Comparative Effectiveness Review
Number 224

Treatment of Depression in Children and Adolescents: A Systematic Review

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.[1] The potential for lasting negative effects of child-onset depression underscores the importance of its early identification, diagnosis, and subsequent treatment.[2]

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.[3] 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.

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.

Agency for Healthcare Research and Quality

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.[4] 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),[5] 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.[6] 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)?

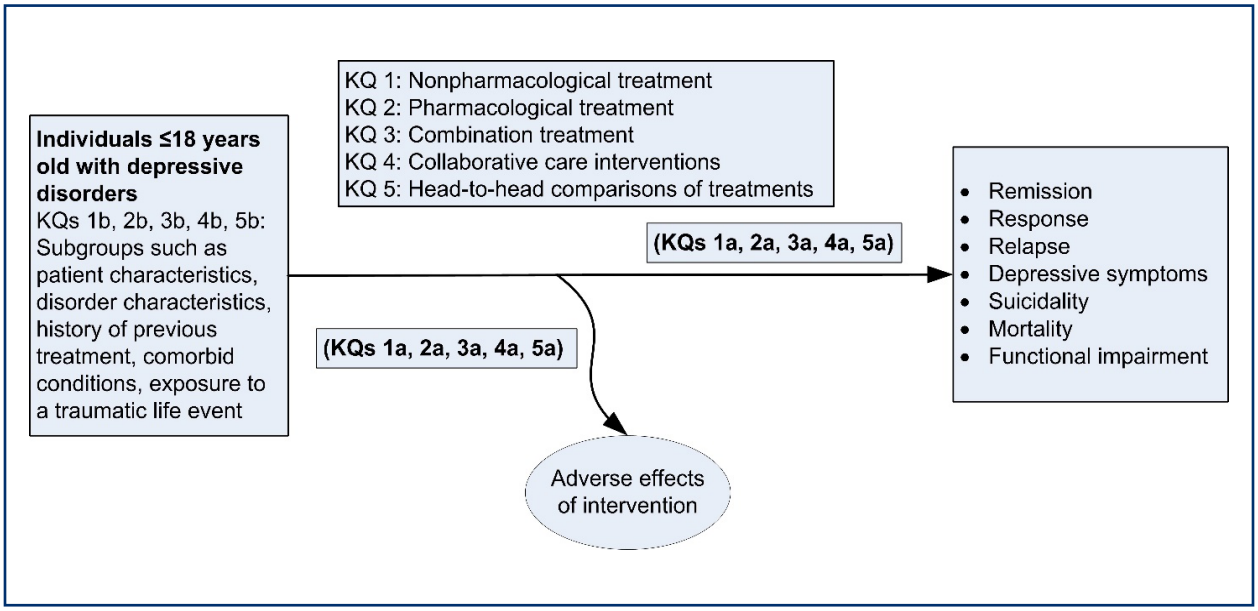
KQ 4a. In adolescents and children, what are the benefits and harms of collaborative care interventions for DDs (MDD, PDD/dysthymic disorders, or DD NOS)?

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*.[7] 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).[8] 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[9] tool for observational studies and the Cochrane RCT tool[10] 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.[11]

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.[12] 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

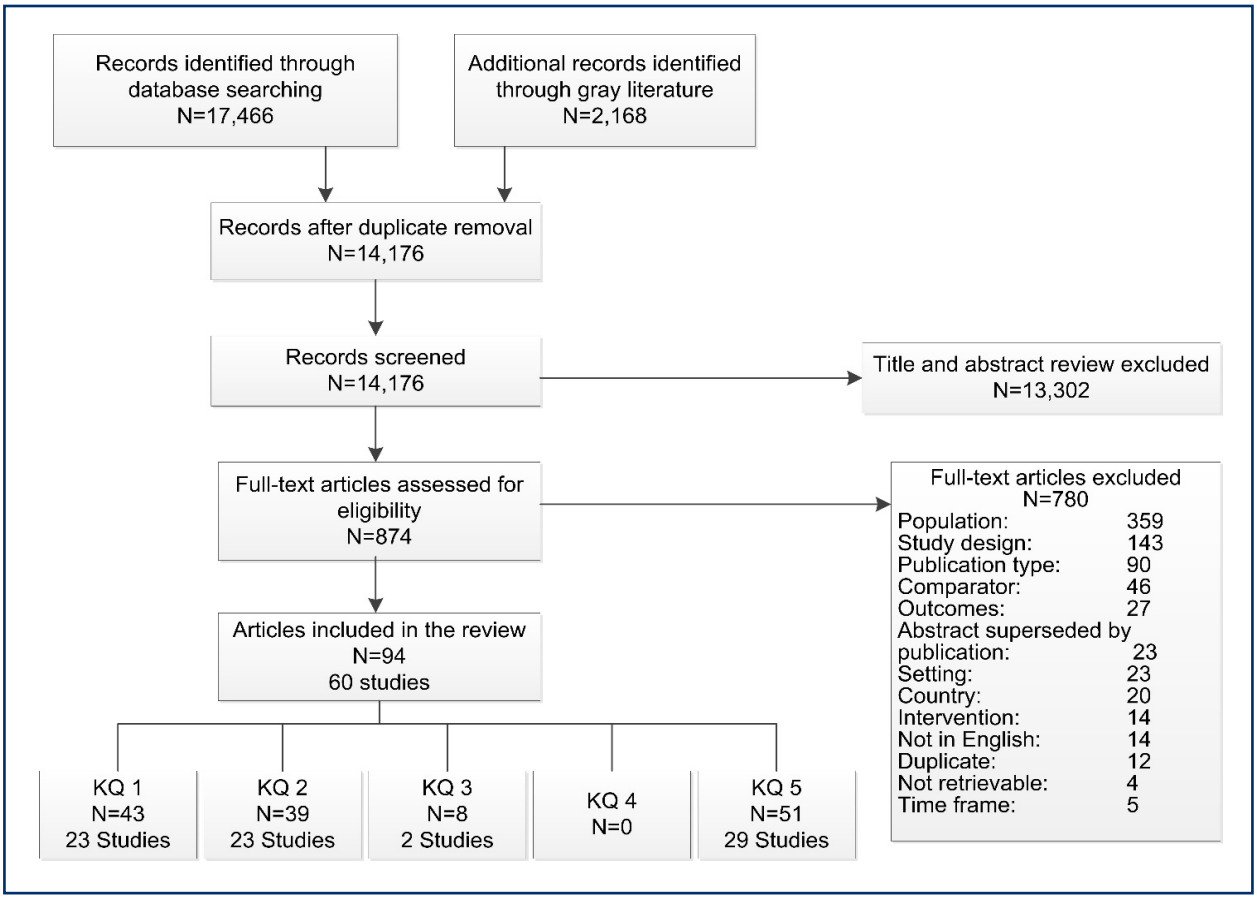
We assessed the applicability of individual studies as well as the applicability of a body of evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[13] We indicated age and type of DD in the analysis and otherwise called out characteristics of the 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 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

Table A. Key characteristics of included studies (continued)

Study Characteristics	Subcharacteristics	Number of Studies	Percent
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	NAa
	Other therapies (IPT, family-based IPT, attachment-based family therapy, family therapy, parent-child interaction therapy)	11	NAa
	Omega-3	2	NAa
	Exercise	1	NAa
	Spirituality	1	NAa

Table A. Key characteristics of included studies (continued)

Study Characteristics	Subcharacteristics	Number of Studies	Percent
KQ 2: Benefits and harms of pharmacological interventions	SSRIs	14	NAa
	SNRIs	5	NAa
	TCAs	4	NAa
	Relapse prevention with fluoxetine versus placebo	2	NAa
	MAOIs	1	NAa
	Venlafaxine plus active control versus placebo plus active control	1	NAa
KQ 3: Benefits and harms of combined interventions	Cognitive behavioral therapy + fluoxetine	1	NAa
	Omega-3 + family therapy	1	NAa
KQ 4: Benefits and harms of collaborative care interventions	Collaborative care interventions	0	NAa
KQ 5: Benefits and harms from head-to-head comparisons of interventions	CBT versus other psychotherapy	3	NAa
	Comparison of psychotherapy delivery methods	7	NAa
	Psychotherapy versus pharmacotherapy	3	NAa
	Psychotherapy plus pharmacotherapy versus psychotherapy	6	NAa

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.[14-16] For pharmacotherapy studies, usual care participants may have received the index medication.[16] For psychotherapy studies, therapists offered treatment that they believed to be effective.[17] Usual care could include therapy, medications, or combined therapy and medications.[18]

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≤28] as response);[19] 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.[20] 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.[21-23] 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.[21, 24]

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[25-27] 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[a]	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)[25]	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)[25]	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)[28]	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)[28]	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)[28]	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)[28]	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)[28]	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD

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

Comparison (Duration of Treatment)	Outcome	Conclusion[a]	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	Relapse	Risk difference (CDRS of 40 or more): -260/1,000; 95% CI, 433 fewer cases to 87fewer cases	1 RCT (n=115)[21, 24]	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents and children with MDD
	Relapse (78 weeks)	Risk difference: 273/ 1,000; 95% CI, 444 fewer cases to 102 fewer cases	1 RCT (n=121)[21, 24]	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)[29]	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)[29]	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)[29]	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)[27]	Imprecision, (small sample size), unknown consistency	Low for benefit	Adolescents or children with MDD, dysthymia, or DD NOS

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

Comparison (Duration of Treatment)	Outcome	Conclusion[a]	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
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)[30]	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)[31]	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD

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

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,[35, 36] 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,[37, 38] 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.[39]

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[23, 34, 40] and escitalopram[33] 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[6, 22, 41-45] and functional status[6, 41, 45-47] 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[a]	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)[23]	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)[23]	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD
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)[33]	Imprecision (wide CIs), unknown consistency	Low for benefit	Adolescents with MDD

Table C. Strength of Evidence for outcomes of pharmacotherapy versus placebo (continued)

Comparison (Duration of Treatment)	Outcome	Conclusion[a]	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
SSRI: Escitalopram 16-20 weeks (continued)	Remission (24 weeks)	Risk difference (CDRS-R): 149/1,000; 95% CI, 40 more cases to 258 more cases	1 RCT (n=311)[33]	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)[48]	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)[33]	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^2=0% Risk difference without high risk-of-bias study, 9 more cases; 95% CI, 23 fewer cases to 42 more cases, N=206[45]	3 RCTs (n=662)[45, 49, 50]	Imprecision (wide CIs), high risk of bias[49, 50]	Low for harms[b, c]	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^2=0% Risk difference without high risk-of-bias study: 70/1,000; 95% CI, 8 more cases to 131 more cases, N=203[45]	3 RCTs (n=658)[45, 49, 50]	Imprecision (wide CIs), high risk of bias[49, 50]	Low for harms	Adolescents or adolescents and children with MDD

Table C. Strength of Evidence for outcomes of pharmacotherapy versus placebo (continued)

Comparison (Duration of Treatment)	Outcome	Conclusion[a]	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^2=9% Risk difference without high risk-of-bias studies: 80/1,000; 95% CI, 16 more to 143 more cases, I^2=0%, N=847	7 RCTs (n=1,525)[6, 22, 41-45]	Imprecision (wide CIs), high risk of bias[41-43]	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^2=0% Risk difference without high risk-of-bias studies: 37/1,000; 95% CI, 26 fewer to 100 more cases, I^2=0%, N=870	4 RCTs (n=1,050)[40, 48, 51, 52]	Imprecision, (wide CIs), high risk of bias[51]	Low for no benefit	Adolescents with MDD
	Functional status, clinician report	SMD (GAF, CGAS), 0.16; 95% CI, 0.03 to 0.29, I^2=0% Without high risk-of-bias studies, SMD: 0.17; 95% CI, 0.02 to 0.33, I^2=0%, N=626	5 RCTs (n=941)[6, 41, 45-47]	Imprecision (wide CIs), high risk of bias[41, 46]	Low for benefit	Adolescents and children with MDD

Table C. Strength of Evidence for outcomes of pharmacotherapy versus placebo (continued)

Comparison (Duration of Treatment)	Outcome	Conclusion[a]	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)	SAEs	Risk difference, 20/1,000; 95% CI, 1 more case to 440 more cases; I^2, 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^2=0%; N=1,358	9 RCTs (n=2,206)[22, 23, 41-43, 45, 47, 52, 53]	Imprecision (wide CIs, few events), high risk of bias[41-43, 53]	Low for harms[b, d]	Adolescents and children with MDD, adolescents with MDD
	Withdrawal due to AEs	Risk difference, 26/1,000; 95% CI, 6 more cases to 45 more cases; I^2, 0% CIs for RR without high risk-of-bias studies span the null	4 RCTs (n=1,296)[48-50, 52]	Serious imprecision, high risk of bias[49, 50]	Low for harms[b]	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)[54, 55]	Serious imprecision (wide CIs, small sample size), inconsistency, high risk of bias[54]	Low for benefit[e]	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)[22, 56]	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)[22, 56]	Imprecision (wide CIs)	Low for no benefit	Adolescents and children with MDD

Table C. Strength of Evidence for outcomes of pharmacotherapy versus placebo (continued)

Comparison (Duration of Treatment)	Outcome	Conclusion[a]	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
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^2=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)[22, 42, 56]	Inconsistency (direction of effect), high risk of bias[42, 57]	Low for no benefit[f]	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)[42]	Imprecision (wide CIs), high risk of bias,[42] unknown consistency	Insufficient for low dose, low for high dose	Adolescents and children with MDD

[a] For CGAS, the 0.5* standard deviation for baseline control arms ranges from 2.5[33] to 3.8.[34] For CDRS-R, the 0.5* standard deviation for baseline or followup control arms ranges from 4.0[31] to 5.7.[29]
[b] 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.
[c] 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).[50]
[d] One study[23] 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.
[e] With the high risk-of-bias studies, the evidence would have been downgraded for inconsistency and imprecision and would have been downgraded to insufficient.
[f] 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%),[45, 49, 50] one study (n=180) reported a substantially increased risk (RD, 95/1000, 95% CI, 22 to 168)[50] 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[58] 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.[55]

The evidence for desvenlafaxine (2 studies)[22, 56] and SNRIs as a class (5 studies, including two venlafaxine studies in a single publication)[22, 42, 56, 57] 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).[42]

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.[35, 36, 41, 46, 59-61] 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.[49] The difference in the incidence of harms between paroxetine and placebo patients was more pronounced in older adolescents than in younger adolescents.[49] 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.[23, 34, 40] 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[a]	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)[23]	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)[23]	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)[40]	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)[34]	Imprecision (small sample size), unknown consistency	Low for benefit	Adolescents with MDD

[a] For CGAS, the 0.5* standard deviation for baseline control arms ranges from 2.5[33] to 3.8.[34] For CDRS-R, the 0.5* standard deviation for baseline or followup control arms ranges from 4.0[31] to 5.7.[2]

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.[23, 34-36, 40, 62, 63]

Combination pharmacotherapy plus psychotherapy may be associated with improved depressive symptoms, remission, and functional status when compared with *psychotherapy* alone.[23, 34-36, 40, 62-65] 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.[23, 34-36, 40, 62, 63, 66-68] 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.[68]

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[a]	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 (CDRSR): 5.76; 95% CI, 3.46 to 8.06	1 RCT (n=220)[23, 34-36, 40, 62, 63]	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)[23, 34-36, 40, 62, 63]	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) (CDRSR): 8.27; 95% CI, 10.59 to -5.95	1 RCT (n=218)[23, 34-36, 40, 62, 63]	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)[64, 65]	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)[23, 34-36, 40, 62, 63]	Imprecision (small sample size), unknown consistency	Low for benefit for combination therapy	Adolescents with MDD

Table E. Strength of evidence for outcomes of comparative effectiveness studies (continued)

Comparison	Outcome	Conclusion[a]	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)	Applicability
Psychotherapy plus pharmacotherapy vs. psychotherapy 8 to 12 weeks (continued)	Functional status	Mean difference (CBT + fluoxetine vs. CBT) (CGAS): 6.60; 95% CI, 3.23 to 9.97	1 RCT (n=185)[23, 34-36, 40, 62, 63]	Imprecision (small sample size), unknown consistency	Low for benefit for combined therapy	Adolescents with MDD
	Depressive symptoms (self-rated)	SMD (CBT + SSRI vs. SSRI, based on CDI, RADS, CESD, and MFQ): 0.15; 95% CI, 0.34 to 0.03, N=450 (4 studies), I^2=0% SMD without high risk-of-bias studies, 0.14; 95% CI, 0.36 to 8.31, N=427, I^2=22%	4 RCTs (n=450)[23, 34-36, 40, 62, 63, 66-68]	Imprecision (wide CIs), inconsistent, high risk of bias[67]	Low for no benefit of adding CBT to SSRIs	Adolescents with MDD
	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)[68]	Imprecision (small sample size), unknown consistency	Low for benefit of adding CBT to bupropion	Adolescents with MDD

Table E. Strength of evidence for outcomes of comparative effectiveness studies (continued)

Comparison	Outcome	Conclusiona	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)	Remission from MDD	Risk difference (combination vs. medication): 140/1,000; 95% CI, 19 more cases to 261 more cases	1 RCT (n=216)[40]	Imprecision (wide CIs, small sample size)	Low for benefit of adding CBT to fluoxetine	Adolescents with MDD

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

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[23] found that CBT was inferior to fluoxetine in groups with lower family income, marked/severe baseline depressive symptom severity, and comorbid ADHD.[35, 36, 69] 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.[70-72]

Discussion

Current recommendations support CBT, combined therapy, and fluoxetine for adolescsents[73] with moderate to severe depression.[74-76] 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.[58] 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.

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Full Report

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