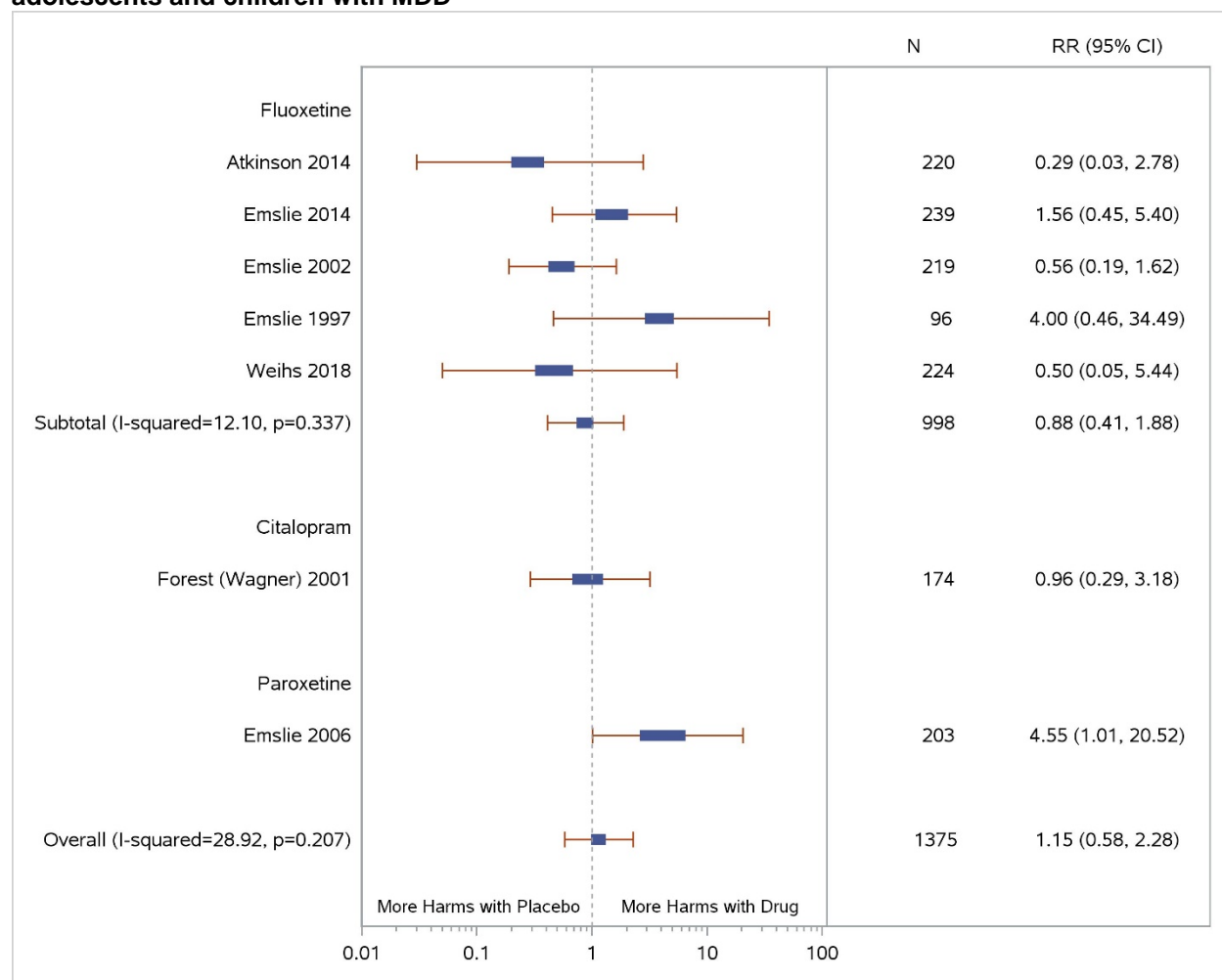
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

**Figure J-23. Pooled estimate of effect of SSRIs on withdrawal due to adverse events for adolescents or children with MDD**



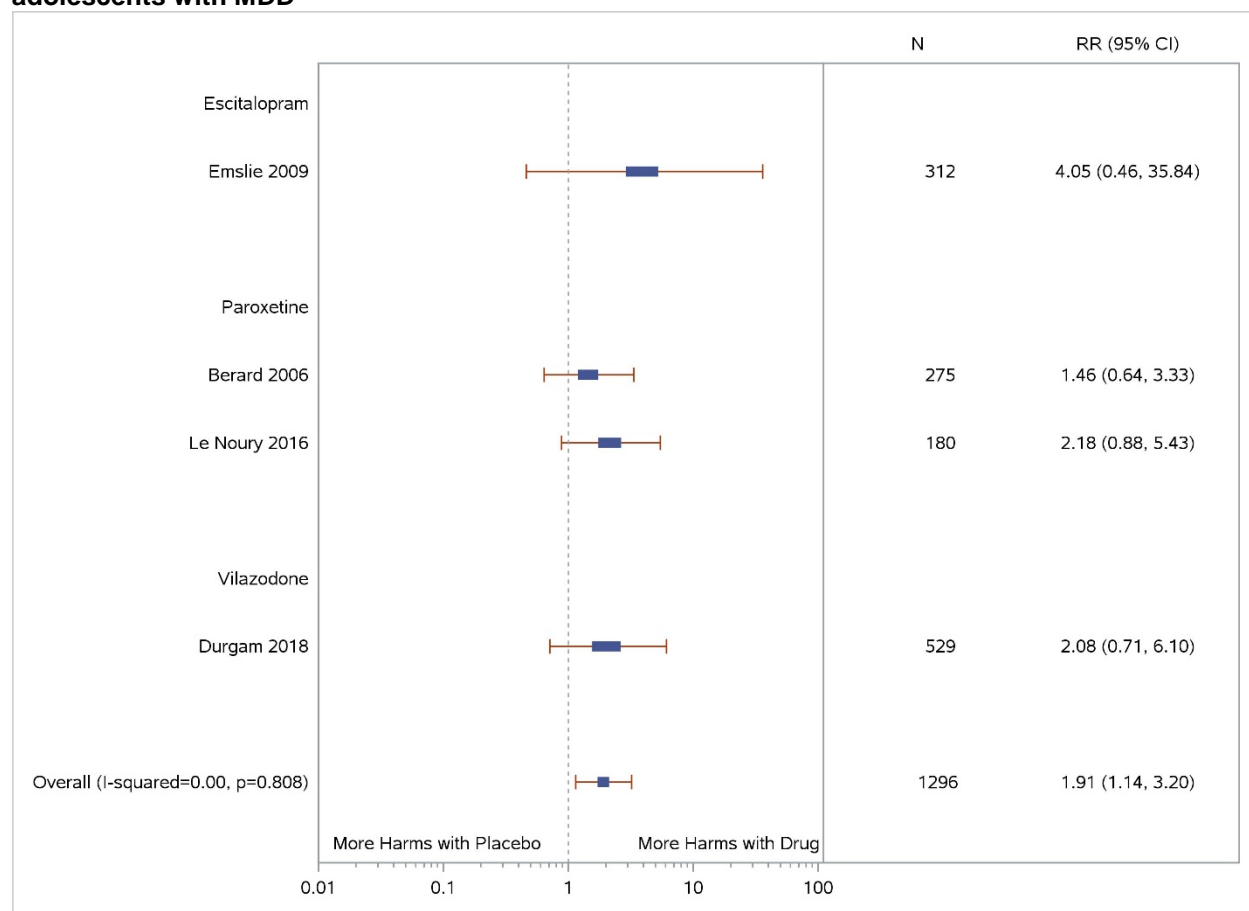
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

**Figure J-24. Pooled estimate of effect of SSRIs on withdrawal due to adverse events for adolescents and children with MDD**



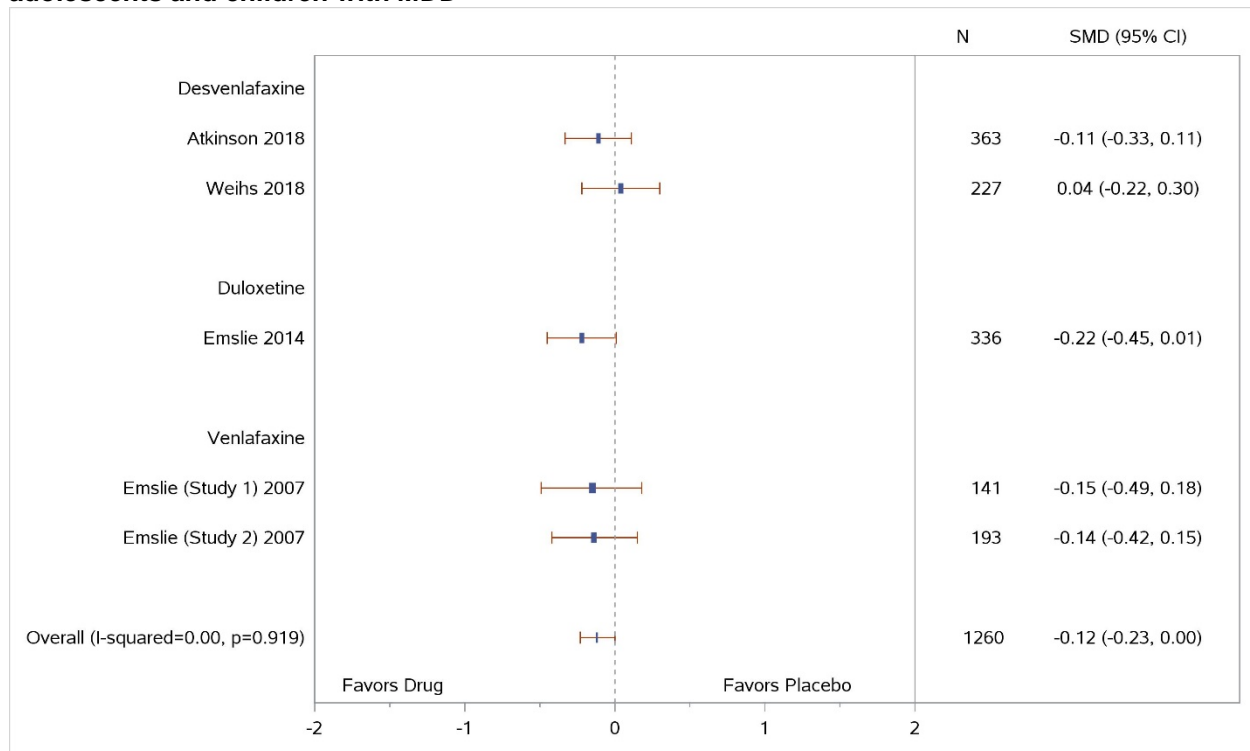
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

**Figure J-25. Pooled estimate of effect of SSRIs on withdrawal due to adverse events for adolescents with MDD**



CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitors.

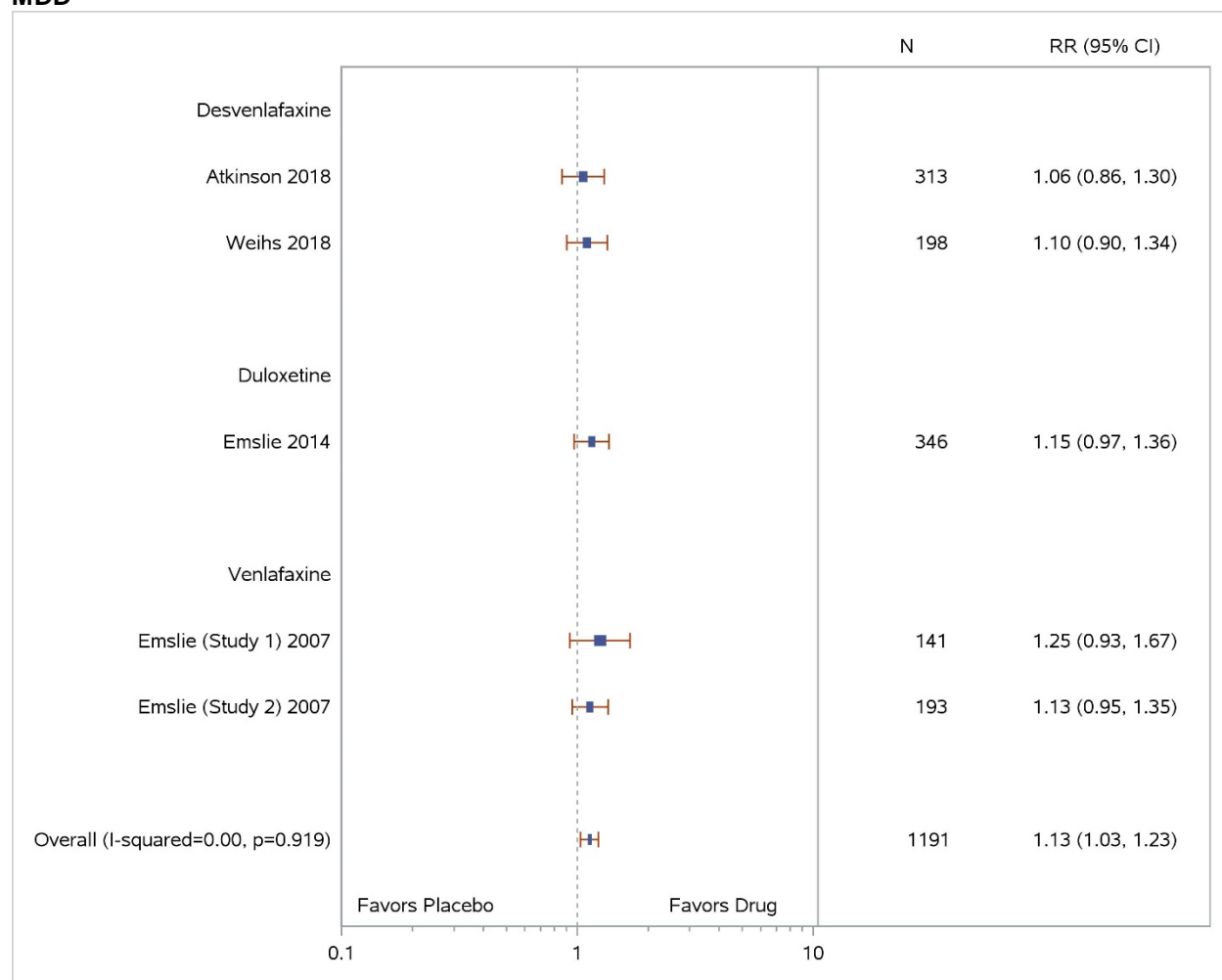
**Figure J-26. Pooled estimate of effect of SNRIs on clinician-rated depression symptoms for adolescents and children with MDD**



CI = confidence interval; MDD = major depressive disorder; N = number; SMD = standardized mean difference; SSRI = serotonin and norepinephrine reuptake inhibitors.

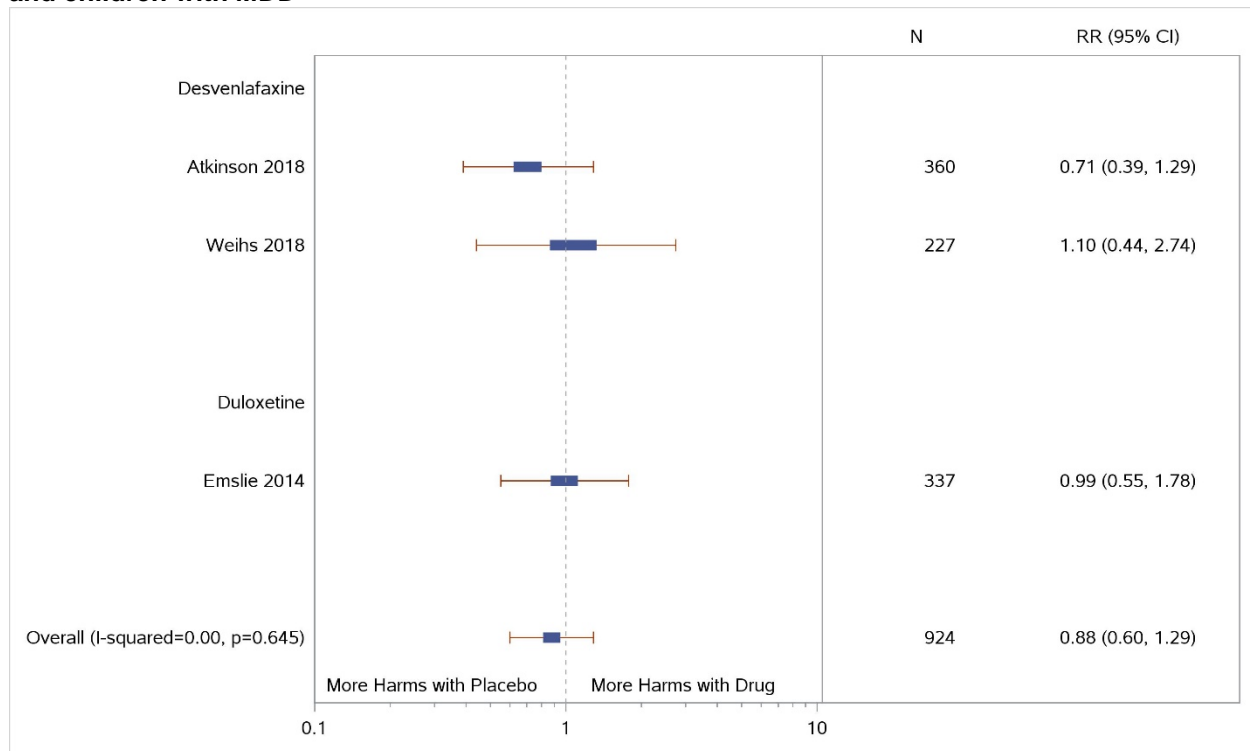


**Figure J-27. Pooled estimate of effect of SNRIs on response for adolescents and children with MDD**



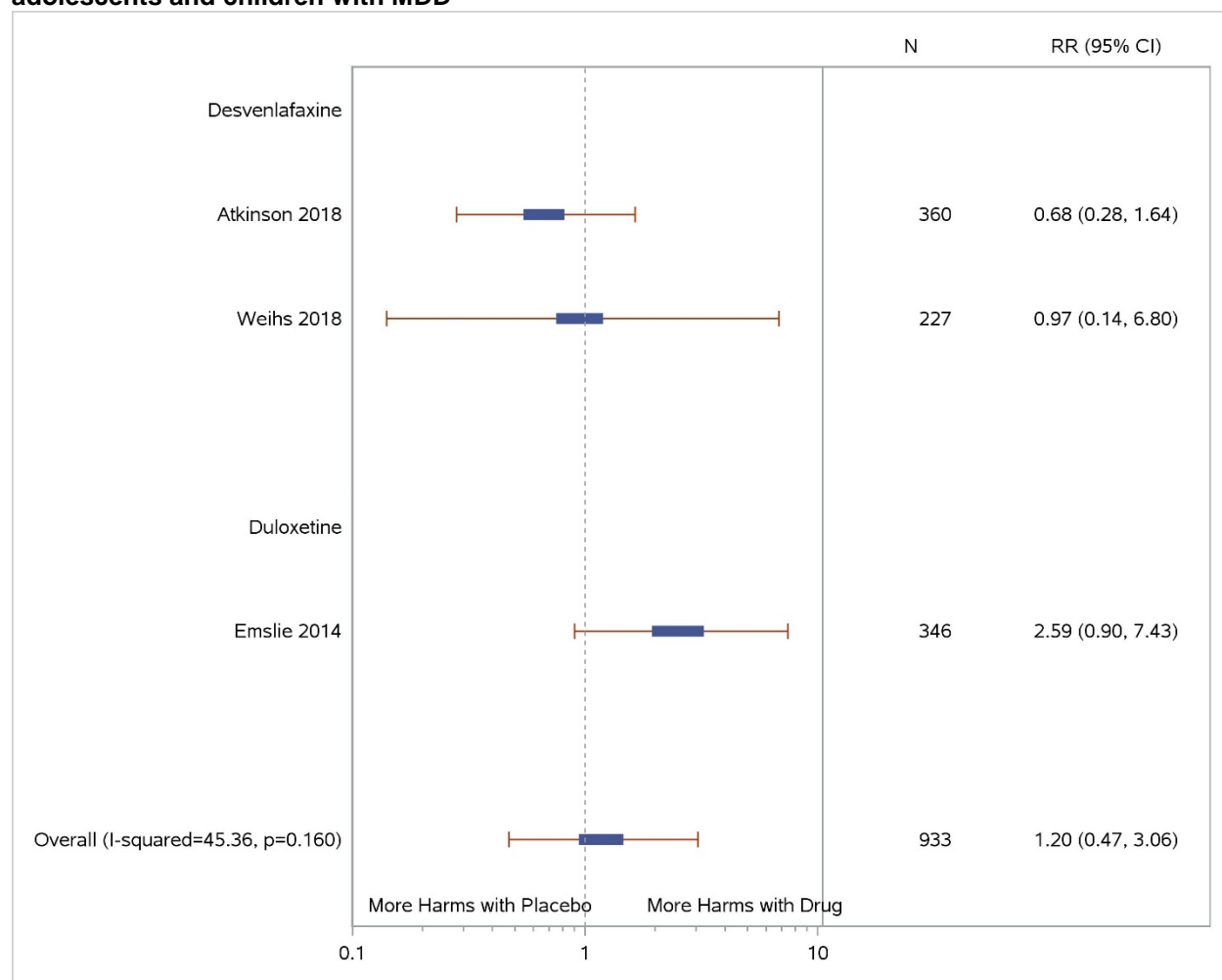
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SNRI = Serotonin and norepinephrine reuptake inhibitors.

**Figure J-28. Pooled estimate of effect of SNRIs on suicidal ideation or behaviors for adolescents and children with MDD**



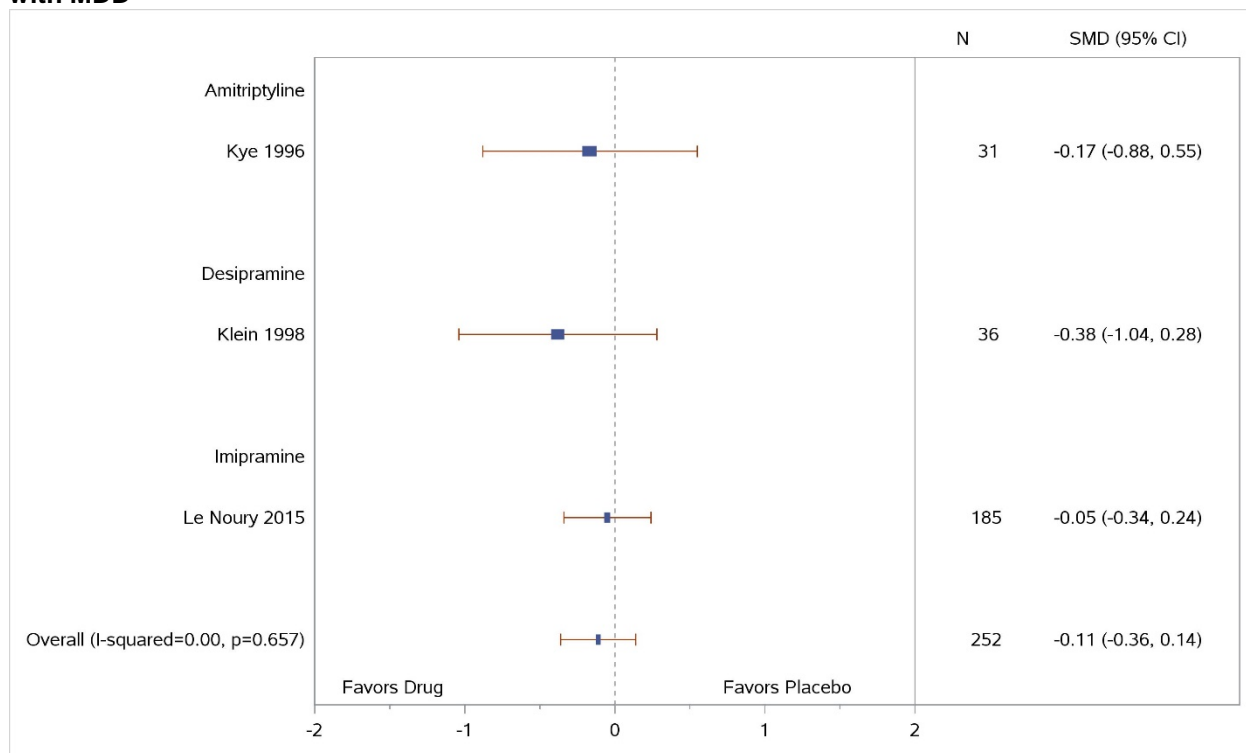
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SNRI = Serotonin and norepinephrine reuptake inhibitors.

**Figure J-29. Pooled estimate of effect of SNRIs on withdrawal due to adverse events for adolescents and children with MDD**



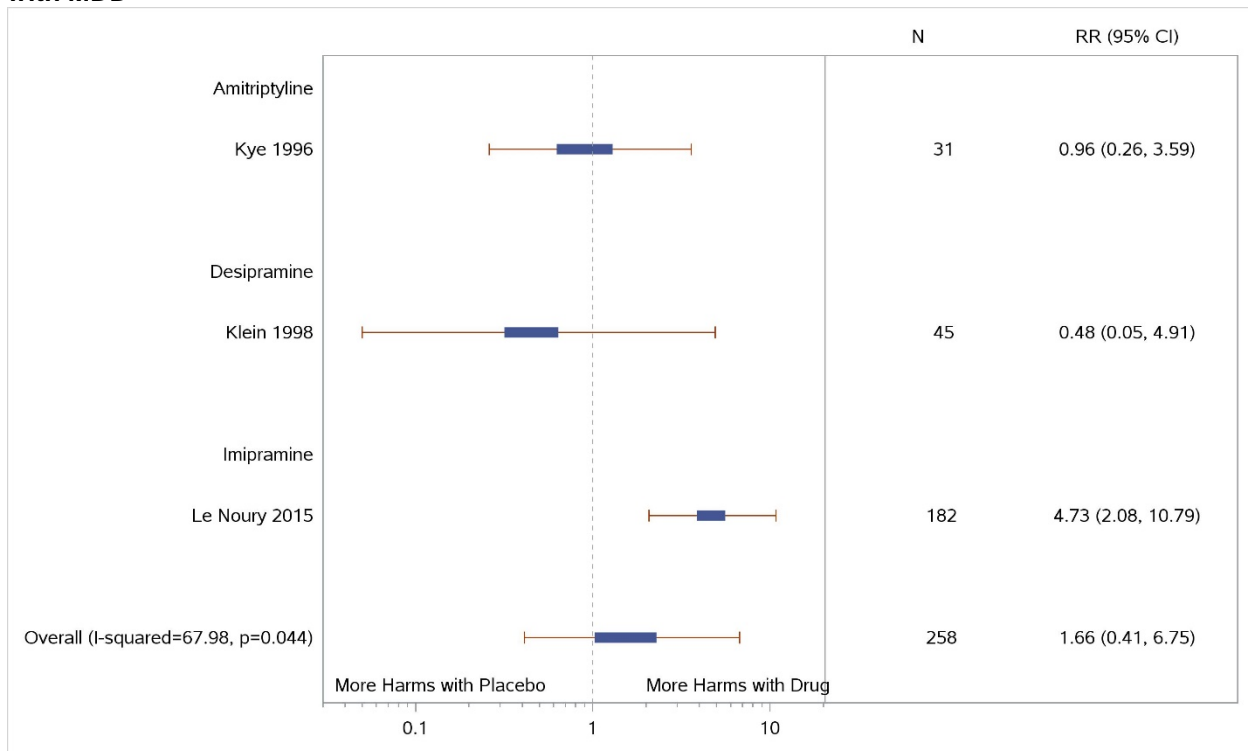
CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; SNRI = Serotonin and norepinephrine reuptake inhibitors.

**Figure J-30. Pooled estimate of effect TCAs on self-rated depression symptoms for adolescents with MDD**



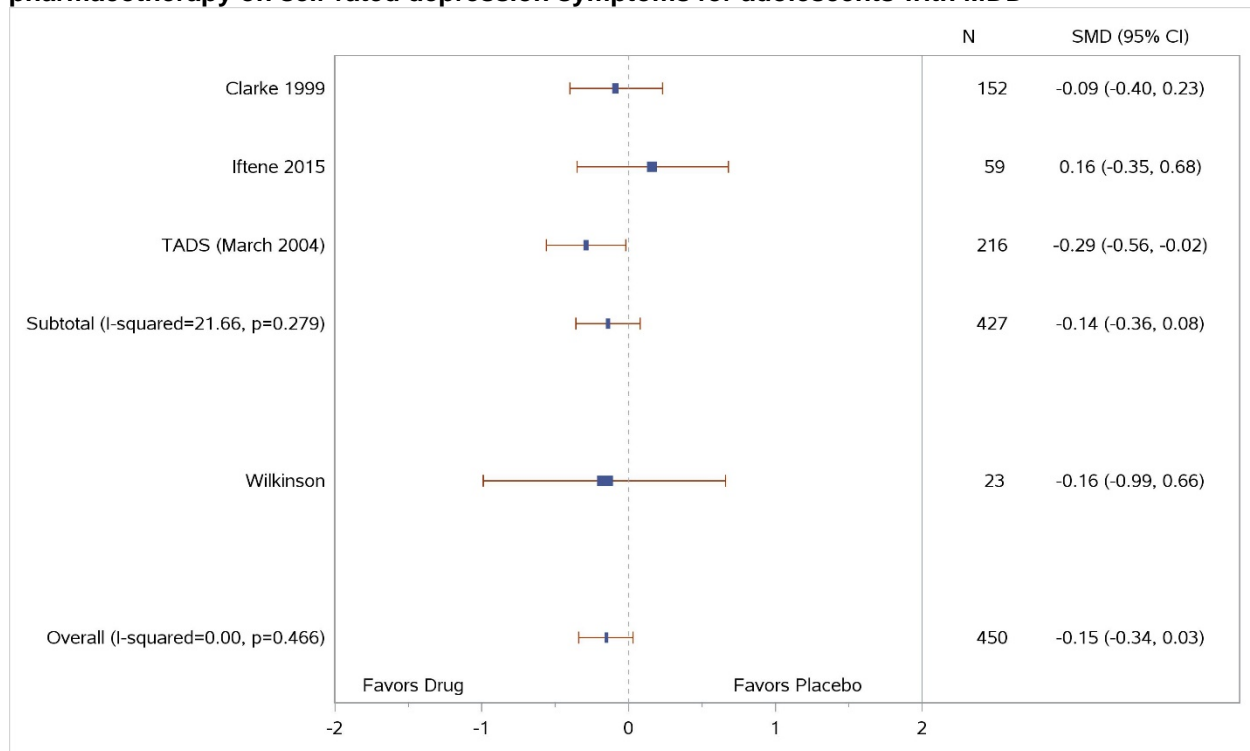
CI = confidence interval; MDD = major depressive disorder; N = number; SMD = standardized mean difference; TCA = tricyclic antidepressants.

**Figure J-31. Pooled estimate of effect TCAs on withdrawal due to adverse events for adolescents with MDD**



CI = confidence interval; MDD = major depressive disorder; N = number; RR = relative risk; TCA = tricyclic antidepressants.

**Figure J-32. Pooled estimate of effect of psychotherapy plus pharmacotherapy versus pharmacotherapy on self-rated depression symptoms for adolescents with MDD**



CI = confidence interval; MDD = major depressive disorder; N = number; SMD = standardized mean difference.

## Appendix K. Appendix References

1. Roseman M, Kloda LA, Saadat N, et al. Accuracy of depression screening tools to detect major depression in children and adolescents: a systematic review. *Can J Psychiatry*. 2016 Dec;61(12):746-57. doi: 10.1177/0706743716651833. PMID: 27310247.
2. Stockings E, Degenhardt L, Lee YY, et al. Symptom screening scales for detecting major depressive disorder in children and adolescents: a systematic review and meta-analysis of reliability, validity and diagnostic utility. *J Affect Disord*. 2015 Mar 15;174:447-63. doi: 10.1016/j.jad.2014.11.061. PMID: 25553406.
3. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004 Aug 18;292(7):807-20. doi: 10.1001/jama.292.7.807. PMID: 15315995.
4. Curry J, Rohde P, Simons A, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1427-39. doi: 10.1097/01.chi.0000240838.78984.e2. PMID: 17135988.
5. Emslie G, Kratochvil C, Vitiello B, et al. Treatment for Adolescents with Depression Study (TADS): safety results. *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1440-55. doi: 10.1097/01.chi.0000240840.63737.1d. PMID: 17135989.
6. Kennard B, Silva S, Vitiello B, et al. Remission and residual symptoms after short-term treatment in the Treatment of Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1404-11. doi: 10.1097/01.chi.0000242228.75516.21. PMID: 17135985.
7. Vitiello B, Rohde P, Silva S, et al. Functioning and quality of life in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1419-26. doi: 10.1097/01.chi.0000242229.52646.6e. PMID: 17135987.
8. Kratochvil CJ, May DE, Silva SG, et al. Treatment response in depressed adolescents with and without co-morbid attention-deficit/hyperactivity disorder in the Treatment for Adolescents with Depression Study. *J Child Adolesc Psychopharmacol*. 2009 Oct;19(5):519-27. doi: 10.1089/cap.2008.0143. PMID: 19877976.
9. Clarke GN, Rohde P, Lewinsohn PM, et al. Cognitive-behavioral treatment of adolescent depression: efficacy of acute group treatment and booster sessions. *J Am Acad Child Adolesc Psychiatry*. 1999 Mar;38(3):272-9. doi: 10.1097/00004583-199903000-00014. PMID: 10087688.
10. Rossello J, Bernal G. The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. *J Consult Clin Psychol*. 1999 Oct;67(5):734-45. PMID: 10535240.
11. Clarke GN, Hornbrook M, Lynch F, et al. Group cognitive-behavioral treatment for depressed adolescent offspring of depressed parents in a health maintenance organization. *J Am Acad Child Adolesc Psychiatry*. 2002 Mar;41(3):305-13. doi: 10.1097/00004583-200203000-00010. PMID: 11886025.
12. Brent DA, Holder D, Kolko D, et al. A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. *Arch Gen Psychiatry*. 1997 Sep;54(9):877-85. PMID: 9294380.
13. Brent DA, Kolko DJ, Birmaher B, et al. Predictors of treatment efficacy in a clinical trial of three psychosocial treatments for adolescent depression. *J Am Acad Child Adolesc Psychiatry*. 1998 Sep;37(9):906-14. doi: 10.1097/00004583-199809000-00010. PMID: 9735610.

14. Shirk SR, Deprince AP, Crisostomo PS, et al. Cognitive behavioral therapy for depressed adolescents exposed to interpersonal trauma: an initial effectiveness trial. *Psychotherapy (Chic)*. 2014 Mar;51(1):167-79. doi: 10.1037/a0034845. PMID: 24377410.
15. Rohde P, Clarke GN, Mace DE, et al. An efficacy/effectiveness study of cognitive-behavioral treatment for adolescents with comorbid major depression and conduct disorder. *J Am Acad Child Adolesc Psychiatry*. 2004 Jun;43(6):660-8. doi: 10.1097/01.chi.0000121067.29744.41. PMID: 15167082.
16. Goodyer IM, Reynolds S, Barrett B, et al. Cognitive-behavioural therapy and short-term psychoanalytic psychotherapy versus brief psychosocial intervention in adolescents with unipolar major depression (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled trial. *Health Technol Assess*. 2017 Mar;21(12):1-94. doi: 10.3310/hta21120. PMID: 28394249.
17. Goodyer IM, Reynolds S, Barrett B, et al. Cognitive behavioural therapy and short-term psychoanalytical psychotherapy versus a brief psychosocial intervention in adolescents with unipolar major depressive disorder (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled superiority trial. *Lancet Psychiatry*. 2017 Feb;4(2):109-19. doi: 10.1016/S2215-0366(16)30378-9. PMID: 27914903.
18. O'Keeffe S, Martin P, Goodyer IM, et al. Predicting dropout in adolescents receiving therapy for depression. *Psychother Res*. 2018 Sep;28(5):708-21. doi: 10.1080/10503307.2017.1393576. PMID: 29084488.
19. O'Keeffe S, Martin P, Goodyer IM, et al. Prognostic implications for adolescents with depression who drop out of psychological treatment during a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2019 Apr 1. doi: 10.1016/j.jaac.2018.11.019. PMID: 30946974.
20. Kennard BD, Emslie GJ, Mayes TL, et al. Cognitive-behavioral therapy to prevent relapse in pediatric responders to pharmacotherapy for major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. 2008 Dec;47(12):1395-404. doi: 10.1097/CHI.0b013e31818914a1. PMID: 18978634.
21. Kennard BD, Emslie GJ, Mayes TL, et al. Sequential treatment with fluoxetine and relapse--prevention CBT to improve outcomes in pediatric depression. *Am J Psychiatry*. 2014 Oct;171(10):1083-90. doi: 10.1176/appi.ajp.2014.13111460. PMID: 24935082.
22. Emslie GJ, Kennard BD, Mayes TL, et al. Continued effectiveness of relapse prevention cognitive-behavioral therapy following fluoxetine treatment in youth with major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. 2015 Dec;54(12):991-8. doi: 10.1016/j.jaac.2015.09.014. PMID: 26598474.
23. Mufson L, Weissman MM, Moreau D, et al. Efficacy of interpersonal psychotherapy for depressed adolescents. *Arch Gen Psychiatry*. 1999 Jun;56(6):573-9. PMID: 10359475.
24. Dietz LJ, Weinberg RJ, Brent DA, et al. Family-based interpersonal psychotherapy for depressed preadolescents: examining efficacy and potential treatment mechanisms. *J Am Acad Child Adolesc Psychiatry*. 2015 Mar;54(3):191-9. doi: 10.1016/j.jaac.2014.12.011. PMID: 25721184.
25. Diamond GS, Reis BF, Diamond GM, et al. Attachment-based family therapy for depressed adolescents: a treatment development study. *J Am Acad Child Adolesc Psychiatry*. 2002 Oct;41(10):1190-6. doi: 10.1097/00004583-200210000-00008. PMID: 12364840.
26. Israel P, Diamond GS. Feasibility of Attachment Based Family Therapy for depressed clinic-referred Norwegian adolescents. *Clin Child Psychol Psychiatry*. 2013;18(3):334-50. doi: 10.1177/1359104512455811. PMID: 108668356. Language: English. Entry Date: 20160426. Revision Date: 20160426. Publication Type: Article.



27. Fristad MA, Vesco AT, Young AS, et al. Pilot randomized controlled trial of Omega-3 and individual-family psychoeducational psychotherapy for children and adolescents with depression. *J Clin Child Adolesc Psychol.* 2019;48(sup1):S105-s18. doi: 10.1080/15374416.2016.1233500. PMID: 27819485.
28. Poole LA, Knight T, Toumbourou JW, et al. A randomized controlled trial of the impact of a family-based adolescent depression intervention on both youth and parent mental health outcomes. *J Abnorm Child Psychol.* 2018 Jan;46(1):169-81. doi: 10.1007/s10802-017-0292-7. PMID: 28374218.
29. Poole LA, Lewis AJ, Toumbourou JW, et al. A multi-family group intervention for adolescent depression: the BEST MOOD program. *Fam Process.* 2017;56(2):317-30. doi: 10.1111/famp.12218. PMID: 2017-25520-002.
30. Tompson MC, Sugar CA, Langer DA, et al. A randomized clinical trial comparing family-focused treatment and individual supportive therapy for depression in childhood and early adolescence. *J Am Acad Child Adolesc Psychiatry.* 2017 Jun;56(6):515-23. doi: 10.1016/j.jaac.2017.03.018. PMID: 28545757.
31. Asarnow JR. Depression in childhood: one year outcomes of family versus individual treatment. *J Am Acad Child Adolesc Psychiatry.* 2018;57(10):S289-S90. doi: 10.1016/j.jaac.2018.07.692. PMID: CN-01653013.
32. Luby J, Lenze S, Tillman R. A novel early intervention for preschool depression: findings from a pilot randomized controlled trial. *J Child Psychol Psychiatry.* 2012 Mar;53(3):313-22. doi: 10.1111/j.1469-7610.2011.02483.x. PMID: 22040016.
33. Hughes CW, Barnes S, Barnes C, et al. Depressed Adolescents Treated with Exercise (DATE): a pilot randomized controlled trial to test feasibility and establish preliminary effect sizes. *Ment Health Phys Act.* 2013 Jun;6(2):119-31. doi: 10.1016/j.mhpa.2013.06.006. PMID: 24244220.
34. Rickhi B, Kania-Richmond A, Moritz S, et al. Evaluation of a spirituality informed e-mental health tool as an intervention for major depressive disorder in adolescents and young adults - a randomized controlled pilot trial. *BMC Complement Altern Med.* 2015 Dec 24;15:450. doi: 10.1186/s12906-015-0968-x. PMID: 26702639.
35. Nemets H, Nemets B, Apter A, et al. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am J Psychiatry.* 2006 Jun;163(6):1098-100. doi: 10.1176/ajp.2006.163.6.1098. PMID: 16741212.
36. Barbe RP, Bridge J, Birmaher B, et al. Suicidality and its relationship to treatment outcome in depressed adolescents. *Suicide Life Threat Behav.* 2004 Spring;34(1):44-55. PMID: 15106887.
37. Rohde P, Seeley JR, Kaufman NK, et al. Predicting time to recovery among depressed adolescents treated in two psychosocial group interventions. *J Consult Clin Psychol.* 2006 Feb;74(1):80-8. doi: 10.1037/0022-006X.74.1.80. PMID: 16551145.
38. Atkinson SD, Prakash A, Zhang Q, et al. A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol.* 2014 May;24(4):180-9. doi: 10.1089/cap.2013.0146. PMID: 24813026.
39. Berard R, Fong R, Carpenter DJ, et al. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol.* 2006 Feb-Apr;16(1-2):59-75. doi: 10.1089/cap.2006.16.59. PMID: 16553529.
40. Durgam S, Chen C, Migliore R, et al. A phase 3, double-blind, randomized, placebo-controlled study of vilazodone in adolescents with major depressive disorder. *Paediatr Drugs.* 2018 Aug;20(4):353-63. doi: 10.1007/s40272-018-0290-4. PMID: 29633166.

41. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997 Nov;54(11):1031-7. PMID: 9366660.
42. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002 Oct;41(10):1205-15. doi: 10.1097/00004583-200210000-00010. PMID: 12364842.
43. Emslie GJ, Wagner KD, Kutcher S, et al. Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2006 Jun;45(6):709-19. doi: 10.1097/01.chi.0000214189.73240.63. PMID: 16721321.
44. Emslie GJ, Ventura D, Korotzer A, et al. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry*. 2009 Jul;48(7):721-9. doi: 10.1097/CHI.0b013e3181a2b304. PMID: 19465881.
45. Findling RL, Robb A, Bose A. Escitalopram in the treatment of adolescent depression: a randomized, double-blind, placebo-controlled extension trial. *J Child Adolesc Psychopharmacol*. 2013 Sep;23(7):468-80. doi: 10.1089/cap.2012.0023. PMID: 24041408.
46. Emslie GJ, Prakash A, Zhang Q, et al. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014 May;24(4):170-9. doi: 10.1089/cap.2013.0096. PMID: 24815533.
47. Findling RL, Pagano ME, McNamara NK, et al. The short-term safety and efficacy of fluoxetine in depressed adolescents with alcohol and cannabis use disorders: a pilot randomized placebo-controlled trial. *Child Adolesc Psychiatry Ment Health*. 2009 Mar 19;3(1):11. doi: 10.1186/1753-2000-3-11. PMID: 19298659.
48. GlaxoSmithKline. A double-blind, multicentre placebo controlled study of paroxetine in adolescents with unipolar major depression. 1998. <http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/038/CN-00497038/frame.html>.
49. Le Noury JL, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *Br Med J*. 2015;351. PMID: 2016-20242-001.
50. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2001 Jul;40(7):762-72. doi: 10.1097/00004583-200107000-00010. PMID: 11437014.
51. Le Noury J, Nardo JM, Healy D, et al. Study 329 continuation phase: safety and efficacy of paroxetine and imipramine in extended treatment of adolescent major depression. *Int J Risk Saf Med*. 2016 Sep 17;28(3):143-61. doi: 10.3233/jrs-160728. PMID: 27662279.
52. Wagner KD, Robb AS, Findling RL, et al. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry*. 2004 Jun;161(6):1079-83. doi: 10.1176/appi.ajp.161.6.1079. PMID: 15169696.
53. Forest Laboratories. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of citalopram in children and adolescents with depression. Forest Laboratories - Clinical Study Register. 2001(1). PMID: CN-00763823.
54. Wagner KD, Jonas J, Findling RL, et al. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J Am Acad Child Adolesc Psychiatry*. 2006 Mar;45(3):280-8. doi: 10.1097/01.chi.0000192250.38400.9e. PMID: 16540812.

55. Weihs KL, Murphy W, Abbas R, et al. Desvenlafaxine versus placebo in a fluoxetine-referenced study of children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2018 Feb;28(1):36-46. doi: 10.1089/cap.2017.0100. PMID: 29189044.
56. Emslie GJ, Heiligenstein JH, Hoog SL, et al. Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 2004 Nov;43(11):1397-405. doi: 10.1097/01.chi.0000140453.89323.57. PMID: 15502599.
57. Emslie GJ, Kennard BD, Mayes TL, et al. Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. *Am J Psychiatry*. 2008 Apr;165(4):459-67. doi: 10.1176/appi.ajp.2007.07091453. PMID: 18281410.
58. Kennard BD, Mayes TL, Chahal Z, et al. Predictors and moderators of relapse in children and adolescents with major depressive disorder. *J Clin Psychiatry*. 2018 Mar/Apr;79(2). doi: 10.4088/JCP.15m10330. PMID: 29474007.
59. Atkinson S, Lubaczewski S, Ramaker S, et al. Desvenlafaxine versus placebo in the treatment of children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2018;28(1):55-65. doi: 10.1089/cap.2017.0099. PMID: 2018-03285-007.
60. Emslie GJ, Findling RL, Yeung PP, et al. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry*. 2007 Apr;46(4):479-88. doi: 10.1097/chi.0b013e31802f5f03. PMID: 17420682.
61. Geller B, Cooper TB, McCombs HG, et al. Double-blind, placebo-controlled study of nortriptyline in depressed children using a "fixed plasma level" design. *Psychopharmacol Bull*. 1989;25(1):101-8. PMID: 2672066.
62. Geller B, Cooper TB, Graham DL, et al. Pharmacokinetically designed double-blind placebo-controlled study of nortriptyline in 6- to 12-year-olds with major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. 1992 Jan;31(1):34-44. doi: 10.1097/00004583-199201000-00007. PMID: 1537779.
63. Klein RG, Mannuzza S, Koplewicz HS, et al. Adolescent depression: controlled desipramine treatment and atypical features. *Depress Anxiety*. 1998;7(1):15-31. PMID: 9592629.
64. Kye CH, Waterman GS, Ryan ND, et al. A randomized, controlled trial of amitriptyline in the acute treatment of adolescent major depression. *J Am Acad Child Adolesc Psychiatry*. 1996 Sep;35(9):1139-44. doi: 10.1097/00004583-199609000-00011. PMID: 8824057.
65. DelBello MP, Hochadel TJ, Portland KB, et al. A double-blind, placebo-controlled study of selegiline transdermal system in depressed adolescents. *J Child Adolesc Psychopharmacol*. 2014 Aug;24(6):311-7. doi: 10.1089/cap.2013.0138. PMID: 24955812.
66. Mandoki MW, Tapia MR, Tapia MA, et al. Venlafaxine in the treatment of children and adolescents with major depression. *Psychopharmacol Bull*. 1997;33(1):149-54. PMID: 9133767.
67. Hirschtritt ME, Pagano ME, Christian KM, et al. Moderators of fluoxetine treatment response for children and adolescents with comorbid depression and substance use disorders. *J Subst Abuse Treat*. 2012 Jun;42(4):366-72. doi: 10.1016/j.jsat.2011.09.010. PMID: 22116008.
68. Kratochvil C, Emslie G, Silva S, et al. Acute time to response in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006 Dec;45(12):1412-8. doi: 10.1097/01.chi.0000237710.73755.14. PMID: 17135986.
69. Barbe RP, Bridge JA, Birmaher B, et al. Lifetime history of sexual abuse, clinical presentation, and outcome in a clinical trial for adolescent depression. *J Clin Psychiatry*. 2004 Jan;65(1):77-83. PMID: 14744173.

70. Dietz LJ, Marshal MP, Burton CM, et al. Social problem solving among depressed adolescents is enhanced by structured psychotherapies. *J Consult Clin Psychol*. 2014 Apr;82(2):202-11. doi: 10.1037/a0035718. PMID: 24491077.
71. Gunlicks-Stoessel M, Mufson L. Innovations in practice: a pilot study of interpersonal psychotherapy for depressed adolescents and their parents. *Child & Adolescent Mental Health*. 2016;21(4):225-30. doi: 10.1111/camh.12167. PMID: 118833587.
72. Jelalian E, Jandasek B, Wolff JC, et al. Cognitive-behavioral therapy plus healthy lifestyle enhancement for depressed, overweight/obese adolescents: results of a pilot trial. *J Clin Child Adolesc Psychol*. 2016 Jun 16:1-10. doi: 10.1080/15374416.2016.1163705. PMID: 27310418.
73. Nelson EL. Cognitive behavioral therapy for childhood depression: a comparison of face-to-face and interactive televideo settings. Dissertation abstracts international. 2004;65(3-b):1558. PMID: CN-00508148.
74. Rohde P, Lewinsohn PM, Seeley JR. Response of depressed adolescents to cognitive-behavioral treatment: do differences in initial severity clarify the comparison of treatments? *J Consult Clin Psychol*. 1994 Aug;62(4):851-4. PMID: 7962890.
75. Spirito A, Wolff JC, Seaboyer LM, et al. Concurrent treatment for adolescent and parent depressed mood and suicidality: feasibility, acceptability, and preliminary findings. *J Child Adolesc Psychopharmacol*. 2015 Mar;25(2):131-9. doi: 10.1089/cap.2013.0130. PMID: 24828247.
76. Trowell J, Joffe I, Campbell J, et al. Childhood depression: a place for psychotherapy. An outcome study comparing individual psychodynamic psychotherapy and family therapy. *Eur Child Adolesc Psychiatry*. 2007 Apr;16(3):157-67. doi: 10.1007/s00787-006-0584-x. PMID: 17200793.
77. Garoff FF, Heinonen K, Pesonen A-K, et al. Depressed youth: treatment outcome and changes in family functioning in individual and family therapy. *J Fam Ther*. 2012 Feb;34(1):4-23. doi: 10.1111/j.1467-6427.2011.00541.x. PMID: 104634633. Language: English. Entry Date: 20120227. Revision Date: 20150711. Publication Type: Journal Article.
78. Iftene F, Predescu E, Stefan S, et al. Rational-emotive and cognitive-behavior therapy (REBT/CBT) versus pharmacotherapy versus REBT/CBT plus pharmacotherapy in the treatment of major depressive disorder in youth; a randomized clinical trial. *Psychiatry Res*. 2015 Feb 28;225(3):687-94. doi: 10.1016/j.psychres.2014.11.021. PMID: 25500320.
79. Melvin GA, Tonge BJ, King NJ, et al. A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *J Am Acad Child Adolesc Psychiatry*. 2006 Oct;45(10):1151-61. doi: 10.1097/01.chi.0000233157.21925.71. PMID: 17003660.
80. Bernstein GA, Borchardt CM, Perwien AR, et al. Imipramine plus cognitive-behavioral therapy in the treatment of school refusal. *J Am Acad Child Adolesc Psychiatry*. 2000 Mar;39(3):276-83. doi: 10.1097/00004583-200003000-00008. PMID: 10714046.
81. Bernstein GA, Anderson LK, Hektner JM, et al. Imipramine compliance in adolescents. *J Am Acad Child Adolesc Psychiatry*. 2000 Mar;39(3):284-91. doi: 10.1097/00004583-200003000-00009. PMID: 10714047.
82. Deas D, Randall CL, Roberts JS, et al. A double-blind, placebo-controlled trial of sertraline in depressed adolescent alcoholics: a pilot study. *Hum Psychopharmacol*. 2000 Aug;15(6):461-9. doi: 10.1002/1099-1077(200008)15:6<461::aid-hup209>3.0.co;2-j. PMID: 12404308.
83. Dietz LJ, Mufson L, Irvine H, et al. Family-based interpersonal psychotherapy for depressed preadolescents: an open-treatment trial. *Early Interv Psychiatry*. 2008 Aug;2(3):154-61. doi: 10.1111/j.1751-7893.2008.00077.x. PMID: 21352148.

84. Clarke G, Debar L, Lynch F, et al. A randomized effectiveness trial of brief cognitive-behavioral therapy for depressed adolescents receiving antidepressant medication. *J Am Acad Child Adolesc Psychiatry*. 2005 Sep;44(9):888-98. PMID: 16113617.
85. Kim SM, Han DH, Lee YS, et al. Combined cognitive behavioral therapy and bupropion for the treatment of problematic on-line game play in adolescents with major depressive disorder. *Comput Human Behav*. 2012;28(5):1954-9. PMID: CN-00853199.
86. Wilkinson PO, Goodyer IM. The effects of cognitive-behavioural therapy on mood-related ruminative response style in depressed adolescents. *Child Adolesc Psychiatry Ment Health*. 2008 Jan 29;2(1):3. doi: 10.1186/1753-2000-2-3. PMID: 18230146.
87. Wilkinson P, Kelvin R, Roberts C, et al. Clinical and psychosocial predictors of suicide attempts and nonsuicidal self-injury in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT). *Am J Psychiatry*. 2011 May;168(5):495-501. doi: 10.1176/appi.ajp.2010.10050718. PMID: 21285141.
88. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA*. 2008 Feb 27;299(8):901-13. doi: 10.1001/jama.299.8.901. PMID: 18314433.
89. Asarnow JR, Emslie G, Clarke G, et al. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. *J Am Acad Child Adolesc Psychiatry*. 2009 Mar;48(3):330-9. doi: 10.1097/CHI.0b013e3181977476. PMID: 19182688.
90. Brent DA, Emslie GJ, Clarke GN, et al. Predictors of spontaneous and systematically assessed suicidal adverse events in the treatment of SSRI-resistant depression in adolescents (TORDIA) study. *Am J Psychiatry*. 2009 Apr;166(4):418-26. doi: 10.1176/appi.ajp.2008.08070976. PMID: 19223438.
91. Heiligenstein JH, Hoog SL, Wagner KD, et al. Fluoxetine 40-60 mg versus fluoxetine 20 mg in the treatment of children and adolescents with a less-than-complete response to nine-week treatment with fluoxetine 10-20 mg: a pilot study. *J Child Adolesc Psychopharmacol*. 2006 Feb-Apr;16(1-2):207-17. doi: 10.1089/cap.2006.16.207. PMID: 16553541.
92. Foster S, Mohler-Kuo M. Treating a broader range of depressed adolescents with combined therapy. *J Affect Disord*. 2018 Dec 1;241:417-24. doi: 10.1016/j.jad.2018.08.027. PMID: 30145512.
93. Foster S, Mohler-Kuo M, Tay L, et al. Estimating patient-specific treatment advantages in the 'Treatment for Adolescents with Depression Study'. *J Psychiatr Res*. 2019 May;112:61-70. doi: 10.1016/j.jpsychires.2019.02.021. PMID: 30856378.
94. Clarke G, DeBar LL, Pearson JA, et al. Cognitive behavioral therapy in primary care for youth declining antidepressants: a randomized trial. *Pediatrics*. 2016 May;137(5). doi: 10.1542/peds.2015-1851. PMID: 27244782.
95. Diamond G, Siqueland L, Diamond GM. Attachment-based family therapy for depressed adolescents: programmatic treatment development. *Clin Child Fam Psychol Rev*. 2003;6(2):107-27. doi: 10.1023/A:1023782510786. PMID: 2003-06174-003.