Effective Health Care Program

Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder

AHRQ

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Comparative Effectiveness Review
Number 161

Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder

Investigators:
Gerald Gartlehner, M.D., M.P.H.
Bradley N. Gaynes, M.D., M.P.H.
Halle R. Amick, M.S.P.H.
Gary Asher, M.D., M.P.H.
Laura C. Morgan, M.A.
Emmanuel Coker-Schwimmer, M.P.H.
Catherine Forneris, Ph.D., ABPP
Erin Boland, B.A.
Linda J. Lux, M.P.A.
Susan Gaylord, Ph.D.
Carla Bann, Ph.D.
Christiane Barbara Pierl, Ph.D., M.P.H.
Kathleen N. Lohr, Ph.D., M.Phil., M.A.

This report is based on research conducted by the RTI International–University of North Carolina Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2012-00008-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 health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well informed decisions and thereby improve the quality of health care 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 Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

Suggested citation: Gartlehner G, Gaynes BN, Amick HR, Asher G, Morgan LC, Coker-Schwimmer E, Forneris C, Boland E, Lux LJ, Gaylord S, Bann C, Pierl CB, Lohr KN. Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder. Comparative Effectiveness Review No. 161. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-2012-00008-I.) AHRQ Publication No. 15(16)-EHC031-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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 health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care 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.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (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.

Richard G. Kronick, Ph.D.
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

Aysegul Gozu, M.D., M.P.H.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Acknowledgments

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent 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 $10,000 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:

Michael J. Barry, M.D.
Massachusetts General Hospital
Boston, MA

Margaret A. Chesney, Ph.D.
University of California, San Francisco
San Francisco, CA

Paul Dallas, M.D., FACP
Virginia Tech Carilion School of Medicine
Roanoke, VA

Steven D. Hollon, Ph.D.
Vanderbilt University
Nashville, TN

Enid Hunkeler, M.A.
Kaiser Permanente Division of Research
Oakland, CA

John R. McQuaid, Ph.D.
San Francisco VA Healthcare System
University of California, San Francisco
San Francisco, CA

Keris Jän Myrick, M.B.A., M.S., Ph.D.c.
National Alliance on Mental Illness
Los Angeles, CA

Rhonda Robinson-Beale, M.D.
OptumHealth Behavioral Solutions
San Francisco, CA

Michael Thase, M.D.
University of Pennsylvania
Philadelphia, PA

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 $10,000 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:

Michael J. Barry, M.D.
Massachusetts General Hospital
Boston, MA

James Blumenthal, Ph.D.
Duke University
Durham, NC

Margaret A. Chesney, Ph.D.*
University of California, San Francisco
San Francisco, CA

Laura Fochtmann, M.D., M.B.I.*
Stony Brook University
Stony Brook, NY

Steven D. Hollon, Ph.D.*
Vanderbilt University
Nashville, TN

John R. McQuaid, Ph.D.*
San Francisco VA Healthcare System
University of California, San Francisco
San Francisco, CA

Michael Thase, M.D.
University of Pennsylvania
Philadelphia, PA

*Also provided comments on the 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 $10,000 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:

Linda Jensen, Ph.D., R.N.
Clarkson College
Board of Directors
National Alliance on Mental Illness
Omaha, NE

Mark Rapaport, M.D.
Emory University
Atlanta, GA

Matthew Rudorfer, M.D.
National Institute of Mental Health
Rockville, MD

Jesse Wright, M.D., Ph.D.
University of Louisville
Louisville, KY

Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder

Structured Abstract

Objective. To compare the benefits and harms of second-generation antidepressants (SGAs), psychological, complementary and alternative medicine, and exercise treatment options as first-step interventions for adult outpatients with acute-phase major depressive disorder (MDD), and as second-step interventions for patients with MDD who did not achieve remission after a first treatment attempt with SGAs.

Data sources. MEDLINE® (via PubMed®), Embase®, the Cochrane Library, AMED (Allied and Complementary Medicine Database), PsycINFO®, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) from January 1, 1990, through January 13, 2015.

Review method. Two investigators independently selected, extracted data from, and rated risk of bias of studies. We graded strength of evidence based on established guidance.

Results. Forty-four trials met inclusion criteria. For benefits across all interventions, we graded the strength of evidence as moderate for only one outcome of one comparison: SGAs compared with cognitive behavioral therapy (CBT). Results indicate that SGAs and CBT had similar effectiveness regarding symptomatic relief in patients with mild to severe MDD.

For risk of harms, we graded the strength of evidence as moderate for some outcomes of three comparisons—namely, SGAs compared with CBT, acupuncture, and St. John's wort. Patients treated with SGAs had a higher risk of experiencing adverse events or discontinuing treatment because of adverse events than patients treated with CBT, acupuncture, or St. John's wort.

Our confidence in the benefits and harms of SGAs compared with the remaining treatment options is low or insufficient, indicating that the bodies of evidence had major or unacceptable deficiencies. Nevertheless, for most comparisons, the overall findings indicated no statistically significant differences in benefits but a lower risk of adverse events for nonpharmacological treatment options. Across all comparisons of interventions, major research gaps pertain to information about the comparative risk of harms and patient-relevant outcomes such as functional capacity and quality of life.

For second-step therapies (i.e., therapy for patients with MDD who did not achieve remission after a first treatment attempt with SGAs), comparative evidence is limited. However, available data suggest that switching to another SGA, switching to cognitive therapy, and augmenting with a particular medication or cognitive therapy are all reasonable options.

Conclusions. Overall, the available evidence indicates that SGAs and CBT do not differ significantly in symptomatic relief as first-step treatments for adult outpatients with moderate to severe MDD. SGAs, in general, lead to a higher risk of adverse events than nonpharmacological treatment options. The evidence is insufficient to form conclusions about differences in serious

adverse events, such as suicidal ideas and behavior. Given comparable effectiveness, the choice of the initial treatment of MDD should consider results of previous treatments, patient preferences, and feasibility (e.g., costs, likely adherence, and availability) following a discussion of the advantages and disadvantages of each treatment option, including risks of particular adverse effects and potential drug interactions. Such shared and informed decisionmaking might enhance treatment adherence and improve treatment outcomes for patients with MDD, especially because treatment continuity is one of the main challenges in treating such patients.

Contents

Figures

Appendixes
Appendix A. Search Strategy
Appendix B. Cochrane Depression, Anxiety and Neurosis Group (CCDAN) Topic List:
    Intervention – Psychological Therapies
Appendix C. Studies Excluded at the Full-Text Review Stage
Appendix D. Risk of Bias Evaluations
Appendix E. Summary of Findings Tables
Appendix F. Studies Included in Network Meta-Analyses
Appendix G. Data From Network Meta-Analyses

Executive Summary

Background

Major depressive disorder (MDD)[1] is the most prevalent and disabling form of depression, affecting more than 16 percent of U.S. adults (lifetime).[2] MDD can be characterized as mild, moderate, or severe based on symptom severity, functional impairment, and level of patient distress;[1] in clinical trials, these distinctions are typically made by scores on a depressive rating instrument.[3] Approximately one-third of patients with MDD are severely depressed,[4] which is associated with depression that is harder to treat, as evidenced by more difficulty in achieving treatment response and remission.[5]

In any given year, nearly 7 percent of the U.S. adult population (approximately 17.5 million people in 2014) experience an episode of MDD that warrants treatment.[2] Most patients receiving care obtain treatment in primary care settings,[6] where second-generation antidepressants (SGAs) are the most commonly prescribed agents.[7] Nonetheless, patients and clinicians may prefer other options, or at least want to be able to consider them. These include psychological interventions, complementary and alternative medicine (CAM) options, and exercise.

The psychological interventions used to treat depressed patients include acceptance and commitment therapy, cognitive therapy (CT), cognitive behavioral therapy (CBT), interpersonal therapy, and psychodynamic therapies. Commonly used CAM interventions for the treatment of patients with MDD include acupuncture, meditation, omega-3 fatty acids, S-adenosyl-L-methionine (SAMe), St. John's wort, and yoga. While acupuncture requires a licensed professional for treatment, the other options may be used in conjunction with a trained provider or be self-administered.

Exercise covers a broad range of activities; they can be done over varying durations of time and singly, in classes, or in informal groups.

About 40 percent of patients treated with SGAs do not respond to initial treatment; approximately 70 percent do not achieve remission during the first-step treatment.[8] Those who do not achieve remission following initial pharmacological treatment require a different treatment strategy. Accordingly, various other interventions—such as medication combinations, psychotherapy, or CAM treatments—are options for patients and clinicians.

Scope and Key Questions

This review for the Effective Health Care Program of the Agency for Healthcare Research and Quality (AHRQ) examines the evidence base for primary care management of MDD for the first two treatment attempts, after which primary care clinicians would consider referral to or consultation by a mental health professional. The specific Key Questions (KQs) are listed below:

KQ 1a. In adult patients with major depressive disorder (MDD) who are undergoing an initial treatment attempt, what is the effectiveness of second-generation antidepressant (SGA) monotherapy compared with the effectiveness of either nonpharmacological monotherapy or combination therapy (involving nonpharmacological treatments with or without an SGA)?

KQ 1b. Does comparative treatment effectiveness vary by MDD severity?

KQ 2a. In adult patients with MDD who did not achieve remission following an initial adequate trial with one SGA, what is the comparative effectiveness of second-step therapies?[a]

KQ 2b. Does comparative treatment effectiveness vary by MDD severity?

KQ 3a. In adult patients with MDD, what are the comparative risks of harms of these treatment options—
1. For those undergoing an initial treatment attempt?
2. For those who did not achieve remission following an initial adequate trial with an SGA?

KQ 3b. Do the comparative risks of treatment harms vary by MDD severity?

KQ 4. Do the benefits and risks of harms of these treatment options differ by subgroups of patients with MDD defined by common accompanying psychiatric symptoms (coexisting anxiety, insomnia, low energy, or somatization) or demographic characteristics (age, sex, race, or ethnicity)?

Methods

Literature Search Strategy

We searched MEDLINE® (via PubMed®), Embase®, the Cochrane Library, AMED (Allied and Complementary Medicine Database), PsycINFO®, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) from January 1, 1990, through January 13, 2015. We used a combination of medical subject headings and title and abstract keywords, focusing on terms to describe the relevant population and interventions of interest. We limited the electronic searches to English-, German-, and Italian-language and human-only studies.

In addition, we manually searched reference lists of pertinent reviews, included trials, and background articles, and searched for gray literature relevant to this review following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* for these steps.[9]

Inclusion and exclusion criteria are presented in Table A.

---

[a] Any comparison that involves an eligible intervention (whether as a monotherapy or a combination therapy) and compares an intervention with one involving an SGA is eligible.

Table A. Inclusion/exclusion criteria

Criteria	Inclusion	Exclusion
Population	Adult (18 years or older) outpatients of all races and ethnicities with MDD during either an initial treatment attempt or a second treatment attempt in patients who did not have remission following an initial adequate trial with an SGA	• Children under age 18 • Patients with perinatal depression, seasonal affective disorder, psychotic depression, or treatment-resistant depression (i.e., 2 or more failures of treatment)
Interventions	Second-generation antidepressants:[a] • Bupropion • Citalopram • Desvenlafaxine • Duloxetine • Fluoxetine • Escitalopram • Fluvoxamine • Levomilnacipran • Mirtazapine • Nefazodone • Paroxetine • Sertraline • Trazodone • Venlafaxine • Vilazodone • Vortioxetine Common depression-focused psychotherapies: • Behavioral therapies/behavior modification • Cognitive behavioral therapies • Integrative therapies (e.g., interpersonal therapy) • Psychodynamic therapies • Third-wave cognitive behavioral therapies Complementary and alternative medicines: • Acupuncture • Meditation (e.g., mindfulness-based stress reduction) • Omega-3 fatty acids • S-adenosyl-L-methionine (SAMe) • St. John's wort (*Hypericum perforatum*) • Yoga Exercise: • Any formal exercise program	Ineligible interventions

Table A. Inclusion/exclusion criteria (continued)

Criteria	Inclusion	Exclusion
Interventions (continued)	Other pharmacotherapies for combination or augmentation: • Atypical antipsychotics (aripiprazole, asenapine maleate, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) • Psychostimulants (amphetamine-dextroamphetamine, armodafinil, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methyphenidate, modafinil) • Buspirone • Levothyroxine (T4) • Lithium • Pindolol • Triiodothyronine (T3)	
Control interventions	For all populations of interest (i.e., KQ 1, KQ 3, and KQ 4): • SGAs vs. psychotherapies • SGAs vs. CAM • SGAs vs. exercise • SGAs vs. SGA + psychotherapies • SGAs vs. SGA + CAM • SGAs vs. SGA + exercise • SGAs vs. combinations of eligible interventions In addition, for populations who did not have remission following an initial adequate trial with an SGA (i.e., KQ 2, KQ 3, and KQ 4): • SGA switch[b] vs. SGA switch • SGA switch[b] vs. nonpharmacological treatment • SGA switch[b] vs. SGA augmentation[c] • SGA augmentation[c] vs. SGA augmentation • SGA augmentation[c] vs. nonpharmacological treatment In addition, for network meta-analyses: • Placebo or other inactive control • Comparisons of eligible interventions without an SGA arm	Ineligible interventions, such as placebo arms
Outcomes	• Benefits: response to treatment, remission, speed of response, speed of remission, relapse, quality of life, functional capacity, reduction of suicidal ideas or behaviors, reduction of hospitalization • Harms: overall adverse events, withdrawals because of adverse events, serious adverse events, specific adverse events (including hyponatremia, seizures, suicidal ideas or behaviors, hepatotoxicity, weight gain, gastrointestinal symptoms, sexual side effects), withdrawals because of specific adverse events, or drug interactions (pharmacological and complementary and alternative treatments)	Studies that do not include at least 1 of the outcomes listed under the inclusion criteria
Timing of intervention	No limitations	Not applicable
Publication language	English, German, Italian	All other languages

Table A. Inclusion/exclusion criteria (continued)

Criteria	Inclusion	Exclusion
Study design	- Original research - Eligible study designs include— - For efficacy/effectiveness: - RCTs - SRs and meta-analyses - In addition, for harms:[d] - Nonrandomized controlled trials - Prospective controlled cohort studies - Retrospective controlled cohort studies - Case-control studies	Case series - Case reports - Nonsystematic reviews - Studies without a control group - Nonrandomized studies with fewer than 500 participants - Post hoc or secondary analyses - Pooled studies
Publication type	Any publication reporting primary data	Publications not reporting primary data

CAM = complementary and alternative medicine; KQ = Key Question; MDD = major depressive disorder; RCT = randomized controlled trial; SGA = second-generation antidepressant; SR = systematic review
[a]SGAs approved for treatment of MDD by the Food and Drug Administration.
[b]Switching to another SGA.
[c]Augmenting with a second SGA, an additional non-SGA medication, or a nonpharmacological treatment.
[d]Nonrandomized studies must have a minimum sample size of 500 participants.

Two trained research team members independently reviewed all titles, abstracts, and eligible full-text articles. We designed, pilot tested, and used a structured data abstraction form to ensure consistency of data abstraction. Trained reviewers initially abstracted data from each study. A senior reviewer then read each abstracted article and evaluated the completeness and accuracy of the data abstraction. We resolved discrepancies by consensus or by involving a third, senior reviewer.

Risk-of-Bias Assessment of Individual Studies

To assess the risk of bias of studies, we used definitions based on AHRQ guidance.[10] We rated the risk of bias for each relevant outcome of a study as low, moderate, or high. To determine risk of bias in a standardized way, we used the Cochrane Risk of Bias tool to appraise randomized controlled trials (RCTs).[11] Two independent reviewers assigned risk-of-bias ratings. They resolved any disagreements by discussion and consensus or by consulting a third, independent party.

Data Synthesis

Throughout this review we synthesized the literature qualitatively. When data were sufficient, we augmented findings with quantitative analyses.

For meta-analyses, we used random-effects (DerSimonian-Laird) and fixed-effects models to estimate comparative effects. We assessed statistical heterogeneity in effects between studies by calculating the chi-squared statistic and Cochran's q. We used the I^2 statistic to estimate the magnitude of heterogeneity. We examined potential sources of heterogeneity using sensitivity analysis or analysis of subgroups. We assessed publication bias by checking study registries and using funnel plots and Kendall's tests. However, given the small number of component studies in our meta-analyses, these tests have low sensitivity to detect publication bias.

Because of the dearth of studies directly comparing interventions of interest, we planned network meta-analyses *a priori*. Our outcome measure of choice was the rate of response on the Hamilton Depression Rating Scale (HAM-D), defined as at least a 50-percent improvement of

scores from baseline. We included all placebo- and active-controlled RCTs detected through our searches that were homogeneous in study populations and outcome assessments and were part of a connected network. We employed a hierarchical frequentist approach using random-effects models.[12,13]

Strength of the Body of Evidence

We graded the strength of evidence (SOE) based on AHRQ guidance established for the Evidence-based Practice Centers.[14] This approach incorporates five key domains: risk of bias, consistency, directness, precision, and reporting bias. Grades (high, moderate, low, insufficient) reflect the strength of the body of evidence for a specific outcome on the comparative benefits and harms of the interventions in this review. During the protocol development, we asked the Technical Expert Panel and the Key Informants to rank the relative importance of outcomes following a process proposed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group.[15] We graded only those outcomes that Technical Expert Panel members and Key Informants deemed as important or critical for decisionmaking.

Applicability

We assessed applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[16] We used the PICOTS (populations, interventions, comparators, outcomes, timing, settings) framework to explore factors that may affect applicability.

Results

We documented the outputs of our literature searches and then described included trials in general terms. We also summarized findings by KQ, dealing with KQ 1 (benefits) and KQ 3 (harms) together, and organized the findings by intervention comparisons.

Results of Literature Searches

Our search strategies identified 7,813 possible articles. We excluded 7,368 references following independent dual title and abstract review, and another 390 references at the full-text review stage. Reasons for exclusion were based on eligibility criteria. Overall, we included 44 trials reported in 55 published articles. Of these, 42 trials pertained to KQ 1a and 5 to KQ 1b. Two trials pertained to KQ 2a, and no trials were identified for KQ 2b. In addition, of the 44 trials, 43 trials pertained to KQ 3a and 1 to KQ 3b; 3 pertained to KQ 4.

For network meta-analyses, we included data from 85 additional published trials and 27 unpublished trials. These trials addressed comparisons of interventions of interest that did not meet eligibility criteria for this report; they did, however, provide common comparators that we could use for network meta-analyses.

Effectiveness and Harms of Treatment Options for Initial Treatment of Patients With Major Depressive Disorder

In all, 42 trials comparing SGAs with nonpharmacological treatment options for MDD provided direct evidence on acute-phase outcomes. Study durations ranged from 4 to 96 weeks. Most patients suffered from moderate to severe major depression. Many of the available trials

had serious methodological limitations. Additionally, few trials adequately assessed harms or reported information on quality of life or functional capacity. The figures provide graphical overviews of response rates (Figure A) and discontinuation rates because of adverse events (Figure B) of SGAs compared with psychological interventions, CAM therapies, and exercise.

Figure A. Comparison of response rates of SGAs compared with other eligible interventions (relative risks and 95% confidence intervals)

Psychological Interventions

SGA vs. CBT	0.91 (0.77, 1.07)	(5 trials, 660 participants, moderate SOE)
SGA vs. CBT + SGA	1.03 (0.85, 1.26)	(2 trials, 174 participants, low SOE)
SGA vs. integrative therapies	1.02 (0.86, 1.22)	(1 trial, 318 participants, low SOE)
SGA vs. third-wave CBT	0.77 (0.64, 0.94)	(2 trials, 243 participants, insufficient SOE)

CAM Interventions

SGA vs. acupuncture	0.75 (0.43, 1.30)	(NWMA of RCTs, low SOE)
SGA vs. acupuncture + SGA	0.82 (0.66, 1.00)	(2 trials, 288 participants, low SOE)
SGA vs. omega -3 fatty acids	1.96 (1.26, 3.05)	(NWMA of RCTs, low SOE)
SGA vs. Omega-3 fatty acids + SGA	0.62 (0.33, 1.14)	(2 trials, 74 participants, insufficient SOE)
SGA vs. SAMe	1.22 (0.66, 2.26)	(NWMA of RCTs, low SOE)
SGA vs. St. John's wort	0.96 (0.83, 1.10)	(9 trials, 1,517 participants, low SOE)

Exercise

SGA vs. exercise	1.86 (0.81, 4.27)	(NWMA of RCTs, low SOE)

0.2   0.5   1   2   5

Favors comparator   *Favors SGA*

CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; NWMA = network meta-analysis; RCT = randomized controlled trial; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant; SOE = strength of evidence

Figure B. Comparison of rates of discontinuation because of adverse events from SGA with other eligible interventions (relative risks and 95% confidence intervals)

Psychological Interventions		
SGA vs. any psychological therapy	2.73 (0.89, 8.38)	(5 trials, 871 participants, moderate SOE)
SGA vs. any psych. therapy + SGA	3.42 (0.73, 16.01)	(2 trials, 176 participants, low SOE)
SGA vs. CBT	2.54 (0.39, 16.47)	(3 trials, 441 participants, low SOE)
SGA vs. CBT + SGA	2.93 (0.72, 11.91)	(2 trials, 176 participants, low SOE)
SGA vs. integrative therapies	0.33 (0.01, 8.06)	(1 trial, 287 participants, insufficient SOE)
SGA vs. third-wave CBT	5.17 (1.60, 16.64)	(2 trials, 243 participants, low SOE)
CAM Interventions		
SGA vs. acupuncture + SGA	0.74 (0.11, 4.90)	(2 trials, 240 participants, low SOE)
SGA vs. omega-3 fatty acids	1.00 (0.07, 14.90)	(1 trial, 40 participants, insufficient SOE)
SGA vs. omega-3 fatty acids + SGA	0.5 (0.05, 5.08)	(1 trial, 40 participants, insufficient SOE)
SGA vs. SAMe	2.63 (0.73, 9.46)	(1 trial, 129 participants, insufficient SOE)
SGA vs. St. John's wort	1.70 (1.12, 2.60)	(9 trials, 1,651 participants, moderate SOE)
Exercise		
SGA vs. exercise	20.96 (1.19, 367.97)	(2 trials, 254 participants, low SOE)
SGA vs. exercise + SGA	1.15 (0.35, 3.72)	(1 trial, 103 participants, low SOE)

CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant; SOE = strength of evidence

Second-Generation Antidepressants Compared With Psychological Interventions

Second-Generation Antidepressants Versus Cognitive Behavioral Therapy

We identified 11 trials (1,566 participants) of interventions categorized by the Cochrane Collaboration Depression, Anxiety and Neurosis (CCDAN) Group Topic List as cognitive behavioral therapies. (Note that numbers do not sum to 11 because of studies with multiple CBT arms. The CCDAN Topic List is shown in Appendix B of the full report.) Six trials employed CBT, four used CT, and one each used problem-solving therapy and rational emotive behavior therapy. Three trials included a combination SGA plus CBT arm. Overall, SGAs and CBT monotherapies led to similar rates of response to treatment (moderate SOE), remission (HAM-D-17 ≤7) (low SOE), and overall discontinuation in patients with moderate to severe MDD after 8 to 16 weeks of followup (moderate SOE). After 24 weeks of followup, however, SGAs led to higher rates of overall discontinuation than CBT (low SOE). Rates of discontinuation because of adverse events following SGAs or CBT were not statistically different (low SOE).

Adding CBT to SGA did not show any benefit in remission or response, as defined previously, and led to similar rates of both overall discontinuation (low SOE) and discontinuation due to adverse events compared with SGA monotherapy (low SOE). The evidence was insufficient to draw conclusions about differences in functional capacity, quality of

life, overall risk of adverse events, suicidal ideas or behaviors, or overall risk of serious adverse events.

Second-Generation Antidepressants Versus Integrative Therapies

The only type of integrative therapy used in the included studies was interpersonal psychotherapy. We identified four trials (872 participants) that compared SGA monotherapy with interpersonal psychotherapy alone. One trial also examined the effect of adding interpersonal psychotherapy to the SGA regimen.

SGAs and interpersonal psychotherapy did not lead to statistically different response or remission rates (HAM-D-17 and HAM-D-21 ≤7) (low SOE). The evidence was insufficient to draw conclusions about differences in suicidal ideas or behaviors, overall risk of adverse events, overall risk of serious adverse events, rates of overall discontinuation, or rates of discontinuation because of adverse events. The combination of SGA and interpersonal psychotherapy had 25-percent higher remission rates than SGA monotherapy (low SOE).

Overall discontinuation rates were similar for SGA monotherapy and the combination of SGA and interpersonal therapy (low SOE). The evidence was insufficient to draw conclusions about differences in functional capacity, quality of life, overall risk of adverse events, suicidal ideas or behaviors, overall risk of serious adverse events, or discontinuation because of adverse events.

Second-Generation Antidepressants Versus Psychodynamic Therapies

Three trials (298 participants) compared SGA monotherapy with short-term (2 to 4 months) psychodynamic therapies (PSYD). One trial (272 participants) compared SGA monotherapy with long-term (24 months) PSYD; that study also examined the effect of adding long-term PSYD to the SGA regimen. SGA monotherapy and short-term PSYD monotherapy did not lead to statistically different rates of remission (HAM-D-17 ≤7) (low SOE) or improvements in functional capacity (low SOE). SGAs and PSYD also led to similar rates of overall discontinuation over 8 to 16 weeks (low SOE), 48 weeks (low SOE), and 96 weeks of followup (low SOE). The evidence was insufficient to draw conclusions about differences in quality of life, overall risk of adverse events, overall risk of serious adverse events, or discontinuation due to adverse events.

Adding long-term (96 weeks) PSYD to SGA treatment led to lower rates of overall discontinuation after 96 weeks of followup compared with SGA monotherapy (low SOE). Suicidal ideas or behaviors did not differ statistically for patients on SGAs, long-term PSYD, or a combination of the two (low SOE). The evidence was insufficient to draw conclusions about differences in functional capacity, quality of life, overall risk of adverse events, overall risk of serious adverse events, or discontinuation due to adverse events.

Second-Generation Antidepressants Versus Third-Wave Cognitive Behavioral Therapy

Two randomized trials (243 participants) compared treatment with an SGA versus treatment with behavioral activation, a type of third-wave cognitive behavioral therapy. Patients on SGAs had nearly three times higher rates of overall discontinuation (low SOE) and more than five times higher rates of discontinuation because of adverse events than those treated with behavioral activation (low SOE). The evidence was mixed with regard to response and remission, and was insufficient to draw conclusions about differences in response, remission,

functional capacity, quality of life, overall risk of adverse events, overall risk of serious adverse events, or suicidal ideas or behaviors.

Severity as a Moderator of Comparative Treatment Effectiveness

Four trials yielded insufficient evidence to determine whether the comparative effectiveness of SGAs versus any psychological treatment changes as a function of MDD severity.

Second-Generation Antidepressants Compared With Complementary and Alternative Medicine Interventions

Second-Generation Antidepressants Versus Acupuncture

Three trials (263 participants), all conducted in China, compared an SGA with either full-body or scalp electroacupuncture. For treatment response, pooled results from direct comparisons and network meta-analysis demonstrated no differences in benefits (low SOE). Two trials (237 participants) examined the effect of adding acupuncture to the SGA treatment regimen. Acupuncture in combination with an SGA had 37-percent higher response rates than SGAs alone (low SOE) but did not differ statistically in remission rates (low SOE).

Compared with SGA monotherapy, the combination of SGAs and acupuncture did not differ statistically in overall discontinuation rates (low SOE), overall rates of adverse events (low SOE), or discontinuation rates because of adverse events (low SOE).

The evidence was insufficient to conclude anything about differences in functional capacity, quality of life, or overall risk of harms. Evidence from meta-analyses of placebo-controlled trials, however, indicated lower overall adverse event rates for acupuncture than SGAs.

Second-Generation Antidepressants Versus Omega-3 Fatty Acids

One trial (40 participants) compared an SGA with omega-3 fatty acids. Network meta-analysis indicated a response rate that was twice as high for patients treated with SGAs as for those receiving omega-3 fatty acids (low SOE).

SGAs and omega-3 fatty acids did not lead to significantly different rates of overall discontinuation (low SOE) or discontinuation because of adverse events (insufficient SOE). Evidence was insufficient to draw conclusions about differences in remission, functional capacity, quality of life, suicidal ideas or behaviors, overall risk of adverse events, or overall risk of serious adverse events.

Two trials (72 participants) examined the effect of adding omega-3 fatty acids to the SGA regimen. Compared with SGA monotherapy, adding omega-3 fatty acids to the SGA regimen led to similar overall discontinuation rates (low SOE). Because of methodological shortcomings, the evidence was insufficient to draw any other conclusions.

Second-Generation Antidepressants Versus S-Adenosyl-L-Methionine

One trial (129 participants) compared an SGA with SAMe. Network meta-analysis indicated response rates that did not differ statistically for patients on SGAs or SAMe (low SOE).

Overall discontinuation rates were also similar between patients treated with SGAs or SAMe (low SOE).

The evidence was insufficient to draw conclusions about differences in remission, functional capacity, quality of life, discontinuation due to adverse events, or overall risk of adverse events.

Second-Generation Antidepressants Versus St. John's Wort

We identified 12 trials (1,806 participants) comparing SGAs with St. John's wort monotherapy. Meta-analysis of nine trials (1,513 participants) indicated similar response rates between SGAs and St. John's wort (low SOE). However, all trials compared St. John's wort with moderate- or low-dose SGA regimens, not fully using the approved range of SGA doses. Meta-analysis of five trials (768 participants) demonstrated similar remission rates for the two treatments (low SOE).

SGAs led to 28-percent higher rates of overall discontinuation (moderate SOE) and 70-percent higher rates of discontinuation because of adverse events (moderate SOE) as St. John's wort. The overall risk of adverse events was 17 percent higher among patients receiving SGAs than those receiving St. John's wort (moderate SOE). In contrast, the risk of serious adverse events did not differ significantly between patients receiving SGAs or St. John's wort (low SOE).

The evidence was insufficient to conclude anything about differences in functional capacity, quality of life, or suicidal ideas or behaviors.

Second-Generation Antidepressants Versus Yoga or Meditation

We identified no eligible trial that compared an SGA with yoga or meditation.

Severity as a Moderator of Comparative Treatment Effectiveness

One trial yielded insufficient evidence to determine whether the comparative effectiveness of SGAs versus SAMe changes as a function of MDD severity.

Second-Generation Antidepressants Compared With Exercise

Two trials (309 participants in active-treatment arms) compared an SGA with aerobic exercise. One trial also examined the effects of adding exercise to the SGA regimen. Rates of remission and discontinuation did not statistically differ for patients treated with SGAs and patients treated with exercise monotherapy (low SOE). Estimates based on network meta-analysis indicated no significant difference in response for patients treated with SGAs and those treated with exercise (low SOE).

Although SGAs and exercise led to similar rates of overall discontinuation (low SOE), rates of discontinuation because of adverse events were 20 times as high for patients treated with SGAs as for those assigned to exercise (low SOE).

The combination treatment of SGAs and exercise led to remission, overall discontinuation rates, and rates of discontinuation because of adverse events that did not differ statistically from those among patients receiving SGA monotherapy (low SOE).

Second-Step Therapy: Effectiveness and Harms of Switching or Augmenting Treatment Options for Patients With Major Depressive Disorder

Switch: Second-Generation Antidepressant Versus Second-Generation Antidepressant

Results from two direct comparisons of second-step therapies involving 1,123 patients who were switched to different SGAs indicate no substantial differences in response rates between

SGAs (moderate SOE). Results from one direct comparison involving 727 patients indicate no substantial difference in remission rates or in the decrease in depressive severity between SGAs (low SOE).

Likewise, results from the same direct comparison of 727 patients indicate no significant difference in overall risk of adverse events (low SOE), rates of discontinuation because of adverse events (moderate SOE), overall risk of serious adverse events (low SOE), and suicidal ideas or behaviors (low SOE).

Switch: Second-Generation Antidepressant Versus Cognitive Therapy

Results from one direct comparison of second-step therapies involving 122 patients who were assigned to switch to a different SGA or to CT indicate no substantial differences in rates of response or remission or in the decrease in depressive severity (low SOE). In addition, rates of discontinuation because of adverse events (low SOE) were similar between SGAs and CT.

Switch: Second-Generation Antidepressant Versus Complementary and Alternative Medicine or Exercise

We did not find any eligible switch evidence comparing an SGA strategy with either CAM or exercise.

Augment: Second-Generation Antidepressant Versus Second-Generation Antidepressant

Results from one direct comparison of second-step therapies involving 565 patients indicate no substantial differences in rates of response or remission between SGAs (low SOE). However, results from one direct comparison involving 565 patients indicate a greater decrease in depressive severity after adding bupropion than buspirone (low SOE). In addition, adding bupropion led to lower rates of discontinuation because of adverse events (moderate SOE) but similar rates of serious adverse events (low SOE) and suicidal ideas or behaviors (low SOE) compared with adding buspirone.

Augment: Second-Generation Antidepressant Versus Cognitive Therapy

Results from one direct comparison of second-step therapies involving 182 patients whose treatment was augmented with a second medication versus augmented with CT indicate no substantial differences in rates of response or remission, or in the decrease in depressive severity (low SOE). The same results also indicate no significant differences in rates of discontinuation because of adverse events (low SOE) or overall risk of serious adverse events (low SOE).

Severity as a Moderator of Comparative Treatment Effectiveness of Second-Step Therapies

One industry-supported secondary analysis involving 396 patients found an insignificant trend toward differences in remission rates for those with severe depression (compared with moderate depression). In contrast, a second secondary analysis involving 727 patients, which was government funded, found that having mild or moderate rather than severe depression did not change the likelihood of remitting after treatment with one versus another SGA (insufficient evidence).

Comparative Benefits and Risks of Harms for Selected Subgroups

No trials were specifically designed to assess differences in our specified subgroups. Overall, only three trials addressing a subgroup of interest met the criteria for inclusion: one of subgroups defined by common accompanying psychiatric symptoms and two of subgroups defined by demographic characteristics. For common accompanying psychiatric symptoms, SGAs produced slightly higher remission rates than interpersonal psychotherapy in patients with a comorbid anxiety disorder but not in those without co-occurring anxiety (insufficient SOE). We had no evidence for any other common accompanying symptoms (insomnia, low energy, or somatization).

For subgroups defined by demographic characteristics, we included two trials. In one trial conducted in older adults, SGAs and St. John's wort led to similar response rates and discontinuation rates because of adverse events (low SOE). The other trial included only minority (predominantly black and Latina) women and showed similar reduction in depressive symptoms between SGAs and CBT (insufficient SOE). We did not identify any trials assessing differences between men and women in effectiveness or harms (insufficient SOE).

No trials at all addressed effectiveness or harms in selected subgroups of patients who did not achieve remission following an initial adequate trial with one SGA (insufficient SOE).

Discussion

Key Findings and Strength of Evidence

Across all interventions, we graded the strength of evidence for benefits as moderate for only one comparison—namely, SGAs compared with CBT. Results from trials of this comparison indicate that SGAs and CBT have similar effectiveness regarding symptomatic relief in patients with mild to severe MDD. For risk of harms, we graded the strength of evidence as moderate for some outcomes of three comparisons—namely, SGAs compared with CBT, acupuncture, and St. John's wort. Patients treated with SGAs had a higher risk of experiencing adverse events or discontinuing treatment because of adverse events than patients treated with CBT, acupuncture, or St. John's wort. The evidence is insufficient to draw conclusions about differences in serious adverse events, such as suicidal ideas and behavior.

Our confidence in findings from the comparisons of remaining treatment options was low or insufficient, indicating that these bodies of evidence had major or unacceptable deficiencies. Nevertheless, for most comparisons the overall findings did not show statistically significant differences in benefits but indicated a lower risk of adverse events for nonpharmacological treatment options. Notable exceptions are omega-3-fatty acids, which appear to have lower effectiveness than SGAs; the combination of SGAs with acupuncture, which appears to have higher response rates than SGA monotherapy; and the combination of SGAs with interpersonal psychotherapy, which appears to have better effectiveness than SGA monotherapy. Our confidence in these findings, however, is low, and results have to be interpreted cautiously. In addition, for many comparisons that are limited to single trials, determining whether similar treatment effects between SGAs and other interventions are based on similar effectiveness or high placebo response rates is impossible. Furthermore, we emphasize that detecting no statistically significant difference does not necessarily mean the treatments are equivalent.

The available data offer no conclusions on how selection of treatment strategies might differ based on a patient's severity of depression. Overall, data do not indicate differences in

comparative effectiveness between SGAs and nonpharmacological interventions for patients with severe MDD. This important question concerning MDD severity, although raised by a few systematic reviews,[17-19] remains without a clear answer.

Beyond the two articles identified comparing switching and augmentation strategies employing a limited number of medication options or CT, the absence of relevant comparative data about which treatment options are most effective for those needing second-step treatment (about 70% of patients with MDD)[20,21] was striking.

Our findings are consistent with several prior systematic reviews and meta-analyses that compared SGAs with nonpharmacological interventions. Most of these reviews, however, included populations that were not eligible for our review, such as patients with minor depression, bipolar disorder, or dysthymia.

Our results are partially consistent with the recommendations of both the American Psychiatric Association[22] and the Department of Veterans Affairs/Department of Defense.[23] These consider both pharmacotherapy and psychotherapy to be appropriate individual first-step treatments for patients with mild to moderate MDD, and state that the combination of pharmacotherapy and psychotherapy may be necessary in cases of moderate to severe depression.

In terms of clinical decisionmaking, the information in this review can be helpful to physicians because they can provide a summary of the available evidence base indicating the advantages and disadvantages of these options, and patients can identify which intervention they would prefer. Some options, such as medication and St. John's wort, would require physician supervision and monitoring, given potential side effects and drug interactions. Moreover, patients who would like to maintain or start an exercise regimen in addition to undergoing SGA therapy can be encouraged to do so. The enhanced potential for increasing physical well-being and expanding social interactions may be an added incentive to encourage an exercise regimen.

Applicability

The scope of this review was limited to trials that enrolled adult patients with MDD. We did not attempt to review literature on interventions for children with MDD or for patients with subthreshold depression (depressive symptoms not severe enough to meet diagnostic criteria for a major depressive episode), dysthymia, psychotic depression, or perinatal depression. The included trials covered populations with mild, moderate, and severe MDD; the majority of participants were women. Most trial populations, however, excluded patients with medical comorbidities or suicidal ideas and behaviors; few trials included elderly patients. We did not find evidence to confirm or refute whether treatments are more or less efficacious for various subgroups (i.e., patients characterized by sex, race, or ethnicity, or individuals with coexisting psychiatric conditions).

With few exceptions, interventions in included trials were in line with clinical practice. Except for some CAM trials in which patients received SGA dosages at the lower end of the recommended range, prescribing patterns and doses in the SGA arms of our evidence base were consistent with clinical practice. Some newer SGAs, such as desvenlafaxine, levomilnacipran, vilazodone, or vortioxetine, have never been compared with psychological or CAM treatments or exercise. Nevertheless, reliable evidence indicates that the comparative effectiveness of SGAs is similar.[24] Consequently, we believe that our findings are applicable across the class of SGAs.

As noted previously, detecting no statistically significant difference does not necessarily mean that the treatments are equivalent. The studies involved were designed to test whether an

outcome for one intervention was different from the outcome for another rather than to test equivalence, which would generally require a much larger sample size. This point is especially relevant for findings with a low SOE. While confidence intervals were relatively narrow and risk ratios were often close to 1 (findings consistent with equivalent outcomes), a conclusion of equivalence cannot be made. Further, while moderate-strength evidence at a group level did not detect a difference between SGAs and CBT, how best to tailor this information to an individual patient is still not clear. Indeed, other potentially relevant indicators (e.g., depressive severity, comorbid psychiatric illness) may favor one over another, but the current evidence base (as indicated in the KQ 1b and 2b findings) is quite limited.

Finally, many trials, particularly for CAM interventions, were conducted outside the United States. Whether and how differences in ethnic or cultural backgrounds and health systems affect the applicability of results to U.S. populations remain uninvestigated and unanswered.

Research Gaps

Across all comparisons of interventions, major research gaps pertain to information about patient-centered outcomes, such as functional capacity and quality of life, and the comparative risk of harms. Lack of information about harms can lead to a biased knowledge base and the potential for decisions that cause more harm than good.

We found no eligible studies that compared SGAs with behavior therapy or behavior modification, humanistic therapies, yoga, or mindfulness interventions. Given the wide use of these types of psychotherapies in clinical practice, further research into their comparative effectiveness with SGAs in treating MDD patients is desirable. For many psychotherapies and all CAM therapies that have been evaluated against an SGA, the data were insufficient because trials did not report important outcomes, most notably quality of life and functional capacity. Future studies should assess remission, response to treatment, quality of life, functional capacity, suicidal ideas and behaviors, and adverse events using standardized measures to allow for more direct comparisons across studies using the same or similar SGAs and psychological interventions. These same deficiencies in the literature extend to the comparative effectiveness of SGAs and both psychological and CAM interventions for treating MDD as a function of depression severity. For CAM interventions, we found that most studies did not include the full range of SGA doses for comparison, and many studies made comparisons with only the very lowest SGA doses. To truly compare any CAM intervention for MDD treatment, future studies will need to incorporate SGA dosing strategies that use the entire SGA dosage range. Finally, a major gap in the evidence is the lack of studies addressing different treatment options for patients who have not achieved remission with first-step therapy. No second-step therapy data at all exist that compare SGA with CAM or exercise treatments. This void in the evidence base is a major one that will perplex and confound clinicians, patients, policymakers, and guideline developers alike.

Conclusions

Overall, the available evidence indicates that SGAs and CBT do not differ significantly in symptomatic relief as first-step treatments for adult outpatients with mild to severe MDD. The evidence is insufficient to draw conclusions about the comparative risk of serious adverse events, such as suicidal ideas and behaviors. Given comparable benefits among treatment options, the choice of the initial treatment of MDD should consider results of previous treatments, patient preferences, and feasibility (e.g., costs, likely adherence, and availability) following a discussion

of the advantages and disadvantages of each treatment option, including risks of particular adverse effects and potential drug interactions.

Differences with respect to adverse events, personal engagement, and costs may be taken into consideration for the choice of a first-step treatment. Such shared and informed decisionmaking might enhance treatment adherence and improve treatment outcomes for patients with MDD, especially because treatment continuity is one of the main challenges in treating such patients. For second-step therapies, although evidence is limited, no clear benefit emerges to suggest that either switching to a particular SGA or CT, or augmenting with a particular medication or CT, is preferable. Available data suggest that switching to another SGA, switching to CT, or augmenting with a particular medication or CT are all reasonable options. The more important decision appears to be simply to try a different evidence-based approach.

Addendum

In the manuscript summarizing the findings of this report for journal submission, we employed a different statistical approach for random effects meta-analyses than in the AHRQ report. We followed journal policy and used restricted maximum likelihood models instead of DerSimonian and Laird methods. As a consequence, point estimates and the width of some confidence intervals for some effect estimates are slightly different between the AHRQ report and journal manuscript. Differences are minor and do not change conclusions.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

2. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003 Jun 18;289(23):3095-105. PMID: 12813115.

3. Khan A, Sambunaris A, Edwards J, et al. Vilazodone in the treatment of major depressive disorder: efficacy across symptoms and severity of depression. Int Clin Psychopharmacol. 2014 Mar;29(2):86-92. PMID: 24247740.

4. Nemeroff CB. The burden of severe depression: a review of diagnostic challenges and treatment alternatives. J Psychiatr Res. 2007 Apr-Jun;41(3-4):189-206. PMID: 16870212.

5. Thase ME. Treatment of severe depression. J Clin Psychiatry. 2000;61 Suppl 1:17-25. PMID: 10703759.

6. Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: The National Academies Press; 2001. www.nap.edu/openbook.php?record_id=10027.

7. Mojtabai R, Olfson M. National patterns in antidepressant treatment by psychiatrists and general medical providers: results from the National Comorbidity Survey Replication. J Clin Psychiatry. 2008 Jul;69(7):1064-74. PMID: 18399725.

8. Gartlehner G, Hansen RA, Morgan LC, et al. Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center, under Contract No. 290-2007-10056-I.) AHRQ Publication No. 12-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm. PMID: 22299185.

9. 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. Chapters available at www.effectivehealthcare.ahrq.gov.

10. Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions; 2012. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2014. Chapters available at www.effectivehealthcare.ahrq.gov.

11. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. PMID: 22008217.

12. Hong H, Carlin BP, Shamliyan TA, et al. Comparing Bayesian and frequentist approaches for multiple outcome mixed treatment comparisons. Med Decis Making. 2013 Jul;33(5):702-14. PMID: 23549384.

13. Jones B, Roger J, Lane PW, et al. Statistical approaches for conducting network meta-analysis in drug development. Pharm Stat. 2011 Nov-Dec;10(6):523-31. PMID: 22213533.

14. Berkman ND, Lohr KN, Ansari M, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update, 2013. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville MD: Agency for Healthcare Research and Quality; 2014. Chapters available at www.effectivehealthcare.ahrq.gov.

15. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol. 2011 Apr;64(4):395-400. PMID: 21194891.

16. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions; 2010. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2014. Chapters available at www.effectivehealthcare.ahrq.gov.

17. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA. 2010 Jan 6;303(1):47-53. PMID: 20051569.

18. Kirsch I, Deacon BJ, Huedo-Medina TB, et al. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008 Feb;5(2):e45. PMID: 18303940.

19. 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.

20. Gaynes BN, Rush AJ, Trivedi MH, et al. Primary versus specialty care outcomes for depressed outpatients managed with measurement-based care: results from STAR*D. J Gen Intern Med. 2008 May;23(5):551-60. PMID: 18247097.

21. Gaynes BN, Lux LJ, Lloyd SW, et al. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review No. 33. (Prepared by RTI International-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016I.). AHRQ Publication No. 11-EHC056-EF. Rockville, MD: Agency for Healthcare Research and Quality; September 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm. PMID: 22091472.

22. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 3rd ed. Arlington, VA; Oct 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf.

23. Department of Veteran Affairs, Department of Defense. VA/DoD Clinical Practice Guideline for Management of Major Depressive Disorder (MDD). May 2009. www.healthquality.va.gov/.

24. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med. 2011 Dec 6;155(11):772-85. PMID: 22147715.

Introduction

Background

Depressive disorders can be serious, disabling illnesses. Major depressive disorder (MDD),[1] defined as the presence of depressed mood or loss of interest or pleasure, along with at least four additional MDD diagnosis criteria or symptoms for at least 2 weeks, is the most prevalent and disabling, affecting more than 16 percent of U.S. adults (lifetime).[2] MDD can be characterized as mild, moderate, or severe based on symptom severity, functional impairment, and level of patient distress;[1] in clinical trials, these distinctions are typically made by scores on a depressive rating instrument.[3] Approximately one-third of patients with MDD are severely depressed,[4] which is associated with depression that is harder to treat, as evidenced by more difficulty in achieving treatment response and remission.[5]

The burden of depressive illnesses, in both human and financial terms, is enormous; depression has become the second leading cause of disability throughout the world.[6,7] MDD, in particular, exerts a negative impact on physical health. It reduces participation in preventive health care activities[8,9] and adherence to medical treatment.[10] It increases the likelihood of chronic conditions such as obesity, smoking, sedentary lifestyles, and hypertension,[11,12] as well as amplifies the risk of cancer[13] and death following myocardial infarction.[11] Mortality rates attributable to MDD and other depressive illnesses are high; approximately 4 percent of adults with a mood disorder die by suicide, and depression precedes about two-thirds of deaths due to suicide.[14]

In 2000, the U.S. economic burden associated with depressive disorders was estimated to be $83.1 billion, a figure that has likely increased during the ensuing 10 years. More than 30 percent of these costs are attributable to direct medical expenses.[14]

In any given year, nearly 7 percent of the U.S. adult population (approximately 17.5 million people in 2014) experiences an episode of MDD that warrants treatment.[2] Approximately one-half of these individuals seek care. Most patients receiving care obtain treatment in primary care settings,[15] where second-generation antidepressants (SGAs) are the most commonly prescribed agents.[16] Patients who initially present to a psychiatric clinic are, in general, similar to those who seek treatment in primary care settings.[17,18]

For patients who do receive care, only 20 percent receive a minimal degree of adequate treatment, based on available evidence-based guidelines as receiving either pharmacotherapy (at least 2 months of an appropriate medication for MDD plus more than four visits to any type of physician) or psychotherapy (at least eight visits with any health care professional lasting an average of at least 30 minutes).[19-21] Such inadequate care might result from actions by the patient (e.g., not adhering to clinician recommendations) and by the clinician (e.g., not providing evidence-based care in concordance with treatment guidelines). Whatever the cause,[20,21] for the general population of patients with MDD, the risk of *undertreatment* can be substantial.

In contrast, for the group receiving pharmacotherapy treatment, *overtreatment* with antidepressant medications poses another potential risk. Several recent studies involving comparisons with placebo controls have highlighted differences in response to pharmacotherapy based on baseline depression severity, suggesting a risk of excessive use of these treatment interventions for patients with mild disease.[22-25] Eligibility criteria for most clinical trials require severely or very severely depressed patients, raising concerns about the generalizability of their results to populations with milder degrees of MDD (which are commonly seen in primary care settings).

Several meta-analyses have reported that as baseline depressive symptoms increase, response to pharmacotherapy improves. One meta-analysis of patient-level data from six randomized controlled trials (RCTs) of antidepressants reported that response to two types of antidepressants (imipramine or paroxetine) begins to outpace placebo response only when baseline scores on the 17-item version Hamilton Depression Rating Scale (HAM-D) exceed 25.[22] In other words, patients with mild MDD who are identified and treated may be at risk of antidepressant overtreatment. Therefore, considering the role of depression severity in MDD on treatment outcomes can be crucial in guiding treatment selection.

Outcomes following an initial, evidence-based treatment with antidepressants in primary care settings are equivalent to those in psychiatric specialty clinics. In each of these types of settings, approximately 30 percent of patients will experience symptom remission (usually defined as a HAM-D score of ≤ 7); about 70 percent will have an inadequate treatment response.[26,27] Providing this latter group (i.e., the remaining 70 percent) with a second treatment attempt led to similar rates of improvement;[28] such interventions can include switching antidepressants or augmenting with a second medication.

These data suggest that outcomes achieved in psychiatric clinics for both an initial treatment attempt and a second attempt are applicable to primary care settings. However, remission decreases to 15 percent for patients who have not yet recovered following two adequate antidepressant trials. This pattern suggests that patients experiencing treatment failure following two adequate trials of antidepressants would benefit from psychiatric referral where clinicians can try more complicated treatment regimens.[29] Accordingly, this systematic review (SR) will focus on the initial two treatment attempts for depressive illness.

Purpose of This Report

Primary care physicians provide the largest number of antidepressant prescriptions and account for most of the near doubling in the use of antidepressants over the past decade.[30] Accordingly, much of this treatment may be for patients with either threshold or mild MDD, suggesting a risk of overtreatment for this group. At the same time, primary care physicians appreciate that other potentially effective interventions are available. According to the topic nominators, primary care physicians require an evidence base identifying the comparative effectiveness of the available treatments for depression to increase the likelihood that treatments are selected and managed correctly. This review will focus on two key issues facing primary care physicians:

1. As an initial treatment choice, how effective are SGAs compared with nonpharmacologic interventions?
2. For patients whose depression did not achieve remission following initial treatment with an SGA, what is the comparative effectiveness of alternative pharmacological and nonpharmacological options? These options include adding a pharmacological or nonpharmacological treatment to the initial medication choice (which we refer to as augmentation) or switching to a different SGA or to a nonpharmacological treatment.

Interventions for MDD

Management of MDD involves three treatment phases (see Figure 1): the acute phase, in which symptoms are treated to remission; the continuation phase, during which remission is sustained until the episode has resolved (ranging from 4 to 9 months); and the maintenance phase, in which treatment is maintained to prevent recurrence of another episode of MDD.

Figure 1. Phases of treatment for major depression
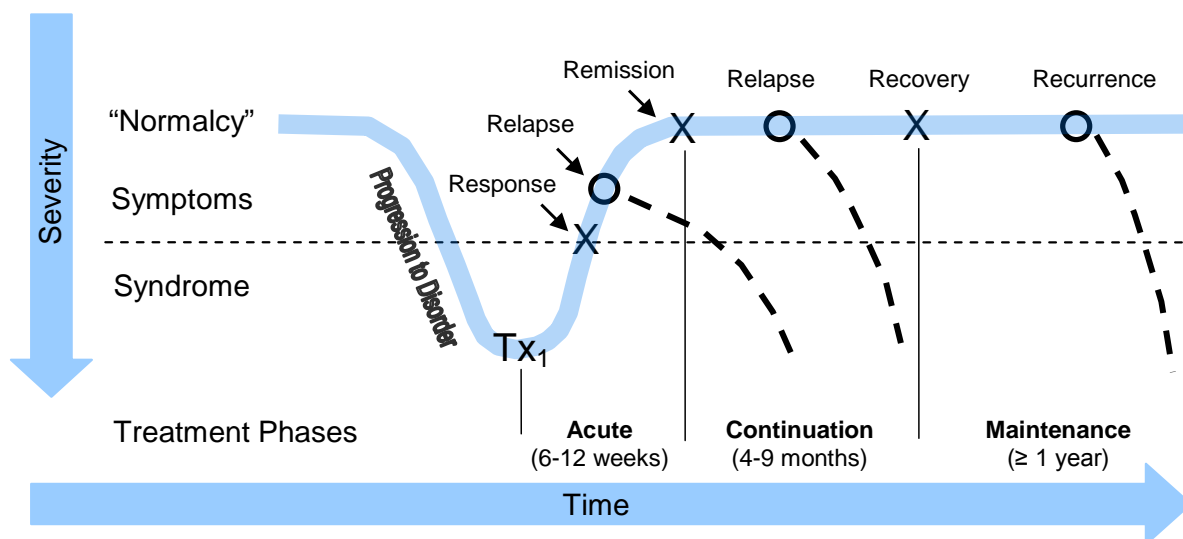
Source: Recreated based on Kupfer, 1991.[31] Tx$_1$=treatment attempt 1; dashed lines indicate hypothetical worsening of depressive severity. Remission, the goal of for treatment, refers to the resolution of depressive symptoms and return to premorbid functioning; response refers to substantial clinical improvement which may or may not reach remission.

Pharmacotherapy remains the primary intervention for MDD patients in primary care. Nonetheless, patients and clinicians may prefer other options (or at least want to be able to consider them). These include psychotherapeutic interventions, complementary and alternative medicine (CAM) options, or exercise. As noted above, clinicians want comparative effectiveness data to help guide treatment selection across these various choices.[32]

We review below the treatment options relevant to this comparative effectiveness review. Given the likelihood of greater benefit of pharmacotherapy for more severely depressed than mildly depressed patients, an important clinical issue is to determine the comparative benefits and harms of SGAs with other treatment options such as psychotherapy, CAM interventions, or exercise as potential monotherapy for patients with mild to severe MDD. A related issue concerns their roles as potential adjuncts to antidepressants for patients with more severe MDD.

Pharmacotherapy for MDD

Pharmacotherapy (e.g., SGAs) dominates the medical management of depressive disorders. This SR will focus on SGAs, which we define as including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, bupropion, mirtazapine, nefazodone, and trazodone. Standard dosing for SGAs available in the United States is shown in Table 1.

Focusing solely on SGAs more accurately represents the pharmaceutical therapies that primary care clinicians prescribe most often.[16,33] Furthermore, because SGAs are most frequently used as first-step therapy, we will examine only comparisons that include SGAs in at least one arm of any given comparative study.

Table 1. SGAs: Usual total daily dosing range and frequency of administration for adults

Generic Name	U.S. Trade Name[a]	Usual Daily Dosing Range	Frequency
Bupropion	Wellbutrin®	200–450 mg	Three times daily
	Wellbutrin SR®	150–400 mg	Twice daily
	Wellbutrin XL®	150–450 mg	Once daily
Citalopram	Celexa®	20–40 mg	Once daily
Desvenlafaxine	Pristiq®	50 mg	Once daily
Duloxetine	Cymbalta®	40–60 mg[b]	Once or twice daily
Escitalopram	Lexapro®	10–20 mg	Once daily
Fluoxetine	Prozac®	10–80 mg	Once or twice daily
	Prozac Weekly®	90 mg (weekly)	Once weekly
Fluvoxamine	Luvox®	50–300 mg	Once or twice daily
Levomilnacipran	Fetzima®	40–120 mg	Once daily
Mirtazapine	Remeron®	15–45 mg	Once daily
	Remeron Sol tab®	15–45 mg	Once daily
Nefazodone	Serzone®	200–600 mg	Twice daily
Paroxetine	Paxil®	20–60 mg	Once daily
	Paxil CR®	12.5–75 mg	Once daily
Sertraline	Zoloft®	50–200 mg	Once daily
Trazodone	Desyrel®	150–400 mg	Three times daily
Venlafaxine	Effexor®	75–375 mg	Two to three times daily
	Effexor XR®	75–225 mg	Once daily
Vilazodone	Viibryd®	40 mg	Once daily
Vortioxetine	Brintellix®	10–20 mg	Once daily

SGA = second generation antidepressant
[a] CR, SR, XL, and XR are registered trademarks referring to controlled-, sustained-, or extended-release dosage forms, respectively.
[b] Doses of duloxetine up to 120 mg were studied in clinical trials, although doses above 60 mg are not believed to have additional efficacy.

Available evidence for MDD does not warrant choosing one SGA over another based on either greater efficacy or greater effectiveness.[33] Only about 60 percent of patients treated with SGAs respond to treatment (meaning specifically that their depressive severity decreases by at least half as measured by a depression rating scale, an improvement that may or may not meet criteria for remission); approximately 30 percent achieve remission during the first-step treatment.[34]

More than 60 percent of patients experience at least one adverse effect during treatment. Although most adverse effects are minor, such as constipation, diarrhea, and dizziness, they frequently lead to discontinuation of treatment.[35]

As documented above, 70 percent of MDD patients do not achieve remission following initial pharmacological treatment, and available data indicate that no one antidepressant performs better than any other. Accordingly, various other interventions—such as medication combinations, psychotherapy, or CAM treatments—are important options for patients and clinicians. In addition, lifestyle changes, for example, increased exercise, have been recommended as adjunctive treatments for MDD.[36,37] Finally, strategies to augment antidepressant medications for those failing an initial treatment attempt may provide better treatment response than single medications alone.[38]

Psychotherapy for MDD

The American Psychological Association recently concluded that the general benefits of the major psychotherapies that have been studied are significant and large.[39-41] Some effects of psychotherapy tend to last longer and to be less subject to relapse requiring additional treatment

than outcomes following pharmacological interventions;[42] however, the effect of depressive severity on these results is not clear. The psychological interventions used to treat depressed patients include acceptance and commitment therapy, cognitive therapy, cognitive behavioral therapy, interpersonal therapy, psychodynamic therapy (PSYD), and other psychotherapies, which may have different customary lengths of treatment. Of note, the optimal frequency and duration of psychotherapy has not been rigorously studied in controlled trials, and different forms of psychotherapy have different customary lengths of treatment. Consequently, there is no clear evidence for what might be considered an adequate or standard course of these therapeutic approaches.[20]

In general, these interventions potentially help people identify how past and present factors may contribute to their depression and teach them how to deal effectively with them. Certain psychological interventions can help individuals identify negative or distorted thought patterns that contribute to feelings of hopelessness and helplessness that accompany depression. These interventions can also help people acquire skills to relieve suffering and prevent later bouts of depression. Among them are developing or strengthening social networks, creating new ways to cope with challenges, and following self-care plans that include positive lifestyle changes. To date, however, little is known about the comparative efficacy and effectiveness or harms of psychological interventions to treat depression.

CAM for MDD

CAM interventions are a growing area of both treatment and research. The term "complementary" refers to using a nonmainstream treatment approach in conjunction with conventional treatments (as complementary medicine), whereas the term "alternative" refers to using a nonmainstream approach in lieu of conventional treatments (as alternative medicine). Although there is currently momentum in the United States to refer to these therapies as Integrative Medicine or Health, as witnessed by the recent name change of the NIH National Center for Complementary and Alternative Medicine (NCCAM) to the National Center for Complementary and Integrative Health (NCCIH), we use the term *CAM* in this report because it more accurately reflects the nature of the study questions in our review. Below, we summarize what is known from randomized, placebo-controlled trials about the efficacy of CAM interventions.[43-45]

Numerous clinical trials and reviews of CAM therapies for depression exist, including several Cochrane reviews.[46-49] In addition to SRs, the American Psychiatric Association Task Force and the Canadian Network for Mood and Anxiety Treatments have issued practice guidelines that incorporate the adjunctive use of several CAM interventions.[50,51] Although the evidence base from high-quality RCTs is limited, sufficient placebo-controlled evidence exists to support St. John's wort for mild to moderate MDD.[52] The evidence base is not as robust for the use of yoga, acupuncture, meditation, S-adenosyl-L-methionine, and omega-3 fatty acids.[48,53-58]

Provision of CAM therapies, with the exception of acupuncture, is largely self-directed and often self-administered. Medical providers are rarely taught to use dietary supplements in clinical practice, so patients are often left self-administering these treatments and rarely seek the advice of a CAM provider.[59] Yoga and meditation are typically offered in classroom settings with trained instructors but home-based video courses are available, and medical providers are rarely involved in administering these as treatments. Acupuncture does require state licensure to practice but may be less available outside of urban centers.[60]

Although evidence-based standard dosing schedules for most dietary supplements do not currently exist, the European Union has produced some guidelines for dosing of St. John's

wort.[43,44] Most sources suggest using an extract standardized to 0.1 percent to 0.3 percent hypericin with a dose of 900 mg daily, usually divided into three doses, to deliver a daily hypericin dose of 1 to 2 mg. Although some clinical trials have demonstrated the importance of additional standardization to 3 percent to 5 percent hyperforin, no guidelines for hyperforin content currently exist because of inconsistent results among trials.[45] In the absence of clear guidelines, protocols followed in clinical trials may define standard practice.

Adverse events are uncommon for most CAM treatments, but potential drug interactions between some dietary supplements and other medications are of some concern. For example, St. John's wort should not be recommended to patients taking any pharmaceutical medications without the advice of a medical provider or pharmacist with expertise in evaluating herb-drug interactions, because it is well documented that the extract is a strong inducer of CYP3A (which can affect the metabolism of many drugs).[61] Importantly, more than one-half of patients with depression are estimated to use some form of CAM therapy, and the majority of patients do not spontaneously disclose CAM use to their care providers, highlighting the necessity for providers to discuss CAM use with their patients being treated for depression.[62]

The comparative effectiveness (either benefits or harms) of CAM and other therapies is not known. As noted for other interventions, the role of depressive severity on these outcomes remains unclear as well.

Exercise for MDD

The use of exercise as either a primary treatment or an augmentation strategy for depression has a growing literature and evidence base. The most comprehensive Cochrane review identified 32 trials involving 1,858 participants with diagnosed MDD;[63] the authors found a moderate clinical benefit of exercise versus no treatment or control. Although small in number, some studies compare exercise with cognitive therapy, medications, and alternative therapies; most find no clear differences in benefits.

This literature continues to evolve. SRs of exercise versus an inactive control suggest small but clinically meaningful benefits (in the elderly a reduction of approximately 20 percent in depressive severity).[64] In addition, recently published clinical trial data indicate that the benefit from exercise is similar to that from sertraline in terms of reducing depressive symptoms in patients with cardiovascular disease and elevated depressive symptoms (but not necessarily MDD), with additional improvements in cardiovascular biomarkers; these findings suggest benefit for both clinical outcomes and quality of life.[65]

Nevertheless, the comparative effectiveness of exercise as either a primary treatment for MDD or an augmentation therapy is unknown. Several clinical trials addressing MDD and exercise are currently under way (http://ccdan.cochrane.org/specialised-register; www.clinicaltrials.gov/), suggesting a need for a review of this area.

Exercise covers a broad range of activities done over varying durations of time and done singly, in classes, or in informal groups. This SR will focus on the benefits and harms of formal exercise activities (a prescribed exercise regimen, either supervised or unsupervised) that enroll people with an explicit diagnosis of MDD because these interventions are the ones most likely to be studied in trials.

Scope and Key Questions

Scope of This Review

This review will examine the evidence base for primary care management of MDD for the first two treatment attempts, after which primary care clinicians would consider referral to or consultation by a mental health professional. The specific Key Questions (KQs) are listed below, and Figure 2 displays the analytic framework that guided our work.

Key Questions

KQ 1a. In adult patients with MDD who are undergoing an initial treatment attempt, what is the effectiveness of second-generation antidepressant (SGA) monotherapy compared with the effectiveness of either nonpharmacological monotherapy or combination therapy (involving nonpharmacological treatments with or without an SGA)?

KQ 1b. Does comparative treatment effectiveness vary by MDD severity?

KQ 2a. In adult patients with MDD who did not achieve remission following an initial adequate trial with one SGA, what is the comparative effectiveness of second-step therapies?[a]

KQ 2b. Does comparative treatment effectiveness vary by MDD severity?

KQ 3a. In adult patients with MDD, what are the comparative risks of harms of these treatment options:
1. For those undergoing an initial treatment attempt?
2. For those who did not achieve remission following an initial adequate trial with an SGA?

KQ 3b. Do the comparative risks of treatment harms vary by MDD severity?

KQ 4. Do the benefits and risks of harms of these treatment options differ by subgroups of patients with MDD defined by common accompanying psychiatric symptoms (coexisting anxiety, insomnia, low energy, or somatization) or demographic characteristics (age, sex, race, or ethnicity)?

---

[a] Any comparison that involves an eligible intervention (whether as a monotherapy or a combination therapy) and compares an intervention with one involving an SGA is eligible. Examples of potential comparisons are listed below.

Figure 2. Analytic framework for treatment of major depressive disorder
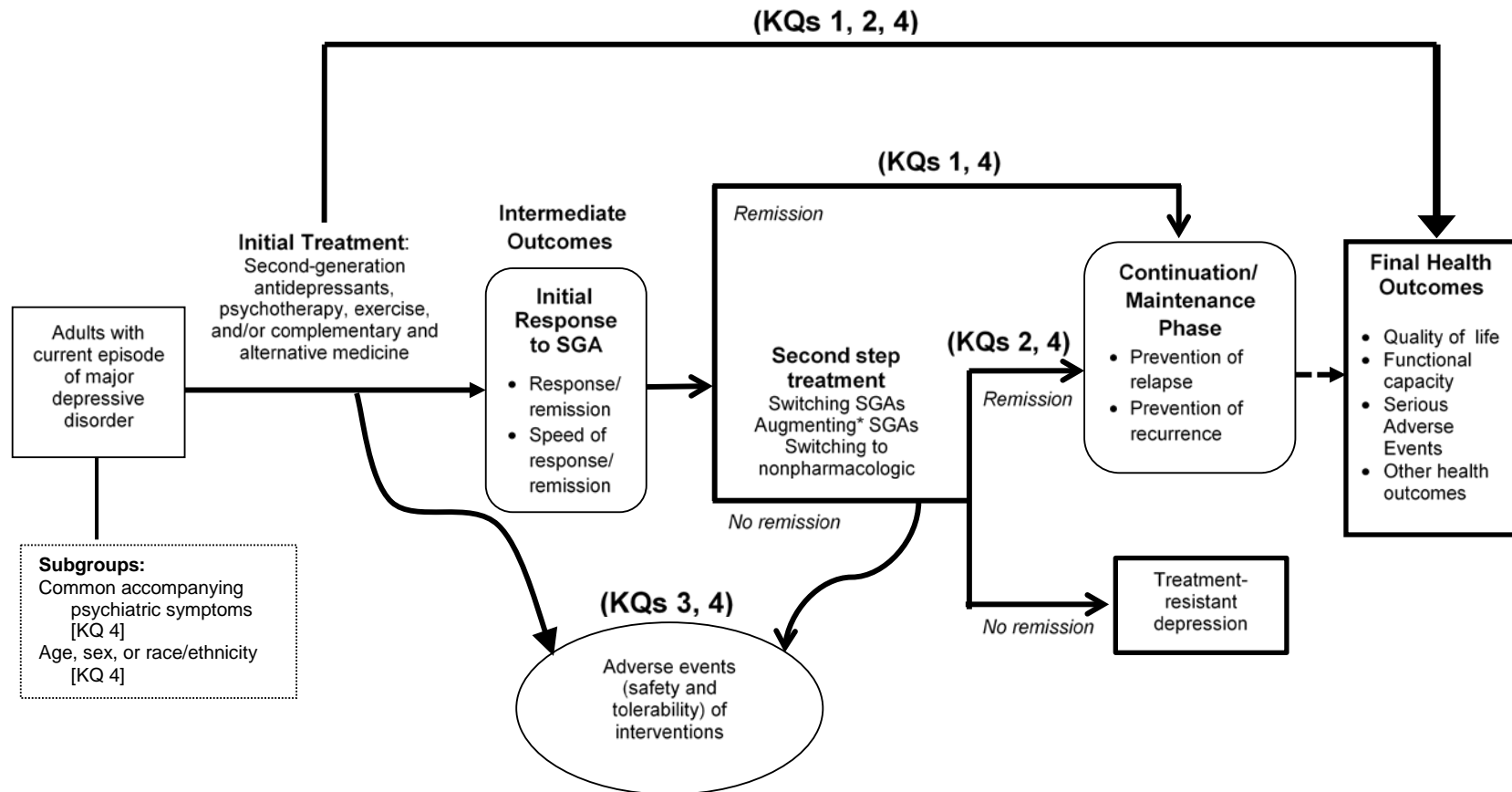
KQ = Key Question; SGA = second-generation antidepressant
*Augmenting with a second SGA, additional medication or a nonpharmacologic treatment.

8

Organization of This Report

The remainder of the review first describes our methods in detail; it then presents the results of our synthesis of the literature with summary tables and the strength of evidence grades for major comparisons and outcomes. The discussion section offers our conclusions, summarizes our findings, and provides other information relevant to interpreting this work for clinical practice and future research.

Appendix A contains the exact search strings for our literature searches. Appendix B presents the typology used to categorize common, depression-focused psychotherapies. Appendix C lists the studies excluded at the stage of reviewing full-text articles with reasons for exclusion. Risk of bias assessments of individual studies in this review are presented in Appendix D. Strength of evidence profiles appear in Appendix E. Published and unpublished trials included in the network meta-analyses on response to treatment are listed in Appendix F. Appendix G presents data from the network meta-analyses.

Methods

The methods for this comparative effectiveness review follow the guidance provided in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (www.effectivehealthcare.ahrq.gov) for the Evidence-based Practice Center (EPC) program. The main sections in this chapter reflect the elements of the protocol established for this review. Certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[66] All methods and analyses were determined a priori.

The AHRQ Effective Health Care (EHC) program's Topic Triage group developed and reviewed the topic; because this group deemed the topic sufficiently relevant, they moved it forward for the Topic Refinement phase. All topics are reviewed and assessed for appropriateness for systematic review (see EHC Web site for information on the process for selecting topics: www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/). Once a topic is assessed and determined to be appropriate for further product development in the EHC program, AHRQ assigns it to a research team. Further development of the topic occurs with the input of key informants and technical experts (see the EHC Web site for information on the research process: www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/).

Topic Refinement and Review Protocol

During the topic refinement, we engaged in a public process to develop a draft and final protocol for the review. We generated an analytic framework, preliminary Key Questions (KQs), and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, settings). Information provided by the topic nominator helped guide our processes. Initially a panel of eight Key Informants gave input on the KQs to be examined; these KQs were posted on AHRQ's Web site for public comment (www.effectivehealthcare.ahrq.gov) from February 3, 2014, through February 24, 2014, and revised as needed. We then drafted a protocol for the systematic review.

In addition, we recruited a panel of technical experts (TEP) to provide high-level content and methodological expertise throughout the development of the review. They represented consumer perspective and professional organizations, researchers, and payers with expertise in psychopharmacology, psychotherapy, complementary and alternative medicine (CAM), and exercise therapies for depression. TEP members participated in one conference call to review the analytic framework, KQs, and PICOTS and in several discussions through email.

Literature Search Strategy

Search Strategy

To identify articles relevant to each KQ, we searched MEDLINE® (via PubMed), EMBASE, the Cochrane Library, AMED (Allied and Complementary Medicine Database), PsycINFO, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) from January 1, 1990, through January 13, 2015, using analogous search terms (Appendix A). We used a combination of medical subject headings and title and abstract key keywords, focusing on terms to describe the relevant population and interventions of interest. An experienced information scientist ran the

searches; another information scientist (EPC librarian) peer-reviewed the searches. We limited the electronic searches to English-, German-, and Italian-language and human-only studies.

In addition to electronic searches, we manually searched reference lists of pertinent reviews, included trials, and background articles on this topic to identify any relevant citations that our searches might have missed. We imported all citations into an EndNote®X6 electronic database.

We searched for "gray literature" relevant to this review following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* for these steps.[67] Sources of gray literature included ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, Drugs@FDA, the European Medicines Agency, the National Institute of Mental Health Web site, the American Psychological Association Web site, Scopus, and the Conference Proceedings Citation Index.

The AHRQ Scientific Resource Center requested scientific information packets from relevant pharmaceutical manufacturing companies, asking for any unpublished studies or data relevant for this systematic review. The AHRQ Scientific Resource Center managed the process of submitting requests for scientific information packets, which contain information about drugs and CAM interventions. We received information packets from Eli Lilly and Company and Merck & Co., Inc.

We investigated any literature suggested by the peer reviewers or the public and, when appropriate using the same methods as described below, incorporated additional studies into the final review.

Inclusion and Exclusion Criteria

We specified our inclusion and exclusion criteria based on the PICOTS identified in topic refinement. Table 2 specifies inclusion and exclusion criteria; subsequent sections define the PICOTS in more detail.

Population(s)

For this review, we included adult (18 years or older) outpatients of all races and ethnicities with MDD during either an initial treatment attempt (KQ 1) or a second treatment attempt in patients who did not achieve remission following an initial adequate trial with a second-generation antidepressant (SGA) (KQ 2).

Subgroups of interest are based on

- common accompanying psychiatric symptoms (anxiety, insomnia, low energy, somatization),
- age,
- sex, and
- race or ethnicity.

Table 2. Inclusion/exclusion criteria

	Inclusion	Exclusion
Population	Adult (18 years or older) outpatients of all races and ethnicities with MDD during either an initial treatment attempt or a second treatment attempt in patients who did not have remission following an initial adequate trial with an SGA	• Children under age 18 • Patients with dysthymia, subthreshold depression, perinatal depression, seasonal affective disorder, psychotic depression, or treatment-resistant depression (i.e., 2 or more failures of treatment)
Geography	No limit	No limit
Date of search	Searches went back until 1990	• Articles published before January 1990
Settings	• Primary, secondary, and tertiary care outpatient settings	• Inpatient settings
Interventions	• As defined in the PICOTS criteria	• First-generation antidepressants • Any other interventions not defined in the PICOTS criteria
Control interventions	• As defined in the PICOTS criteria	• Ineligible interventions (see PICOTS criteria)
Outcomes	• As defined in the PICOTS criteria	• Studies that do not include at least 1 of the outcomes listed under the inclusion criteria
Timing of intervention	• No limitations	• NA
Publication language	• English, German, Italian	• All other languages

Study design	• Original research
	• Eligible study designs include:
	• For efficacy/effectiveness
	  - RCTs
	  - SRs and meta-analyses
	• In addition for harms[a]
	  - Nonrandomized controlled trials
	  - Prospective controlled cohort studies
	  - Retrospective controlled cohort studies
	  - Case-control studies
	  - Nonrandomized studies
		• Case series
		• Case reports
		• Nonsystematic reviews
		• Studies without a control group
		• Nonrandomized studies with fewer than 500 participants
		• Post hoc or secondary analyses
		• Pooled studies

Publication type	• Any publication reporting primary data	• Publications not reporting primary data

MDD = major depressive disorder; RCT = randomized controlled trial; SGA = second-generation antidepressant;
SR = systematic review
[a] Nonrandomized studies must have a minimum sample size of 500 participants.

We did not include studies that exclusively focused on patients with dysthymia, subthreshold depression, bipolar depression, perinatal depression, chronic depression, seasonal affective disorder, psychotic depression, or treatment-resistant depression (i.e., two or more treatment failures). We classified severity of depression of patients following a categorization that is outlined in Table 3. There are no agreed-upon thresholds to categorize severity. We used information from the QIDS Data Center[68] as the basis for our categorizations, but we also include categories for the most commonly used measure, the Hamilton Rating Scale for Depression (HAM-D),[17] from a study directly comparing the HAM-D to a semistructured interview and the Clinical Global Impression of Severity.[69] Hence, these ranges should be considered a guide to severity rather than a definitive categorization.

Table 3. Categories of depressive severity[68,69]

Instrument	None/Mild	Moderate	Severe/Very Severe
HAM-D$_{17}$	≤ 13/16	14–19/17–23	≥ 20/≥ 24
HAM-D$_{21}$	≤ 15	16–22	≥ 23
HAM-D$_{24}$	≤ 18	19–26	≥ 27
MADRS	≤ 19	20–34	≥ 35
BDI	≤ 18	18–29	≥ 30
QID-SR	≤ 10	11–15	≥ 16

BDI = Beck Depression Inventory; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; QID-SR = Quick Inventory of Depressive Symptomatology—Self-Report
For HAM-D$_{17}$, the first number or range indicates data from the QIDS Data Center,[68] whereas the second number or range is from the Zimmerman et al. study.[69] The remaining instrument categories are all from the QIDS Data Center.

Interventions

For patients with acute-phase MDD and an initial treatment attempt, we were interested in common depression-focused psychotherapies, common CAM interventions, and exercise

1. as monotherapies
2. in combination with one another, or
3. in combination with SGAs.

For patients who did not achieve remission following an initial adequate trial with an SGA, we were also interested in second-step therapies that involve an eligible intervention (whether as a monotherapy or a combination therapy). Table 4 presents interventions that were eligible for this report. Appendix B gives a more detailed description of common depression-focused psychotherapies.

Table 4. Eligible interventions for major depressive disorders

Second-Generation Antidepressants[a]	Common Depression-Focused Psychotherapies	Complementary and Alternative Medicines	Exercise	Other Pharmacotherapies for Combination or Augmentation
- Bupropion - Citalopram - Desvenlafaxine - Duloxetine - Fluoxetine - Escitalopram - Fluvoxamine - Levomilnacipran - Mirtazapine - Nefazodone - Paroxetine - Sertraline - Trazodone - Venlafaxine - Vilazodone - Vortioxetine	- Behavioral therapies/behavior modification - Cognitive behavioral therapies - Integrative therapies (e.g., interpersonal therapy) - Psychodynamic therapies - Third-wave cognitive behavioral therapies	- Acupuncture - Meditation (e.g., mindfulness-based stress reduction) - Omega-3 fatty acids - S-adenosyl-L-methionine (SAMe) - St. John's wort (Hypericum perforatum) - Yoga	Any formal exercise program	- Atypical antipsychotics (aripiprazole, asenapine maleate, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) - Psychostimulants (amphetamine-dextroamphetamine, armodafinil, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methyphenidate, modafinil) - Buspirone - Levothyroxine (T4) - Lithium - Pindolol - Triiodo-thyronine (T3)

FDA = Food and Drug Administration; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant
[a] SGAs approved for treatment of MDD by the U.S. FDA.

One difficulty that arises with systematic reviews that include a variety of psychological interventions is how to categorize them. When different frameworks are used to organize and categorize the interventions in systematic reviews, the ability to draw conclusions between them

can be substantially diminished. The Cochrane Collaborative Depression, Anxiety and Neurosis (CCDAN) Group has developed a framework for categorizing psychological interventions which it uses in its reviews.[70] In an effort to enhance consistency of categorization of psychotherapies in this review and our ability to compare our findings to those of other large reviews, we have used the first six categories and descriptions of the CCDAN Group's framework: Behavior/Behavior Modification, Cognitive Behavioral Therapy, Third-Wave Cognitive Behavioral Therapy, Psychodynamic Therapies, Humanistic Therapies, and Integrative Therapies (which often combine elements of the other categories, including Cognitive Behavioral Therapy and Psychodynamic Therapies).[70] We did not include the categories of Systemic Therapies or Other Psychologically-Oriented Interventions because these categories reflect the mode of delivery as opposed to the type of therapy. Appendix B presents the CCDAN classification in more detail.

Comparators

For KQ 1, we were interested in direct comparisons of eligible interventions with SGAs as single interventions. Except for network meta-analyses, we excluded studies that did not include SGA monotherapies in at least one arm of the study. For KQ 2, we were also interested in studies that modified an existing SGA strategy and compared it with nonpharmacological interventions other pharmacological treatment strategies, or combinations of nonpharmacological and pharmacological strategies. These second-step therapies could involve a switch to a new treatment or augmentation of an existing treatment. We excluded studies that did not involve an SGA (whether as a new monotherapy or as part of a combination therapy). Table 5 lists possible head-to-head comparisons of eligible interventions with SGAs.

Table 5. Possible comparisons of eligible interventions with second-generation antidepressants

For all populations of interest (i.e., KQ 1, KQ 3, and KQ 4)
SGAs vs. psychotherapies
SGAs vs. CAM
SGAs vs. exercise
SGAs vs. SGA + psychotherapies
SGAs vs. SGA + CAM
SGAs vs. SGA + exercise
SGAs vs. combinations of eligible interventions
In addition for populations who did not achieve remission following an initial adequate trial with an SGA (i.e., KQ 2, KQ 3, and KQ 4):
SGA switch[a] vs. SGA switch[a]
SGA switch[a] vs. nonpharmacological treatment
SGA switch[a] vs. SGA augmentation[b]
SGA augmentation[b] vs. SGA augmentation[b]
SGA augmentation[b] vs. nonpharmacological treatment
In addition for network meta-analyses (KQ1):
Any eligible intervention vs. placebo
Any eligible intervention vs. any other eligible intervention

CAM = complementary and alternative medicine; KQ = Key Question; SGA = second-generation antidepressant; vs. = versus
[a]Switching to another SGA.
[b]Augmenting with a second SGA, for an additional non-SGA medication, or a nonpharmacological treatment.

Outcomes

In general, we were interested in patient-relevant health outcomes. In collaboration with the Technical Expert Panel (TEP) and the Key Informants, we selected the following outcomes as relevant for this report.

- Benefits: response to treatment, remission, speed of response, speed of remission, relapse, quality of life, functional capacity, reduction of suicidal ideas or behaviors, reduction of hospitalization
- Harms: overall adverse events, withdrawals because of adverse events, serious adverse events, specific adverse events (including hyponatremia, seizures, suicidal ideas or behaviors, hepatotoxicity, weight gain, gastrointestinal symptoms, sexual side effects), or drug interactions (pharmacological and complementary and alternative treatments)

In addition, during the protocol development, we asked the TEP and the Key Informants to rank the relative importance of these outcomes following a process proposed by the GRADE Working Group.[71] We used SurveyMonkey© for an anonymous ranking of the relative importance of outcomes. Participants used a 9-point Likert scale to rank outcomes into three categories: (1) critical for decisionmaking, (2) important but not critical for decisionmaking, and (3) of low importance for decisionmaking. Table 6 lists the 11 outcomes (seven benefits, four harms) that respondents viewed as either critical or important for decisionmaking. For average ratings, 9 would indicate greatest importance and 1 least importance.

Table 6. Outcomes rated as critical or important for decisionmaking

Category for Decisionmaking	Outcomes	Average Ratings
Critical	Reduction of suicidal ideas or behaviors	8.00
	Quality of life	7.57
	Response to treatment	7.43
	Remission	7.29
	Functional capacity	7.29
	Risk of serious adverse events	7.14
Important	Overall risk of adverse events	6.43
	Speed of remission	6.14
	Risk of drug interactions	5.71
	Speed of response	5.71
	Risk of discontinuing treatment because of adverse events	5.43

Timing

We had no limitations on study duration or length of followup.

Setting

We included outpatients from primary, secondary, and tertiary care settings.

Study Selection

Two trained research team members independently reviewed all titles and abstracts identified through searches for eligibility against our inclusion/exclusion criteria using AbstrackR®.[72] Studies marked for inclusion underwent full-text review. For studies without adequate information at the title/abstract stage to determine inclusion or exclusion, we retrieved the full text and then made the determination. All results at both title/abstract and full-text review stages were tracked in an EndNote® bibliographic database (Thomson Reuters, New York, NY).

We retrieved and reviewed the full text of all articles retained during the title/abstract phase. Two trained team members independently reviewed each full-text article for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agreed that a study did not meet the eligibility criteria, we excluded the study. If the reviewers disagreed, conflicts were resolved by discussion and consensus or by consulting a third member of the review team.

We recorded the reason that each excluded full-text publication did not satisfy the eligibility criteria. If the information in published articles was insufficient to permit us to decide about inclusion or exclusion, we contacted authors for further clarification. Appendix C gives the bibliography of excluded studies and reasons for exclusion.

For this review, results from low risk of bias head-to-head trials provide the strongest evidence to compare interventions of interest with respect to benefits and harms. In addition to head-to-head studies, we included placebo-controlled trials for network meta-analysis. For harms (i.e., evidence pertaining to safety, tolerability, and adverse events), we intended to examine data from both randomized and nonrandomized studies; however, we found no eligible nonrandomized studies. (Throughout this report we use "harms" as a summary term for adverse events and unwanted effects, as suggested by the CONSORT [Consolidated Standards of Reporting Trials] statement.[73])

Data Extraction

We designed, pilot-tested, and used a structured data abstraction form to ensure consistency of data abstraction. Trained reviewers initially abstracted data from each study. A senior reviewer then read each abstracted article and evaluated the completeness and accuracy of the data abstraction. We resolved discrepancies by consensus or by involving a third, senior reviewer.

We abstracted the following data from included trials: study design, eligibility criteria, intervention, additional medications allowed, funder of the study, methods of outcome assessment, population characteristics (such as age, sex, race, ethnicity, or coexisting anxiety), sample size, attrition, and outcomes of interest. We recorded intention-to-treat results (ITT; i.e., all patients are analyzed as randomized with missing values imputed) if available. For studies eligible for quantitative analyses, we contacted authors if reported data were incomplete or missing.

Risk of Bias Assessment of Individual Studies

To assess the risk of bias of studies, we used definitions based on AHRQ guidance.[74] We rated the risk of bias for each relevant outcome of a study as low, moderate, or high. In general terms, results of a study with low risk of bias are considered to be valid. Medium risk of bias implies some confidence that the results represent true treatment effect. The study is susceptible to some bias, but the problems are not sufficient to invalidate the results (i.e., no flaw is likely to cause major bias). A study with high risk of bias has significant methodological flaws (e.g., stemming from serious errors in design or analysis) that may invalidate its results. Ratings of risk of bias are not comparable across study designs. That is, a low risk of bias nonrandomized study does not necessarily equal a low risk of bias randomized controlled trial (RCT). We take limitations of certain study designs into consideration when we grade the strength of the evidence.

We included all eligible studies regardless of risk of bias in this review. For quantitative analyses, however, we used studies with high risk of bias only for sensitivity analyses.

To determine risk of bias in a standardized way, we used the Cochrane Risk of Bias tool to appraise randomized controlled trials RCTs.[75] For nonrandomized studies, we employed criteria outlined by Deeks et al.[76] For systematic reviews with meta-analyses we used the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) tool.[77]

Two independent reviewers assigned risk of bias ratings. They resolved any disagreements by discussion and consensus or by consulting a third, independent party. Time constraints precluded our contacting study authors for clarification of methodological questions. Appendix D presents risk of bias assessments of individual studies included in this review.

Data Synthesis

Throughout this review we synthesized the literature qualitatively. When data were sufficient, we augmented findings with quantitative analyses. We conducted meta-analyses of data for head-to-head comparisons for trials that were fairly homogenous in study populations and outcome assessments. We also conducted network meta-analyses to compare pharmacological with nonpharmacological interventions when direct head-to-head evidence was sparse or entirely lacking.

Meta-Analysis of Direct Comparisons

To determine whether quantitative analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance.[78]

For all analyses, we used random-effects and fixed-effects models to estimate comparative effects. We used DerSimonian & Laird models for random effects analyses. For efficacy, we were able to conduct meta-analyses on three outcomes relating to benefits:

1. the relative risk of achieving response (as defined by authors, most commonly defined as a 50 percent or greater improvement from baseline) on the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Åsberg Depression Rating Scale (MADRS) at study endpoint
2. the relative risk of achieving remission (as defined by authors, most commonly defined as a HAM-D score of < 7) at study endpoint
3. the weighted mean difference of changes on HAM-D

For harms, we conducted meta-analyses on the relative risk of

1. experiencing an adverse event
2. experiencing a serious adverse event,
3. discontinuing treatment,
4. discontinuing treatment because of harms
5. discontinuing treatment because of lack of efficacy

Because studies reported very few and sometimes no events for risk of suicidal ideas or behaviors, we used Peto's odds ratio as an outcome measure for meta-analyses on the comparative risk of suicidal ideas and behaviors.

Evidence indicates that no substantial differences in benefits exist among SGAs;[33] therefore, in all meta-analyses we compared SGAs as a class with other interventions of interest. When we conducted meta-analyses, we assessed statistical heterogeneity in effects between studies by calculating the chi-squared statistic and Cochran's q. We used the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity) to estimate the magnitude of heterogeneity. We examined potential sources of heterogeneity using sensitivity analysis or analysis of subgroups. For quantitative analyses, we conducted sensitivity analyses including high risk of bias studies. Planned stratifications or categories for subgroup analyses included the subgroups listed in the analytic framework (Figure 2).

We assessed publication bias using funnel plots and Kendall's tests. However, given the small number of component studies in our meta-analyses, these tests have low sensitivity to detect publication bias.

We ran all meta-analyses with both random- and fixed-effects models. In cases where results were very similar, we report results from random-effects models. If not, we report results from both random- and fixed-effects models. All meta-analyses were conducted using Comprehensive Meta-analysis, version 3.2.

Network Meta-Analyses

Because we were aware of the dearth of studies directly comparing some interventions of interest, we planned a priori with pre-specified criteria to conduct network meta-analyses on response to treatment with a hierarchical frequentist approach using random effects models.[79,80] Evidence suggests that network meta-analyses agree with head-to-head trials if component studies are similar and treatment effects are expected to be consistent in patients in different trials.[81] Nevertheless, results have to be interpreted cautiously.

To conduct network meta-analyses, we included all placebo- and active-controlled RCTs that were homogenous in study populations and outcome assessments and were part of a connected network. We built on a database of relevant RCTs of a previous report on the comparative efficacy and safety of SGAs.[33] For drugs and most CAM interventions, we included only double-blinded RCTs. For interventions where double blinding was not possible (e.g., psychological intervention or yoga), we required that outcomes assessors had to be blinded. For network meta-analyses, we excluded studies conducted exclusively in subjects who were older than 55 years of age because evidence indicates that older patients have a smaller treatment benefit than younger patients.

Our outcome measure of choice was response to treatment on the HAM-D (defined as a 50 percent improvement of scores from baseline). We chose this outcome because most studies used the HAM-D and reported data on response to treatment. We recalculated response rates for each study using the number of all randomized patients as the denominator to reflect a true ITT analysis. With this approach, we attempted to correct variations in results of modified ITT analyses encountered in individual studies.

The data provided information on the probability of the response of treatment j out of K possible treatments in study i (p_{ij}). We applied a generalized linear model with random effects. The logit for the random effects model[79,80,82] can be expressed as:

$$logit(p_{ij}) = \mu_i + \delta_{ij} + \sum_{k=1}^{K} \frac{\delta_{ik}}{K}$$

where all $\delta_{i1}=1$ and $(\delta_{i2} ..., \delta_{ik}) \sim N[(d_2, ..., d_k), \sum]$.

We fit all models using PROC GLIMMIX in SAS version 9.3, specifying a binomial likelihood and logit link function. For ease of interpretation, we present the relative risks and 95 percent confidence intervals of outcomes of interest for all possible comparisons among our treatments of interest.

Strength of Evidence of the Body of Evidence

We graded the strength of evidence based on the guidance established for the EPC Program.[83] 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, and reporting bias. For some scenarios, it also considers other optional domains that may be relevant: a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect).

Grades reflect the strength of the body of evidence to answer KQs on the comparative benefits and harms of the interventions in this review. Table 7 defines the four grades of strength of evidence.[83] Two trained reviewers assessed each domain for each key outcome; differences were resolved by consensus. One of the two reviewers was always a senior researcher with experience in grading strength of evidence. Following GRADE guidance, we graded the strength of evidence for eight outcomes deemed by the Technical Expert Panel (TEP) and the Key Informants to be of most importance for decisionmaking (see section on outcomes in Inclusion and Exclusion Criteria). Because we found little evidence on overall risk of adverse events, we also graded overall discontinuation rates and discontinuation rates because of adverse events. We used the Guideline Development Tool (www.guidelinedevelopment.org/) to grade the strength of evidence in a standardized manner and to develop summary of findings tables.

Table 7. Definition of strength of evidence grades

Grade	Definition
High	We are very confident that the estimate of effect lies close to the *true effect* for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the *true effect* for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the *true effect* for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the *true effect*.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Applicability

We assessed applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[84] We used the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age of enrolled populations, sex of enrolled populations (e.g., fewer men may be enrolled in some studies), and race or ethnicity of enrolled populations.

Peer Review and Public Commentary

The AHRQ Task Order Officer and an AHRQ associate editor (a senior member of another EPC) reviewed the draft report before peer review and public comment. The draft report (revised as needed) was sent to invited peer reviewers and simultaneously uploaded to the AHRQ Web site where it was available for public comment for 28 days.

We collated all reviewer comments (both invited and from the public) and addressed them individually. We documented all our responses to these comments in a disposition of comments document, which will be posted on the AHRQ EHC program Web site about 3 months after Web publication of the evidence report. The authors of the report have final discretion as to how the

report will be revised based on the reviewer comments, with oversight by the Task Order Officer and associate editor.

Results

Introduction

This chapter begins with the results of our literature search and a general description of the included trials. It is then organized by Key Question (KQ 1 through KQ 4). For each KQ, we give an overview, the key points, and more detailed syntheses of the literature organized by intervention comparisons. We also restate the actual issue for that particular KQ.

In each KQ section, we present a table with characteristics of included trials and results of the main outcomes. More details about included trials can be found at the Systematic Review Data Repository (http://srdr.ahrq.gov/). In Appendix E, we also present "summary of findings" tables that give the main results (effect sizes) for outcomes ranked as critical or important for decisionmaking and the respective strength of evidence (SOE) grades. Appendix G presents data from the network meta-analyses.

Trials that we reviewed reported outcomes data based on an array of commonly used mental health–related measures and assessment tools. Table 8 lists abbreviations of mental health assessment tools encountered in this literature. Important outcomes typically encountered included response to treatment, remission, and changes on depression measures and occasionally quality of life or functional status.

Table 8. Abbreviations and full names of mental health and other assessment tools

Abbreviation	Full Name of Instrument
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory-II
HAM–A–X[a]	Hamilton Rating Scale for Anxiety
HAM–D–X[a]	Hamilton Rating Scale for Depression
MADRS	Montgomery-Åsberg Depression Rating Scale
QIDS-SR-X[a]	Quick Inventory of Depressive Symptomatology-Self Report
WAIS-III	Wechsler Adult Intelligence Scale-III

[a] X indicates the number of items in the scale.

Results of Literature Searches

Our search strategies identified 7,813 possible articles. From that pool, we excluded 7,368 references following independent dual title and abstract review and another 390 references at the full-text review stage. Reasons for exclusion were based on eligibility criteria. Appendix C lists articles excluded during full-text review with reasons for exclusion. Figure 3 documents the disposition of the articles identified from searches.

Description of Included Trials

Overall, we included 44 trials reported in 55 published articles. Of these, 42 trials pertained to KQ 1a and five to KQ 1b. Two trials pertained to KQ 2a, and none was identified for KQ 2b. In addition, of the 44 trials, 43 trials pertained to KQ 3a and one to KQ 3b. Finally, three trials pertained to KQ 4.

Figure 3. PRISMA diagram for treatment of major depressive disorders

```
┌────────────────────────────────┐   ┌────────────────────────────────┐
│ # of records identified through │   │ # of additional records         │
│ database searching (after        │   │ identified through other        │
│ duplicates removed):             │   │ sources:                        │
│ 7,797                            │   │ 16                              │
└────────────────────────────────┘   └────────────────────────────────┘
                  │                                  │
                  └──────────────┬───────────────────┘
                                 ▼
              ┌────────────────────────────────────┐
              │ Total # of title/abstracts screened:│
              │ 7,813                                │
              └────────────────────────────────────┘
                                 │
                                 ├──────────────────────────►  ┌──────────────────────────┐
                                 │                              │ # of records excluded:    │
                                 │                              │ 7,368                     │
                                 ▼                              └──────────────────────────┘
              ┌────────────────────────────────────┐
              │ # of full-text articles assessed for │
              │ eligibility:                         │
              │ 445                                  │
              └────────────────────────────────────┘
                                 │
                                 ├──────────────────────────►
                                 │
                                 ▼
              ┌────────────────────────────────────┐
              │ # of trials included in evidence     │
              │ synthesis:                           │
              │ 44 (55 articles)                     │
              └────────────────────────────────────┘
```

# of records excluded, with reasons: 390

Ineligible publication type:	59
Ineligible population(s):	84
Ineligible or no intervention(s):	34
Ineligible study design:	49
Ineligible or no comparison(s):	131
Ineligible outcome(s):	10
Does not answer a KQ:	5
SR without relevant MA:	7
Abstract only:	11

KQ = Key Question; MA = meta-analysis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SR = systematic review.

To obtain unreported data of interest from included published trials, we sent e-mails soliciting additional data to 31 authors (current contact information for three authors was unavailable). Sixteen authors responded to our query, but many could not provide data because they were no longer available. Ultimately, we obtained additional outcomes data for ten trials.

Trials included for this report had various funding sources. The majority of funding came from government agencies and industry sources, with many trials funded by a mix of sources. Table 9 describes funding sources for each included trial.

Table 9. Reported sources of funding for included trials

Funding Categories	Number of Trials
Multiple sources	10[85-94]
Government	13[95-107]
Industry	10[108-117]
Academic	3[118-120]
Foundation or nonprofit organization	2[87,121,122]
Professional organization	0
Funding source not reported	6[123-128]

For network meta-analyses, we included data from 127 published and unpublished trials. Fifteen of these trials also provide direct evidence for KQ1a; the remaining 112 trials (85 published, 27 unpublished) are included in network meta-analyses only. These trials addressed comparisons of interventions of interest that did not meet eligibility criteria for this report (e.g., SSRIs versus SNRIs or placebo-controlled trials); they did, however, provide common comparators that we could use for network meta-analyses. Appendix F lists published and unpublished trials included in the network meta-analyses. Figure 4 is a visual presentation of the network of trials included for network meta-analyses. Nodes are weighted according to the number of studies including the respective interventions. Lines represent the available direct comparisons. In this network, SGAs were the most commonly available comparator, followed by placebo (abbreviated as PLA in the figure).

Figure 4. Network of trials included for network meta-analyses
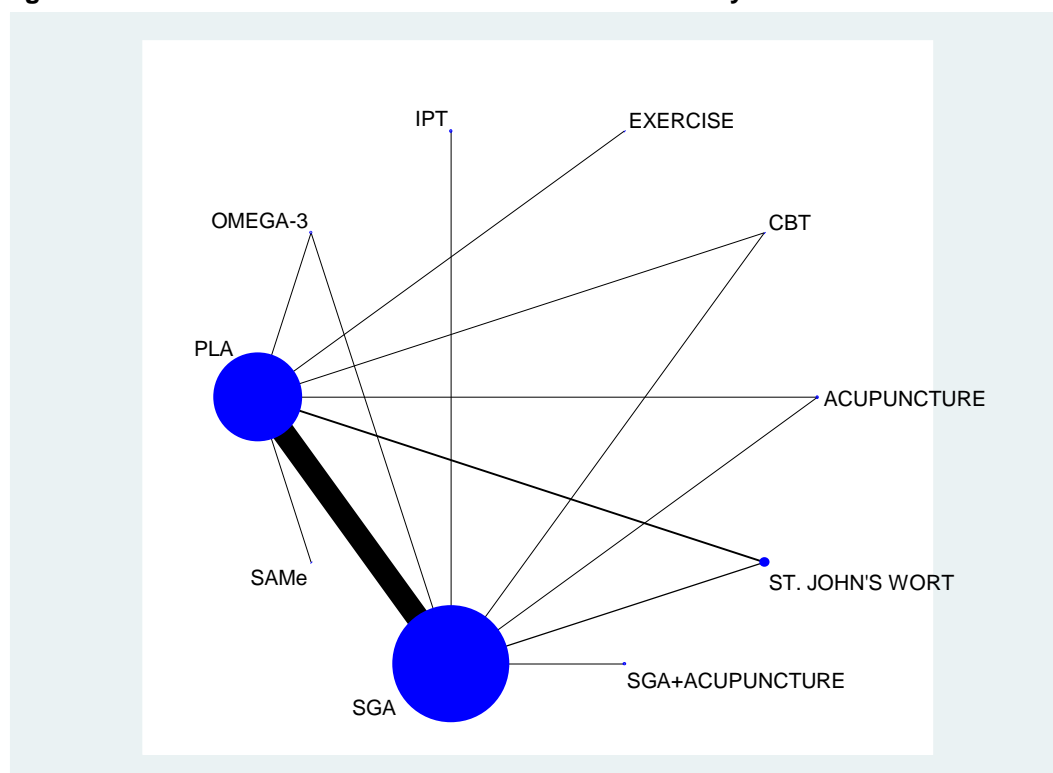
CBT = cognitive behavioral therapy; IPT = interpersonal psychotherapy; PLA = placebo; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant.

KQ 1. First-Step Therapy: Second-Generation Antidepressants Compared With Nonpharmacological Therapies

KQ 1a deals with adult patients with acute-phase MDD receiving an initial treatment attempt (also referred to as first-step therapy) with an SGA. It examines the effectiveness of the SGA compared with i) the effectiveness of either nonpharmacological interventions used alone or ii) various combinations of SGAs and one of the nonpharmacological treatments. KQ 1b examines whether treatment effectiveness varies by MDD severity. The nonpharmacological interventions for this KQ are psychological interventions, complementary and alternative medicine (CAM) interventions, and exercise.

In all, 42 trials comparing SGAs with nonpharmacological treatment options provided direct evidence on acute-phase outcomes (as depicted in Figure 1 in the introduction). Study durations ranged from 4 to 96 weeks, though most data for this comparative effectiveness review were reported between 8 and 24 weeks. The results of studies that reported longer-term outcomes (including off-treatment relapse and recurrence) are described in each treatment comparison section. Most patients suffered from moderate to severe major depression. Many of the available trials had serious methodological limitations. Additionally, few trials reported information on quality of life or functional capacity. We present results from network meta-analyses on response to treatment if we could not find sufficient eligible head-to-head evidence or if direct head-to-head evidence had substantial flaws or limitations (insufficient SOE) and network meta-analyses yielded findings with stronger SOE. We present a summary of results of network meta-analyses in Appendix G. For network meta-analyses we used 127 placebo- or active-controlled trials; 15 provided direct evidence as well.

Key Points: Second-Generation Antidepressants Compared With Psychological Interventions

- SGAs and cognitive behavioral therapy (CBT) monotherapy led to similar response rates after 8 to 16 weeks of treatment in patients with moderate to severe MDD (comparisons from five RCTs, moderate SOE); there was little difference in effect size for remission rates for SGAs and CBT between 12 and 16 weeks of treatment (four comparisons from three RCTs, low SOE).
- Adding CBT to SGA treatment did not lead to statistically different response and remission rates compared with SGA monotherapies in patients with moderate to severe MDD after 12 weeks of treatment (two RCTs, low SOE).
- SGAs and integrative therapies (interpersonal psychotherapy [IPT]) did not lead to statistically different response rates (one RCT, low SOE) in patients with moderate to severe MDD after 8 to 12 weeks of treatment. Remission rates were mixed in terms of direction and significance (two RCTs, low SOE).
- Adding IPT to SGA treatment resulted in higher remission rates compared with SGA monotherapy in patients with moderate to severe MDD after 12 weeks of treatment (one RCT, low SOE).
- SGAs and short-term psychodynamic therapies (PSYD) monotherapy did not lead to statistically different remission rates in patients with moderate MDD following 16 weeks of treatment (one RCT, low SOE).

- We did not find any eligible trials comparing SGAs with behavior therapies or humanistic therapies (insufficient SOE).

Key Points: Second-Generation Antidepressants Compared With Complementary and Alternative Medicine Interventions

- SGAs and acupuncture monotherapy did not lead to statistically different response rates in patients with severe MDD following 6 weeks of treatment (two RCTs, network meta-analysis, low SOE).
- Adding acupuncture to SGA treatment improved treatment responses compared with SGAs alone in patients with severe MDD after 6 weeks of treatment (2 RCTs, low SOE), but did not lead to statistically different rates of remission (1 RCT, low SOE).
- SGAs led to higher response rates than monotherapy with omega-3 fatty acids in patients with severe MDD (network meta-analysis, low SOE).
- SGAs and S-adenosyl-L-methionine (SAMe) did not lead to statistically different response rates in patients with moderate MDD following 12 weeks of treatment (one RCT, network meta-analysis, low SOE).
- SGAs and St. John's wort monotherapy led to similar response (nine trials, low SOE) and remission rates (five trials, low SOE) in patients with moderate to severe MDD after 4 to 12 weeks of treatment
- We did not find any eligible trials comparing SGAs with meditation or yoga (insufficient SOE).

Key Points: Second-Generation Antidepressants Compared With Exercise

- SGAs and exercise did not lead to statistically different rates of response (network meta-analysis, low SOE) or remission in patients with moderate MDD, following 16 weeks of treatment (two trials, low SOE).
- Adding exercise to SGA treatment did not lead to statistically different remission rates compared with SGA monotherapy in patients with moderate MDD, following 16 weeks of treatment (one trial, low SOE).

Key Points: Severity as a Moderator of Comparative Treatment Effectiveness

- The evidence is inconclusive as to whether the comparative effectiveness of SGAs versus psychological treatments changes as a function of MDD severity (four trials, insufficient SOE).
- The evidence is insufficient to draw conclusions about the effect of severity of disease on the comparative effectiveness SGAs and CAM interventions (one RCT, insufficient SOE).

Figures 5 and 6 graphically display relative risks of response and remission rates of SGAs compared with other interventions.

Figure 5. Comparison of response of SGAs compared with other eligible interventions (relative risks and 95% confidence intervals)

Psychological Interventions

SGA vs. CBT	0.91 (0.77, 1.07)	(5 trials, 660 participants, moderate SOE)
SGA vs. CBT + SGA	1.03 (0.85, 1.26)	(2 trials, 174 participants, low SOE)
SGA vs. integrative therapies	1.02 (0.86, 1.22)	(1 trial, 318 participants, low SOE)
SGA vs. third-wave CBT	0.77 (0.64, 0.94)	(2 trials, 243 participants, insufficient SOE)

CAM Interventions

SGA vs. acupuncture	0.75 (0.43, 1.30)	(NWMA of RCTs, low SOE)
SGA vs. acupuncture + SGA	0.82 (0.66, 1.00)	(2 trials, 288 participants, low SOE)
SGA vs. omega -3 fatty acids	1.96 (1.26, 3.05)	(NWMA of RCTs, low SOE)
SGA vs. Omega-3 fatty acids + SGA	0.62 (0.33, 1.14)	(2 trials, 74 participants, insufficient SOE)
SGA vs. SAMe	1.22 (0.66, 2.26)	(NWMA of RCTs, low SOE)
SGA vs. St. John's wort	0.96 (0.83, 1.10)	(9 trials, 1,517 participants, low SOE)

Exercise

SGA vs. exercise	1.86 (0.81, 4.27)	(NWMA of RCTs, low SOE)

0.2   0.5   1   2   5

Favors comparator   Favors SGA

CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; KQ = Key Question; NWMA = network meta-analysis; RCT = randomized controlled trial; SAMe = S-adenosyl-L-methionine SGA = second-generation antidepressant; SOE = strength of evidence; vs. = versus.

Figure 6. Comparison of remission rates of SGAs compared with other eligible interventions (relative risks and 95% confidence intervals)
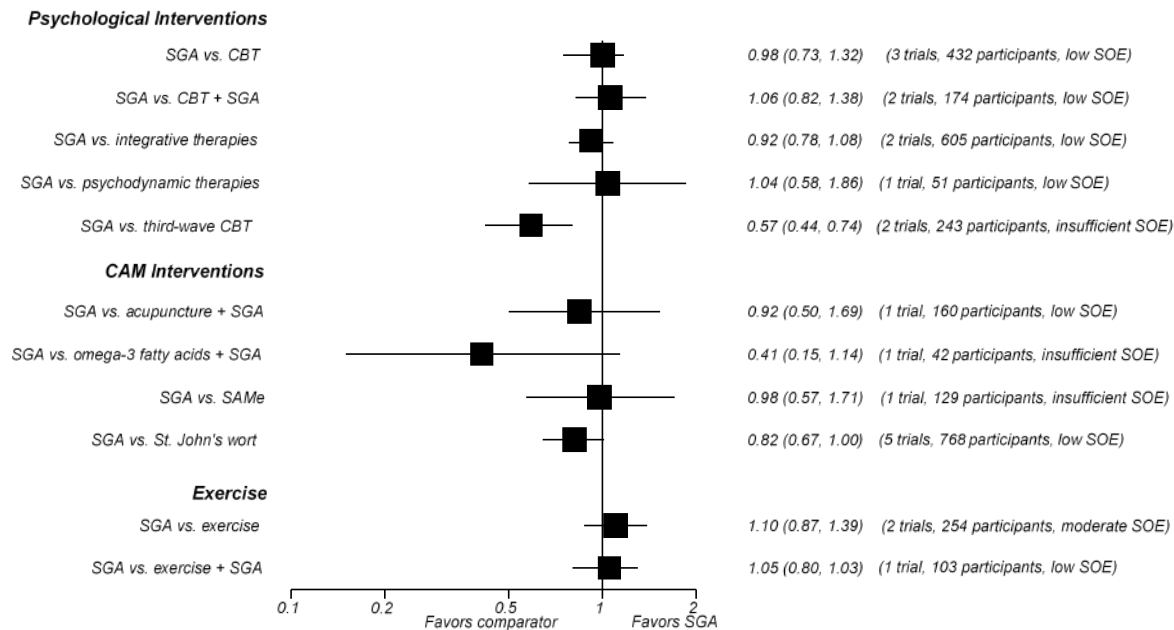
CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; KQ = Key Question; NWMA = network meta-analysis; RCT = randomized controlled trial; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant; SOE = strength of evidence; vs. = versus.

Detailed Synthesis: KQ 1

In this section, we present findings for both KQs 1a and 1b. The first subsection below (KQ 1a) concerns comparisons of SGAs with various other therapeutic interventions—namely, psychological therapies, CAM interventions, and exercise—as initial options for treating patients with acute-phase MDD (KQ 1a). In all cases, comparisons involve monotherapies for both the SGAs and the alternative interventions. In some cases, the comparisons involve SGA monotherapy with various combinations of SGAs and the alternative. The second subsection below (KQ 1b) examines the question of whether outcomes differ by the severity of MDD.

Table 10 provides the number of included trials by eligible comparison. We included any trial that met eligibility criteria, regardless of the risk of bias rating. In our syntheses, however, we place more emphasis on trials with low or medium risk of bias because of the presumed higher certainty of findings. In Appendix E we present "summary of findings" tables of important outcomes. These tables are intended for guideline development and give basic information on the available evidence, show absolute and relative effect measures, and present SOE grades for outcomes that the TEP and key informants deemed as most important for decisionmaking.

Table 10. Number of included trials by type of comparison

Comparison Category	Comparisons for KQ 1	Number of Trials and Citations
SGA vs. Psychological interventions	SGA vs. Behavior therapies/behavior modification	0
	SGA vs. CBT	11[87,90,95,97-100,102,108,119,121,129]
	SGA vs. Humanistic therapies	0
	SGA vs. Integrative therapies	4[85,88,89,103]
	SGA vs. Psychodynamic therapies	4[86,96,101,116]
	SGA vs. Third-wave CBTs	2[97,118]
SGA vs. CAM	SGA vs. Acupuncture	5[91,105,122-124]
	SGA vs. Omega-3 fatty acids	2[106,120]
	SGA vs. SAMe	1[104]
	SGA vs. St. John's wort	12[92,109-114,117,125-128]
	SGA vs. Meditation	0
SGA vs. Exercise	SGA vs. Yoga	0
	SGA vs. Exercise	2[93,94]

CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; KQ = Key Question; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant

KQ 1a. Second-Generation Antidepressants Compared With Psychological Interventions

In this section, we categorize types of psychotherapy according to the Cochrane Collaboration Depression, Anxiety and Neurosis Review Group (CCDAN) classification system (see Appendix B).[70] We address CBT, integrative therapies (interpersonal psychotherapy), PSYD, and third-wave CBTs. Most of these trials compare monotherapies; when relevant, we also present information about an SGA monotherapy with some form of a combination of SGA and the relevant psychological treatment.[130]

Description of Included Trials

In all, 20 primary RCTs (reported in 25 articles) compared SGAs with a psychological treatment and provided data for KQ 1a.[85-90,95-103,108,116,118,119,121,129,131-134] Trials are grouped according to the type of psychotherapy compared with the SGA. They are listed within this chapter's tables first by subtype of psychotherapy (if applicable) and then alphabetically by SGA. We found no trials eligible for KQ 1a that compared an SGA with behavior therapy or behavior modification or with humanistic therapies.

Five trials[86,88,100,103,121] were conducted in primary care settings; the remainder took place in mental health care locations. Most trials were funded by the government; seven trials[85,88-90,100,108,116] received at least partial funding from the pharmaceutical industry. Six trials[88,95-97,99,100,129] took place solely in the United States; other countries included Brazil,[101] Canada,[90,98,108] England,[121] Finland,[86] Germany,[102] Iran,[118,119] Italy,[103] Romania,[87] and The Netherlands.[89,116] One trial was conducted in both the United States and Italy.[85]

Generally, patients were between 18 and 65 years of age; most trials reported a mean age between 35 and 45 years. In all trials, the majority of patients were female. One trial enrolled only women.[100] In the few trials that reported race or ethnicity, three[88,96,100] included more than 33 percent nonwhite patients. All trials reported mean baseline depressive severity of at least a moderate degree; most trials reported mean baseline HAM-D-17 scores between 16 (moderate depression) and 23 (severe). The total daily dose of each SGA medication was within the usual ranges prescribed for adults.

Second-Generation Antidepressants Compared With Behavior Therapies/Behavior Modification Therapies

We found no eligible trials that compared an SGA with behavior therapy/behavior modification.

Second-Generation Antidepressants Compared With Cognitive Behavioral Therapy

Table 11 describes the 11 included trials (13 publications) of an SGA compared with a CBT (grouped by therapy subtype and in alphabetical order by first author). Six trials employed CBT,[90,95,98,100,102,108] four used cognitive therapy (CT),[87,97,99,119] and one each used problem solving therapy (PST)[121] and rational emotive behavior therapy (REBT).[87,133] Trial counts exceed 11 because one trial had both cognitive therapy (CT) and REBT arms.[87] All but one trial compared SGA monotherapy with CBT alone; Lam and colleagues compared SGA monotherapy with SGA plus CBT.[108] Two trials included an additional comparison of SGA monotherapy with a combination of SGA and CBT.[119,121] Treatment duration ranged from 8 weeks to 1 year; some trials also reported followup results once patients were off- treatment.

One trial was rated overall low risk of bias,[108] five were rated medium risk,[87,97,99,100,121,129] and five trials were rated high.[90,95,98,102,119] Reasons for high risk of bias ratings included high attrition without proper handling of missing data, high differential attrition between treatment arms, potentially meaningful differences in baseline characteristics between treatment groups, potential reporting bias, and little or no information on randomization and allocation procedures. In two cases, we applied a second risk of bias rating for specific outcomes: one medium-risk trial[99] was rated high for change in HAM-D score, and one overall high-risk trial[102] was rated medium for remission and response because we could use data from the full sample for those outcomes.[102] Full risk of bias assessments for included trials are found in Appendix D.

Table 11. Second-generation antidepressants versus cognitive behavioral therapy: Trial characteristics, main outcomes, and risk of bias ratings

Trial and Type of Psychotherapy	N[a] Duration (Weeks)	Total Sample Mean Baseline Severity	SGA Dose: mg/day Psychotherapy Type: Number of Sessions	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
David et al., 2008[87] Sava et al., 2009[133] CT	112 14 treatment; 36 followup	HAM-D-17: 22.5	Fluoxetine: 40 to 80 CT: 20	At 14 weeks: 58 vs. 63 p>0.05	At 14 weeks: 47 vs. 50 p>0.05	-12.6 vs. -14.3 p>0.05	Medium
David et al., 2008[87] Sava et al., 2009[133] REBT	113 14 treatment; 36 followup	HAM-D-17: 22.5	Fluoxetine: 40 to 80 REBT: 20	At 14 weeks: 58 vs. 65 p>0.05	At 14 weeks: 47 vs. 44 p>0.05	-12.6 vs. -14.3 p>0.05	Medium
DeRubeis et al., 2005[99] Leykin et al., 2007[134] Landen-berger, 2002[129] CT	180 8[c]	HAM-D-17: 23.4	Paroxetine: 10 to 50 CT: 20 to 28	50 vs. 43 p=0.40	NR	Effect size estimate: 0.16 (favors SGA) p=0.46	Medium for response and remission; high for change in HAM-D[d]
Dimidjian, 2006[97] CT	145 16	HAM-D-17: 20.7	Paroxetine: 10 to 50 CT: 24	43 versus 58 p=NR	27 versus 42 p=NR	NR[e]	Medium
Hegerl, 2010[102] CBT	48 10	HAM-D-17: 16.1	Sertraline: 50 to 200 CBT: 14	54 vs. 64 p=NR	NR	-6.5 vs. -8.8 p=NR	Medium for response and remission; high for change in HAM-D
Kennedy et al., 2007[90] CBT	31 16	HAM-D-17: 20.5	Venlafaxine: 75 to 225 CBT: 16	64 vs. 41 p=NR	57 vs. 29 p=NR	-12.9 vs. -10.8 p=NR	High[f]

Table 11. Second-generation antidepressants versus cognitive behavioral therapy: Trial characteristics, main outcomes, and risk of bias ratings (continued)

Trial and Type of Psychotherapy	N[a] Duration (Weeks)	Total Sample Mean Baseline Severity	SGA Dose: mg/day Psychotherapy Type: Number of Sessions	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
Lam et al., 2013[108] CBT	105 12	MADRS: 27.6	Escitalopram: 10 to 20 CBT (via telephone): 8 + escitalopram: 10 to 20	61 vs. 63 p=0.86	53 vs. 56[g] p=0.74	MADRS: -14.3 vs. -15.7 p=0.60	Low
McGrath et al., 2013[95] CBT	82 12	HAM-D-17: 18.8	Escitalopram: 10 to 20 CBT: 16	60 vs. 57 p=NR	28 vs. 29 p=NR	NR	High[h]
Mynors-Wallis et al., 2000[121] PST	151 52	HAM-D-17: 20.3	Fluvoxamine: 100 to 150 or Paroxetine: 10 to 40 PST (provided by GP): 6 PST (provided by nurse): 6 PST (provided by nurse): 6 + fluvoxamine: 100 to 150 or paroxetine: 10 to 40	At 12 weeks 78 vs. 64 vs. 69 vs. 74 p=NR	At 12 weeks 67 vs. 51 vs. 54 vs. 60 p=NR	-14.0 vs. -12.0 vs. -11.8 vs. -12.3 p>0.05	Medium
Segal et al., 2006[98] CBT	301 24 treatment; 96 followup	HAM-D-17: 19.5	Sertraline: 50 to 200 or paroxetine: 20 to 50 or venlafaxine: 75 to 225 CBT: 20	At 24 weeks: 80 vs. 72 p=NR	At 24 weeks[i] 71 vs. 61 p=NR	NR	High[j]

Table 11. Second-generation antidepressants versus cognitive behavioral therapy: Trial characteristics, main outcomes, and risk of bias ratings (continued)

Trial and Type of Psychotherapy	N[a] Duration (Weeks)	Total Sample Mean Baseline Severity	SGA Dose: mg/day Psychotherapy Type: Number of Sessions	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
Shamsaei et al., 2008[119] CT	120 8	BDI: 42.8	Citalopram: 20 CT: 8 Citalopram: 20 + CT: 8	NR	NR	NR	High[k]
WECare[100] CBT	178 4[l]	HAM-D (version NR): 16.9	Paroxetine: 10 to 50 CBT: 8	NR	NR	-5.0 vs. -2.1 p=0.17	Medium

BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CT = cognitive therapy; GP = general practitioner; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; mg = milligram; N = number; NR = not reported; PST = problem solving therapy; REBT = rational emotive behavior therapy; SGA = second-generation antidepressant; vs. = versus
[a] Total number of randomized participants in relevant arms of trial.
[b] Response (≥50 percent decrease in depressive severity) and remission (as defined by authors of individual trials) are measured using the HAM-D unless indicated otherwise.
[c] Nonresponders were switched to and/or augmented with another pharmacotherapy at 8 weeks.
[d] For dropouts, only the data gathered prior to attrition were used in continuous outcome models.
[e] Continuous data were only provided stratified by depression severity. Those results are presented in KQ 1b.
[f] High attrition, completers analysis, difference in baseline age between groups.
[g] Response was defined as ≥50 percent decrease in MADRS; remission was defined as MADRS ≤12.
[h] High attrition, completers analysis, no baseline data for part of the population.
[i] Definition of response was not reported.
[j] Very high attrition, completers analysis, unclear randomization method.
[k] Several important aspects of study design and analysis not reported.
[l] Although patients received SGA for 8 weeks, only the 4-week time point was reported.

Second-Generation Antidepressant Versus Cognitive Behavioral Therapy: Monotherapy Comparisons

We conducted random-effects meta-analyses of trials rated low or medium risk of bias for three outcomes: (1) remission (three trials [four comparisons];[87,97,121,129] 432 patients), (2) response (five trials [six comparisons];[87,97,99,102,121,129] 660 patients), and (3) change in HAM-D-17 score (three trials [four comparisons];[87,100,121] 427 patients). We also performed sensitivity analyses for those outcomes including additional trials rated high risk of bias.[90,95,98]

For remission, we included results measured between 12 and 16 weeks; all trials compared an SGA with CBT, and all trials defined remission based on a HAM-D-17 score of either less than 7[87] or less than or equal to 7.[97,99,121] One trial[97] also required a score less than or equal to 10 on the Beck Depression Inventory for remission. Patients treated with SGAs had numerically lower but not significantly different remission rates than patients on CBT (40.7 percent versus 47.9 percent; relative risk [RR], 0.98; 95% CI, 0.73 to 1.32; Figure 7). We found similar results when we stratified by subtype of CBT (CT versus PST versus REBT). Our sensitivity analysis included one additional SSRI trial,[95] a trial of an SNRI (venlafaxine),[90] and a trial that allowed patients to receive either an SSRI or an SNRI.[98] Our sensitivity analysis yielded a similar, nonsignificant difference.

Figure 7. SGA versus cognitive behavioral therapy: Remission
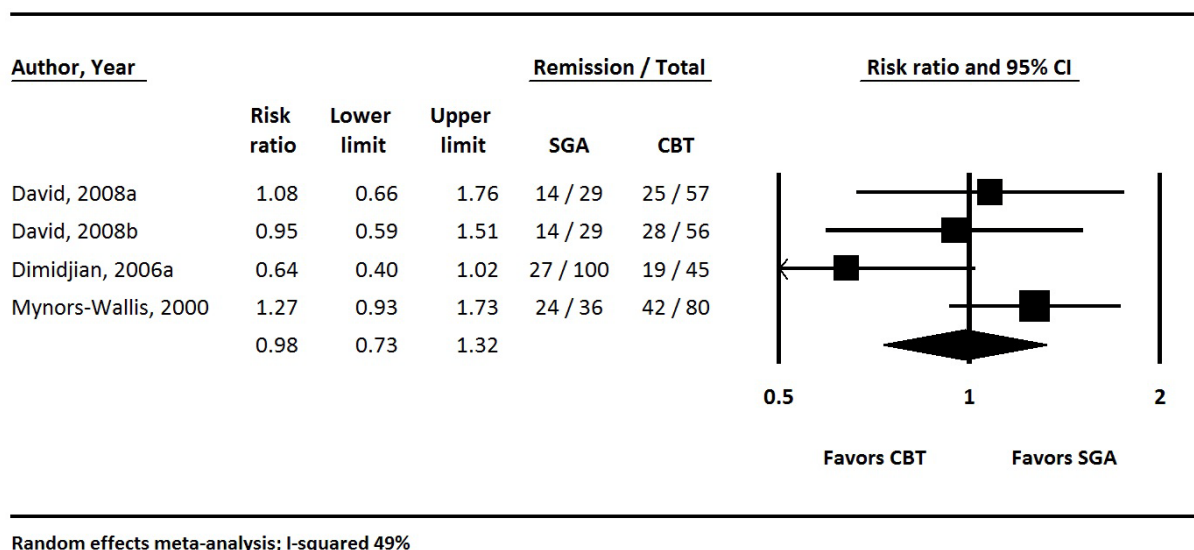
Author, Year	Risk ratio	Lower limit	Upper limit	Remission / Total SGA	Remission / Total CBT
David, 2008a	1.08	0.66	1.76	14 / 29	25 / 57
David, 2008b	0.95	0.59	1.51	14 / 29	28 / 56
Dimidjian, 2006a	0.64	0.40	1.02	27 / 100	19 / 45
Mynors-Wallis, 2000	1.27	0.93	1.73	24 / 36	42 / 80
	0.98	0.73	1.32		

Random effects meta-analysis; I-squared 49%

CBT = cognitive behavioral therapy; CI = confidence interval; SGA = second-generation antidepressant

For response, we included results measured between 8 and 16 weeks. Trials defined response as a 50 percent or greater reduction in HAM-D-17 score from baseline. Treatment effects were similar for SGAs and CBT (44.2 percent versus 45.5 percent; RR, 0.91; 95% CI, 0.77 to 1.07; Figure 8). We found similar results when we stratified by subtype of CBT and by time point (<12 weeks versus 12 to 16 weeks). The sensitivity analysis including three high risk of bias studies[90,95,98] yielded a similarly nonstatistically significant difference in response between SGAs and CBT.

Figure 8. SGA versus cognitive behavioral therapy: Response
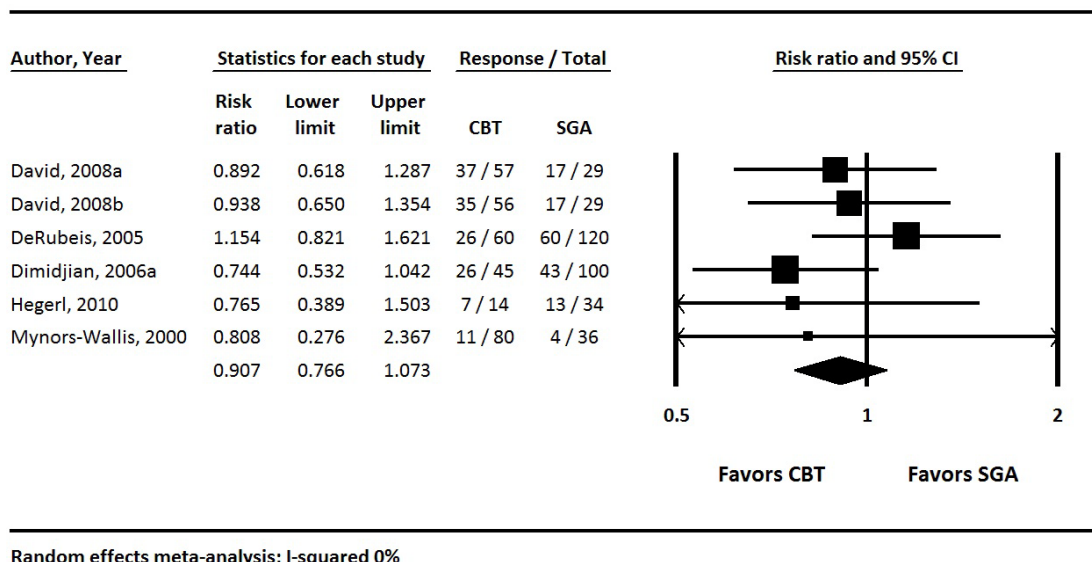
Author, Year	Statistics for each study			Response / Total		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	CBT	SGA	
David, 2008a	0.892	0.618	1.287	37 / 57	17 / 29	
David, 2008b	0.938	0.650	1.354	35 / 56	17 / 29	
DeRubeis, 2005	1.154	0.821	1.621	26 / 60	60 / 120	
Dimidjian, 2006a	0.744	0.532	1.042	26 / 45	43 / 100	
Hegerl, 2010	0.765	0.389	1.503	7 / 14	13 / 34	
Mynors-Wallis, 2000	0.808	0.276	2.367	11 / 80	4 / 36	
	0.907	0.766	1.073			

Favors CBT   Favors SGA

Random effects meta-analysis; I-squared 0%

CBT = cognitive behavioral therapy; CI = confidence interval; SGA = second-generation antidepressant

Our weighted mean difference analysis of the three trials that reported change in HAM-D-17 scores at 8 weeks or longer found no statistically significant difference between SGAs and CBT (WMD, -0.38; 95% CI, -2.87 to 2.10; Figure 9), although heterogeneity was somewhat high ($I^2 =$ 44.3 percent). Potential sources of heterogeneity include variation between CBT subtypes (included trials used CT,[87] PST,[121] and REBT[87]) and type of provider delivering the psychotherapy (general practitioner[121] versus psychologists or psychiatrists[87,100]).We performed a sensitivity analysis that included the study that reported HAM-D-17 results at 4 weeks[100]; doing so changed the direction of effect but not to a clinically or statistically significant degree (WMD, 0.57; 95% CI, -1.86 to 3.00). In addition, the heterogeneity increased to 62.9 percent. Further sensitivity analyses were not possible owing to too few trials. Adding the high risk of bias trials to the model yielded no difference in comparative effectiveness.

Figure 9. SGA versus cognitive behavioral therapy: Change in HAM-D-17

Study name	Statistics for each study			Sample size		Difference in means and 95% CI
	Difference in means	Lower limit	Upper limit	SGA	CBT	
David, 2008a	-1.700	-5.066	1.666	29	57	
David, 2008b	-1.700	-4.975	1.575	29	56	
Mynors-Wallis, 2000	2.000	-1.023	5.023	36	42	
	-0.380	-2.870	2.109			

Random effects meta-analysis; I-squared 44%
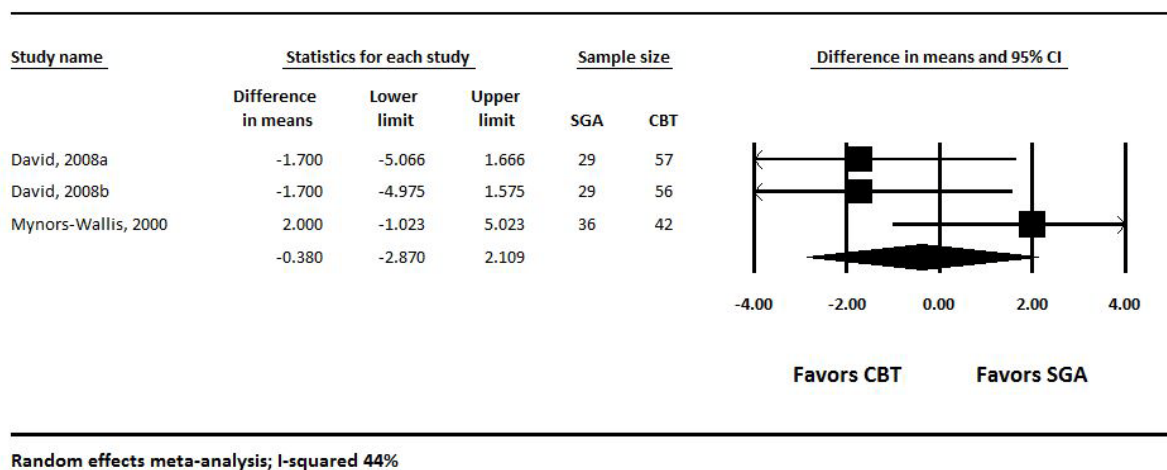
CBT = cognitive behavioral therapy; CI = confidence interval; HAM-D = Hamilton Depressive Scale; SGA = second-generation antidepressant

Two trials, both rated medium risk of bias, reported response, remission, or change in HAM-D-17 score at time points beyond 16 weeks. In one,[87] patients receiving either REBT or CT reported higher rates of remission and response at 6 months than patients taking fluoxetine, although neither difference was statistically significant. At 6 months, patients receiving REBT or CT reported significantly lower HAM-D-17 scores than the patients taking fluoxetine. In the trial that compared either fluvoxamine or paroxetine with PST,[121] rate of remission at 1 year was higher in the PST arms, although rate of response at 1 year was higher in the SGA arm. In that trial, patients' HAM-D-17 scores continued to decline, with 1-year scores being lower in the PST arms than the SGA arm. Again, these differences failed to reach statistical significance.

With respect to other health outcomes, three trials reported relapse rates during off-treatment followup.[87,97,98] Two trials defined relapse as symptom levels meeting criteria for MDD; the third[97] defined relapse as either a HAM-D-17 score of 14 or greater or a psychiatric status rating of 5 or greater during the first year of followup. During the followup period of that trial, patients who had initially received CT did not receive any treatment, and patients who had received SGA were randomized to continue SGA or be withdrawn to pill placebo.

In one medium risk of bias trial,[87] 10.6 percent of patients treated with fluoxetine relapsed within 6 months, compared with 2.1 percent and 6.1 percent of patients treated with REBT and CT, respectively. In the other medium risk of bias trial,[97] the rates of relapse were 39 percent for prior CT, 53 percent for patients who were on SGA and continued to receive it during followup, and 59 percent for patients who received SGAs during acute phase but were withdrawn to placebo during followup. Prior CT was significantly different from followup placebo (p=0.02). In the trial rated high risk of bias,[98] 47 percent of remitted patients treated with an SGA and 39 percent of remitted patients treated with CBT relapsed within 18 months.

Finally, one of the medium risk of bias trials[97] reported recurrence during the second year of followup, defined as either a HAM-D-17 score of 14 or greater or a psychiatric status rating of 5 or greater among those who did not relapse during year 1 of followup. The rates of recurrence during year 2 were 24 percent for prior CT and 52 percent for patients who were on SGAs during the acute phase. Owing largely to small numbers of patients in each group (17 in each group), the difference was not statistically significant, and results should be interpreted with caution. The

single trial that reported measures of functional capacity used the Social Adjustment Scale;[121] SGA and PST did not differ at end of treatment or at 40-week off-treatment followup.

Second-Generation Antidepressant Versus Cognitive Behavioral Therapy: Combination Comparisons

Three trials compared SGA monotherapy with a combination of SGA and CBT.[108,119,121] The two that measured response and remission reported no statistically significant between-group differences in rates of either outcome.[108,121] Table 11 also presents effect estimates and the respective SOE grades for response and remission. All three trials reported change in depression scale score between baseline and endpoint, but only one[119] reported a significant between-group difference—namely, a smaller decrease in scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) for patients on citalopram alone compared with patients treated with citalopram plus CT. This trial, however, was rated high risk of bias, whereas the other two were rated low[108] and medium[121] risk of bias.

The trial that compared escitalopram alone with escitalopram plus telephone CBT measured several work-related outcomes.[108] Patients receiving the combination of escitalopram and telephone CBT reported greater improvement on three of four work functioning measures. The authors reported found no between-group differences in reduction of hours of work missed, although both groups reported a decrease at the end of treatment. In the trial that compared SGA alone with the combination of SGA and PST, there was no between-group difference in the Social Adjustment Scale at end of treatment or at 40-week off-treatment followup.[121]

Second-Generation Antidepressants Compared With Humanistic Therapies

We found no eligible trials that compared an SGA with humanistic therapies.

Second-Generation Antidepressants Compared With Integrative Therapies

The only type of integrative therapy used in the included studies was interpersonal psychotherapy (IPT). Table 12 describes the four included trials (five publications) of an SGA compared with IPT.[85,88,89,103,131] One trial also included a combination SGA+IPT arm.[89] Two trials took place outside the United States;[89,103] two were conducted in outpatient primary care clinics.[88,103] Three of the four trials received a combination of industry and government funding.[85,88,89,131]

Table 12. Second-generation antidepressants versus interpersonal psychotherapy: Trial characteristics, main outcomes, and risk of bias ratings

Trial	N[a] Duration (weeks)	Total Sample Mean Baseline Severity	SGA Dose: (mg/day) Psychotherapy Type: Number of Sessions	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
Blom et al., 2007[89]	207 12	HAM-D-17: 20.1	Nefazodone: 400 to 600 IPT: 12 Nefazodone: 400 to 600 + IPT: 12	NR	Nefazodone + IPT vs. nefazodone: OR (95% CI) 3.22 (1.02 to 10.12) Other comparisons NR p>0.10	-5.4 vs. -6.9 vs. -8.1 p=NR	Medium
Frank et al., 2011[85] Rucci, 2011[131]	318 12	HAM-D-17: 20.0	Escitalopram: 10 to 20 IPT: NR	At 6 weeks: 62.7 vs. 61.3 p=NR At 12 weeks: NR	At 12 weeks: 46.8 vs. 42.5 p=NR	NR	High[c]
Menchetti et al., 2014[103]	287 8	HAM-D-21: 17.3	Citalopram: 10 to 60 or Sertraline: 25 to 200 IPT: 6 to 8	NR	45 vs. 59 p=0.021	NR	Medium
Raue et al., 2009[88]	60 24	HAM-D-24: 23.7	Escitalopram: 10 to 20 IPT: 14	NR	At 12 weeks: NR; p=NS	At 24 weeks: 18.9 vs. 14.0 p=0.05	High[d]

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; IPT = interpersonal psychotherapy; mg/day = milligram per day; N = number; NR = not reported; OR = odds ratio; SGA = second-generation antidepressant; vs. = versus.

[a] Total number of randomized participants in relevant arms of trial
[b] Response (≥50 percent decrease in depressive severity) and remission (as defined by authors of individual trials) are measured on the Hamilton Depression Rating Scale.
[c] No methods of randomization/allocation reported, unclear if outcome assessors were masked, and median duration of illness was much higher in SGA arm (10.8 years) than in IPT arm (3.5 years).
[d] Very little information provided about procedures/methods, randomization was to a treatment by way of preference congruence.

Patients ranged between 18 and 66 years of age, and the samples comprised at least 72 percent females. Trial enrollment ranged from 60 to 318 patients. Treatment duration ranged from 8 to 24 weeks. None of the trials reported posttreatment followup results. The two trials rated high risk of bias provided few details about trial methods.[85,88] Full risk of bias assessments for included trials are found in Appendix D.

Second-Generation Antidepressants Versus Integrative Therapies (Interpersonal Psychotherapy): Monotherapy Comparisons

Of the four trials that met eligibility criteria, two trials, one medium risk of bias[103] and one high risk of bias,[85] reported rates of remission (HAM-D-17 ≤7 and HAM-D-21 ≤7, respectively). In the medium risk of bias trial, remission at 2 months was significantly lower in the SGA group (45.1 percent) than in the IPT group (58.7 percent; p=0.021). This trial reported no other main outcomes. The study rated high risk of bias[85] reported similar rates of remission for SGA and IPT (46.8 percent and 42.5 percent, respectively). That study was the only one to report rates of response, which were similar for SGA and IPT: 62.7 percent and 61.3 percent, respectively.

We did not find enough trials to pool data for any depression outcomes. Our network meta-analysis yielded a relative risk of response that indicated similar treatment effects between SGAs and IPT (RR, 1.01; 95% CI, 0.63 to 1.6).

Second-Generation Antidepressants Versus Integrative Therapies (Interpersonal Psychotherapy): Combination Comparisons

In the sole trial that compared SGAs with a combination of SGA and IPT (N=97), rated medium risk of bias, nefazodone alone was associated with a significantly lower odds ratio (OR) of remission (HAM-D-17 ≤ 8) than the combination of nefazodone and IPT at 8 weeks, although the 95% CI was very wide (low SOE, small sample size, very wide CI).[89] The combination was also associated with a greater decrease in the HAM-D-17 at 12 weeks than either therapy alone (presumably not significant, p not reported); also, the reported result does not meet the minimum clinically meaningful difference of 3 points advocated by the National Institute of Health and Care Excellence.[37]

Second-Generation Antidepressants Compared With Psychodynamic Therapies

Table 13 describes the four included trials (five articles) of an SGA compared with PSYD of various sorts.[86,96,101,116,132] Of these four trials, one included an additional treatment arm that combined fluoxetine and PSYD.[101] One trial took place in the United States;[96] three were conducted in outpatient psychiatry clinics,[96,101,116] and one was conducted in a primary care setting.[86,132] Three trials were funded in part by a government agency.[86,96,101]

Subjects ranged in age between 18 and 66 years of age; the samples comprised at least 72 percent females. Trial enrollment ranged from 51 to 272 patients. Three trials compared SGA monotherapy with short-term (2 to 4 months) PSYD; the fourth compared SGA monotherapy with long-term (24 months) PSYD. All four trials were rated medium risk of bias.

Table 13. Second-generation antidepressants versus psychodynamic therapies: Trial characteristics, main outcomes, and risk of bias ratings

Trial	N[a] Duration (Weeks)	Total Sample Mean Baseline Severity	SGA Dose: (mg/day) Psychotherapy Type: Number of Sessions	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
Barber et al., 2012[96]	106 8[c]	HAM-D-17: 19.4	Sertraline: 50 to 200 Supportive-expressive therapy: 20	At 8 weeks: 61.8 vs. NR p=NR	NR	NR	Medium
Bastos et al., 2013[101]	272 96	BDI: 26.8	Fluoxetine: 20 to 60 Long-term psychodynamic psychotherapy: weekly Fluoxetine: 20 to 60 + long-term psychodynamic psychotherapy: weekly	NR	NR	NR	Medium
Dekker et al., 2008[116]	141 8	HAM-D-17: 20.1	Venlafaxine: 75 to 225 Short-term psychodynamic supportive psychotherapy: 16	NR	NR	-4.23 vs. -2.00 p=0.039	Medium
Salminen et al., 2008[86]	51 16	HAM-D-17: 18.6	Fluoxetine: 20 to 40 Short-term psychodynamic supportive psychotherapy: 16	NR	48 vs. 46 p=NR	-11.2 vs. -11.0 p=0.87	Medium

BDI = Beck Depression Inventory; HAM-D = Hamilton Depression Rating Scale; mg/day = milligram per day; N = number; NR = not reported; SGA = second-generation antidepressant; vs. = versus

[a] Total number of randomized participants in relevant arms of trial
[b] Response and remission (as defined by authors of individual trials) are measured on the Hamilton Depression Rating Scale (HAM-D.) the BDI.
[c] Treatment duration was 16 weeks, but only the week 8 results are relevant for this key question.

Second-Generation Antidepressants Versus Psychodynamic Therapies: Monotherapy Comparisons

One trial reported rate of remission as measured by either the HAM-D-17 or criteria specified by the *Diagnostic and Statistical Manual*, fourth edition (DSM-IV);[86] treatment groups did not differ significantly. In the one trial that reported response rate,[96] 61.8 percent of sertraline patients responded to treatment at 8 weeks, but the response rate for supportive-expressive therapy patients was not reported. (In that trial, nonresponders to sertraline were switched to a different medication at week eight, but no such switch in treatment was made in the psychotherapy arm.) Therefore, we are unable to report results for second medication in the latter.

Two trials, both comparing short-term PSYD with an SGA, reported changes in HAM-D-17.[86,116] In both, HAM-D-17 scores decreased more for SGA patients than for PSYD patients; the difference, however, was statistically significant in only one (-4.2 versus -2.0; p=0.04).[116] A third trial measured depressive symptoms with the Beck Depression Inventory (BDI), but results had not been published at the time of this report.[101]

Two trials[86,101] reported measures of functional and/or neuropsychological capacity. In one,[86] both the fluoxetine and short-term PSYD groups improved significantly on the Social and Occupational Functioning Assessment Scale, but the between-group difference was not significant. In the same trial, the proportion of patients on sick leave at 16 weeks was higher in the SGA group than in the short-term PSYD group (12.0 percent versus 43.8 percent), although the difference was not statistically significant. The other study measured several domains of the Wechsler Adult Intelligence Scale, third edition (WAIS-III) at time points between 6 and 24 months.[101] Few statistically significant between-group differences were reported, all of which favored long-term PSYD.

Second-Generation Antidepressants Versus Psychodynamic Therapies: Combination Comparisons

The trial that compared fluoxetine with the combination of fluoxetine and long-term (24 month) PSYD[101] only reported neurocognitive changes. In it, none of the differences in WAIS-III domains between fluoxetine and the combination of fluoxetine and long-term PSYD were statistically significant.

Second-Generation Antidepressants Compared With Third-Wave Cognitive Behavioral Therapy

Two trials compared an SGA (sertraline and paroxetine) with a third-wave CBT (namely, 16 sessions of behavioral activation).[97,118] One took place in an outpatient psychiatry clinic in Iran over 49 weeks and received funding from two academic institutions; the other was conducted in the United States and funded by the government. The American study also contained a cognitive therapy arm as reported earlier in this section. The American study was rated medium risk of bias, and the Iranian study as high risk. The samples ranged from 100 to 143 patients (see Table 14), and 66 to 85 percent of participants were female. Dimidjian et al. allowed a full range of paroxetine (10 mg to 50 mg/day), but Moradveisi et al. capped the dosage of sertraline at 100 mg/day—half the maximum dosage typically allowed for MDD.

Both studies defined remission as HAM-D-17 ≤ 7 and BDI ≤ 10. The Iranian study reported much higher rates of both response and remission compared with the American study (see Table 14). In fact, we find it suspicious that over 90 percent of patients in both treatment groups in

Moradveisi et al. reported response (between-group p=0.42). However, if one assumes that trial dropouts failed to respond, then rates of response are 66.0 percent for SGA and 88.0 percent for behavioral activation (BA) CBT. In the American study, paroxetine and BA CBT were associated with roughly similar rates of response at 16 weeks.

In the American study, authors found a greater rate of remission for BA CBT patients—nearly half—compared with patients taking paroxetine (27%). The Iranian study authors also reported that fewer patients taking sertraline were in remission at 13 weeks, compared with patients receiving BA CBT (68.6 percent versus 91.1 percent; p<0.01). With the same assumption of trial dropouts as treatment failures, the rates of remission in the Iranian study were 48.0 percent and 82.0 percent, respectively. However, these results should be interpreted with caution because of the potentially insufficient dosage of sertraline allowed.

Both studies reported followup data beyond the acute treatment phase. In one,[118] at the 49-week followup, roughly half as many SGA patients as BA CBT patients reported at least a 50 percent reduction in symptoms (46.5 percent versus 88.6 percent; p<0.01). Similarly, fewer than half the number of SGA patients than BA CBT patients were in remission at 49 weeks (27.9 percent versus 65.9 percent; p<0.01). If one assumes that trial dropouts failed to remit, then rates of remission are 24.0 percent for SGA and 58.0 percent for BA CBT. With the same assumption for response, the rates are 40.0 percent and 78.0 percent, respectively. Among patients who were in remission at 13 weeks, more SGA patients relapsed (defined as "no longer meeting the remission criterion [scores less than or equal to 7 on the HAM-D and less than or equal to 10 on the BDI]") during 49 weeks of followup than BA CBT patients (60.0 percent versus 27.8 percent; p=0.02). Again, these results should be interpreted with caution in light of the upper limit of the sertraline dosage.

In the other,[97] patients who had initially received BA did not receive any treatment, and patients who had received SGA were randomized to continue SGA or be withdrawn to pill placebo. In that study, relapse was defined as either HAM-D-17 score of 14 or greater or psychiatric status rating of 5 or greater during the first year of followup.

During the first year of followup of that trial, the rates of relapse were 50 percent for prior BA, 53 percent for patients who were on SGA and continued to receive it during followup, and 59 percent for patients who received SGA during acute phase but were withdrawn to placebo during followup.

Finally, one of the trials[97] reported recurrence during the second year of followup, defined as either a HAM-D-17 score of 14 or greater or a psychiatric status rating of 5 or greater among those who did not relapse during year 1 of followup. The rates of recurrence during year 2 were 26 percent for prior BA and 52 percent for patients who were on SGA during the acute phase. Owing largely to small numbers of patients (12 in prior BA and 17 in prior SGA), the difference was not statistically significant, and results should be interpreted with caution.

Table 14. Second-generation antidepressants versus third-wave cognitive behavioral therapy: Trial characteristics, main outcomes, and risk of bias ratings of trials

Trial	N[a] Duration (Weeks)	Total Sample Mean Baseline Severity	SGA Dose: mg/day Psychotherapy Type: Number of Sessions	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
Dimidjian, 2006[97] BA CBT	143 16	HAM-D-17: 20.7	Paroxetine: 10 to 50 BA: 24	43 versus 51 p=NR	27 versus 49 p=NR	NR[c]	Medium
Moradveisi, 2013[118] BA CBT	100 49	HAM-D-17: 21.4	Sertraline: 100 BA: 16	At 13 weeks 98 vs. 94 p=0.42	At 13 weeks 69 vs. 91 p<0.01	At 13 weeks -14.2 vs. -17.3 p<0.01	High[d]

BA = behavioral activation; BDI = Beck Depression Inventory; HAM-D = Hamilton Depression Rating Scale; N = number; SGA = second-generation antidepressant; vs. = versus

[a] Total number of randomized participants in relevant arms of trial.

[b] Response was defined as at least a 50 percent reduction from baseline on both the HAM-D and the BDI-II. Remission was defined as scores of less than 8 on the HAM-D and less than 11 on the BDI.

[c] Continuous data were only provided stratified by depression severity. Those results are presented in KQ 1b.

[d] High attrition; dosage capped below the upper limit of typically prescribed range.

KQ 1a. Second-Generation Antidepressants Compared With Complementary and Alternative Medicine Interventions

Description of Included Trials

We evaluated four CAM therapies: acupuncture, omega-3 fatty acids, SAMe, and St. John's wort. All involved a comparison of an SGA with the CAM therapy of interest as monotherapy. When data were available, we also included an evaluation of an SGA with a combination of a CAM therapy plus an SGA. For all reports, the SGA was an SSRI; however, the term *SGA* has been used throughout for consistency. We defined acupuncture broadly to include techniques provided by trained practitioners that provide stimulation to meridian points using traditional needles. We elected to group trials of manual and electroacupuncture together because of the paucity of publications in this area and the uncertainty surrounding any meaningful differences between the two techniques for treating patients with depression.

We identified 20 primary RCTs (22 articles) comparing an SGA with a CAM therapy for treating patients with MDD.[91,92,104-106,109-114,117,120,122-128,135,136] Five trials (six articles) evaluated acupuncture (503 participants), two trials evaluated omega-3 fatty acids (102 participants), one trial evaluated SAMe (189 participants), and 12 trials (13 articles) evaluated St. John's wort (1,806 participants). About one-half of the trials (11 of 20) compared fluoxetine with a CAM therapy. Other SGAs involved sertraline (3 trials), paroxetine (2), citalopram (2), and escitalopram (1). Importantly, many of these trials used moderate or low antidepressant doses. Trials enrolled participants according to a criteria-based diagnosis of MDD based on the DSM-IV or the DSM revised third edition (DSM-III-R) and a predefined cutoff point of the HAM-D. Most participants had moderate to severe depression as measured by the HAM-D. All trials excluded patients who had additional Axis I disorders, high suicidal risk, or progressive medical diseases or who used psychotherapy, electroconvulsive therapy, or psychotropic medications.

Second-Generation Antidepressants Compared With Acupuncture

Table 15 describes the five trials (six articles, two reporting on substantially the same participants) that compared patients treated with an SGA to those treated with acupuncture monotherapy or with acupuncture plus an SGA. All trials took place in China. Four sets of analyses were funded by Chinese government agencies;[91,105,122,135] the other two did not report their funding sources.[123,124] Trial enrollment ranged from 75 to 160 participants. All trials performed primary outcome evaluations at 6 weeks.

Four trials used fluoxetine; the Qu et al. and Chen et al. trials used paroxetine. Trials employed a variety of experimental designs–including a variety of types of acupuncture, points used, and frequency of treatment. Three trials used the HAM-D-24[91,122,124] and two used the HAM-D-17.[105,123] Chen et al.[135] reported on essentially the same dataset as the Qu et al. trial;[105] also, it described outcomes for only the SCL-90 (Symptom Checklist 90), so we excluded it from meta-analyses.

43

Table 15. Second-generation antidepressants versus acupuncture: Study characteristics, main outcomes, and risk of bias ratings

Trial	N[a] Duration (Weeks)	Mean Baseline HAM-D Score	SGA Dose: mg/day Type of Acupuncture: Number of Sessions	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Risk of Bias Rating
Huang et al., 2005[122]	98 6	24.1	Fluoxetine (20–40) Scalp EA (36)	65 vs.56 p=NR	NR	Medium
Qu et al., 2013[105] Chen et al., 2014[135c]	160 6	24.4	Paroxetine (10–40) Paroxetine + MA (18) Paroxetine + EA (18)	42 vs. 70 (MA) vs.70 (EA) p=0.004 for SGA vs. MA or EA	22.9 vs.22.6 (MA) vs 28.6 (EA) p=0.72	Medium
Song et al., 2007[124]	90 6	25.3	Fluoxetine (20) EA (30)	NR	NR	High[d]
Sun et al., 2013[91e]	75 6	23.3	Fluoxetine (20) EA #1 (30) EA #2 (30)	60 vs.75 vs. 75 p=0.16	NR	High[f]
Zhang et al., 2009[123]	80 6	24.1	Fluoxetine (20–30) + sham MA (30) Fluoxetine (10) + MA (30)	80 vs. 78 p=0.79	NR	Medium

EA = electroacupuncture; HAM-D = Hamilton Depression Rating Scale; MA = manual acupuncture; mg/day = milligram per day; N = number; NR = not reported; SGA = second-generation antidepressant; vs. = versus
[a] Total number of randomized participants in relevant arms of trial.
[b] Response and remission are measured on the Hamilton Depression Rating Scale (HAM-D).
[c] The Chen et al. trial had substantial overlap of participants (n=105) with the Qu et al. trial.
[d] Very little information provided on randomization procedures and analytic methods.
[e] Trial included two active electroacupuncture groups, with different sets of points, designed to treat depression.
[f] High differential attrition; completers analysis.

Second-Generation Antidepressants Versus Acupuncture: Monotherapy Comparisons

One medium risk of bias trial compared fluoxetine (20 to 40 mg/day) with scalp electroacupuncture (36 sessions).[122] This trial recruited participants from four university-based hospitals. After 6 weeks, participants treated with fluoxetine or scalp electroacupuncture reported similar response rates (65 percent versus 56 percent, p-value not reported). A second trial, which we rated high risk of bias, reported fewer treatment responses with fluoxetine (20 mg/day) than electroacupuncture (30 sessions) (60 percent versus 75 percent, p=0.16).[91]

Results from network meta-analyses indicated no difference in response rates between patients treated with acupuncture and those treated with SGAs (RR, 0.75; 95% CI, 0.43 to 1.30).

Second-Generation Antidepressants Versus Acupuncture: Combination Comparisons

Two medium risk of bias RCTs compared SGA monotherapy with a combination of acupuncture and an SGA.[105,123] Qu et al. compared paroxetine (10–40 mg/d) with manual acupuncture (18 sessions) plus paroxetine and also with electroacupuncture (18 sessions) plus paroxetine. Response to treatment was significantly lower for paroxetine than for both combination acupuncture arms (42 percent versus 70 percent or 70 percent, p=0.004); the trial found no differences in remission among the three treatment arms (22.9 percent versus 22.6 percent or 28.6 percent, p=0.72). Zhang et al. compared fluoxetine (20 to 30 mg/day) plus sham acupuncture (30 sessions) with fluoxetine (10 mg/day) plus acupuncture (30 sessions). Response to treatment did not differ between the trial arms (80 percent versus 78 percent, p=0.79).

Second-Generation Antidepressants Compared With Omega-3 Fatty Acids

Second-Generation Antidepressants Versus Omega-3 Fatty Acids: Monotherapy Comparisons

One high risk of bias RCT compared fluoxetine with either EPA (eicosapentaenoic acid, 1,000 mg/day) or DHA (docosahexaenoic acid) monotherapy or a combination of EPA (1,000 mg/day) and fluoxetine (20 mg/day) (n=60).[120] This trial took place in Iran, recruited participants from a psychiatric hospital, and received funding from its local academic institution. After 8 weeks, patients treated with fluoxetine or omega-3 fatty acid supplements reported similar response rates (50 percent versus 56 percent, p=0.43).

Results from network meta-analyses indicated statistically significantly higher response rates for patients treated with SGAs as for patients treated with omega-3 fatty acids (RR, 1.96; 95% CI, 1.26 to 3.05).

Second-Generation Antidepressants Versus Omega-3 Fatty Acids: Combination Comparisons

Two trials compared patients treated with either fluoxetine or citalopram with patients treated with combinations of omega-3 fatty acids plus an SGA; we rated both these trials as high risk of bias (Table 16). One trial took place in the United States (funded by the National Institutes of Health) and recruited participants from outpatient referrals and local advertisements.[106] The other trial was from Iran (described above).[120] Combined, the trials evaluated 90 participants receiving either SGA monotherapy or the combination intervention; patient ages ranged from 18 to 65 years, and about 70 percent were female; the interventions took place over an 8-week period. Omega-3 fatty acid supplements consisted of either 1,000 mg daily of pure EPA[120] or a

combination of 1,800 mg EPA, 400 mg DHA, and 200 mg other omega-3 fatty acids daily.[106] Primary outcome evaluations were based on the HAM-D.

Table 16. Second-generation antidepressants versus omega-3 fatty acids: Study characteristics, main outcomes, and risk of bias ratings

Trial	N[a] Duration (Weeks)	Mean Baseline HAM-D Score	SGA Dose: mg/day Fatty Acid Dose: mg/day	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Risk of Bias Rating
Gertsik et al., 2012[106]	42 8	25.3	Citalopram: 20–40 EPA: 1,800 + DHA 400 + other 200 + citalopram 20-40	14 vs. 17 NR	18 vs. 44 NR	High[c]
Jazayeri et al., 2008[120]	48 8	30.0	Fluoxetine: 20 EPA: 1,000 Fluoxetine: 20 + EPA 1,000	50 vs. 56 vs. 81[d] p=0.43, p=0.005, p=0.009	NR	High[e]

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HAM-D = Hamilton Depression Rating Scale; mg/day = milligram per day; N = number; NR = not reported; vs. = versus

[a] Total number of randomized participants in relevant arms of trial.
[b] Response and remission are measured on the Hamilton Depression Rating Scale (HAM-D).
[c] Unclear randomization methods; high attrition; completers analysis.
[d] Fluoxetine versus EPA versus fluoxetine + EPA. P-values are for fluoxetine versus EPA, fluoxetine versus combination, and EPA versus combination, respectively.
[e] Unclear randomization methods; high attrition; completers analysis.

In the U.S. trial, at 8 weeks, changes in HAM-D favored the combination of omega-3 fatty acid supplement plus citalopram over citalopram monotherapy (data not reported, p<0.05).[106] The Iran trial reported superior 8-week treatment response rates for combination treatment with EPA plus fluoxetine (81 percent) over rates for either fluoxetine (50 percent) or EPA (56 percent) alone (p=0.005).[120] Similarly, the combination treatment produced greater reductions in HAM-D over 8 weeks than either monotherapy (data not reported, p=0.005). In summary, participants treated with a combination of omega-3 fatty acids plus SGA were more likely to benefit than participants treated with either SGA or omega-3 monotherapy.

Second-Generation Antidepressants Compared With S-Adenosyl-L-Methionine

One trial (high risk of bias) compared escitalopram (10 to 20 mg/day) to SAMe (1,600 to 3,200 mg/day).[104] The National Institutes of Health supplied funding. The trial recruited participants from outpatient referrals and local advertisements to academic hospitals in two U.S. locations. Patients ranged in age from 17 to 79 years. The sample was 50 percent female. The trial evaluated outcomes, based on the HAM-D, after 12 weeks of treatment.

Second-Generation Antidepressants Versus S-Adenosyl-L-Methionine: Monotherapy Comparisons

Treatment groups did not differ significantly in treatment response (34 percent versus 36 percent, p>0.05), remission (28 percent versus 28 percent, p>0.05), or reduction in HAM-D scores over time (6.3 versus 6.1, p-value not reported) (see Table 17). Results of our network meta-analyses also reported similar response rates for patients treated with SGAs and patients treated with SAMe (RR, 1.22; 95% CI, 0.66 to 2.26).

Table 17. Second-generation antidepressants versus SAMe: Study characteristics, main outcomes, and risk of bias ratings

Trial	N[a] Duration (Weeks)	Mean Baseline HAM-D Score	SGA Dose: mg/day SAMe Dose: units	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Risk of Bias Rating
Mischoulon et al., 2014[104]	129 12	19.2	Escitalopram: 10–20 SAMe: 1,600–3,200	34 vs. 36 p>0.05	28 vs. 28 p>0.05	High[c]

[a] Total number of randomized participants in relevant arms of trial.

[b] Response and remission are measured on the Hamilton Depression Rating Scale (HAM-D).

[c] High attrition.

Second-Generation Antidepressants Versus S-Adenosyl-L-Methionine: Combination Comparisons

We did not find any trials comparing SGA monotherapy with a combination therapy of SGAs and SAMe. Data were insufficient to estimate the comparative benefits of SGA monotherapy with combination SAMe plus SGA using network meta-analyses.

Second-Generation Antidepressants Compared With St. John's Wort (*Hypericum perforatum*)

Overall, 12 trials (13 articles) compared an SGA with St. John's wort (Table 18). Trials used a variety of commercially available standardized extracts (LI-160, WS5570, Ze117, STW3, Calmigen, Iperisan, Swiss herbal remedies), most often standardized to 0.12 to 0.28 percent hypericin; doses ranged from 300 mg to 1,800 mg of the standardized extract daily. Nine trials included 900 mg within their dosing range. Six trials used fluoxetine for comparison,[109,112,114,117,127,128] four used sertraline,[92,111,113,126] one used paroxetine,[110] and one used citalopram[125] (see Table 18 for dosages). Of the trials included in meta-analyses, none used an SGA dose at the maximum recommended strength and most used doses at the low end of the dosage range. In all, these trials provided data on 1,806 participants, predominantly with severe depression. Three trials took place in outpatient psychiatry clinics,[109,110,112] six trials in outpatient primary care clinics,[111,114,117,125,126,128] and three trials did not report the source of patients beyond outpatient communities.[92,113,127] Five trials were conducted in Germany;[110,114,125,126,128] three in the United States;[92,109,113] and one each in Brazil,[112] Canada,[111] Denmark,[127] and Sweden.[117] The maker of the supplement sponsored seven trials;[109-114,117] the U.S. government sponsored one.[92] Treatment duration ranged from 4 to 12 weeks. Most trials had a medium risk of bias, although we rated three trials as high[109,112,113] and two trials as low risk of bias.[117,125] In two cases, we gave a medium risk of bias rating to high-risk trials when evaluating response and remission.[109,113] We attempted to contact all study authors for additional study information and received additional data for two studies.[92,111]

Second-Generation Antidepressants Versus St. John's Wort: Monotherapy Comparisons

Overall, treatment effects with respect to treatment response, remission, and magnitude of change on the HAM-D scale were similar between patients treated with SGAs or St. John's wort. We did not find any evidence with respect to other outcomes of interest such as quality of life or functional capacity.

We conducted random-effects meta-analyses of nine low or medium risk of bias trials that reported data on response (1,517 participants), typically defined as ≥50 percent decrease in HAM-D.[92,110,111,113,114,117,125-127] Patients treated with SGAs and those receiving St. John's wort had similar response rates (51.7 percent versus 54.4 percent; RR, 0.96; 95% CI, 0.83 to 1.10) after 4 to 12 weeks of treatment (Figure 10). Sensitivity analysis using SGA dose or treatment duration showed no statistical difference between SGA and St. John's wort. Sensitivity analysis stratified by St. John's wort preparation demonstrated a difference for Ze 117[114] in favor of St. John's wort when compared with other preparations (RR, 0.66; 95% CI, 0.51 to 0.87) but was used in only a single trial. When stratifying by study country of origin, we found no statistical difference in estimates between studies conducted in Germany and non-German countries (RR, 0.90; 95% CI, 0.76 to 1.06 RR, 1.07; 95% CI, 0.85 to 1.33, respectively).

Table 18. Second-generation antidepressants versus St. John's wort: Trial characteristics, main outcomes, and risk of bias ratings

Trial	N[a] Duration (Weeks)	Mean Baseline HAM-D Score	SGA Dose (mg/day) St. John's Wort Formulation (mg/day)	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Risk of Bias Rating
Behnke et al., 2002[127]	70 6	20.4	Fluoxetine 40 Calmigen 300	66 vs. 55 p=0.41	NR	Medium
Bjerkenstedt et al., 2005[117]	113 4-6	24.7	Fluoxetine 20 LI160 900	37 vs. 38 NS	28 vs. 24 NR	Low
Brenner et al., 2000[113]	30 7	21.5	Sertraline 50–75 LI160 600–900	40 vs. 47 NS	NR	High[c,d]
Davidson et al., 2002[92]	224 8	22.7	Sertraline 50–100 LI160 900–1,500	24 vs. 14 NR	25 vs. 24 NR	Medium
Fava et al., 2005[109] Papakostas et al., 2007[136e]	92 12	19.6	Fluoxetine 20 LI160 900	NR	30 vs. 38 NS	High[c,f]
Gastpar et al., 2005[126]	241 12	22.1	Sertraline 50 STW3 612	69 vs. 74 NS	NR	Medium
Gastpar et al., 2006[125]	258 6	21.9	Citalopram 20 STW3-VI 900	56 vs. 54 p=0.63	NR	Low
Harrer et al., 1999[128 g]	161 6	NR	Fluoxetine 10 LoHyp-57 400	72 vs. 71 NR	NR	Medium
Moreno et al., 2006[112]	40 8	NR	Fluoxetine 20 Iperisan 900	55 vs. 20 p=0.02	12 vs. 35 NR	High[h]

Table 18. Second-generation antidepressants versus St. John's wort: Trial characteristics, main outcomes, and risk of bias ratings (continued)

Trial	N[a] Duration (Weeks)	Mean Baseline HAM-D Score	SGA Dose (mg/day) St. John's Wort Formulation (mg/day)	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Risk of Bias Rating
Schrader et al., 2000[114]	240 6	19.6	Fluoxetine 20 Ze117 500	40 vs. 60 p=0.05	NR	Medium
Szegedi et al., 2005[110]	251 6	25.5	Paroxetine 20–40 WS5570 900–1,800	73 vs. 86 p=0.08	43 vs. 61 p=0.02	Medium
van Gurp et al., 2002[111]	90 12	19.3	Sertraline 50–100 Swiss herbal remedies 900–1,800	NR	NR	Medium

HAM-D = Hamilton Depression Rating Scale; mg/day = milligrams per day; N = number; NR = not reported; NS = reported as not significant; SGA = second-generation antidepressants; vs. = versus

[a] Total number of randomized participants in relevant arms of trial.

[b] Response and remission are measured on the HAM-D.

[c] For dichotomous outcomes (e.g., response and remission), we rated the risk of bias for these trials medium because dropouts were counted as remission failures.

[d] High attrition, unclear randomization methods.

[e] Not included in meta-analyses because it is a reanalysis of Fava et al. (2005).[109]

[f] High attrition, unclear randomization methods.

[g] Not included in response and remission meta-analyses because of the age of trial population (60 to 80 years).

[h] Completers analysis.

Figure 10. SGA versus St. John's wort: Response

Author, Year	Statistics for each study			Response / Total		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	SGA	SJW	
Behnke, 2002	1.31	0.84	2.06	21 / 35	16 / 35	
Bjerkenstedt, 2005	0.93	0.57	1.50	20 / 56	22 / 57	
Brenner, 2000	0.86	0.38	1.95	6 / 15	7 / 15	
Davidson, 2002	1.22	0.91	1.63	55 / 111	46 / 113	
Gastpar, 2005	1.07	0.87	1.32	72 / 118	70 / 123	
Gastpar, 2006	1.03	0.83	1.29	71 / 127	71 / 131	
Schrader, 2000	0.66	0.51	0.87	45 / 114	75 / 126	
Szegedi, 2005	0.84	0.70	1.02	73 / 126	86 / 125	
van Gurp, 2002	0.88	0.61	1.29	23 / 45	26 / 45	
	0.96	0.83	1.10			

Favors SJW   Favors SGA

Random effects meta-analysis; I-squared 47%

CI = confidence interval; SGA = second-generation antidepressants; SJW = St. John's wort

Likewise, random-effects meta-analyses of five low or medium risk of bias trials (768 participants) showed similar remission rates (typically defined as HAM-D ≤7) for participants on SGAs or St. John's wort (30.2 percent versus 36.2 percent; RR, 0.82; 95% CI, 0.67 to 1.00) after 4 to 12 weeks of treatment (Figure 11).[92,109-111,117] Sensitivity analysis including one high risk of bias trial[112] (40 participants) produced similar findings (29.4 percent versus 33.2 percent; RR, 0.88; 95% CI, 0.68 to 1.13).

Figure 11. SGA versus St. John's wort: Remission
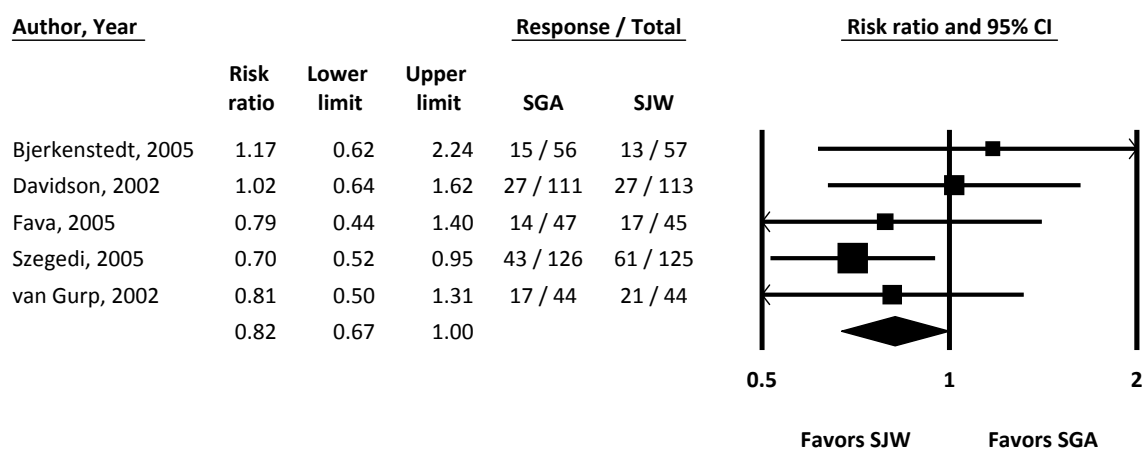
Author, Year	Risk ratio	Lower limit	Upper limit	Response / Total SGA	Response / Total SJW	Risk ratio and 95% CI
Bjerkenstedt, 2005	1.17	0.62	2.24	15 / 56	13 / 57	
Davidson, 2002	1.02	0.64	1.62	27 / 111	27 / 113	
Fava, 2005	0.79	0.44	1.40	14 / 47	17 / 45	
Szegedi, 2005	0.70	0.52	0.95	43 / 126	61 / 125	
van Gurp, 2002	0.81	0.50	1.31	17 / 44	21 / 44	
	0.82	0.67	1.00			

Favors SJW   Favors SGA

Random effects meta-analysis; I-squared 0%

CI = confidence interval; SGA = second-generation antidepressants; SJW = St. John's wort

Seven trials with low or moderate risk of bias reported data on change in HAM-D scores (1,369 participants).[92,109-111,114,125-127] We found similar HAM-D reductions for patients treated with an SGA and those treated with St. John's wort (Figure 12; mean difference -0.45; 95% CI, -1.45 to 0.55). Sensitivity analysis including two high risk of bias trials indicated no difference in conclusions (mean difference -0.65; 95% CI, -1.62 to 0.33).

Figure 12. SGA versus St. John's wort: Change in HAM-D-17

Study name	Difference in means	Lower limit	Upper limit	Sample size SGA	Sample size SJW	Difference in means and 95% CI
Behnke, 2002	-1.30	-3.87	1.27	35	35	
Davidson, 2002	1.60	0.10	3.10	109	113	
Gastpar, 2005	0.30	-0.99	1.59	118	123	
Gastpar, 2006	-0.10	-1.54	1.34	127	131	
Schrader, 2000	-0.86	-1.84	0.12	114	126	
Szegedi, 2005	-3.00	-5.15	-0.85	126	125	
van Gurp, 2002	-1.30	-4.35	1.75	43	44	
	-0.45	-1.45	0.55			

-8.00   -4.00   0.00   4.00   8.00

Favors SJW   Favors SGA
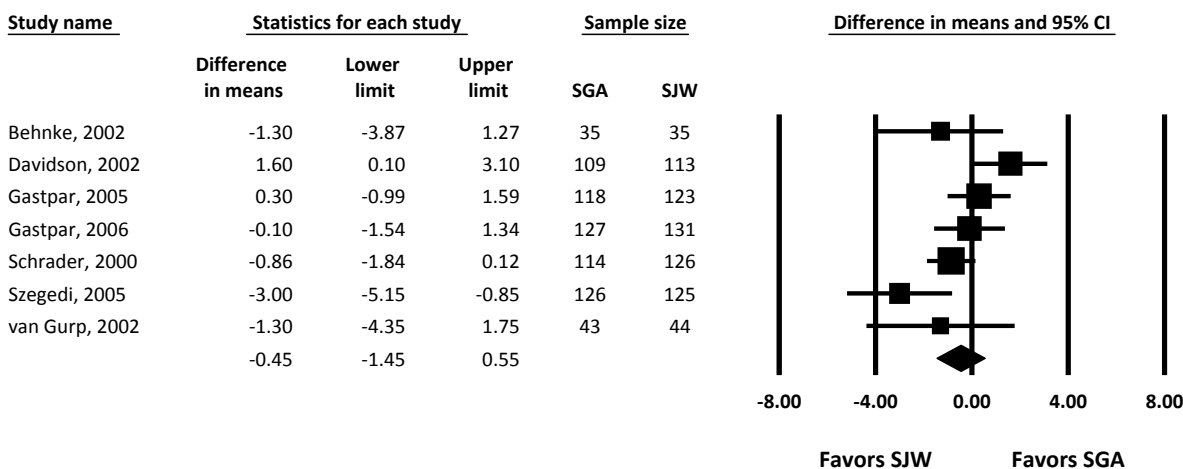
Random effects meta-analysis; I-squared 61%

CI = confidence interval; HAM-D = Hamilton Depression Scale for Depression; SGA = second-generation antidepressants; SJW = St. John's wort.

Second-Generation Antidepressants Versus St. John's Wort: Combination Comparisons

We did not find any trials comparing SGA monotherapy with a combination therapy of St. John's wort and SGAs. Data were insufficient to estimate the comparative benefits with network meta-analyses.

Second-Generation Antidepressants Compared With Yoga

We found no eligible trials that compared an SGA with yoga.

Second-Generation Antidepressants Compared With Meditation

We found no eligible trials that compared an SGA with meditation therapy.

KQ 1a. Second-Generation Antidepressants Compared With Exercise Interventions

We identified two primary RCTs (four articles) comparing an SGA with an aerobic exercise intervention for treating patients with MDD.[93,94,137,138] The same group of researchers conducted both trials; we rated both as medium risk of bias (Table 19). Both trials evaluated sertraline compared with aerobic exercise; the earlier trial also evaluated the efficacy of sertraline alone compared with sertraline plus aerobic exercise.[93] The trials enrolled patients according to a criteria-based diagnosis of MDD based on DSM-IV;[70] they excluded patients who had additional Axis I disorders, high suicidal risk, or progressive medical diseases; who were involved in regular exercise; or who were undergoing psychiatric treatment. Both trials used the HAM-D 17 to assess MDD severity at baseline and at 16 weeks. Participants had depression of moderate severity at baseline as measured by the HAM-D. Grants from the National Institutes of Health and Pfizer Pharmaceuticals funded both studies.

Table 19. Second-generation antidepressants versus exercise: Study characteristics, main outcomes, and risk of bias ratings

Trial	N[a] Duration	Mean Baseline HAM-D Score	SGA Dose (mg/day) Exercise Type (Frequency of Sessions)	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Quality of Life, Functional Capacity and Significance Level	Risk of Bias Rating
Blumenthal et al., 1999[93] Babyak et al., 2000[139]	156 16-week treatment; 6-month followup	NR Per group: range from 17 to 19	Sertraline 50–200 Aerobic exercise (3 times per/week) Sertraline + aerobic exercise (3 times per week)	At 16 weeks: NR	68.8 vs. 60.4 vs. 65.5 p=0.67	Life satisfaction p=NS	Medium
Blumenthal et al, 2007[94] Hoffman et al., 2008[138]	153 16-week treatment	NR Per group: range from 16 to 17	Sertraline 50–200 Supervised aerobic exercise (3 times per week) Home-based aerobic exercise (3 times per week)	At 16 weeks: NR	47 vs. 45 vs. 40 p=0.646	Neurocognitive tests battery p=NS	Medium

HAM-D = Hamilton Depression Rating Scale; mg/day = milligrams per day; N = number; NR = not reported; NS = reported as not significant, SGA = second-generation antidepressants; vs. = versus

[a] Total number of randomized participants in relevant arms of trial.

[b] Response (≥50 percent decrease in depressive severity) and remission (as defined by authors of individual trials) are measured using the HAM-D unless indicated otherwise.

The trials included 309 participants total randomized to active treatment arms, recruited from the community into an outpatient facility at an academic medical center. In the earlier trial, participants ranged from 50 to 77 years of age (mean, 57 years); 57 percent of the sample was female. In the 2007 trial, participants' mean age was 52 years, and 51 percent were female.

Both trials compared a 50–200 mg daily sertraline dose with a supervised aerobic exercise program of 45 minutes three times weekly over 16 weeks. The aerobic exercise program consisted of a 10-minute warm-up exercise period followed by 30 minutes of continuous walking or jogging at an intensity that would maintain heart rate at 70 percent to 85 percent of heart rate reserve, followed by 5 minutes of cool-down exercises. In addition, the Blumenthal et al., 1999[93] trial compared the sertraline and supervised exercise arms, individually, with an arm combining sertraline with supervised exercise. In contrast, the Blumenthal et al., 2007[94] trial used a four-armed design—adding a home-based exercise program arm and a placebo pill arm. The primary outcome for both trials was the remission rate at 16 weeks (no longer meeting MDD criteria and HAM-D <8). At baseline and 16 weeks of treatment, participants also underwent a graded exercise treadmill test to measure exercise capacity and tolerance. The trial reported additional secondary outcomes: anxiety, self-esteem, life satisfaction, and dysfunctional attitudes in the 1999 trial and neurocognitive improvement in the 2007 trial.

Second-Generation Antidepressants Versus Aerobic Exercise: Monotherapy Comparisons

Neither trial found a statistically significant difference in remission rates between sertraline alone and aerobic exercise alone: 68.8 percent (sertraline) versus 60.4 percent (exercise) in the 1999 trial and 47 percent (sertraline) versus 45 percent (supervised exercise) versus 40 percent (home-based exercise) in the 2007 trial. All three active groups in the 2007 trial tended to have higher remission rates than the placebo control group (31 percent) (p=0.057). The crude pooled risk ratio comparing sertraline treatment with the exercise conditions (pooling data from the two exercise groups in the 2007 trial with the one exercise-only group in the 1999 trial, a total of three arms) was 1.10 (95% CI, 0.87 to 1.39). All active treatment groups in the 2007 trial showed a clinically and statistically significant decline (p<0.0001) in HAM-D scores from baseline to 16 weeks; the sertraline group decreased by 6.1, supervised exercise by 7.2, home-based exercise by 7.1, and placebo by 6.1 points. There were no between-group differences in this decline (p=0.321). The 1999 trial found the magnitude of the decline in HAM-D to be comparable across groups; it did not provide specifics. Neither trial reported response rates. Based on network meta-analyses, patients in the SGA and exercise groups had similar response rates (RR 1.86; 95% CI, 0.81 to 4.27).

In both trials, patients receiving sertraline showed significantly lower levels of aerobic capacity (peak VO_2), as well as shorter treadmill times, than patients in the exercise groups (p<0.001). The Blumenthal et al. 1999 trial also assessed anxiety, self-esteem, life satisfaction, and dysfunctional attitudes. Although both the sertraline and the exercise groups improved, the groups did not differ on these measures. The companion report to the 2007 trial[138] found little evidence of between-group differences in neurocognitive measures; exercise participants performed better than those on sertraline on tests of executive function (Trail-making Test, p=0.02; Ruff 2 & 7 test, p=0.03) but not on measures of verbal memory or verbal fluency/working memory.

In a sensitivity analysis, the magnitudes of the RRs are slightly attenuated with inclusion of trials with a high risk of bias, but the interpretations do not change.

Second-Generation Antidepressants Versus Aerobic Exercise: Combination Comparisons

A single trial, Blumenthal et al. 1999,[93] included an arm comparing sertraline alone to a combination of sertraline plus exercise; it had 48 participants in the sertraline-alone group and 55 in the combined sertraline plus exercise group. Data were insufficient to estimate comparative benefits of SGA monotherapy versus combination therapy with SGA and exercise using network analysis. Patients in the sertraline-only group showed minimal (<3 percent) improvement in aerobic capacity; those in the combined group improved by 9 percent. The two groups did not differ in improvements in anxiety, self-esteem, life satisfaction, or dysfunctional attitudes scores.

KQ 1b. Effect of Severity: Second-Generation Antidepressants Compared With Psychological Interventions

Description of Trials

In all, four RCTs compared SGA with a psychological treatment and provided data for KQ 1b (Table 20).[96,97,103,118] We rated three trials medium risk of bias[96,97,103] and one trial as high risk of bias.[97,118] One medium risk of bias trial compared SGA with either of two psychological treatments.[97] Included trials compared an SGA with a CBT (cognitive therapy),[97,118] a third-wave CBT (behavioral activation),[97] a PSYD,[96] and an integrative therapy (interpersonal therapy).[103] We found no trials eligible for KQ 1b that compared a SGA with behavior therapy/behavior modification or with a humanistic therapy.

Table 20. SGAs versus psychological interventions by depression severity: Trial characteristics, main outcomes, and risk of bias ratings of trials

Author, Year Type of Psychotherapy	N[a] Duration (Weeks)	MDD Severity Definition and Mean Baseline Severity	SGA Dose (mg/day) Psycho-therapy Type: (Number of Sessions)	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Mean Change (SD) in HAM-D and Significance Level	Risk-of Bias Rating
Dimidjian 2006[97] Cognitive therapy	145 16	Low: HAM-D-17 ≤19 Mean: SGA: 16.98 CT: 16.65 High: HAM-D ≥20 Mean: SGA: 23.79 CT: 23.16	Paroxetine: 50 CT: 24[c]	Low: Paroxetine: 47 CT: 60 p=NS High: Paroxetine: 40 CT: 56 p=NS	Low: Paroxetine: 33 CT: 50 p=0.45 High: Paroxetine: 23 CT: 36 p=0.012	Low: Paroxetine: -8.53 (NR) CT: -9.46 (NR) p=NR High: Paroxetine: -15.16 (NR) CT: -12.39 (NR) p=NR	Medium
Menchetti et al., 2014[103] Integrative psychotherapy (IPT)	287 8	HAM-D-21 <18 vs. HAM-D-21 ≥18 Mean: SGA: 17.5 IPT: 17.1	Citalopram: 10–60 or sertraline 25–200 IPT: 6 to 8	NR	HAM-D <18: SGA: 56 IPT: 75 p=NR but is statistically significant (SRD=0.19; 95% CI, 0.04 to 0.34) HAM-D ≥18: SGA: 46 IPT: 40 p=NR but is not statistically significant (SRD = -0.06; 95% CI, -0.24 to 0.12)	NR	Medium

Table 20. SGAs versus psychological interventions by depression severity: Trial characteristics, main outcomes, and risk of bias ratings of trials (continued)

Author, Year Type of Psychotherapy	N[a] Duration (Weeks)	MDD Severity Definition and Mean Baseline Severity	SGA Dose (mg/day) Psycho-therapy Type: (Number of Sessions)	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Mean Change (SD) in HAM-D and Significance Level	Risk-of Bias Rating
Barber et al., 2012[96] Psychodynamic Psychotherapy (Supportive expressive therapy)	106 8[d]	Baseline HAM-D-17 score <19 vs. HAM-D-17 >20 Mean: SGA: 19.0 SET: 19.9	Sertraline: 50–200 SET: 20	NR	NR	Limiting the analysis to patients with high depression severity revealed no differences in rate of change of HAM-D	Medium
Moradveisi et al., 2013[118] Third-wave CBT (Behavioral activation)	100 49	Baseline HAM-D-17 score included in regression model. Mean: SGA: 21.62 BA: 21.12	Sertraline: 100 BA: 16	NR	NR	β (95% CI): -2.03 (-3.01 to -1.05) p<0.001	High[e]
Dimidjian et al., 2006[97] Third-wave CBT (Behavioral activation)	143 16	Low: HAM-D-17 <19 Mean: SGA: 16.98 BA: 17.28 High: HAM-D-17 >20 Mean: SGA: 23.79 BA: 23.16	Paroxetine: 50 BA: 24	Low: Paroxetine: 47 BA: 39 p=NS High: Paroxetine 40 BA 60 p=NS	Low: Paroxetine: 33 BA: 39 p=NS High: Paroxetine: 23 BA: 56 p=0.002	Low: Paroxetine: -8.53 (NR) BA: -9.36 (NR) p=NR High: Paroxetine: -15.16 (NR) BA: -15.60 (NR) p=NR	Medium

BA = behavioral activation; CBT = cognitive behavioral therapy; CI = confidence interval; CT = cognitive therapy; HAM-D = Hamilton Rating Scale for Depression; IPT = interpersonal psychotherapy; MDD = major depressive disorder; mg/day = milligrams per day; N = number; NR = not reported; SD = standard deviation; SET = supportive expressive therapy; SGA = second-generation antidepressant; SRD = standardised rate difference; vs. = versus

[a] Total number of randomized participants in relevant arms of trial.

[b] Response and remission (as defined by authors of individual trials) are measured on the Hamilton Depression Rating Scale (HAM-D) or indicated otherwise.

[c] This trial contained a fourth placebo control arm.

[d] Treatment duration was 16 weeks, but only the week 8 results are relevant for this KQ.

[e] High attrition; dosage capped below the upper limit of typically prescribed range.

Two of the trials were conducted in the United States,[96,97] and two were conducted in other countries: one in Iran[118] and one in Italy.[103] Two of the trials took place in outpatient primary care settings;[97,103] two were conducted in outpatient psychiatry clinics.[96,118] Three of the trials were funded entirely or in part by the government.[96,97,103] Three trials did not provide any information on treatment fidelity,[96,103,118] and only one trial reported adequate treatment fidelity.[97] None of the trials reported on functional capacity, quality of life, reduction of suicidality, relapse, or hospitalization. None of the trials excluded individuals with any comorbid anxiety disorder, although one trial reported that they did not include subjects with a primary diagnosis of panic disorder or obsessive-compulsive disorder.[97]

None of the trials was designed to answer the primary question of whether depressive severity was a modifier of the comparative effectiveness of SGAs versus psychotherapy. However, two trials prespecified their plan to use depressive severity as a moderator.[97,103] The methods to analyze whether outcome measured by depressive severity varied. One trial stratified its sample into a high- and low-severity subgroup and assessed the comparative benefits of the SGAs versus psychotherapy within each subgroup.[97] Another trial examined potential moderators of remission with logistic modeling, including stratification of high versus low severity as one possible predictor.[103] A third trial used a mixed regression analysis model that tested whether the baseline depressive severity score moderated outcomes.[118] Finally, one trial used hierarchical linear modeling to determine whether depressive severity had a moderating effect, considering both the full sample as well as the subgroup with higher depressive severity.[96]

Generally, patient age ranged between 18 and 50 years old; trials reported a mean age between 31.4[118] and 44.9 years.[103] In all trials, the majority of the patients were female. Two trials reported minority status (18.3 percent[97] and 48.1 percent[96]).

Impact of Severity on Various Outcomes

One medium risk of bias trial (n=145), with one arm comparing paroxetine and CT, conducted subgroup analyses in patients with low- and high-severity MDD.[97] For the subgroup with high-severity MDD (i.e., those with a HAM-D-17 $\geq$20), those receiving paroxetine were less likely to achieve remission of MDD than those receiving CT (23 percent versus 36 percent, p=NS).[97] For the subgroup with low-severity MDD (i.e., those with a HAM-D-17 $\leq$19); remission rates did not differ significantly for patients treated with paroxetine or CT. Efficacy did not differ significantly between treatments in either subgroup when measured by treatment response or change in HAM-D-17. Because of the small sample size and the fact that authors conducted multiple parallel comparisons of subgroups and not a test of interaction, findings might be attributable to chance and need to viewed cautiously.

One medium risk of bias trial (n=287) reported subgroup analyses of patients with low- or high-severity MDD at baseline who were treated with either an SGA or IPT.[103] From regression analyses, Menchetti and colleagues[103] reported that the likelihood of remission varied as a function of depression severity; only those with less severe depression saw a worse outcome from SGA than from IPT. For patients with baseline HAM-D-21 <18, those receiving 2 months of citalopram or sertraline were 19 percent less likely to achieve remission than those receiving IPT (Standardised Rate Difference [SRD], 0.19; 95% CI, 0.04 to 0.34), consistent with a small-to-moderate effect size (ES = 0.25).[103] However, for patients with high-severity MDD (HAM-D-20 $\geq$18), the likelihood of remission did not differ between the two treatment groups [SRD, -0.06; 95% CI, -0.24 to 0.12].[103] The trial did not report treatment response or change in HAM-D score.

One medium risk of bias trial and one high risk of bias trial[97,118] compared an SGA with behavioral activation and provided subgroup analyses that considered the effects of depressive severity on treatment outcome. In one trial (n=100), Moradveisi and colleagues used regression modeling to assess the effect of baseline severity on change in depressive severity.[118] The difference in treatment effects between the two types of interventions increased as a function of severity. In patients with less severe MDD at baseline, the difference in treatment effects at weeks 4, 13, and 49 were minimal. However, as baseline severity increased, patients receiving sertraline had less improvement in depressive severity as measured by both HAM-D and BDI at each followup point.[118]

The medium risk of bias trial (n=143) reported on the effect of baseline depressive severity on all three main outcomes.[97] In this trial, the authors reported that for subjects with high-severity MDD (defined as HAM-D-17 $\geq$20), those receiving paroxetine were less likely to remit than those receiving BA (23 percent versus 56 percent, p=0.002). In those with low-severity MDD, remission rates did not differ to a statistically significant degree between the two treatment groups. For the other two outcomes, treatment response or change in HAM-D-17 score, having either high- or low-severity MDD did not produce different outcomes for the two interventions.

One medium risk of bias trial (n=106) that compared supportive–expressive psychotherapy conducted subgroup analyses in high- and low-severity patients.[96] The trial did not report on either response to treatment or remission. Although the authors did not report specific changes in HAM-D scores stratified by subgroup, they did analyze depression severity as a potential moderator of change in HAM-D scores. Limiting the analysis to patients with high depression severity revealed no differences in rate of change of HAM-D. We contacted trial authors for additional data but did not receive any supplementary information.

Comparative Efficacy for Critical Efficacy Outcomes by Baseline Severity for Psychological Interventions and Second-Generation Antidepressants

We further investigated the role of depressive severity on outcomes by considering all trials from KQ 1a that both directly compared psychological interventions to SGAs and reported on key effectiveness outcomes (response, remission, and/or functional capacity). These studies did not directly assess depressive severity as a moderator; however, one might observe whether there is evidence of a relation between mean baseline depressive severity and the comparative effectiveness of the interventions (Table 21). We were not able to stratify by whether the depressive severity of the populations was specifically "moderate" or "severe," because most populations were mixed (i.e., they had both moderate and severely depressed populations mixed together). Rather, for each comparison we list the range of mean baseline depressive severity and the findings. Of note, we found no differences in the comparative effectiveness between SGAs and psychological treatments in patients with moderate to severe MDD, which is consistent with findings of the few studies that we have for KQ 1b. However, as with our earlier KQ 1b findings, the evidence was very limited.

Table 21. Comparative efficacy for critical efficacy outcomes by baseline severity for psychological interventions and second-generation antidepressants

Comparisons	Baseline MDD Severity	Comparative Effectiveness for Critical Efficacy Outcomes	Strength of Evidence
SGA vs. CBT	Moderate to severe	Response: No statistically significant differences	Moderate
		Remission: No statistically significant differences	Low
		Functional capacity: No statistically significant differences	Low
SGA vs. CBT + SGA	Moderate to severe	Response: No statistically significant differences	Low
		Remission: No statistically significant differences	Low
		Functional capacity: Favors CBT + SGA combination	Low
SGA vs. IT	Moderate to severe	Response: No statistically significant differences	Low
		Remission: No statistically significant differences	Low
SGA vs. IT + SGA	Moderate to severe	Remission: Favors SGA	Low
SGA vs. PSYD	Moderate	Remission: No statistically significant differences	Low
		Functional capacity: No statistically significant differences	Low

CBT = cognitive behavioral therapy; IT = integrative therapy; SGA = second-generation antidepressant; PSYD = psychodynamic therapy.

KQ 1b. Effect of Severity: Second-Generation Antidepressants Compared With Complementary and Alternative Medicine Interventions

One trial compared SGA with a CAM therapy for treating patients with MDD.[104] Participants were enrolled according to a criteria-based diagnosis of MDD based on either the DSM-IV or the DMS-III-R and a predefined cutoff point for the HAM-D. Most participants had moderate to severe depression as measured by the HAM-D. Patients were excluded who had additional Axis I disorders, high suicidal risk, or progressive medical diseases or who used psychotherapy, electroconvulsive therapy, or psychotropic medications.

Second-Generation Antidepressants Compared With S-Adenosyl-L-Methionine

One trial (Table 22), rated medium risk of bias, compared escitalopram (10 to 20mg/day) with SAMe (1,600 to 3,200 mg/day). The National Institutes of Health supplied funding. The trial recruited participants (N=129) from outpatient referrals and local advertisements to academic hospitals in two U.S. locations. Participant age ranged from 17 to79 years; the sample was 50 percent female. The trial evaluated outcomes, based on the HAM-D, after 12 weeks of treatment. Mean (SD) baseline HAM-D score was 19.2 (4.7) with a range from 4 to 32. No statistically significant interaction appeared between baseline HAM-D score and treatment groups for reduction in HAM-D scores over time (p=NS).

Table 22. SGAs versus SAMe by depression severity: Trial characteristics, main outcomes, and risk of bias ratings of trials

Trial	N[a] Duration (Weeks)	Mean Baseline HAM-D Score	SGA Dose (mg/day) and SAMe Dose (mg/day)	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Reduction in HAM-D by Baseline Score[c]	Risk of Bias Rating
Mischoulon et al., 2014[104]	189 12	19.2	Escitalopram 10–20 SAMe 1,600–3,200	NR	NR	p=NS	High[d]

HAM-D = Hamilton Depression Rating Scale; mg = milligram; N = number; NR = not reported; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant

[a] Total number of randomized participants in relevant arms of trials.

[b] Response and remission are measured on the Hamilton Depression Rating Scale (HAM-D).

[c] Interaction between baseline HAM-D score and overall reduction in HAM-D over 12 weeks.

[d] High attrition.

Comparative Efficacy for Critical Efficacy Outcomes by Baseline Severity for Complementary and Alternative Interventions, Exercise, and Second-Generation Antidepressants

As with our psychological intervention comparison, we further investigated the role of depressive severity on outcomes by considering all trials from KQ 1a that directly compared CAM interventions or exercise to SGAs and reported on key effectiveness outcomes (i.e., response, remission, and/or functional capacity) (Table 23). Again, we found no differences in treatment effects in populations with moderate or severe MDD, which is consistent with findings of the few studies that we have for KQ 1b. This evidence, too, was extremely limited.

Table 23. Comparative efficacy for critical efficacy outcomes by baseline severity for complementary and alternative interventions, exercise, and second-generation antidepressants

Comparisons	Baseline MDD Severity	Comparative Effectiveness for Critical Efficacy Outcomes	Strength of Evidence
SGA vs. Acupuncture	Severe	Response: No statistically significant differences	Low
SGA vs. Acupuncture + SGA	Severe	Response: Favors acupuncture + SGA combination	Low
		Remission: No statistically significant differences	Low
SGA vs. Omega-3 fatty acids	Severe	Response: Favors SGA	Low
SGA vs. SAMe	Moderate	Response: No statistically significant differences	Low
SGA vs. St. John's wort	Moderate to severe	Response: No statistically significant differences	Low
		Remission: No statistically significant differences	Low
SGA vs. Exercise	Moderate	Response: No statistically significant differences	Low
		Remission: No statistically significant differences	Low
SGA vs. Exercise + SGA	Moderate	Remission: No statistically significant differences	Low

MDD = major depressive disorder; mg = milligram; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant.

KQ 2. Second-Step Therapy: Switching or Augmentation Strategies Involving a Second-Generation Antidepressant

KQ 2a addresses adult patients with acute-phase MDD who fail to recover after an initial treatment with an SGA (also referred to as second-step therapy). It examines the effectiveness of any eligible intervention (whether as a monotherapy or an augmentation therapy) that has been compared with one involving an SGA. The comparison can involve either switching to different treatment (pharmacological or nonpharmacological) or augmenting the initial SGA with a second treatment (pharmacological or nonpharmacological).

As with KQ 1, the nonpharmacological interventions for this KQ include psychological interventions, CAM interventions, and exercise. For augmentation, however, the pharmacological options increase; augmentation of the initial SGA can involve adding either a second SGA or an eligible non-SGA medication (e.g., buspirone). KQ 2b examines whether treatment effectiveness varies by MDD severity.

In all, two trials provided data that compared eligible second-step treatment strategies. Both used the HAM-D to measure outcome; neither reported quality of life or functional status outcomes. One trial compared switching to one SGA versus switching to a different SGA.[115] The other trial, the STAR*D study, provided data for multiple comparisons that were reported in three articles. These analyses allowed the comparison of four eligible second-step treatment strategies: switching to one SGA versus switching to a different SGA,[140] switching to CBT versus switching to any one of three SGAs,[107] augmenting with a second medication versus augmenting with CBT,[107] and augmenting with one non-SGA medication versus augmenting with an SGA.[141]

We found no eligible switch trials directly comparing SGAs with either CAM or exercise, nor did we find any eligible augmentation trials comparing SGAs with CAM or exercise. Moreover, we found no direct comparison of switching strategies versus augmentation strategies. Because of an insufficient number of eligible studies, we could not perform a network meta-analysis on response to treatment for second-step therapies that compared eligible second-step therapies with placebo.

Key Points: Switching Strategies

- When switching to a different SGA as a second-step therapy, various SGAs produce similar response rates (two RCTs, moderate SOE), similar remission rates (one RCT, low SOE), and a similar decrease in depressive severity (one RCT, low SOE).
- Switching to cognitive therapy does not produce statistically different rates of response (one RCT, low SOE) or remission (one RCT, low SOE) compared with switching to a different SGA.
- We did not find any eligible switch evidence comparing an SGA strategy with either CAM or exercise.

Key Points: Augmentation Strategies

- When augmenting with a second medication as a second-step therapy, adding a non-SGA augmenting medication does not lead to statistically different rates of response (one RCT, low SOE) or remission rate (one RCT, low SOE) compared with augmenting with a second SGA; augmentation with bupropion leads to a greater decrease in depressive severity than with buspirone (one RCT, low SOE).
- Augmenting with cognitive therapy does not produce statistically different rates of response (one RCT, low SOE), remission (one RCT, low SOE), or decrease in depressive severity compared with augmenting with an SGA.
- We did not find any eligible augmentation evidence comparing adding a second medication with adding either CAM or exercise.

Key Points: Severity as a Moderator of Comparative Treatment Effectiveness of Second-Step Therapies

- For second-step therapies, the evidence is insufficient to draw conclusions about the effect of severity of disease on the comparative effectiveness of switching to different SGAs as measured by remission rates (secondary analyses of two RCTs, insufficient SOE).

- For second-step therapies, we did not find any eligible evidence about the effect of severity of disease on the comparative effectiveness of switching to a different SGA versus switching to any nonpharmacological treatment.
- For second-step therapies, we did not find any eligible evidence about the effect of severity of disease on the comparative effectiveness of any augmentation strategies.

Detailed Synthesis: KQ 2

This section presents findings for both KQs 2a and 2b. KQ 2a concerns comparisons of "next step" treatment options. These can include comparisons of switch strategies against each other, augmentation strategies against each other, or switch versus augmentation strategies, as long as at least one arm involved an SGA. Eligible switch or augmentation strategies can involve eligible psychotherapies, CAM, or exercise interventions. KQ 2b examines the question of whether the comparative effectiveness of these strategies differs by the severity of MDD.

Table 24 provides the number of included trials by eligible comparison. The evidence base for KQ 2a provided limited data (two trials reported in three articles) that addressed four comparisons—two switch and two augmentation—and involved only medications and psychotherapy. In the analyses comparing medications, specific medications were assessed head-to-head (e.g., sertraline versus bupropion); in the studies comparing medications to psychotherapy, however, the analyses grouped all medications into a single medication variable. No eligible studies involved CAM treatments or exercise. Further, the number of relevant placebo-controlled studies was insufficient to allow a network meta-analysis. In Appendix E, we present "summary of findings" tables of important outcomes. These tables are intended mainly for readers involved in developing clinical practice guidelines; they give basic information on the available evidence, show absolute and relative effect measures, and present SOE grades for each outcome on which we had evidence.

Table 24. Number of included trials by type of comparison

Comparison Category	Comparisons for KQ 2	Number of Trials and Citations
Switch	SGA switch[a] vs. SGA switch[a]	2[115,140]
	SGA switch[a] vs. nonpharmacological switch	1[107]
Augmentation	SGA augmentation[b] vs. SGA augmentation[b]	1[141]
	SGA augmentation[b] vs. nonpharmacological switch	1[107]

KQ = Key Question; SGA = second-generation antidepressant; vs. = versus

[a]Switching to another SGA.

[b]Augmenting with a second SGA, an additional non-SGA medication, or a nonpharmacological treatment.

KQ 2a. Switching or Augmentation Strategies

Description of Included Trials

In all, two trials provided four comparison studies reported in four articles. All four comparisons reported in three of the articles[107,140,141] involved data from the STAR*D study, which had multiple arms allowing several comparisons following a treatment failure. A different independent study reported data comparing various SGA switches.[115]

The Lenox-Smith and Jiang trial was conducted in a single outpatient psychiatry setting in Great Britain and was funded by the pharmaceutical industry. The STAR*D comparison

involved outpatients from 41 psychiatric (60 percent) and primary care (40 percent) settings in the United States and was government funded.

Generally, patients were between 18 and 65 years of age (mean ages between 41 and 43 years). In both, the majority of patients were female. Mean baseline depressive severity was at least moderate. STAR*D comparisons involved mean baseline HAM-D scores between 15.8 and 17.8; the Lenox-Smith and Jiang trial had greater depression severity, with a mean HAM-D score of approximately 26 (severe). The total daily dose of each SGA medication reached or exceeded the minimum recommended dose for that medication as prescribed for adults, and the maximal dose did not exceed that noted in FDA labelling.

Whereas the Lenox-Smith and Jiang trial was a relatively standard RCT, the STAR*D study employed an equipoise randomization scheme that allowed some degree of patient preference. STAR*D was designed to allow multiple randomized comparisons of second-step therapies; the three relevant comparisons reported here[107,140,141] all involved patients who did not remit following 3 months of treatment with citalopram. Patients could not refuse a specific medication choice, but patients did have the option of refusing any of the available treatment strategies (switch to another SGA, switch to cognitive therapy, augment with a second medication, or augment with cognitive therapy), as long as at least two treatment options remained to allow randomization.

Second-Generation Antidepressant Switch Compared With Second-Generation Antidepressant Switch

Table 25 describes the trial characteristics, main outcomes, and risk of bias ratings for these analyses. The Lenox-Smith and Jiang trial lasted 12 weeks, with 396 patients randomized to one of two treatment arms.[115] The trial compared venlafaxine ER (doses ranged from 75 to 300 mg daily; mean daily dose was 191 mg) to citalopram (20 to 60 mg; mean daily dose, 51 mg). The investigators measured response with the HAM-D; they did not report response rate for the two study arms but instead stated that response did not differ (reported as p=0.953). They did not report remission rate or time to remission for any outcome. The decrease in depressive severity, whether measured by HAM-D, MADRS (p=0.5002), or CGI-S (p=0.3014), did not differ by groups. We rated the risk of bias as low.

The Rush et al. study lasted an average of 14 weeks; it randomized 727 patients into one of three treatment arms.[140] The switch comparison randomized patients to either bupropion SR (150 to 400 mg; mean daily dose at end of study was 282 mg), sertraline (50 to 200 mg; mean daily dose at end of study was 136 mg), or venlafaxine XR (37.5 mg to 375 mg; mean daily dose at end of study was 194 mg). Response rates did not differ by treatment arm; as reported for the QIDS-SR, they ranged from 26.1 percent to 28.2 percent (p-value not reported). Similarly, remission rates did not differ between treatment arms, whether reported for either the HAM-D (p=0.16) or the QIDS-SR (p-value not reported). The mean change in HAM-D score was not reported; however, the percentage decrease in QIDS-SR was reported and did not differ among the three groups. Neither the time to response (ranging from 5.5 to 7.0 weeks) nor the time to remission (5.4 to 6.2 weeks) differed among the three options.

We rated this study as medium risk of bias, as we did for all the STAR*D studies described below, for two reasons: less than 80 percent of the sample provided outcomes at study completion and because the mean medication doses ultimately prescribed indicated that some medications did not reach the maximal dose recommended in the protocol so that comparable

adequate doses may not have been achieved among the various arms. Appendix C documents the full risk of bias assessments for included trials.

Second-Generation Antidepressant Switch Compared With a Nonpharmacological Treatment Switch (Psychotherapy)

Thase et al. reported a STAR*D-based comparison (rated medium risk of bias) of switching to an SGA versus switching to a nonpharmacological strategy, namely CT[107] (Table 25). Randomization to a different SGA could assign patients to receive sertraline (50 mg to 200 mg; mean daily dose at end of study was 137 mg), bupropion SR (150 mg to 400 mg, mean daily dose at end of study was 270 mg), or venlafaxine XR (37.5 mg to 375 mg, mean daily dose at end of study was 221 mg); however, the comparisons of SGA with CT consolidated the medications into a single SGA group variable. Response rates assessed on the QIDS-SR showed no difference between SGA and CT (26.7 percent versus 22.2 percent p=0.84). Similarly, remission rates did not differ by treatment arm, whether measured by the HAM-D (27.9 percent versus 25.0 percent, p=0.69) or by the QIDS-SR (26.7 percent versus 30.6 percent, p=0.90).

Table 25. Second-generation antidepressant switch versus another second-step switch strategy: Trial characteristics, main outcomes, and risk of bias ratings

Trial	N[a] Duration (Weeks)	Mean Baseline Severity (SD)	SGA Dose: mg/day	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
Lenox-Smith and Jiang, 2008[115]	396 12	HAM-D: Venlafaxine ER: 28.6 (5.7) Citalopram: 28.8 (5.4) MADRS: Venlafaxine ER: 30.8 (5.7) Citalopram: 30.9 (6.1)	Venlafaxine ER: 75 to 300 Citalopram: 20 to 60	Response rate NR; text stated no difference in HAM-D response, p=0.953	NR	HAM-D -17.0 vs. -16.5, p=0.4778	Low
Rush et al., 2006[140] STAR*D	727 14	HAM-D: 18.9 (7.3)	Bupropion SR: 150 to 400 Sertraline: 50 to 200 Venlafaxine XR: 37.5 to 375	QIDS-SR: 26.1 vs. 26.7 vs. 28.2 p=NR	HAM-D: 21.3 vs. 17.6 vs. 24.8, p=0.16 QIDS-SR: 25.5 vs. 26.6 vs. 25.0, p=NR	HAM-D NR, although % decrease in QIDS-SR is presented as 16.4% versus 21.9% versus 16.9%, p=NR	Medium
Thase et al., 2007[107] STAR*D	122 14	HAM-D Medication: 17.7(6.6) CT: 16.4 (6.2)	Medication: Sertraline: 50 to 200 Bupropion SR: 150 to 400 Venlafaxine XR: 37.5 to 375 CT: 16 sessions	QIDS-SR (Medication versus CT [Medication consolidated into a single response rate]): 26.7 versus 22.2 p=0.84	HAM-D (Medication versus CT [Medication consolidated into a single response rate]): 27.9 versus 25.0, p=0.69 QIDS-SR: 26.7 versus 30.6, p=0.90	HAM-D (Medication versus CT: NR % decrease in QIDS-SR is presented as 46.2% versus 40.7%, p=0.90	Medium

CT = cognitive therapy; ER = extended release; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; mg = milligram; N = number; NR = not reported; QIDS-SR = Quick Inventory of Depressive Symptoms – Self Report-16; SD = standard deviation; SGA = second-generation antidepressant; SR = sustained release; STAR*D = Sequenced Treatment Alternatives to Relieve Depression Study; vs. = versus; XR = extended release

[a] Total number of randomized participants in relevant arms of trials.

[b] Response (≥50 percent decrease in depressive severity) and remission (as defined by authors of individual trials) are measured using the HAM-D unless indicated otherwise.

HAM-D change in depressive severity was not reported, but the percentage decrease in QIDS–SR-16 did not differ between the groups (46.2 percent versus 40.7 percent, p=0.90). Neither the time to response nor remission differed for these two switch strategies.

Second-Generation Antidepressant Augmentation Compared With Second-Generation Antidepressant Augmentation

One eligible trial (another from the STAR*D series, also rated medium risk of bias) compared an SGA augmentation strategy with another SGA augmentation strategy (Table 25).[141]

This augmentation comparison randomized patients to the addition of either bupropion SR (150 mg to 400 mg, mean daily dose at end of study was, 268 mg) or buspirone, a nonbenzodiazepine anxiolytic (15 mg/60 mg; mean daily dose at end of study was 41 mg). Response rates did not differ by treatment arm; as reported for the QIDS-SR (31.8 percent versus 26.9 percent, p=0.21). Remission rates also did not differ (29.7 percent versus 30.1 percent, p=0.93, on HAM-D; 39.0 percent versus 32.9 percent, p=0.13, on QIDS-SR). The investigators did not report the mean change in HAM-D score; they did report the percentage decrease in QIDS-SR as favoring bupropion over buspirone (decrease of 25.3 percent versus 17.1 percent, p<0.04). Neither the time to response (ranging from 6.3 to 6.8 weeks) nor the time to remission (ranging from 5.4 to 6.3 weeks) differed between the two augmentation options.

Second-Generation Antidepressant Augmentation With Pharmacological Treatment Compared With Second-Generation Antidepressant Augmentation With Nonpharmacological Treatment Switch (Psychotherapy)

One eligible trial compared an SGA augmentation with a nonpharmacological SGA augmentation strategy, CT (Table 26).[107]

This augmentation comparison randomized patients to the addition of either a medication (bupropion SR, an antidepressant [150 to 400 mg, mean daily dose at end of study was 283 mg], or buspirone [15 to 60 mg, mean daily dose at end of study was 45.1 mg]) or CT (16 sessions). Response rates did not differ by treatment arm, as reported by the QIDS-SR (28.2 percent versus 35.4 percent, p=0.25). Remission rates also did not differ by HAM-D (33.3 percent versus 23.1 percent, p=0.20) or by QIDS-SR (33.3 percent versus 30.8 percent, p=0.78). Although the mean change in HAM-D score was not provided, the percentage decrease in QIDS-SR revealed no difference between the percentage decrease in depressive severity (39.6 percent versus 40.5 percent, p=0.83). Patients assigned to medication group did not differ from the CT group in terms of time to response; however, those receiving medication reached remission faster than those receiving CT (40.1 days versus 55.3 days, p=0.022).

Second-Step Switch Strategy Compared With Any Augmentation Strategy

We found no eligible trials that directly compared a SGA switch strategy with an augmentation strategy.

Network Meta-Analysis of Either Switch or Augmentation Comparisons Versus Placebo

We did not have enough eligible studies to conduct a network meta-analysis of the relevant treatment options compared with placebo.

Table 26. Second-generation antidepressant augmentation versus another second-generation augmentation strategy: Trial characteristics, main outcomes, and risk of bias ratings

Trial	N[a] Duration (Weeks)	Total Sample Mean Baseline Severity (SD)	SGA Dose: mg/day or Psychotherapy Type: Number of Sessions	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Mean Change in HAM-D Score from Baseline and Significance Level	Risk of Bias Rating
Trivedi et al., 2006[141] STAR*D	565 14	HAM-D: 15.8 (7.1)	Bupropion SR: 150 to 400 Buspirone: 15 to 60 mg	QIDS-SR: 31.8 versus 26.9 p=0.21	HAM-D: 29.7 versus 30.1, p=0.93 QIDS-SR: 39.0 versus 32.9, p=0.13	NR, although % decrease in QIDS-SR presented as 25.3% versus17.1%, p<0.04	Medium
Thase et al., 2007[107] STAR*D	182 14	HAM-D: Medication: 16.0 (6.7) CT: 17.8 (5.7)	Medication: Bupropion SR: 150 to 400 Buspirone: 15 to 60 CT: 16 sessions	QIDS-SR (Medication versus CT [Medication consolidated into a single response rate]): 28.2 versus 35.4 p=0.25	HAM-D (Medication versus CT [Medication consolidated into a single response rate]): 33.3 versus 23.1, p=0.20 QIDS-SR: 33.3 versus 30.8, p=0.78	HAM-D (Medication versus CT): NR Although % decrease in QIDS-SR presented as 39.6% versus 40.5%, p=0.83	Medium

CT = cognitive therapy; HAM-D = Hamilton Depression Rating Scale; N = number; NR = not reported; QIDS-SR = Quick Inventory of Depressive Symptoms – Self Report; SD = standard deviation; SR = sustained release; vs. = versus; STAR*D = Sequenced Treatment Alternatives to Relieve Depression Study; vs. = versus

[a] Total number of randomized participants in relevant arms of trials.

[b] Response (≥50 percent decrease in depressive severity) and remission (as defined by authors of individual trials) are measured using the HAM-D unless indicated otherwise.

KQ 2b. Effect of Severity on the Comparative Effectiveness of Second-Step Therapies

We identified two secondary analyses that addressed how depressive severity might moderate the comparative effectiveness of SGAs. Both involved trials described for KQ 2a,[115,140] although the analysis in one case was published in a separate STAR*D article.[142]

The Lenox-Smith and Jiang trial[115] performed secondary analyses to determine whether comparative effectiveness varied by the level of depression severity (severe versus moderate). In patients with moderate depression (HAM-D≤31), depressive outcomes did not differ measured by either HAM-D or MADRS. However, in the group with HAM-D>31, some clinical outcomes seemed better in patients receiving venlafaxine (produced by the trial sponsor) than in those receiving citalopram. Remission rates favored venlafaxine, although the difference was not statistically significant (31.6 percent versus 16.4 percent, p=0.08). Changes in depressive severity were better following venlafaxine treatment as measured by HAM-D (p=0.04) but not by MADRS (p=0.09).

A secondary analysis of the original 727 patients in the SGA switch analysis explored whether several variables, including depressive severity, might differentially moderate the effectiveness of the medications being compared.[140] The analysis assessed the effect of mild or moderate versus severe depression (defined as QIDS-SR≥16) on remission rates. The odds of remission for patients with severe depression (relative to mild/moderate) were lower for all three medications (bupropion SR 0.38, sertraline 0.38, venlafaxine XR 0.25), but the differences among the medications were not statistically significant (p=0.70).

KQ 3. Comparative Risks of Treatment Harms

In this section, we distinguish adverse events from serious adverse events based on the Food and Drug Administration (FDA) classification. FDA defines adverse events as any medical occurrence associated with the use of an intervention, whether or not it is considered related to the intervention.[143] A serious adverse event is any medical occurrence that results in death, is life threatening, requires hospitalization, results in persistent or significant disability or incapacity, or is a congenital birth defect. We also report the findings of the one eligible trial providing information about how the risk of harms for our interventions of interest varies by baseline severity of MDD.[97] The trial's authors collected data to address this issue but reported findings only qualitatively.

As we have done in previous sections, here we provide an overview of the articles, including the number of trials, for each comparison (Table 27); key points; and a detailed synthesis. All trials are of low or medium risk of bias except if noted otherwise. In Appendix E, we present summary of findings tables for the important outcomes. These tables describe basic information on the available evidence, summarize differences in risks of harms using absolute and relative effect measures, and present the SOE grades for each outcome.

Table 27. Number of trials for each comparison of interest

Comparison Category	Comparison Intervention	Number of Trials
SGA vs. Psychological interventions	SGA vs. Behavior therapies/behavior modification	0
	SGA vs. CBT	10[87,90,95,97-100,102,108,119,121,129]
	SGA vs. Humanistic therapies	0
	SGA vs. Integrative therapies	4[85,88,89,103]
	SGA vs. Psychodynamic therapies	4[86,96,101,116]
	SGA vs. Third-wave CBTs	2[97,118]
SGA vs. Complementary and alternative medicine	SGA vs. Acupuncture	5[91,105,122-124]
	SGA vs. Omega-3 fatty acids	2[106,120]
	SGA vs. SAMe	1[104]
	SGA vs. St. John's wort	12[92,109-114,117,125-128]
	SGA vs. Meditation	0
	SGA vs. Yoga	0
SGA vs. Exercise	SGA vs. Exercise	2[93,94]
SGA switch vs. SGA switch	Switch to citalopram from different SSRI vs. Switch to venlafaxine from different SSRI	1[107]

CBT = cognitive behavioral therapy; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant; SSRI = serotonin-specific reuptake inhibitor; vs. = versus

Overview

We analyzed adverse events data from 43 head-to-head efficacy trials. Table 27 summarizes the number of trials that contributed information to the assessment of the comparative risks of harms.

As described in more detail in the Methods section, we intended to include data from head-to-head trials *and* nonrandomized trials for assessing comparative risk of harms. However, we did not find any nonrandomized trials that met our eligibility criteria.

Few trials that examined the comparative effectiveness of SGAs with other eligible treatment options adequately assessed differences in harms. Three trials, two of psychological interventions[100,119] and one of acupuncture,[124] did not report any data on harms. None of the trials that reported harms data used objective scales such as the UKU-SES (Utvalg for Kliniske Undersogelser Side Effect Scale) or the SAFTEE-SI (Systematic Assessment for Treatment of Emergent Events-Specific Inquiry). Most trials combined spontaneous patient-reported adverse events with a regular clinical examination by an investigator. Determining whether assessment methods were unbiased and adequate was often difficult. Rarely did authors report whether adverse events were prespecified and defined. Short trial durations and small sample sizes also limited the validity of adverse event assessment in many trials.

No trials were designed to assess specific adverse events as primary outcomes. Detailed information on included trials can be found in KQ 1.

Key Points

Second-Generation Antidepressants Compared With Psychological Interventions

- Psychological interventions as a class led to numerically higher overall discontinuation rates than SGAs, although the difference was not statistically significant (7 RCTs, moderate SOE). Discontinuations because of adverse events also occurred numerically

less often after psychological interventions than SGAs, but the between-group difference was not statistically significant (5 RCTs, moderate SOE). Patients given SGAs had a numerically but not statistically significantly higher risk of suicidal ideas or behaviors than those receiving psychological interventions (4 RCTs, low SOE).

- The combination of psychological interventions as a class and SGAs did not produce statistically different discontinuation rates compared with patients treated with SGA monotherapy after 12 weeks of followup (3 RCTs, low SOE). In contrast, overall discontinuation rates were lower following SGA monotherapy than following combination treatment after 96 weeks of followup (1 RCT, low SOE). Adding psychological interventions to SGA treatment did not produce statistically different rates of discontinuation because of adverse events compared with SGA monotherapy after 12 weeks of followup (2 RCTs, low SOE).

- We did not find any eligible trials comparing behavior therapies with SGAs (insufficient SOE).

- CBT and SGAs led to similar overall discontinuation rates after 8-14 weeks of followup (4 RCTs, moderate SOE). After 24 weeks of followup, SGAs led to higher overall discontinuation rates than CBT (1 RCT, low SOE). Rates of discontinuation because of adverse events (3 RCTs, low SOE) were numerically but not statistically significant lower for patients receiving CBT than those given SGAs.

- Adding CBT to SGA treatment did not lead to statistically different rates of overall discontinuation and discontinuation because of adverse events compared with SGA monotherapy (2 RCTs each, both low SOE).

- We did not find any eligible trials comparing humanistic therapies with SGAs (insufficient SOE).

- The evidence was insufficient to draw conclusions about any outcomes for integrative therapy (interpersonal therapy) alone or in combination with SGAs compared with SGA monotherapy.

- Short-term psychodynamic therapy (PSYD) did not lead to statistically different rates of overall discontinuation compared with SGAs over the course of 8-16 weeks (3 RCTs, low SOE). Long-term PSYD also did not lead to statistically different rates of overall discontinuation compared with SGAs over the course of 48 weeks or 96 weeks of followup (1 RCT each, both low SOE). Long-term PSYD did not lead to statistically different rates of suicidal ideas or behaviors compared with SGAs after 96 weeks of followup (1 RCT low SOE).

- Adding long-term PSYD to SGA treatment led to lower rates of overall discontinuation compared with patients receiving SGA monotherapy after 96 weeks of followup (1 RCT, low SOE). The addition of long-term PSYD to SGA treatment did not lead to statistically different rates of suicidal ideas or behaviors compared with SGA monotherapy after 96 weeks of followup (1 RCT, low SOE).

- Third-wave CBT led to lower rates of overall discontinuation (2 RCTs, low SOE) and discontinuation because of adverse events (2 RCTs, low SOE) than SGAs.

- The evidence was insufficient to draw conclusions about the comparative overall risk of serious adverse events between psychological interventions in general and SGAs.

Second-Generation Antidepressants Compared With Complementary and Alternative Medicines

- The evidence was insufficient to draw conclusions about the comparative rates of harms and overall discontinuation between acupuncture and SGAs. (1 RCT, insufficient SOE). However, indirect evidence from a systematic review that included depressive disorders other than MDD indicated that acupuncture had a lower overall risk of harms than SGAs (21 RCTs, moderate SOE).
- Adding acupuncture to SGA treatment led to an overall risk of adverse events (1 RCT, low SOE), overall discontinuation rates (2 RCTs, low SOE), and rates of discontinuation because of adverse events (2 RCTs, low SOE) that were similar to those among patients receiving SGA monotherapy.
- Omega-3 fatty acids did not lead to statistically different rates of overall discontinuation (1 RCT, low SOE). We were unable to draw conclusions about how rates of discontinuation because of adverse events compared with SGAs and omega-3 fatty acids monotherapies (1 RCT, insufficient SOE).
- Adding omega-3 fatty acids to SGA treatment also did not lead to statistically different rates of overall discontinuation (1 RCT, low SOE). However, we were unable to draw conclusions about how rates of discontinuation because of adverse events compared between SGA monotherapy and the combination of omega-3 fatty acids and SGAs.
- SAMe did not lead to statistically different overall discontinuation rates compared with patients treated with SGAs (1 RCT, low SOE).
- St. John's wort led to lower rates of overall discontinuation (9 RCTs, moderate SOE) and discontinuation because of adverse events (9 RCTs, moderate SOE) than did SGAs. The overall risk of adverse events was also lower among patients receiving St. John's wort than those receiving SGAs, although this difference was statistically nonsignificant (8 RCTs, moderate SOE). In contrast, the risk of serious adverse events did not differ between patients receiving St. John's wort and those receiving SGAs (4 RCTs, low SOE).
- We did not find any eligible trials comparing meditation or yoga with SGAs (insufficient SOE).

Second-Generation Antidepressant Switching Strategies Following Failure of an Initial Adequate SGA Trial

- Switching to citalopram and switching to venlafaxine led to similar risks of overall harms and overall discontinuation rates (1 RCT each, both low SOE).
- Switching to bupropion, sertraline, or venlafaxine and switching to CT following treatment failure with citalopram led to similar rates of discontinuation because of adverse events (1 RCT, low SOE).

Second-Generation Antidepressant Augmentation Strategies

- Bupropion augmentation of citalopram led to lower rates of discontinuation because of adverse events than buspirone augmentation (1 RCT, moderate SOE), but both augmentation strategies led to similar rates of serious adverse events (1 RCT, low SOE) and suicidal ideas or behaviors (1 RCT, low SOE).

- Bupropion or buspirone augmentation of citalopram led to numerically higher, but not statistically different, rates of discontinuation because of adverse events than CT augmentation (1 RCT, low SOE). Both augmentation strategies also produced statistically similar rates of serious adverse events (1 RCT, low SOE).

Second-Generation Antidepressants Compared With Exercise

- Exercise and SGAs led to similar overall discontinuation rates (2 RCTs, moderate SOE). Discontinuation rates because of adverse events were lower for exercise than SGAs (2 RCTs, low SOE).
- Adding exercise to SGA treatment led to overall discontinuation rates and discontinuation rates because of adverse events that were similar to those among patients receiving SGA monotherapy (1 RCT each, both low SOE).

Figures 13, 14, and 15 graphically display relative risks of SGAs compared with other interventions for overall harms, overall discontinuation, and discontinuation because of adverse events.

Figure 13. Comparison of overall risk of harms of SGAs with other eligible interventions (relative risks and 95% confidence intervals)
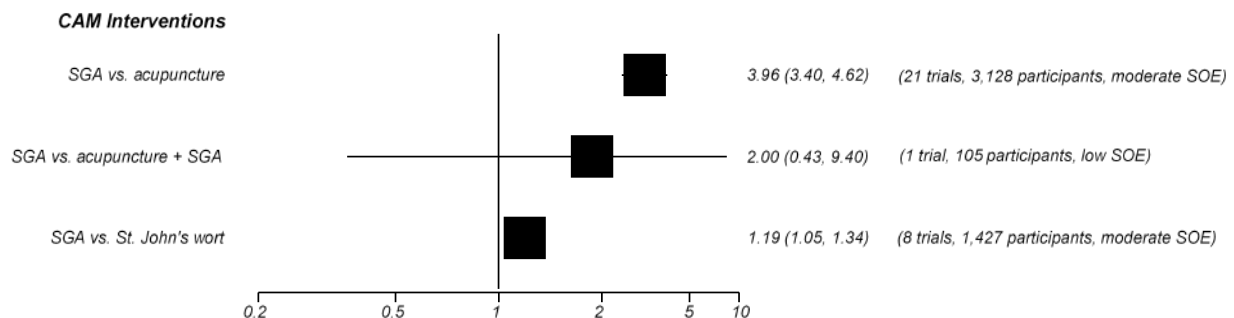
CAM = complementary and alternative medicine; SGA = second-generation antidepressant; SOE = strength of evidence; vs. = versus

Figure 14. Comparison of overall discontinuation rates from SGAs with other eligible interventions (relative risks and 95% confidence intervals)

Psychological Interventions	
SGA vs. any psychological therapy	1.47 (0.94, 2.30) (7 trials, 1,092 participants, moderate SOE)
SGA vs. CBT	1.00 (0.59, 1.69) (4 trials, 611 participants, moderate SOE)
SGA vs. CBT + SGA	0.77 (0.37, 1.60) (2 trials, 176 participants, low SOE)
SGA vs. integrative therapies	1.38 (0.83, 2.30) (2 trials, 384 participants, insufficient SOE)
SGA vs. integrative therapies + SGA	1.11 (0.64, 1.93) (1 trial, 96 participants, low SOE)
SGA vs. PSYD	1.01 (0.68, 1.52) (3 trials, 298 participants, low SOE)
SGA vs. PSYD + SGA	0.48 (0.27, 0.85) (1 trial, 182 participants, low SOE)
SGA vs. third-wave CBT	2.76 (1.40, 5.41) (2 trials, 243 participants, low SOE)
CAM interventions	
SGA vs. acupuncture	0.03 (0.00, 0.56) (1 trial, 50 participants, insufficient SOE)
SGA vs. acupuncture + SGA	1.11 (0.50, 2.46) (2 trials, 240 participants, low SOE)
SGA vs. omega-3 fatty acids	1.00 (0.23, 4.37) (1 trial, 40 participants, low SOE)
SGA vs. omega-3 fatty acids + SGA	2.38 (0.81, 6.98) (2 trials, 82 participants, low SOE)
SGA vs. SAMe	1.19 (0.78, 1.80) (1 trial, 129 participants, low SOE)
SGA vs. St. John's wort	1.28 (1.01, 1.62) (9 trials, 1,651 participants, moderate SOE)
Exercise	
SGA vs. exercise	0.87 (0.48, 1.59) (2 trials, 254 participants, low SOE)
SGA vs. exercise + SGA	0.73 (0.31, 1.73) (1 trial, 103 participants, low SOE)

0.01   0.1 0.2   0.5 1   2   5   10

Higher risk with comparator   Higher risk with SGA

CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; KQ = Key Question; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant; SOE = strength of evidence; vs. = versus

Figure 15. Comparison of discontinuation because of adverse events rates of SGA with other eligible interventions (relative risks and 95% confidence intervals)

Psychological Interventions		
SGA vs. any psychological therapy	2.73 (0.89, 8.38)	(5 trials, 871 participants, moderate SOE)
SGA vs. any psych. therapy + SGA	3.42 (0.73, 16.01)	(2 trials, 176 participants, low SOE)
SGA vs. CBT	2.54 (0.39, 16.47)	(3 trials, 441 participants, low SOE)
SGA vs. CBT + SGA	2.93 (0.72, 11.91)	(2 trials, 176 participants, low SOE)
SGA vs. integrative therapies	0.33 (0.01, 8.06)	(1 trial, 287 participants, insufficient SOE)
SGA vs. third-wave CBT	5.17 (1.60, 16.64)	(2 trials, 243 participants, low SOE)
CAM Interventions		
SGA vs. acupuncture + SGA	0.74 (0.11, 4.90)	(2 trials, 240 participants, low SOE)
SGA vs. omega-3 fatty acids	1.00 (0.07, 14.90)	(1 trial, 40 participants, insufficient SOE)
SGA vs. omega-3 fatty acids + SGA	0.5 (0.05, 5.08)	(1 trial, 40 participants, insufficient SOE)
SGA vs. SAMe	2.63 (0.73, 9.46)	(1 trial, 129 participants, insufficient SOE)
SGA vs. St. John's wort	1.70 (1.12, 2.60)	(9 trials, 1,651 participants, moderate SOE)
Exercise		
SGA vs. exercise	20.96 (1.19, 367.97)	(2 trials, 254 participants, low SOE)
SGA vs. exercise + SGA	1.15 (0.35, 3.72)	(1 trial, 103 participants, low SOE)

0.01   0.10.2 0.5 1 2   5 10   100   1000
Higher risk with comparator   Higher risk with SGA

CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; KQ = Key Question; SAMe = S-adenosyl-L-methionine SGA = second-generation antidepressant; SOE = strength of evidence; vs. = versus

KQ 3a. Comparative Risks of Harms Between Pharmacological and Nonpharmacological Interventions

Detailed Synthesis: Overall Risk of Experiencing Harms and Discontinuation of Treatment

This section provides a detailed synthesis of the comparative risk of experiencing harms and discontinuing treatment. In general, reporting of adverse events was scarce, and we were able to draw only a few conclusions with certainty from the available evidence. Even common adverse events associated with SGAs, such as diarrhea, dizziness, dry mouth, headache, insomnia, nausea, vomiting, and weight gain, were rarely assessed or reported. Similarly, few trials addressed adverse events that are commonly associated with psychotherapies, such as worsening of symptoms or onset of new depression-associated symptoms.

Second-Generation Antidepressants Compared With Psychological Interventions

We first present the available evidence on the comparative risk of harms for SGAs and psychological treatments as a class. Next, we summarize the evidence for each included

psychological intervention. As in KQ 1, we use classifications of the Cochrane Collaboration Depression, Anxiety and Neurosis Review Group.[70]

Second-Generation Antidepressants Compared With Any Psychological Interventions

Second-Generation Antidepressants Versus Any Psychological Intervention: Monotherapy Comparisons

We conducted meta-analyses of low or medium risk of bias studies comparing overall discontinuation rates, discontinuation rates because of lack of efficacy, and discontinuation rates because of adverse events for patients treated with any SGA compared with those treated with any psychological intervention. Interventions for these comparisons were limited to fluoxetine, fluvoxamine, paroxetine, and sertraline (for the SGAs) and behavioral activation, cognitive therapy, problem solving therapy, rational emotive behavior therapy, and short-term psychodynamic psychotherapy (for the psychological interventions).

Overall discontinuation rates were numerically, but not statistically, higher following SGAs than psychological interventions, according to our random-effects meta-analysis (15.4 percent versus 11.4 percent; RR, 1.47; 95% CI, 0.94 to 2.30; Figure 16). When we used a fixed-effects meta-analytic model, however, the difference in overall discontinuation rates became statistically significant (RR, 1.41; 95% CI, 1.01 to 1.97).

Figure 16. SGA versus psychological interventions as a class: Overall discontinuation rates

Study name	Risk ratio	Lower limit	Upper limit	SGA	Psychotherapy
David, 2008a	1.20	0.31	4.67	3 / 29	5 / 57
David, 2008b	1.18	0.30	4.59	3 / 29	5 / 56
DeRubeis, 2005	0.72	0.33	1.59	13 / 120	9 / 60
Dimidjian, 2006a	2.69	0.94	7.68	13 / 50	4 / 43
Dimidjian, 2006b	2.25	0.87	5.85	13 / 50	5 / 45
Menchetti, 2014	2.15	0.84	5.50	13 / 144	6 / 143
Moradveisi, 2013	3.00	1.18	7.63	15 / 50	5 / 50
Mynors-Wallis, 2000	0.58	0.26	1.30	6 / 36	23 / 80
Salminen, 2008	2.08	0.42	10.37	4 / 25	2 / 26
	1.47	0.94	2.30		

Random effects meta-analysis; I-squared 40%
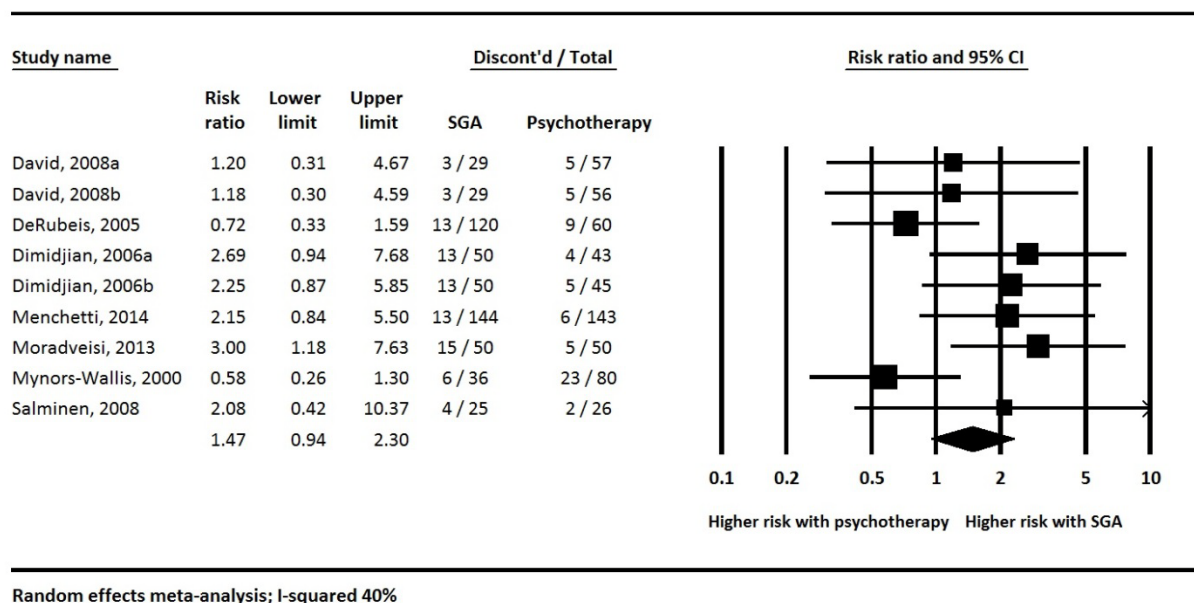
CI = confidence interval; Discont'd = discontinued; SGA = second-generation antidepressant

Discontinuation rates because of lack of efficacy were numerically lower for patients treated with SGAs than for patients treated with psychological interventions, even though the difference did not reach statistical significance (2.1 percent versus 6.3 percent; RR, 0.52; 95% CI, 0.18 to 1.46; Figure 17).

80

Figure 17. SGA versus psychological interventions as a class: Discontinuation rates because of lack of efficacy

| Study name | Statistics for each study | | | Discontinued / Total | | Risk ratio and 95% CI |
	Risk ratio	Lower limit	Upper limit	SGA	Psychotherapy	
DeRubeis, 2005	0.25	0.05	1.33	2 / 120	4 / 60	
Dimidjian, 2006a	2.25	0.23	22.08	3 / 50	1 / 45	
Dimidjian, 2006b	2.15	0.22	21.08	3 / 50	1 / 43	
Menchetti, 2014	0.33	0.01	8.06	0 / 144	1 / 143	
Mynors-Wallis, 2000	0.07	0.00	1.08	0 / 36	16 / 80	
Salminen, 2008	0.52	0.05	5.38	1 / 25	2 / 26	
	0.52	0.18	1.46			
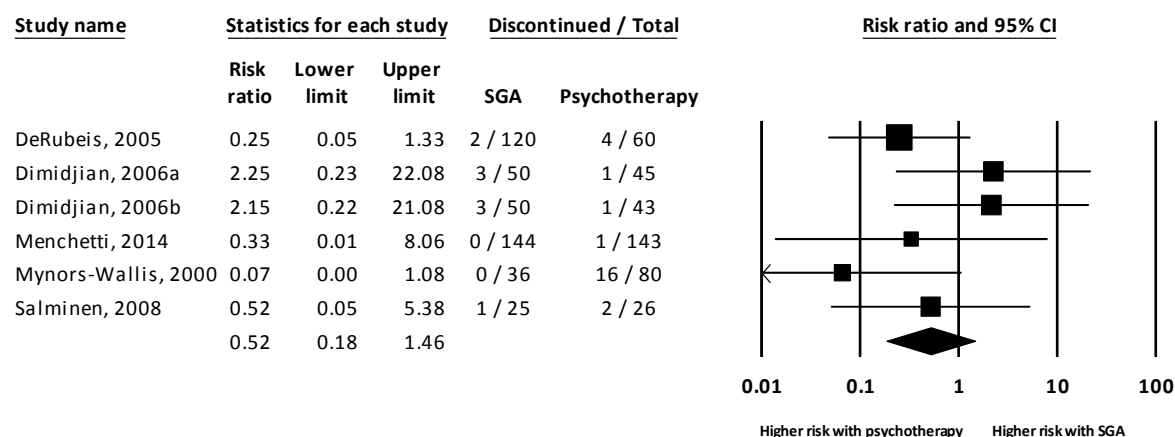
Random effects meta-analysis; I-squared 16%

CI = confidence interval; SGA = second-generation antidepressant.

In contrast, discontinuation rates because of adverse events were more than twice as high for patients receiving SGAs than for those treated with psychological interventions, but the difference was not statistically significant (7.1 percent versus 2.1 percent; RR, 2.73; 95% CI, 0.89 to 8.38; Figure 18). The numbers of events of discontinuation because of lack of efficacy and discontinuation because of adverse events, however, were low; therefore, results should be interpreted with caution.

Figure 18. SGA versus psychological interventions as a class: Discontinuation rates because of adverse events

| Study name | Statistics for each study | | | Discont'd / Total | | Risk ratio and 95% CI |
	Risk ratio	Lower limit	Upper limit	SGA	Psychotherapy	
DeRubeis, 2005	0.63	0.17	2.24	5 / 120	4 / 60	
Dimidjian, 2006a	5.59	0.71	44.10	7 / 50	1 / 43	
Dimidjian, 2006b	5.85	0.74	46.20	7 / 50	1 / 45	
Menchetti, 2014	0.33	0.01	8.06	0 / 144	1 / 143	
Moradveisi, 2013	6.00	1.41	25.44	12 / 50	2 / 50	
Mynors-Wallis, 2000	10.95	0.54	222.37	2 / 36	0 / 80	
	2.73	0.89	8.38			
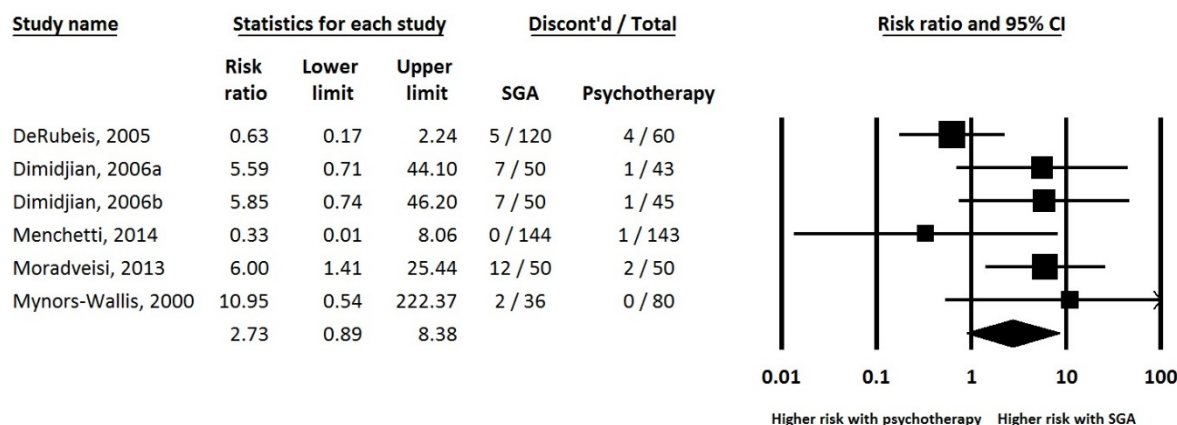
Random effects meta-analysis; I-squared 48%

CI = confidence interval; Discont'd = discontinued; SGA = second-generation antidepressant

For sensitivity analyses, we added five high risk of bias trials to the meta-analytic models.[89,90,95,102,116] The results of the analyses of overall discontinuation rates (RR, 1.16; 95% CI, 0.82 to 1.64) and discontinuation because of adverse events (RR, 2.55; 95% CI, 0.43 to 15.01) remained consistent with the results of their respective primary analyses presented above. No high risk of bias trials reported on discontinuation because of lack of efficacy. When a fixed-effects meta-analytic model was used, the difference between SGAs and psychological interventions in the sensitivity analysis became statistically significant for discontinuation because of adverse events[97,102] (RR, 2.66; 95% CI, 1.31 to 5.39).

Second-Generation Antidepressants Versus Any Psychological Treatment: Combination Comparisons

Four trials, including one with a high risk of bias,[89] comparing SGAs with combinations of SGAs and psychological interventions reported information on adverse events.[89,101,108,121] SGAs included fluvoxamine, paroxetine, escitalopram, nefazodone, and fluoxetine, and psychological interventions included CBT, interpersonal therapy (IPT), and long-term psychodynamic therapy. After 12 weeks, overall discontinuation rates were similar for patients treated with SGAs (9.4 percent to 16.7 percent) and those treated with psychotherapy (15.4 percent to 17.1 percent).[108,121] In contrast, rates of discontinuation because of adverse events were numerically, but not statistically, higher among patients treated with escitalopram, fluvoxamine, or paroxetine (5.7 percent to 11.1 percent) than the same SGAs used in combination with CBT (0.0 percent to 3.8 percent).[108,121] The high risk of bias trial found similar results after 12 weeks of treatment whether patients received SGAs (36.2 percent) or IT (32.7 percent).[89]

Second-Generation Antidepressants Compared With Behavior Therapy/Behavior Modification

We found no eligible trials that compared an SGA with behavior therapy/behavior modification.

Second-Generation Antidepressants Compared With Cognitive Behavioral Therapy

Of 11 trials included for KQ 1a, 9 reported limited data on adverse events (see KQ 1, Table 11 for more details on trial design and dosing).[87,90,95,97-99,102,108,121,129,133]

Second-Generation Antidepressants Versus Cognitive Behavioral Therapy: Monotherapy Comparisons

Eight trials, of which four had a high risk of bias rating,[90,95,98,102] provided limited information on the comparative risk of harms of SGA monotherapy compared with CBT.[87,90,95,97-99,102,121,129,133] In these trials, SGAs were limited to escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine. None of the trials provided information on the comparative risk of specific adverse events, even common adverse events of SGAs. Only one trial reported in two publications provided data on the proportions of patients who experienced any adverse events.[87,133] About 15.7 percent of patients treated with an SGA experienced adverse events as did 0.9 percent of patients treated with CBT. Particularly for SGAs, reported adverse event rates appear to underestimate substantially the actual risk. A comprehensive systematic assessment of the risk of harms for SGAs reported that an average of 60 percent of patients treated with SGAs experience at least one adverse event during treatment.[33]

Overall discontinuation rates were similar for patients treated with SGAs or CBT (16.0 percent versus 15.8 percent; RR, 1.00; 95% CI, 0.59 to 1.69, Figure 19). The findings did not change when stratified by time point (<12 weeks versus 12 to 16 weeks). Discontinuation rates because of lack of efficacy were numerically, but not statistically significantly, lower for patients treated with SGAs than for those treated with CBT (2.4 percent versus 11.4 percent; RR, 0.36; 95% CI, 0.06 to 2.21, Figure 20). In contrast, discontinuation rates because of adverse events were numerically higher for patients on SGAs than for patients treated with CBT, but the difference did not reach statistical significance (7.8 percent versus 2.7 percent; RR, 2.54; 95% CI, 0.39 to 16.47, Figure 21). The numbers of events for discontinuation because of lack of efficacy and discontinuation because of adverse events were very low. Therefore, results should be interpreted with caution.

Figure 19. SGA versus cognitive behavioral therapy: Overall discontinuation rates

Study name	Risk ratio	Lower limit	Upper limit	SGA	Psychotherapy
David, 2008a	1.20	0.31	4.67	3 / 29	5 / 57
David, 2008b	1.18	0.30	4.59	3 / 29	5 / 56
DeRubeis, 2005	0.72	0.33	1.59	13 / 120	9 / 60
Dimidjian, 2006	2.25	0.92	5.50	25 / 100	5 / 45
Mynors-Wallis, 2000	0.58	0.26	1.30	6 / 36	23 / 80
	1.00	0.59	1.69		
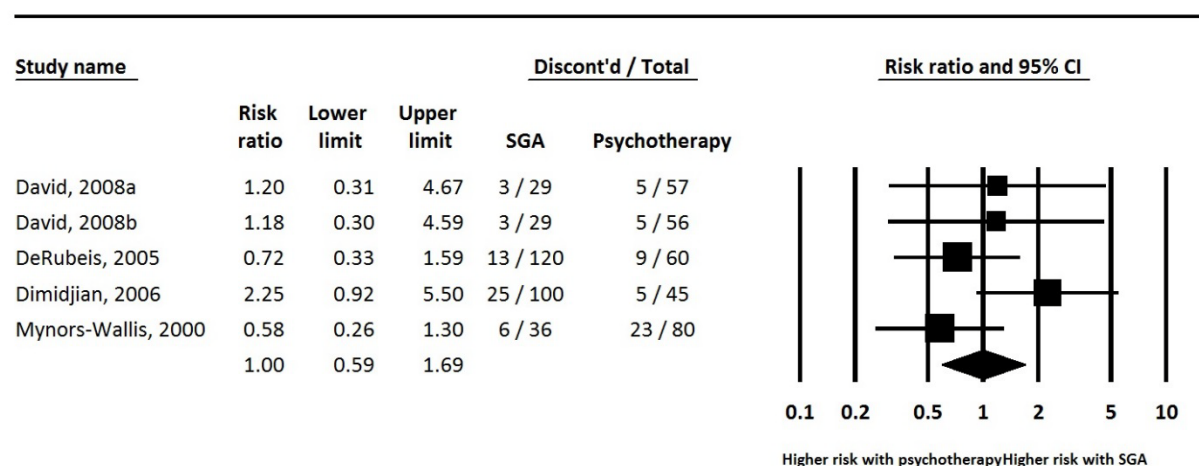
Random effects meta-analysis; I-squared 30%

CBT = cognitive behavioral therapy; CI = confidence interval; Discont'd = discontinued; SGA = second-generation antidepressant

Figure 20. SGA versus cognitive behavioral therapy: Discontinuation rates because of lack of efficacy

Study name	Risk ratio	Lower limit	Upper limit	SGA	Psychotherapy	Risk ratio and 95% CI
DeRubeis, 2005	0.25	0.05	1.33	2 / 120	4 / 60	
Dimidjian, 2006a	2.25	0.23	22.08	3 / 50	1 / 45	
Mynors-Wallis, 2000	0.07	0.00	1.08	0 / 36	16 / 80	
	0.36	0.06	2.21			
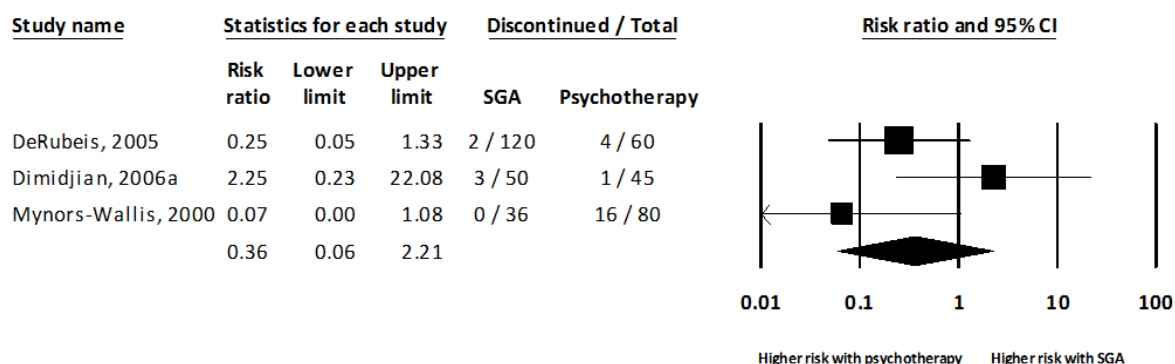
Random effects meta-analysis; I-squared 51%

CBT = cognitive behavioral therapy; CI = confidence interval; SGA = second-generation antidepressant

Figure 21. SGA versus cognitive behavioral therapy: Discontinuation rates because of adverse events

Study name	Risk ratio	Lower limit	Upper limit	SGA	Psychotherapy	Risk ratio and 95% CI
DeRubeis, 2005	0.63	0.17	2.24	5 / 120	4 / 60	
Dimidjian, 2006	5.85	0.79	43.37	13 / 100	1 / 45	
Mynors-Wallis, 2000	10.95	0.54	222.37	2 / 36	0 / 80	
	2.54	0.39	16.47			
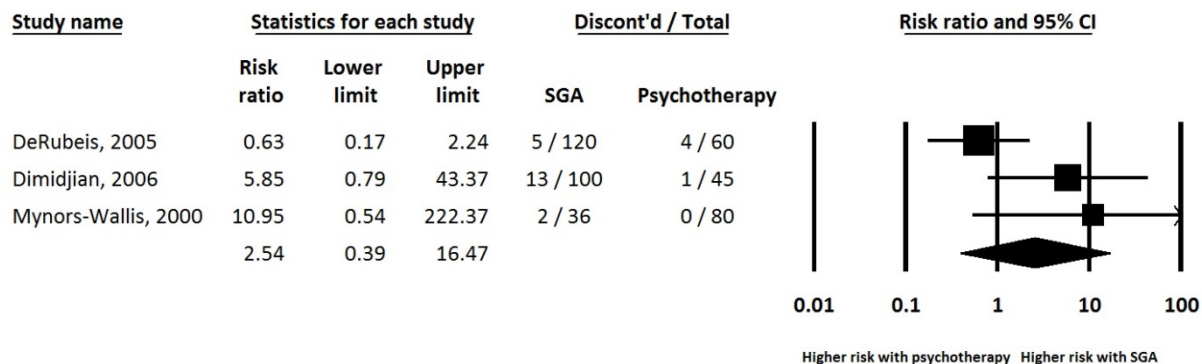
Random effects meta-analysis; I-squared 62%

CBT = cognitive behavioral therapy; CI = confidence interval; Discont'd = discontinued; SGA = second-generation antidepressant

In sensitivity analyses, we added high risk of bias trials to the meta-analytic models.[90,95,102] The differences in overall discontinuation rates (RR, 0.98; 95% CI, 0.72 to 1.35) and rates of discontinuation because of adverse events (RR, 2.97; 95% CI, 0.69 to 12.81) remained similar to the original analyses. As in the primary analysis, the findings of the sensitivity analysis for overall discontinuation did not change when stratified by time point (<12 weeks versus 12 to 16 weeks).[97,102]

Second-Generation Antidepressants Versus Cognitive Behavioral Therapy: Combination Comparisons

The only trial that compared an SGA (escitalopram) with a combination of escitalopram and telephone CBT did not report information on specific adverse events.[108] After 12 weeks, overall discontinuation rates (13.0 percent versus 23.0 percent) were numerically lower for patients treated with SGAs than for those treated with the combination regimen. Discontinuation rates because of adverse events were similar for the two treatment groups (6.0 percent versus 4.0 percent).

Second-Generation Antidepressants Compared With Humanistic Therapies

We found no eligible trials that compared an SGA with humanistic therapies.

Second-Generation Antidepressants Compared With Integrative Therapies

Of four trials of integrative therapies included in KQ 1, all evaluating IPT only, none provided information on the comparative risk of specific adverse events.[85,88,89,103,131] Two trials provided limited data on discontinuation rates comparing patients receiving SGAs with patients receiving IPT (see KQ 1, Table 12 for more details on trial design and dosing).[85,89,103,131]

Second-Generation Antidepressants Versus Interpersonal Psychotherapy: Monotherapy Comparisons

Neither of the two available trials comparing SGAs (nefazodone, citalopram, or sertraline) with IPT reported on specific adverse events. Discontinuation rates ranged from 9.0 percent to 36.0 percent for patients treated with SGAs (citalopram, escitalopram, or nefazodone) and from 14.0 percent to 32.0 percent for patients receiving IPT.[89,103] Only one study reported any discontinuations because of adverse events, in which a single patient withdrew because of medical problems.[103]

Second-Generation Antidepressants Versus Interpersonal Therapy: Combination Comparisons

One trial compared an SGA (nefazodone) with a combination of nefazodone and IPT.[89] Authors did not report any data on adverse events except overall discontinuation rates, which were similar between the nefazodone monotherapy and combination treatment groups after 12 weeks of followup (36.0 percent versus 32.6 percent, respectively).

Second-Generation Antidepressants Compared With Psychodynamic Therapies

None of the four trials included for KQ 1 reported on the risk of specific adverse events (see KQ 1, Table 13 for more details on trial design and dosing).[86,96,101,116,132]

Second-Generation Antidepressants Versus Psychodynamic Therapies: Monotherapy Comparisons

Four trials compared SGA monotherapies (fluoxetine, sertraline, venlafaxine) with PSYD.[86,96,101,116,132] One small trial (N=51) comparing fluoxetine monotherapy with short-term PSYD reported that overall rates of adverse events were similar for patients receiving either treatment (4.0 percent versus 8.0 percent) after 16 weeks of followup.[86] Overall discontinuation rates ranged from 14.3 percent to 36.4 percent for patients treated with SGAs (fluoxetine, sertraline, or venlafaxine) and from 19.2 percent to 26.8 percent for patients who received short-

or long-term PSYD across all followup durations. None of the four trials reported any data on discontinuation because of adverse events.

Second-Generation Antidepressants Versus Psychodynamic Therapies: Combination Comparisons

The only trial that compared an SGA monotherapy (fluoxetine) with a combination of fluoxetine and long-term PSYD did not report any data on differences in adverse events.[101] After 96 weeks, patients receiving fluoxetine and long-term PSYD together had overall discontinuation rates that were half those of patients receiving SGA monotherapy (15.4 percent versus 31.9 percent, respectively).

Second-Generation Antidepressants Compared With Third-Wave Cognitive Behavioral Therapy

Second-Generation Antidepressants Versus Third-Wave Cognitive Behavioral Therapy: Monotherapy Comparisons

Two trials[97,118] compared SGAs (paroxetine or sertraline) with third-wave CBT. Neither study reported overall risks of adverse events. Overall discontinuation rates ranged from 25.0 percent to 30.0 percent for patients treated with SGAs and from 9.3 percent to 10.0 percent for patients who received third-wave CBT. Similarly, rates of discontinuation because of adverse events were higher among patients treated with SGAs than those treated with third-wave CBT, ranging from 13.0 percent to 24.0 percent and from 2.3 percent to 4.0 percent, respectively.

Second-Generation Antidepressants Versus Third-Wave Cognitive Behavioral Therapy: Combination Comparisons

We did not find any trials addressing this comparison.

Second-Generation Antidepressants Compared With Complementary and Alternative Medicines

Second-Generation Antidepressants Compared With Acupuncture

For the comparison of SGAs with acupuncture, four efficacy trials reported data on harms or discontinuation rates.[91,105,123,135] We rated one trial as high risk of bias.[91] Overall, the available data were sparse and prevented us from drawing any firm conclusions about the comparative risk of harms between SGAs and acupuncture. One trial reported overall rates of adverse events.[135] Even adverse events that are specifically associated with acupuncture, such as fainting after needle insertion, needle-related pain, or transmission of blood-borne infectious disease due to inadequate sterilization practices, were not reported consistently. Likewise, typical SGA-associated adverse events, such as nausea, diarrhea, headache, and dizziness, were not reported adequately.

Second-Generation Antidepressants Versus Acupuncture: Monotherapy Comparisons

Two trials,[91,122] one rated medium risk of bias,[122] one high risk of bias,[91] compared fluoxetine with acupuncture (electroacupuncture, see KQ 1, Table 15 for more details on trial design and dosing). The medium risk of bias study collected data on overall adverse events but not on the type of discontinuation. Results showed that the rates of any adverse event were similar between patients treated with fluoxetine (4.2 percent) and those treated with acupuncture (6.0 percent).[122]

The high risk of bias study reported that overall discontinuation rates were substantially lower for patients treated with fluoxetine than those treated with acupuncture (0.0 percent versus 36.0 percent, respectively).[91]

A systematic review that did not meet our eligibility criteria because it included depressive disorders other than MDD provided the most comprehensive assessment of the comparative risk of harms between SGAs and acupuncture.[144] Based on evidence from 21 RCTs, the authors reported that adverse event rates were statistically significantly higher in patients treated with SGAs than in those receiving active or sham acupuncture.[144] Overall, 40.0 percent of patients treated with SGAs reported adverse events compared with 10.0 percent of patients undergoing acupuncture (p<0.001). The most commonly reported adverse events of patients treated with an SGA were headache, insomnia, and tiredness. Patients treated with acupuncture reported needling pain, dizziness, and nausea as the most common adverse events.

Second-Generation Antidepressants Versus Acupuncture: Combination Comparisons

Two trials compared SGA monotherapy (fluoxetine or paroxetine) with a combination of an SGA with acupuncture (see KQ 1, Table 15 for more details on trial design and dosing).[105,123,135] One trial reported no statistically significant differences in specific adverse events, such as headache, dizziness, insomnia, and somnolence.[105,135] The other trial did not report any data on adverse events.[123]

Overall discontinuation rates were similar for patients treated with SGAs (10.0 percent to 10.4 percent) compared to those treated with a combination of an SGA with acupuncture (5.0 percent to 10.7 percent). Rates of discontinuation because of adverse events ranged from 0.0 percent to 3.4 percent and did not differ significantly between treatment groups.[105,123]

Second-Generation Antidepressants Compared With Omega-3 Fatty Acids

Second-Generation Antidepressants Versus Omega-3 Fatty Acids: Monotherapy Comparisons

An Iranian trial (high risk of bias) compared fluoxetine with omega-3 fatty acids (EPA, see KQ 1, Table 16 for more details on trial design and dosing).[120] The authors did not report whether the risks of specific adverse events differed in any statistically significant way between patients treated with fluoxetine and patients treated with EPA monotherapy. For the two treatment groups, rates of overall discontinuation (both 15.0 percent) and discontinuation because of adverse events (both 5.0 percent) were the same.

Second-Generation Antidepressants Versus Omega-3 Fatty Acids: Combination Comparisons

Two trials (both high risk of bias) compared SGAs (citalopram or fluoxetine) with combinations of SGAs and omega-3 fatty acids (see KQ 1, Table 16 for more details on trial design and dosing).[106,120] Overall, the available data on harms were sparse and did not allow us to draw firm conclusions about the comparative risk of harms between SGA monotherapy and the combination of SGAs with omega-3 fatty acids. Fluoxetine monotherapy and combined fluoxetine and EPA treatment groups did not differ significantly in rates of overall discontinuation (20.0 percent versus 20.0 percent) or discontinuation because of adverse events (5.0 percent versus 10.0 percent, respectively).

Second-Generation Antidepressants Compared With S-Adenosyl-L-Methionine (SAMe)

Second-Generation Antidepressants Versus SAMe: Monotherapy Comparisons

Only one trial that compared an SGA (escitalopram) with SAMe (see KQ 1, Table 17 for more details on trial design and dosing) reported on discontinuation rates.[104] Overall discontinuation rates (44.6 percent versus 37.5 percent, respectively) and discontinuation rates because of adverse events (12.3 percent versus 4.7 percent, respectively) were numerically higher for patients treated with escitalopram than for those treated with SAMe. The differences, however, did not reach statistical significance.

Second-Generation Antidepressants Versus SAMe: Combination Comparisons

We found no eligible trials that compared an SGA with a combination of SGA and SAMe.

Second-Generation Antidepressants Compared With St. John's Wort

All 12 trials comparing SGAs with St. John's wort provided data on harms or discontinuation rates (see KQ 1, Table 18 for more details on trial design and dosing).[92,109-114,117,125-128] Two trials were rated as high risk of bias.[112,113]

Second-Generation Antidepressants Versus St. John's Wort: Monotherapy Comparisons

Enough data were available to warrant meta-analyses of overall rates of adverse events and rates of overall discontinuation, discontinuation because of adverse events and because of lack of efficacy, and overall rates of serious adverse events.

Patients treated with SGAs experienced higher overall rates of adverse events, overall discontinuation, and discontinuation because of adverse events than patients treated with St. John's wort. Discontinuation rates because of lack of efficacy were similar between the treatment groups. In the following paragraphs, we describe the results of these meta-analyses in more detail.

Eight trials, all assigned a low or medium risk of bias rating, reported overall rates of adverse events.[110,111,114,117,125-128] SGAs were limited to citalopram, fluoxetine, paroxetine, and sertraline. Our random-effects meta-analysis indicated a numerically but not statistically significantly higher overall risk of adverse events for patients treated with SGAs than those treated with St. John's wort (46.6 percent versus 39.3 percent, respectively; RR, 1.17; 95% CI, 0.95 to 1.44; Figure 22).

Figure 22. SGA versus St. John's wort: Overall risk for adverse events

Author, Year	Statistics for each study			AEs / Total		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	SGA	SJW	
Behnke, 2002	0.91	0.62	1.33	20 / 35	22 / 35	
Bjerkenstedt, 2005	1.60	1.05	2.46	31 / 57	20 / 59	
Gastpar, 2005	0.85	0.67	1.06	60 / 118	74 / 123	
Gastpar, 2006	1.40	1.00	1.96	53 / 127	39 / 131	
Harrer, 1999	1.22	0.62	2.42	16 / 84	12 / 77	
Schrader, 2000	1.72	1.01	2.94	28 / 114	18 / 126	
Szegedi, 2005	1.38	1.15	1.66	96 / 126	69 / 125	
van Gurp, 2002	0.86	0.61	1.21	25 / 45	29 / 45	
	1.17	0.95	1.44			

0.5   1   2

Higher risk with SJW   Higher risk with SGA

Random effects meta-analyses; I-squared 66%

AEs = adverse events; CI = confidence interval; SGA = second-generation antidepressant(s); SJW = St. John's wort

Of note, a high degree of heterogeneity was present because three trials found a *higher* rate of overall adverse events for patients treated with St. John's wort, although none of these trials' risk ratios were statistically significant.[111,126,127] An exploratory analysis to identify the cause of the heterogeneity did not reveal any systematic differences between these three trials and the five showing a higher rate with SGAs; we surmise that the between-trial differences can probably be attributed to chance.

All 12 trials comparing SGAs with St. John's wort extracts, of which three had a high risk of bias rating,[109,112,113] reported overall discontinuation rates. Random-effects meta-analysis findings based on low and medium risk of bias trials showed that patients treated with SGAs had a statistically significantly higher risk of overall discontinuation than those treated with St. John's wort (15.5 percent versus 11.8 percent, respectively; RR, 1.28; 95% CI, 1.01 to 1.62; Figure 23). The results of our sensitivity analysis, which included the three high risk of bias trials, were similar (17.5 percent versus 13.6 percent, respectively; RR, 1.25; 95% CI, 1.02 to 1.54; forest plot not shown).

Figure 23. SGA versus St. John's wort: Overall discontinuation rates
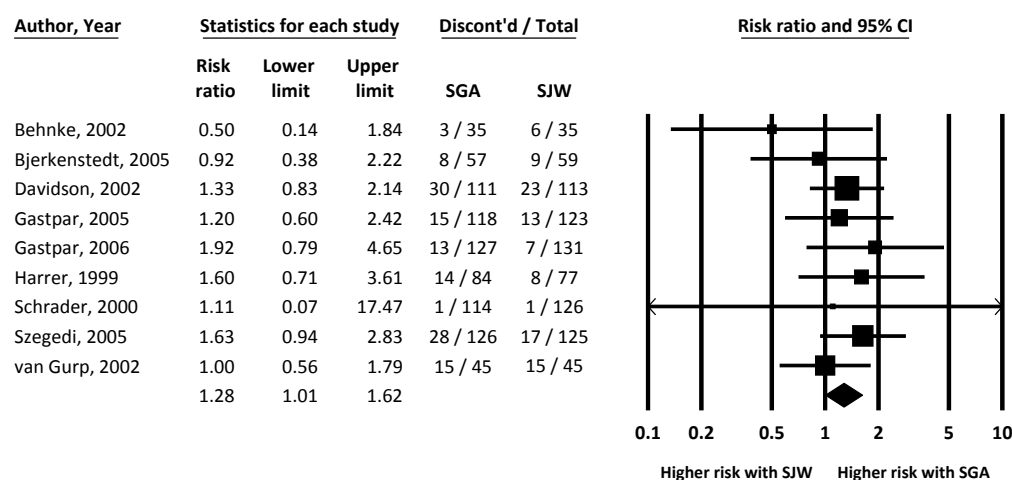
Author, Year	Statistics for each study			Discont'd / Total		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	SGA	SJW	
Behnke, 2002	0.50	0.14	1.84	3 / 35	6 / 35	
Bjerkenstedt, 2005	0.92	0.38	2.22	8 / 57	9 / 59	
Davidson, 2002	1.33	0.83	2.14	30 / 111	23 / 113	
Gastpar, 2005	1.20	0.60	2.42	15 / 118	13 / 123	
Gastpar, 2006	1.92	0.79	4.65	13 / 127	7 / 131	
Harrer, 1999	1.60	0.71	3.61	14 / 84	8 / 77	
Schrader, 2000	1.11	0.07	17.47	1 / 114	1 / 126	
Szegedi, 2005	1.63	0.94	2.83	28 / 126	17 / 125	
van Gurp, 2002	1.00	0.56	1.79	15 / 45	15 / 45	
	1.28	1.01	1.62			

Higher risk with SJW   Higher risk with SGA

Random effects meta-analyses; I-squared 0%

CI = confidence interval; Discont'd = discontinued; SGA = second-generation antidepressant; SJW = St. John's wort

Eleven of 12 trials, of which two were rated high risk of bias,[109,113] reported rates of discontinuation because of adverse events.[92,109-111,113,114,117,125-128] Our random-effects meta-analysis found a statistically significantly higher rate of discontinuation because of adverse events among patients treated with SGAs than those treated with St. John's wort (6.9 percent versus 3.8 percent, respectively; RR, 1.70; 95% CI, 1.12 to 2.60; Figure 24). Our sensitivity analysis, which included the same two high risk of bias trials mentioned above, found similar statistically significant results (SGA: 6.8 percent versus St. John's wort: 3.8 percent; RR, 1.69; 95% CI, 1.12 to 2.54; data not shown).

Figure 24. SGA versus St. John's wort: Discontinuation because of adverse events

Author, Year	Statistics for each study			Discont'd / Total		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	SGA	SJW	
Behnke, 2002	1.00	0.15	6.71	2 / 35	2 / 35	
Bjerkenstedt, 2005	1.04	0.27	3.94	4 / 57	4 / 59	
Davidson, 2002	2.55	0.50	12.84	5 / 111	2 / 113	
Gastpar, 2005	2.08	0.73	5.92	10 / 118	5 / 123	
Gastpar, 2006	2.84	0.93	8.68	11 / 127	4 / 131	
Harrer, 1999	1.22	0.44	3.36	8 / 84	6 / 77	
Schrader, 2000	3.31	0.14	80.52	1 / 114	0 / 126	
Szegedi, 2005	1.98	0.61	6.42	8 / 126	4 / 125	
van Gurp, 2002	1.40	0.48	4.08	7 / 45	5 / 45	
	1.70	1.12	2.60			

Higher risk with SJW   Higher risk with SGA

Random effects meta-analyses; I-squared 0%

AEs = adverse events; CI = confidence interval; Discont'd = discontinued; SGA = second-generation antidepressant(s); SJW = St. John's wort

Six trials reported rates of discontinuation because of lack of efficacy.[92,110,111,125,126,128] Our random-effects meta-analysis found similar rates of discontinuation because of a lack of efficacy between patients treated with SGAs and those treated with St. John's wort (2.3 percent versus 2.4 percent, respectively; RR, 0.91; 95% CI, 0.44 to 1.88; Figure 25).

Figure 25. SGA versus St. John's wort: Discontinuation rates because of lack of efficacy
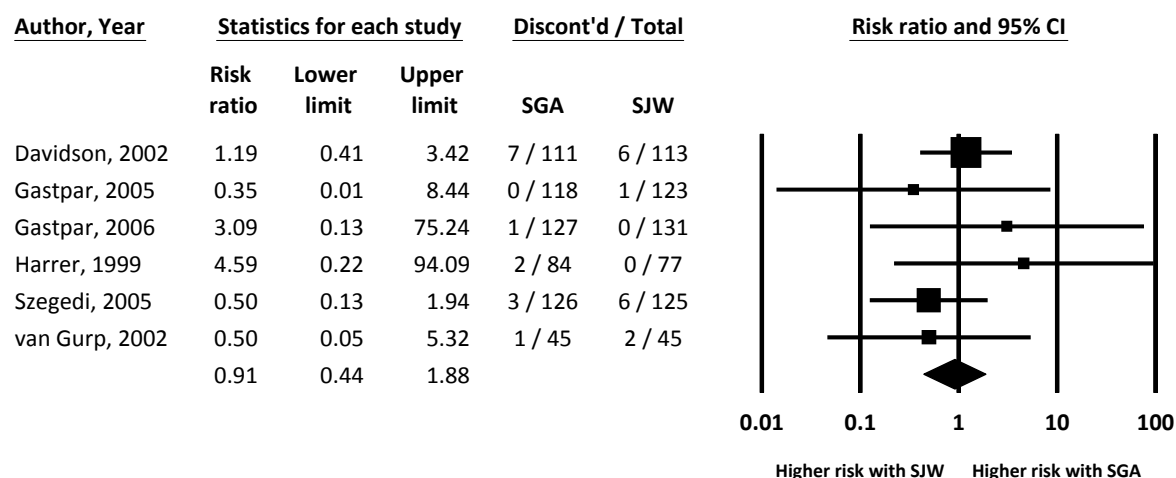
Author, Year	Statistics for each study			Discont'd / Total		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	SGA	SJW	
Davidson, 2002	1.19	0.41	3.42	7 / 111	6 / 113	
Gastpar, 2005	0.35	0.01	8.44	0 / 118	1 / 123	
Gastpar, 2006	3.09	0.13	75.24	1 / 127	0 / 131	
Harrer, 1999	4.59	0.22	94.09	2 / 84	0 / 77	
Szegedi, 2005	0.50	0.13	1.94	3 / 126	6 / 125	
van Gurp, 2002	0.50	0.05	5.32	1 / 45	2 / 45	
	0.91	0.44	1.88			

0.01   0.1   1   10   100

Higher risk with SJW   Higher risk with SGA

Random effects meta-analyses; I-squared 0%

CI = confidence interval; Discont'd = discontinued; SGA = second-generation antidepressant; SJW = St. John's wort

Second-Generation Antidepressants Versus St. John's Wort: Combination Comparisons
We did not find any trials addressing this comparison.

Second-Generation Antidepressants Compared With Exercise

As in previous sections, we first present the available evidence on the comparative risk of harms for SGAs compared with exercise, followed by the available evidence for SGAs compared with combination treatments of SGA and exercise.

Second-Generation Antidepressants Versus Exercise: Monotherapy Comparisons
Two trials comparing sertraline with exercise provided limited data about the comparative risk of harms (see KQ 1, Table 19, for more details on trial design and dosing).[93,94] Neither trial adequately reported on specific adverse events. One trial reported that, of 36 adverse events that investigators assessed, only the difference in the rates of diarrhea reached statistical significance.[94] Overall discontinuation rates were similar between patients treated with sertraline and those enrolled in the exercise programs (14.4 percent versus 16.6 percent, respectively). Patients on sertraline, however, had statistically significantly higher rates of discontinuation because of adverse events than patients in the exercise programs (6.2 percent versus 0.0 percent, respectively; RR, 20.96; 95% CI, 1.19 to 367.97).

Second-Generation Antidepressants Versus Exercise: Combination Comparisons
One of these trials compared sertraline with a combination of sertraline and exercise.[93] Authors did not report information on specific adverse events. Patients treated with sertraline or

a combination with exercise had similar rates of overall discontinuation (14.6 percent versus 20.0 percent, respectively) and discontinuation because of adverse events (10.4 percent versus 9.1 percent, respectively).[93]

Second-Generation Antidepressant Switching Strategies

In this section, we present the available evidence on the comparative risk of harms from SGA switch strategies compared with other switch strategies following failure of an adequate SGA trial.

Second-Generation Antidepressant Switch Versus Second-Generation Antidepressant Switch

Two trials, one of which used data from the STAR*D study,[140] compared the risks of harms of different SGA switching strategies.[115,140] Specifically, one trial found that overall rates of adverse events (57.5 percent versus 63.1 percent, respectively; p=NR) and overall discontinuation (24.5 percent versus 20.9 percent, respectively; p=NR) were similar regardless of whether patients switched to citalopram or to venlafaxine.[115] The other trial found that rates of discontinuation because of adverse events were similar regardless of which SGA treatment was switched to—bupropion (27.2 percent), sertraline (21.0 percent), or venlafaxine (21.2 percent)—following treatment failure with citalopram (p=NR).[140]

Second-Generation Antidepressant Switch Versus Nonpharmacological Treatment Switch (Psychotherapy)

One trial based on the STAR*D study compared the risks of harms from an SGA switching strategy (bupropion or buspirone) with a CT switching strategy following an initial citalopram treatment failure.[107] Rates of discontinuation because of adverse events were numerically higher for patients who received an SGA switch (26.7 percent) compared with those who switched to CT (16.7 percent) (p=0.34). No data on the overall risk of adverse events or overall discontinuation rates were reported.

Second-Generation Antidepressant Augmentation Strategies

In this section, we present the available evidence on the comparative risk of harms from SGA augmentation strategies compared with other augmentation strategies following failure of an adequate SGA trial.

Second-Generation Antidepressant Augmentation Versus Second-Generation Antidepressant Augmentation

One trial based on the STAR*D study compared the risk of harms from bupropion augmentation or buspirone augmentation following the treatment failure of citalopram.[141] Patients who received bupropion augmentation (12.5 percent) were statistically significantly less likely to discontinue treatment because of adverse events than those receiving buspirone augmentation (20.6 percent) (p<0.001). Neither overall discontinuation rates nor rates of adverse events were reported.

Second-Generation Antidepressant Augmentation With Pharmacological Treatment Versus Second-Generation Antidepressant Augmentation With Nonpharmacological Treatment Augmentation (Psychotherapy)

A single trial compared the risk of harms from an SGA augmentation (bupropion or buspirone) or augmentation with CT following the treatment failure of citalopram.[107] Rates of discontinuation because of adverse events were numerically more than twice as high following SGA augmentation than after CT augmentation, but the difference was not statistically significant (18.8 percent versus 9.2 percent, respectively; p=0.0863). Neither overall discontinuation rates nor rates of adverse events were reported.

Second-Step Switch Strategy Compared With Any Augmentation Strategy

We found no eligible trials that directly compared an SGA switch strategy with an augmentation strategy.

Detailed Synthesis: Risk of Experiencing Serious Adverse Events

Our included trials reported the incidence of serious adverse events even less frequently than more common adverse events. This could reflect the inherent rarity of serious problems, but the majority of our trials also failed to report whether any serious adverse events took place at all, and none indicated how they defined serious adverse events. Overall, 19 trials (23 articles) provided some data on these events.[85,88,92,96,99,101-103,106-111,115-117,125,126,129,131,140,141]

Second-Generation Antidepressants Compared With Psychological Interventions

Ten trials comparing SGA monotherapy with psychotherapy alone or in combination with SGAs provided explicit information about the occurrence or nonoccurrence of serious adverse events.[85,88,96,97,99,101,103,107,108,116,129,131] None of these trials compared between-group differences in the rates of serious events.

Second-Generation Antidepressants Compared With Any Psychological Intervention

Second-Generation Antidepressants Versus Any Psychological Intervention: Monotherapy Comparisons

Eight trials reported the occurrence of one or more serious adverse events;[85,88,97,99,102,103,107,116,129,131] of these, seven reported data on suicidal ideas or behaviors.[85,88,97,99,102,103,116,129,131] Rates of suicidal ideas or behaviors ranged from 1.0 percent to 9.0 percent for patients treated with SGAs, and from 0.0 percent to 19.0 percent for patients receiving psychological treatments. One RCT conducted a comprehensive assessment of suicidal ideas or behaviors in patients treated with SGAs (escitalopram) or integrative therapy, specifically IPT.[85,131] We received data from the authors of one RCT that evaluated the presence of suicidal ideas or behaviors at all study timepoints, including baseline,[88] as well as data from the authors of three other RCTs that reported the incidence of suicidal ideas or behaviors at posttreatment followup.[102,103,116]

We were able to conduct meta-analyses of overall rates of suicidal ideas or behaviors using all seven of the above trials that reported relevant data, three of which had a high risk of bias.[85,88,97,102,131] These trials all compared patients receiving SGAs (paroxetine or sertraline)

with those receiving different psychotherapies (CBT, IPT, short-term PSYD, and third-wave CBT). Our primary analysis including only the four low and medium risk of bias trials[97,99,103,116,129] did not show a statistically significant difference in the rate of suicidal ideas or behaviors between the two groups (9.0 percent versus 7.5 percent, respectively; RR, 1.36; 95% CI, 0.87 to 2.14; Figure 26).

Figure 26. SGA versus any psychological treatment: Rates of suicidal ideas or behaviors

Study name	Statistics for each study			Events / Total		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	SGA	Psychotherapy	
Dekker, 2008	1.01	0.47	2.19	11 / 70	11 / 71	
DeRubeis, 2005	2.52	0.12	51.69	2 / 120	0 / 60	
Dimidjian, 2006a	1.80	0.06	52.52	1 / 50	0 / 45	
Dimidjian, 2006b	1.73	0.06	50.21	1 / 50	0 / 43	
Menchetti, 2014	1.55	0.87	2.78	25 / 144	16 / 143	
	1.36	0.87	2.14			

Random effects meta-analysis; I-squared 0%
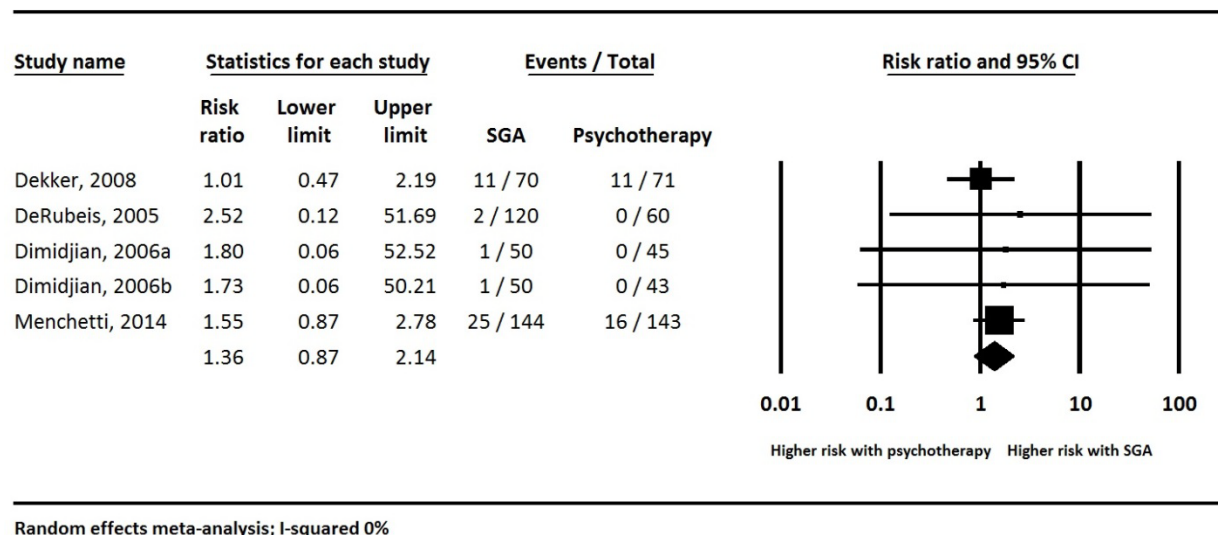
CI = confidence interval; SGA = second-generation antidepressant(s)

In our sensitivity analyses, we included the three high risk of bias trials mentioned above. The results were statistically similar to those of the primary analysis (RR, 0.83; 95% CI, 0.47 to 1.46).

Second-Generation Antidepressants Versus Any Psychological Intervention: Combination Comparisons

Only a single trial with a medium risk of bias compared the risk of any serious adverse events following SGA monotherapy or SGA treatment in combination with psychotherapy.[101] Specifically, the rate of suicidal ideas or behaviors in patients treated with fluoxetine (4.4 percent) exceeded that of patients treated with long-term psychodynamic therapy (1.1 percent). While this was a fourfold difference, these findings should be interpreted with caution because of the very small number of events taking place.

Second-Generation Antidepressants Compared With Behavior Therapy/Behavior Modification

We did not find any trials comparing an SGA with behavior therapy/behavior modification.

Second-Generation Antidepressants Compared With Cognitive Behavioral Therapy

Second-Generation Antidepressants Versus Cognitive Behavioral Therapy: Monotherapy Comparisons

Three trials comparing an SGA (paroxetine or sertraline) with CBT reported data on serious adverse events.[97,99,102,129] A total of 9 patients experienced serious events, all but two of whom had received SGAs. Three committed suicide,[97,99,129] one attempted suicide,[99,129] one exhibited an unspecified type of suicidal ideas or behaviors[102], and two experienced severe allergic reactions or severe but unspecified adverse events.[99,129] Both patients who were receiving CBT also exhibited an unspecified type of suicidal ideas or behaviors.[102]

Second-Generation Antidepressants Versus Cognitive Behavioral Therapy: Combination Comparisons

Only one trial comparing SGAs with a combination of SGAs and CBT reported data on serious adverse events.[107,108] In this trial, patients did not experience any serious events whether they were receiving escitalopram alone or escitalopram in combination with CBT.[108]

Second-Generation Antidepressants Compared With Humanistic Therapies

We found no trials addressing this comparison.

Second-Generation Antidepressants Compared With Integrative Therapies

Second-Generation Antidepressants Versus Integrative Therapies (IPT only): Monotherapy Comparisons

Three trials compared SGAs (citalopram, escitalopram, or sertraline) and IPT and provided data about serious adverse events.[85,88,103,131] In one trial, among patients who had no suicidal ideation at baseline but who developed it during the trial, 15.4 percent of patients were receiving IPT and 5.2 percent were receiving SGAs at the onset of their suicidal ideation.[85,131] No serious adverse events took place in another trial, which compared patients receiving escitalopram with those receiving IPT.[103] Unpublished data from the authors of the third, high risk of bias trial showed that a numerically greater proportion of patients treated with SGAs no longer endorsed suicidal ideas or behaviors than did patients treated with IPT.[88]

Second-Generation Antidepressants Versus Integrative Therapies (IPT Only): Combination Comparisons

We found no trials addressing this comparison.

Second-Generation Antidepressants Compared With Psychodynamic Therapies

Second-Generation Antidepressants Versus Psychodynamic Therapies: Monotherapy Comparisons

Three trials, two of which had a high risk of bias,[101,116] comparing SGAs with short-term or long-term PSYD provided information about serious adverse events.[96,101,116] Patients treated with SGAs (15.7 percent) and those treated with short-term supportive PSYD (15.5 percent) experienced suicidal ideas or behaviors at similar rates during 8 weeks of followup (p=NR).[116] In the other high risk of bias trial, patients receiving fluoxetine (4.4 percent) and those receiving long-term PSYD (3.3 percent) experienced similar rates of suicidal ideas or behaviors at the 96-

week followup (p=NR).[101] In the third trial comparing sertraline or venlafaxine and short-term PSYD, no patients experienced serious adverse events.[96]

Second-Generation Antidepressants Versus Psychodynamic Therapies: Combination Comparisons

One high risk of bias trial comparing SGAs with a combination of SGAs and long-term PSYD provided information about serious adverse events.[101] Patients receiving fluoxetine (4.4 percent) and those receiving long-term PSYD (1.1 percent) experienced similar rates of suicidal ideas or behaviors at the 96-week followup (p=NR).[101]

Second-Generation Antidepressants Compared With Third-Wave CBT

A single trial comparing an SGA (paroxetine) with third-wave CBT (behavioral activation) reported data on serious adverse events.[97] Specifically, one patient receiving paroxetine (1.0 percent) committed suicide, while no patients receiving third-wave CBT reported suicidal ideas or behaviors (p=NR).

Second-Generation Antidepressants Compared With Complementary and Alternative Medicines

Nine RCTs[92,106,109-111,117,120,125,126] comparing SGA monotherapy with CAM interventions alone or in combination with SGAs provided information about serious adverse events.

Second-Generation Antidepressants Compared With Acupuncture

No information about serious adverse events was available from trials comparing SGAs with acupuncture.

Second-Generation Antidepressants Versus Omega-3 Fatty Acids

Second-Generation Antidepressants Versus Omega-3 Fatty Acids: Monotherapy Comparisons

A single high risk of bias trail comparing SGAs (fluoxetine) with omega-3 fatty acids provided information about serious adverse events.[120] A single patient (5 percent) treated with omega-3 fatty acids reported suicidal ideation, while no patients treated with SGAs experienced suicidal ideas or behaviors.

Second-Generation Antidepressants Versus Omega-3 Fatty Acids: Combination Comparisons

No information about serious adverse events was available from trials comparing SGAs with omega-3 fatty acids except for one trial (high risk of bias) that compared citalopram with omega-3 fatty acids in combination with citalopram and DHA.[106] In this trial, no patients experienced serious adverse events.

Second-Generation Antidepressants Compared With S-Adenosyl-L-Methionine

No information about serious adverse events was available from the sole trial comparing SGAs with SAMe.[104]

Second-Generation Antidepressants Compared With St. John's Wort

Second-Generation Antidepressants Versus St. John's Wort: Monotherapy Comparisons

Seven trials comparing SGAs with various extracts of St. John's wort provided data on serious adverse events.[92,109-111,117,125,126]

Enough data were available to warrant meta-analyses of overall rates of serious adverse events. Specifically, we included five of the above trials in our analyses (one rated high risk of bias[109]). These trials all compared patients receiving different SGAs (citalopram, fluoxetine, paroxetine, or sertraline) with those receiving St. John's wort.[109-111,125,126] Our primary analysis with only low and medium risk of bias trials did not show a statistically significant difference in the rate of serious adverse events between the two groups (1.2 percent versus 1.7 percent, respectively, for SGAs or St. John's wort; Peto OR [odds ratio], 0.66; 95% CI, 0.12 to 3.58; Figure 27). Including the remaining, high risk of bias trial[109] in the sensitivity analysis did not affect the original findings (SGAs: 1.1 percent versus St. John's wort: 1.7 percent; OR, 0.55; 95% CI, 0.12 to 2.47; forest plot not shown). Because of the low number of events, results should be interpreted with caution.

Figure 27. SGA versus St. John's wort: Serious adverse events
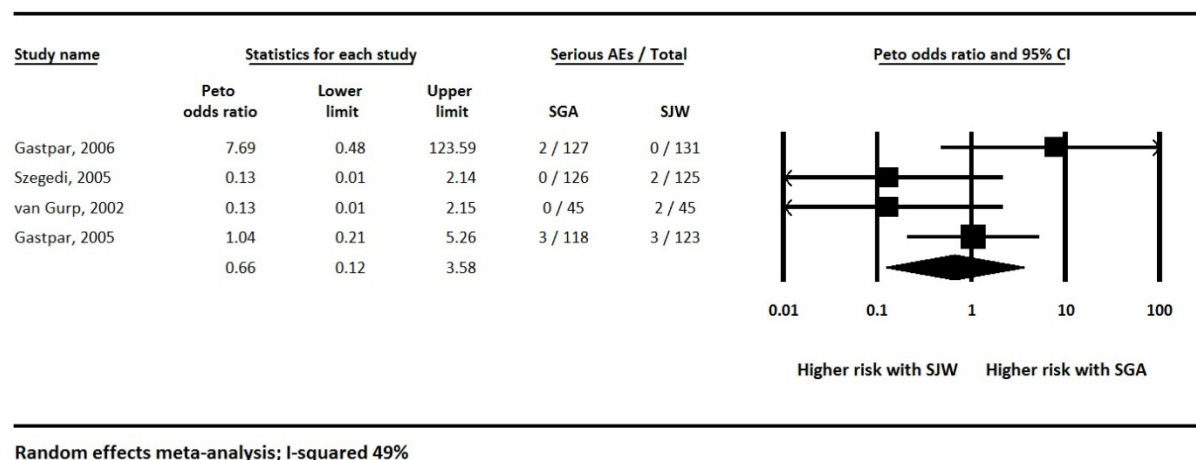
Study name	Statistics for each study			Serious AEs / Total		Peto odds ratio and 95% CI
	Peto odds ratio	Lower limit	Upper limit	SGA	SJW	
Gastpar, 2006	7.69	0.48	123.59	2 / 127	0 / 131	
Szegedi, 2005	0.13	0.01	2.14	0 / 126	2 / 125	
van Gurp, 2002	0.13	0.01	2.15	0 / 45	2 / 45	
Gastpar, 2005	1.04	0.21	5.26	3 / 118	3 / 123	
	0.66	0.12	3.58			

Random effects meta-analysis; I-squared 49%

CI = confidence interval; SGA = second-generation antidepressant; SJW = St. John's wort

Second-Generation Antidepressants Versus St. John's Wort: Combination Comparisons

We did not find any trials addressing this comparison.

Second-Generation Antidepressants Compared With Exercise

No information about serious adverse events was available from trials comparing SGAs with exercise.

Second-Generation Antidepressant Switching Strategies

Three trials comparing an SGA switch strategy with an SGA or nonpharmacological therapy switch strategy following failure of an adequate SGA trial provided information about serious adverse events.[107,115,140]

Second-Generation Antidepressant Switch Versus Second-Generation Antidepressant Switch

Two trials compared the risks of serious adverse events from SGA switching strategies with different SGA switching strategies,[115,140] but only one reported the occurrence of any serious adverse events.[140] This trial, which compared switching from citalopram to bupropion, sertraline, or venlafaxine, reported rates of serious adverse events ranging from 2.1 percent to 4.2 percent, although they did not differ significantly.[140]

Second-Generation Antidepressant Switch Versus Nonpharmacological Treatment Switch (Psychotherapy)

One trial compared switching from citalopram to a different SGA (sertraline, bupropion, or venlafaxine) with switching to CBT [107] Only patients receiving SGA switching (2.3 percent) experienced any serious adverse events, although this rate was not statistically significantly different from that of patients receiving CT switching (p=1.00). None of the events were psychiatric in nature.

Second-Generation Antidepressant Augmentation Strategies

In this section, we present the available evidence on the comparative risk of harms from SGA augmentation strategies compared with other augmentation strategies following failure of an initial adequate SGA trial.

Second-Generation Antidepressant Augmentation Versus Second-Generation Antidepressant Augmentation

One trial compared the risk of serious adverse events from bupropion augmentation or buspirone augmentation following the treatment failure of citalopram.[141] Patients who received bupropion augmentation (3.6 percent) and those receiving buspirone augmentation (4.2 percent) had similar overall rates of serious adverse events (p=0.71). Of these, 1.1 percent and 2.1 percent were psychiatric in nature, respectively (p=NR). Rates of suicidal ideas or behaviors were also similar between groups (0.4 percent versus 1.4 percent, respectively; p=NR).

Second-Generation Antidepressant Augmentation With Pharmacological Treatment Versus Second-Generation Antidepressant Augmentation With Nonpharmacological Treatment Augmentation (Psychotherapy)

A single trial compared the risk of serious adverse events from an SGA augmentation (bupropion or buspirone) or augmentation with CT.[107] Patients augmenting citalopram with CT following a treatment failure experienced numerically and statistically similar rates of serious adverse events compared with patients receiving an SGA augmentation (6.2 percent versus 3.4 percent, p=0.46). Rates of psychiatric serious adverse events were numerically, but not statistically, greater among patients receiving CT augmentation than patients receiving SGA augmentation (6.2 percent versus 0.9 percent, p=0.06).

Second-Step Switch Strategy Compared With Any Augmentation Strategy

We found no eligible trials that directly compared an SGA switch strategy with an augmentation strategy.

KQ 3b. Variation in Risk of Harms by Severity of Major Depressive Disorder

Detailed Synthesis: Overall Risk of Experiencing Harms and Discontinuation of Treatment

A single trial comparing SGAs with CBT and third-wave CBT provided qualitative information about baseline MDD severity as a moderator of the risk of adverse events.[97] Specifically, the risk of adverse events in patients treated with SGAs did not differ by baseline severity except in two cases: higher-severity patients experienced more nausea but less diarrhea than lower-severity patients. Because of the small sample size of this trial and the risk for chance findings, results should be interpreted with caution.

Detailed Synthesis: Risk of Experiencing Serious Adverse Events

We did not find any trials addressing the potential role of baseline MDD severity as a moderator of risk of experiencing serious adverse events.

KQ 4. Comparative Benefits and Risks of Harms for Selected Subgroups

Overview

In this section, we focus on the comparative benefits and harms of SGAs with psychotherapy, CAM, or exercise for treating MDD in selected subpopulations. Specific subgroups were defined by common accompanying psychiatric symptoms (coexisting anxiety, insomnia, low energy, or somatization) or by demographic characteristics (age, sex, or race or ethnicity).

As we have done in previous sections, here we provide an overview of the articles, including the number of trials for each comparison (listed in Table 28); key points; and a detailed synthesis. In Appendix E, we present "summary of findings" tables for a set of outcomes identified as especially important. These tables describe basic information on the available evidence and present the SOE grades for each outcome.

No trials were specifically designed to assess differences in our specified subgroups. Overall, as documented in Table 28, only three trials addressing a subgroup of interest met the criteria for inclusion. As described in Methods, we broadened eligibility criteria to include placebo-controlled trials for preplanned mixed treatment comparisons. However, we did not have sufficient data on any subgroup to conduct mixed treatment comparisons and meta-regression analyses.

No trials at all addressed efficacy or harms in selected subgroups of patients who did not achieve remission following an initial adequate trial with one SGA.

Table 28. Number of included trials for all subgroups by type of comparison

Comparison Category	Comparisons	Number of Trials
SGA vs. Psychological Interventions	SGA vs. Behavior therapies/behavior modification	0
	SGA vs. CBT	1[100]
	SGA vs. Humanistic therapies	0
	SGA vs. Integrative therapies	1[103]
	SGA vs. Psychodynamic therapies	0
	SGA vs. Third-wave CBTs	0
SGA vs. Complementary and Alternative Medicine	SGA vs. Acupuncture	0
	SGA vs. Omega-3 fatty acids	0
	SGA vs. SAMe	0
	SGA vs. St. John's wort	1[128]
	SGA vs. Meditation	0
	SGA vs. Yoga	0
SGA vs. Exercise	SGA vs. Exercise	0

CBT = cognitive behavioral therapy; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant

Key Points: Common Accompanying Psychiatric Symptoms

- SGAs produced slightly higher remission rates than IPT in patients with a comorbid anxiety disorder but not in those without co-occurring anxiety (one RCT, insufficient SOE). We did not find any evidence comparing SGAs with any other nonpharmacological interventions in subgroups with comorbid anxiety (insufficient SOE).
- We did not identify any eligible trials for subgroups with accompanying insomnia, low energy, or somatization (insufficient SOE).

Key Points: Age

- St. John's wort did not lead to statistically different response rates compared with SGAs after 6 weeks of treatment in older adults with MDD (one RCT, low SOE for no differences); both groups reported adverse events, and discontinuation rates attributable to adverse events were similar (low SOE for no differences).
- We did not find any eligible evidence comparing SGAs with other CAM interventions by age (i.e., acupuncture, meditation, omega-3 fatty acids, SAMe, or yoga) (all insufficient SOE).
- We did not find any eligible evidence comparing SGAs with psychological interventions by age (insufficient SOE).

Key Points: Sex

- We did not identify any trials assessing differences between men and women in efficacy or harms (insufficient SOE).
- SGAs and CBT showed similar reduction in depressive symptoms in a trial that included only minority women (insufficient SOE).

Key Points: Race or Ethnicity

- No trials directly compared the efficacy, effectiveness, or harms of SGAs with eligible psychotherapy, CAM, or exercise interventions among patients of different races or ethnicities (insufficient SOE).

Detailed Synthesis: Common Accompanying Psychiatric Symptoms

Second-Generation Antidepressant Compared With Psychotherapy Interventions

One trial comparing SGAs with IPT assessed differences in patients with and without comorbid anxiety disorders.[103] The trial was conducted in primary care settings in New Zealand. SGA produced higher remission rates than IPT in patients with a comorbid anxiety disorder but not in patients without co-occurring anxiety. Because of the small sample size of this trial and the potential for chance findings, these results should be interpreted cautiously.

No trials reported evidence on risk of harms.

We found no eligible trials in subgroups of MDD patients with other common accompanying psychiatric symptoms (insomnia, low energy, or somatization).

Table 29 provides detailed information on included trials for all subgroups.

Table 29. Second-generation antidepressants versus nonpharmacological therapies in subgroups: Trial characteristics, main outcomes, and risk of bias ratings

Trial Subgroup of Interest	N[a] Duration (Weeks)	Mean Baseline HAM-D Score	SGA: mg/day Comparator: mg/day *or* Number of Sessions	Response[b] (%) and Significance Level	Remission[b] (%) and Significance Level	Risks of Harms	Risk of Bias Rating
Menchetti et al., 2014[103] Accompanying psychiatric symptoms (anxiety)	287 8	17.3	Citalopram: 10 to 60 or Sertraline: 25 to 200 Interpersonal psychotherapy: 6 to 8	NR	Comorbid anxiety disorder: 70 vs. 65 SRD= -0.05; 95% CI, -0.33 to 0.23 No comorbid anxiety disorder: 46 vs. 67 SRD=0.21; 95% CI, 0.04 to 0.38	NR	Medium
Women Entering Care (WECare), 2003[100] Minority women	178 8[c]	16.9[d]	Paroxetine: 10 to 50 Cognitive behavioral therapy: 8	NR	NR	NR	Medium
Harrer et al., 1999[128] Older adults	161 6	NR	Fluoxetine: 10 St. John's wort: 400	72 vs. 71 p=NR	NR	Discontinued treatment because of adverse drug reactions: 8 vs. 6	Medium

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; N = number; NR = not reported; SGA = second-generation antidepressant; SRD = standardized rate difference; vs. = versus

[a] Total number of randomized participants in relevant arms of trial.
[b] Response and remission are measured on the HAM-D.
[c] Results reported at 4 weeks.
[d] Mean baseline score includes participants randomized to community referral intervention.

Second-Generation Antidepressant Compared With Complementary and Alternative Medicine Interventions

We found no eligible trials in subgroups with accompanying psychiatric symptoms.

Second-Generation Antidepressant Compared With Exercise Interventions

We found no eligible trials in subgroups with accompanying psychiatric symptoms.

Detailed Synthesis: Age

No trials directly compared the efficacy, effectiveness, or harms of SGAs with eligible psychotherapy, CAM, or exercise interventions in older adults (55 years of age or older) and the general population. We identified one trial that exclusively enrolled older adults; it assessed response, remission, and harms for SGAs compared with St. John's wort.[128] We did not find any evidence about other outcomes of interest such as quality of life or functional capacity.

Second-Generation Antidepressant Compared With Complementary and Alternative Medicine Interventions

One trial conducted in a primary care setting randomized older adults (60 to 80 years of age) to fluoxetine or St. John's wort for 6 weeks. Both treatments produced similar response rates and reductions in HAM-D scores.[128] In addition, discontinuation because of harms was similar for both groups.

Second-Generation Antidepressant Compared With Exercise Interventions

No trials meeting our eligibility criteria compared SGAs with exercise. We identified post-hoc analysis from a trial in adults 55 years or older. Even though this analysis does not meet criteria for inclusion, we briefly describe it here because of the paucity of evidence on subgroups. This analysis found no significant difference between sertraline and exercise in neurocognitive function in older adults.[138]

Detailed Synthesis: Sex

Second-Generation Antidepressant Compared With Psychotherapy Interventions

We did not identify any trials assessing differences between men and women in efficacy or harms. One trial (described in KQ 1) randomized low-income minority women to SSRI or CBT for 8 weeks.[100] Both interventions improved patients' depressive symptoms. At month 6, SSRI-treated participants reported lower depressive symptoms and better instrumental role functioning than those treated with CBT.

Second-Generation Antidepressant Compared With Complementary and Alternative Medicine Interventions

We found no eligible evidence.

Second-Generation Antidepressant Compared With Exercise Interventions

We found no eligible evidence.

Detailed Synthesis: Race or Ethnicity

We did not identify any trials assessing benefits or harms of second-generation antidepressants with eligible psychotherapy, CAM, or exercise interventions across races or ethnic groups.

Discussion

This chapter summarizes the key findings and how they relate to published findings and current clinical practices and policies. We also briefly examine the applicability of our findings and their implications for decisionmaking. We comment on limitations of both the review process and the entire evidence base as a segue into our discussion of research gaps in this field.

Key Findings and Strength of Evidence

Pharmacotherapy (particularly second-generation antidepressants [SGAs]) is the primary intervention for treating patients with major depressive disorder (MDD) in primary care. Nonetheless, primary care patients and clinicians may prefer other options (or at least want to be able to consider them). These include psychotherapeutic interventions, complementary and alternative medicine (CAM) options, exercise, or a combination of these treatments. Our report provides a comprehensive summary of the available evidence on comparative effectiveness and risk of harms of commonly used pharmacological and nonpharmacological treatments for MDD.

In this review we focus on two key issues that primary care physicians commonly face:
1. How do different treatment options compare as an initial treatment choice, and how effective are SGAs compared with nonpharmacological interventions?
2. For patients whose depression did not achieve remission following initial treatment with an SGA, what is the comparative effectiveness of alternative pharmacological and nonpharmacological options?

Overall, the available evidence was characterized by substantial methodological shortcomings and a lack of adequate assessment of harms. In addition, outcomes reporting bias often appeared to be an issue. For example, publications frequently did not report remission and adverse events, yet trials on treatment of patients with MDD are unlikely to fail to assess these outcomes.

The available evidence base has some clear limitations. Some nonpharmacological interventions have never been compared with any SGAs. Very limited evidence is available to address the comparative effectiveness of second-step therapies (i.e., treatment options for patients who did not achieve remission after an initial treatment trial). Further, the role of depression severity as a moderator of comparative treatment effectiveness, whether for first- or second-step therapies, has received very little direct testing in head-to-head trials.

Nevertheless, we were able to draw some conclusions. Because reliable evidence supports similar effectiveness within the class of SGAs, our conclusions are likely valid for the entire class of SGAs.

Comparative Benefits and Harms of Treatment Options for Initial Treatment of Patients With Major Depressive Disorder

Across all interventions, we graded the strength of evidence (SOE) as moderate for only one comparison: namely, SGAs compared with cognitive behavioral therapy (CBT). Results from trials of this comparison indicate that SGAs and CBT have similar effectiveness regarding symptomatic relief in patients with mild to severe MDD. For risk of harms, we graded the SOE as moderate for some outcomes of three comparisons, namely SGAs compared with CBT, acupuncture, and St. John's wort. For all three comparisons, patients treated with SGAs had a higher risk of experiencing adverse events or discontinuing treatment because of adverse events

than patients treated with CBT, acupuncture, and St. John's wort. The evidence is insufficient to draw conclusions about differences in serious adverse events such as suicidal ideas and behavior.

Our confidence in findings from the remaining comparisons of SGAs with other treatment options was low or insufficient, indicating that these bodies of evidence had major or unacceptable deficiencies. Nevertheless, for most comparisons the overall findings did not show a statistically significant difference in effectiveness but did indicate a lower risk of adverse events for nonpharmacological treatment options. Notable exceptions are omega-3 fatty acids, which appear to have lower effectiveness than SGAs, and the combination of SGAs with acupuncture, which appears to have greater effectiveness than SGA monotherapy. Our confidence in these findings, however, is low and results have to be interpreted cautiously. In addition, for many comparisons that are limited to single trials, determining whether similar treatment effects between SGAs and other interventions are based on similar effectiveness or high placebo response rates is impossible.

The available data offers no conclusions on how selection of treatment strategies might differ based on a patient's severity of depression. Overall, data do not indicate differences in the comparative effectiveness between SGAs and nonpharmacological interventions for patients with severe MDD. This important question concerning MDD severity, although, raised by a few systematic reviews,[22-24] remains without a clear answer.

Beyond the two articles identified comparing switching and augmentation strategies employing a limited number of medication options or CT, the absence of relevant comparative data about which treatment options are most effective for those needing second-step treatment (about 70% of patients with MDD)[26,27] was striking. Table 30 summarizes our main findings and the respective certainty that we have about these findings, presented as SOE grades (high, moderate, low, or insufficient).[83] In this table, we do not present comparisons for which we found no studies whatsoever or for which we were unable to estimate the comparative effectiveness with network meta-analyses. We discuss the summary of findings in more detail below.

Table 30. Summary of findings with strength of evidence: Comparative benefits and harms of second-generation antidepressants and other treatment options as an initial choice for the treatment of patients with major depressive disorders

Comparison and Outcome of Interest		Strength of Evidence[a]	Findings
SGA versus CBT monotherapy	Remission	Low	Results from direct comparisons in 3 trials indicate that no substantial differences in remission exist between SGAs and CBT monotherapy.
	Response	Moderate	Results from direct comparisons in 5 trials indicate that no substantial differences in response exist between SGAs and CBT monotherapy.
	Functional capacity	Low	Results from 1 trial indicate that no substantial differences in functional capacity exist between SGAs and CBT monotherapy.
	Overall risk of adverse events	Insufficient	Based on 1 trial with few events, the evidence is insufficient to draw conclusions.
	Overall discontinuation of treatment (8-14 weeks)	Moderate	Results from direct comparisons in 4 trials indicate that no significant differences exist in overall discontinuation between patients treated with SGAs and those treated with CBT.
	Overall discontinuation of treatment (24 weeks)	Low	Results from 1 trial indicate that patients treated with SGAs are more likely to discontinue treatment for any reason than those treated with CBT.
	Discontinuation of treatment because of adverse events	Low	Results from direct comparisons in 3 trials indicate that patients treated with SGAs experience a numerically but not statistically significant higher rate of discontinuation because of adverse events than those treated with CBT.
	Serious adverse events	Insufficient	Based on 2 trials with few events, the evidence is insufficient to draw conclusions.
	Suicidal ideas and behavior	Insufficient	Based on 3 trials with few events, the evidence is insufficient to draw conclusions.
SGA versus SGA + CBT	Remission	Low	Results from direct comparisons in 2 trials indicate that no substantial differences in remission exist between SGAs and SGAs combined with CBT.
	Response	Low	Results from direct comparisons in 2 trials indicate that no substantial differences in response exist between SGAs and SGAs combined with CBT.
	Functional capacity	Low	Results from 1 trial indicate that the combination of SGA with CBT results in greater improvement on 3 of 4 work functioning measures than SGA alone.
	Overall discontinuation of treatment	Low	Results from direct comparisons in 2 head-to-head trials indicate that no significant differences exist in overall discontinuation between patients treated with SGAs and those treated with CBT.
	Discontinuation of treatment because of adverse events	Low	Results from direct comparisons in 2 head-to-head trials indicate that no significant differences exist in discontinuation because of adverse events between patients treated with SGAs and those treated with CBT.

Table 30. Summary of findings with strength of evidence: Comparative benefits and harms of second-generation antidepressants and other treatment options as an initial choice for the treatment of patients with major depressive disorders (continued)

Comparison and Outcome of Interest		Strength of Evidence[a]	Findings
SGA versus IT monotherapy	Remission	Low	Results from direct comparisons in 2 trials indicate that no substantial differences in remission exist between SGAs and interpersonal therapy monotherapy.
	Response	Low	Results from 1 trial indicate that no substantial differences in response exist between SGAs and interpersonal therapy monotherapy.
	Overall discontinuation of treatment	Insufficient	Based on 2 trials with few events, the evidence is insufficient to draw conclusions.
	Discontinuation of treatment because of adverse events	Insufficient	Based on 1 trial with few events, the evidence is insufficient to draw conclusions.
	Suicidal ideas and behavior	Insufficient	Based on 2 trials with few events, the evidence is insufficient to draw conclusions.
SGA versus SGA + IT	Remission	Low	Results from 1 trial indicate that a substantial difference in remission favoring SGAs combined with interpersonal therapy exists, but the confidence interval is very wide.
	Overall discontinuation of treatment	Insufficient	Based on 1 with very few events, the evidence is insufficient to draw conclusions.
	Subgroup with anxiety	Insufficient	Based on 1 trial, the evidence is insufficient to draw conclusions for benefits or harms.
SGA versus PSYD monotherapy	Remission	Low	Results from 1 trial indicate that no substantial differences in remission exist between SGAs and PSYD monotherapy.
	Functional capacity	Low	Results from direct comparisons based on 2 trials indicate that few substantial differences in functional capacity exist between SGAs and PSYD monotherapy.
	Overall discontinuation of treatment (8 to 16 weeks)	Insufficient	Results from direct comparisons in 3 head-to-head trials indicate that no significant differences exist in overall discontinuation after 8-16 weeks of followup between patients treated with SGAs and those treated with PSYD monotherapy.
	Overall discontinuation of treatment (48 weeks)	Low	Results from direct comparisons in 1 head-to-head trial indicate that no significant differences exist in overall discontinuation after 48 weeks of followup between patients treated with SGAs and those treated with PSYD monotherapy.
	Overall discontinuation of treatment (96 weeks)	Low	Results from direct comparisons in 1 head-to-head trial indicate that no significant differences exist in overall discontinuation after 96 weeks of followup between patients treated with SGAs and those treated with PSYD monotherapy.
	Suicidal ideas and behavior	Insufficient	Based on 1 trial with few events, the evidence is insufficient to draw conclusions.

Table 30. Summary of findings with strength of evidence: Comparative benefits and harms of second-generation antidepressants and other treatment options as an initial choice for the treatment of patients with major depressive disorders (continued)

Comparison and Outcome of Interest		Strength of Evidence[a]	Findings
SGA versus SGA + PSYD	Functional capacity	Low	Results from 1 trial indicate that no substantial differences in the effects on WAIS-III measures exist between patients treated with SGAs and those treated with SGAs plus PSYD.
	Overall discontinuation of treatment	Low	Results from direct comparisons in 1 head-to-head trial indicate that overall discontinuation is more likely among patients treated with SGAs than those treated with SGAs plus PSYD.
	Suicidal ideas and behavior	Low	Results from direct comparisons based on a single head-to-head trial indicate that no significant differences exist in suicidal ideas and behavior between patients treated with SGAs and those treated with SGAs plus PSYD.
SGA versus third-wave CBT	Remission	Insufficient	Based on 2 trials, the evidence is insufficient to draw conclusions.
	Response	Insufficient	Based on 2 trials, the evidence is insufficient to draw conclusions.
	Overall discontinuation of treatment	Low	Results from direct comparisons in 2 head-to-head trials indicate that overall discontinuation is significantly more likely among patients treated with SGAs than those treated with third-wave CBT.
	Discontinuation of treatment because of adverse events	Low	Results from direct comparisons in 2 head-to-head trials indicate that discontinuation of treatment because of adverse events is significantly more likely among patients treated with SGAs than those treated with third-wave CBT.
	Suicidal ideas and behavior	Insufficient	Based on 1 trial with few events, the evidence is insufficient to draw conclusions.
SGA versus acupuncture monotherapy	Response	Low	Results from direct comparisons based on 2 head-to-head trials, as well as network meta-analysis, indicate that no substantial differences in response exist between patients treated with SGA and those treated with acupuncture monotherapy.
	Overall risk of adverse events: direct evidence	Insufficient	Based on 1 trial with few events, the evidence is insufficient to draw conclusions.
	Overall risk of adverse events: indirect evidence	Moderate	Results from a systematic review of 21 trials indicate that patients treated with SGAs experience a significantly higher overall risk of adverse events than those treated with acupuncture. However, this systematic review of 21 trials did not meet our eligibility criteria because some trials included depressive disorders other than MDD.
	Overall discontinuation of treatment	Insufficient	Based on 1 of 2 available trials with few events, the evidence is insufficient to draw conclusions.

Table 30. Summary of findings with strength of evidence: Comparative benefits and harms of second-generation antidepressants and other treatment options as an initial choice for the treatment of patients with major depressive disorders (continued)

Comparison and Outcome of Interest		Strength of Evidence[a]	Findings
SGA versus SGA + acupuncture	Remission	Low	Results from direct comparisons in 1 head-to-head trial indicate that no substantial differences in remission exist between patients treated with SGAs and those treated with acupuncture combination therapy.
	Response	Low	Results from direct comparisons in 2 head-to-head trials indicate higher response rates for patients treated with SGAs plus acupuncture than patients treated with SGAs alone.
	Overall risk of adverse events	Low	Results from direct comparisons based on 1 head-to-head trial indicate that no significant differences exist in overall risk of adverse events between patients treated with SGAs and those treated with acupuncture plus SGAs.
	Overall discontinuation of treatment	Low	Results from direct comparisons in 2 head-to-head trials indicate that no significant differences exist in overall discontinuation between patients treated with SGAs and those treated with SGAs plus acupuncture.
	Discontinuation of treatment because of adverse events	Low	Results from direct comparisons based on 2 head-to-head trials indicate that no significant differences exist in discontinuation because of adverse events between patients treated with SGAs and those treated with SGAs plus acupuncture.
SGA versus Omega-3 fatty acids monotherapy	Response	Low	Results from network meta-analysis indicate higher response rates for patients treated with SSRIs than for those receiving omega-3 fatty acids.
	Overall discontinuation of treatment	Low	Results from direct comparisons in 1 head-to-head trial indicate that no substantial differences exist in overall discontinuation between patients treated with SGAs and those treated with omega-3 fatty acids.
	Discontinuation of treatment because of adverse events	Low	Results from direct comparisons in 1 head-to-head trial indicate that no substantial differences exist in overall discontinuation between patients treated with SGAs and those treated with omega-3 fatty acids.
	Suicidal ideas and behavior	Insufficient	Based on 1 trial with few events, the evidence is insufficient to draw conclusions.
SGA versus SGAs + Omega-3 fatty acids	Remission	Insufficient	Based on 1 trial, the evidence is insufficient to draw conclusions.
	Response	Insufficient	Based on 2 trials, the evidence is insufficient to draw conclusions.
	Overall discontinuation of treatment	Low	Results from direct comparisons in 2 head-to-head trials indicate that no substantial differences in overall discontinuation between patients treated with SGAs and those with treated with SGAs plus omega-3 fatty acids.
	Discontinuation of treatment because of adverse events	Insufficient	Results from direct comparisons in 1 trial with few events, the evidence is insufficient to draw conclusions.

Table 30. Summary of findings with strength of evidence: Comparative benefits and harms of second-generation antidepressants and other treatment options as an initial choice for the treatment of patients with major depressive disorders (continued)

Comparison and Outcome of Interest		Strength of Evidence[a]	Findings
SGAs versus SAMe monotherapy	Remission	Insufficient	Based on 1 trial, the evidence is insufficient to draw conclusions.
	Response	Low	Results from direct comparisons in 1 trial and our network meta-analysis indicate that no substantial differences in response exist between SGA and SAMe monotherapy.
	Overall discontinuation of treatment	Low	Results from direct comparisons in 1 head-to-head trial indicate that no significant differences exist in overall discontinuation between patients treated with SGAs and those treated with SAMe.
	Discontinuation of treatment because of adverse events	Insufficient	Based on 1 trial with few events, the evidence is insufficient to draw conclusions.
SGA versus St. John's wort monotherapy	Remission	Low	Results from direct comparisons based on 5 head-to-head trials indicate that no substantial differences in remission exist between patients treated with SGA and those treated with St. John's wort monotherapy.
	Response	Low	Results from direct comparisons in 9 head-to-head trials indicate that no apparent differences in response exist between patients treated with SGAs and those treated with St. John's wort monotherapy.
	Overall risk of adverse events	Moderate	Results from direct comparisons in 8 head-to-head trials indicate that patients treated with SGAs experience a significantly higher overall risk of adverse events than those treated with St. John's wort.
	Overall discontinuation of treatment	Moderate	Results from direct comparisons in 9 head-to-head trials indicate that patients treated with SGAs experience significantly higher rates of overall discontinuation than those treated with St. John's wort.
	Discontinuation of treatment because of adverse events	Moderate	Results from direct comparisons in 9 head-to-head trials indicate that patients treated with SGAs experience significantly higher rates of discontinuation because of adverse events than those treated with St. John's wort.
	Serious adverse events	Low	Results from direct comparisons in 4 head-to-head trials indicate that no significant differences exist in the occurrence of serious adverse events between patients treated with SGAs and those treated with St. John's wort.
	Suicidal ideas and behavior	Insufficient	Based on 2 trials with few events, the evidence is insufficient to draw conclusions.
	Subgroup based on older age	Low	Results from 1 trial in older adults indicate similar response rates and discontinuation rates because of adverse events for patients treated with SGAs and those treated with St. John's wort.

111

Table 30. Summary of findings with strength of evidence: Comparative benefits and harms of second-generation antidepressants and other treatment options as an initial choice for the treatment of patients with major depressive disorders (continued)

Comparison and Outcome of Interest		Strength of Evidence[a]	Findings
SGA versus exercise monotherapy	Remission	Low	Results based on direct comparisons in 2 trials reveal no significant difference in remission between patients treated with SGAs and those treated with exercise therapy.
	Response	Low	Estimates based on network meta-analysis reveal no significant difference in response between patients treated with SGAs and those treated with exercise therapy.
	Overall discontinuation of treatment	Low	Results from direct comparisons in 2 head-to-head trials indicate that no significant differences exist in overall discontinuation between patients treated with SGAs and those treated with exercise.
	Discontinuation of treatment because of adverse events	Low	Results from direct comparisons in 2 head-to-head trials indicate that patients treated with SGAs experience significantly higher rates of discontinuation because of adverse events than those treated with exercise.
SGA versus exercise + SGA	Remission	Low	Results based on direct comparison from 1 trial reveal no significant difference in effectiveness between SGA and SGAs plus exercise.
	Overall discontinuation of treatment	Low	Results from direct comparisons in 1 head-to-head trial indicate that no significant differences exist in overall discontinuation between patients treated with SGAs and those treated with SGAs plus exercise.
	Discontinuation of treatment because of adverse events	Low	Results from direct comparisons in 1 head-to-head trial indicate that no significant differences exist in discontinuation because of adverse events between patients treated with SGAs and those treated with SGAs plus exercise.

CBT = cognitive behavioral therapy; IT = integrative therapies; MMD = major depressive disorder; PSYD = psychodynamic therapies; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant; SOE = strength of evidence; SSRI = selective serotonin reuptake inhibitor; third-wave CBT = third-wave cognitive behavioral therapy; vs. = versus
[a]SOE grades (high, moderate, low, or insufficient) are based on methods guidance for the AHRQ EPC program.[83]

For psychotherapies, the available evidence based on 20 randomized controlled trials (RCTs) with 3,000 patients suggests similar beneficial treatment effects of SGAs and psychotherapies, either alone or in combination. Except for SGAs compared with CBT, however, the SOE was low or insufficient, indicating a strong uncertainty associated with these findings.

With respect to risk of harms, SGAs often had higher rates of adverse events or discontinuation rates because of adverse events than psychotherapies. For most of these comparisons, the SOE was also low or insufficient. For example, the evidence was insufficient to draw any conclusions about the comparative risk for serious adverse events. Reasons for low or insufficient SOE grades reflected mainly levels of risk of bias for individual trials and lack of precision of results that encompassed substantial benefits for both interventions.

Many trials had methodological shortcomings such as high dropout rates or lack of blinding of outcome assessors that reduced our confidence in the results. In addition, few trials adequately determined or reported differences in harms. Some comparisons were based on single trials with small sample sizes, which led to indeterminate results because of wide confidence intervals that

encompassed appreciable benefits for both comparators. The best available evidence for psychological interventions with moderate SOE was SGAs compared with CBT monotherapy. We found no statistically significant difference in treatment effects on response or remission in our analysis of trials that we rated as low or medium risk of bias trials, although a sensitivity analysis of remission that included three trials that we rated high risk of bias yielded a result that favored SGAs.

For the comparison of SGAs with CAM interventions, we identified 20 RCTs including 2,600 patients comparing an SGA with one of six CAM therapies for treating patients with MDD. Individual trials faced the same methodological issues as trials for psychological interventions. In addition, all trials of CAM interventions used either moderate or low SGA doses as comparators. We rated nearly half of them as high risk of bias (nine trials). Few trials adequately assessed and reported the risk of harms. Because of the lack of evidence and the methodological limitations of many head-to-head trials, we relied on both direct evidence and network meta-analyses to draw conclusions. With the exception of omega-3 fatty acids, beneficial effects appeared to be similar for SGAs and CAM interventions; however, results for comparisons of SGAs with acupuncture, S-adenosyl-L-methionine (SAMe), and St. John's wort are limited to low SOE, indicating substantial uncertainty of findings. Network meta-analyses resulted in higher response rates for SGAs than omega-3 fatty acids.

Based on two RCTs with low SOE, we found that the beneficial treatment effects of SGAs and exercise, either alone or in combination, were not significantly different. In one trial, patients in the exercise groups reported a slightly lower risk of side effects (diarrhea) than those treated with SGAs.

We did not find any trials on behavior therapy and behavior modification, meditation, or yoga that met our eligibility criteria.

Comparative Benefits and Harms as a Function of Baseline Depressive Severity

The evidence was insufficient to draw any firm conclusions about comparative differences in benefits and harms among interventions of interest as a function of depressive severity. Table 31 summarizes our findings and the respective certainty that we have about these findings, presented as SOE grades (high, moderate, low, or insufficient).[83]

Table 31. Summary of findings with strength of evidence: Variation in effectiveness by severity for second-generation antidepressants compared with other treatments for patients with major depressive disorder

Comparison and Outcome of Interest		Strength of Evidence[a]	Findings
SGA versus CBT monotherapy	Remission	Insufficient	Based on 1 trial, the evidence is insufficient to draw conclusions.
	Response	Insufficient	Based on 1 trial, the evidence is insufficient to draw conclusions.
SGA versus IT monotherapy	Remission	Insufficient	Based on 1 trial, the evidence is insufficient to draw conclusions.
SGA versus Third-wave CBT	Remission	Low	Results from 1 trial with a small sample size indicate that patients with high-severity MDD treated with behavioral activation experience a significantly higher rate of remission than those treated with SGAs, but results did not indicate a difference in remission for patients with low-severity MDD.
	Response	Low	Results from 1 trial with a small sample size indicate that baseline severity exerts no significant difference on response between SGA and behavioral activation.
SGAs versus SAMe	Remission	Insufficient	Based on 1 trial, the evidence is insufficient to draw conclusions.
	Response	Insufficient	Based on 1 trial, the evidence is insufficient to draw conclusions.

AHRQ = Agency for Healthcare Research and Quality; CBT = cognitive behavioral therapy; EPC = Evidence-based Practice Center; IT = integrative therapies; MDD = major depressive disorder; SAMe = S-adenosyl-L-methionine; SGA = second-generation antidepressant; SOE = strength of evidence; third-wave CBT = third-wave cognitive behavioral therapy
[a]SOE grades (high, moderate, low, or insufficient) are based on methods guidance for the AHRQ EPC program.[83]

Comparative Benefits and Harms of Alternative Pharmacological and Nonpharmacological Options for Patients Whose Depression Did Not Achieve Remission Following Initial Treatment With a Second-Generation Antidepressant

Table 32 summarizes our findings and the respective certainty that we have about these findings, presented as SOE grades (high, moderate, low, or insufficient).[83] Comparisons only involved medications and CT; no eligible trials involving CAM or exercise interventions were identified.

Two trials involved 1,992 patients and provided data for four comparisons. All findings suggested little difference in benefit for depression regardless of whether a switch or augmentation strategy was used or whether medications or cognitive therapy (CT) were involved. Both trials suffered from attrition rates of more than 20 percent, and all comparisons other than SGA switch compared with SGA switch were based on data from one study. For all the comparisons except one, the SOE was low, indicating limited confidence that the estimate of effect lies close to the true effect for these outcomes.

Table 32. Summary of findings with strength of evidence: Comparative benefits of second-generation antidepressants and other treatment options as a second-step choice for the treatment of major depressive disorder (KQ 2a)

Comparison and Outcome of Interest		Strength of Evidence[a]	Findings
Switch strategies: SGA switch versus SGA switch	Response	Moderate	Results from 2 direct comparisons involving 1,123 patients indicate no substantial differences in response rates between SGAs.
	Remission	Low	Results from 1 direct comparison involving 727 patients indicate no substantial difference in remission rates between SGAs.
	Decrease in depressive severity	Low	Results from 1 direct comparison involving 727 patients indicate no substantial differences in decrease in depressive severity between SGAs.
	Discontinuation because of adverse events	Moderate	Results from 1 direct comparison involving 727 patients indicate no substantial differences in rates of discontinuation because of adverse events between SGAs.
	Serious adverse events	Low	Results from 1 direct comparison involving 727 patients indicate no substantial differences in rates of serious adverse events between SGAs.
	Suicidal ideas or behavior	Low	Results from 1 direct comparison involving 727 patients indicate no substantial differences in rates of suicidal ideas or behavior between SGAs.
Switch strategies: SGA switch versus CT switch	Response, remission, and change in depressive severity	Low	Results from 1 direct comparison of switching to a different SGA versus switching to CT involving 122 patients indicate no substantial differences in rates of response or remission or in the decrease in depressive severity.
	Discontinuation because of adverse events	Low	Results from 1 direct comparison of switching to a different SGA versus switching to CT involving 122 patients indicate no substantial differences in rates of discontinuation because of adverse events.
	Serious adverse events	Insufficient	Based on 1 trial with few events, the evidence is insufficient to draw conclusions.
Augmentation strategies: SGA augment versus SGA augment	Response and remission	Low	Results from 1 direct comparison involving 565 patients indicate no substantial differences in rates of response or remission between SGAs.
	Decrease in depressive severity	Low	Results from 1 direct comparison involving 565 patients indicate a greater decrease in depressive severity after adding bupropion than buspirone.
	Discontinuation because of adverse events	Moderate	Results from 1 direct comparison involving 565 patients indicate lower rates of discontinuation because of adverse events after adding bupropion than buspirone.
	Serious adverse events	Low	Results from 1 direct comparison involving 565 patients indicate similar rates of serious adverse events after adding bupropion or buspirone.
	Suicidal ideas and behavior	Low	Results from 1 direct comparison involving 565 patients indicate similar rates of suicidal ideas and behavior after adding bupropion or buspirone.

Table 32. Summary of findings with strength of evidence: Comparative benefits of second-generation antidepressants and other treatment options as a second-step choice for the treatment of major depressive disorder (KQ 2a) (continued)

Comparison and Outcome of Interest		Strength of Evidence[a]	Findings
Augmentation strategies: SGA augment versus CT augment	Response, remission, and change in depressive severity	Low	Results from 1 direct comparison involving 182 patients of augmenting with a second medication versus augmenting with CT indicate no substantial differences in rates of response or remission or in the decrease in depressive severity.
	Discontinuation because of adverse events	Low	Results from 1 direct comparison involving 182 patients of augmenting with a second medication versus augmenting with CT indicate no substantial differences in rates of discontinuation because of adverse events.
	Serious adverse events	Low	Results from 1 direct comparison involving 182 patients of augmenting with a second medication versus augmenting with CT indicate no substantial differences in rates of serious adverse events.

CT = cognitive therapy; KQ =Key Question; SGA = second-generation antidepressant; SOE = strength of evidence; vs. = versus
[a]SOE grades (high, moderate, low, or insufficient) are based on methods guidance for the AHRQ EPC program.[83]

Comparative Benefits and Harms of Second-Step Therapies as a Function of Baseline Depressive Severity

The evidence was insufficient to draw any conclusions about differences in benefits and harms among second-step interventions of interest as a function of depressive severity. Table 33 summarizes our findings.

Table 33. Summary of findings with strength of evidence: Second-generation antidepressants compared with other treatments for major depressive disorder—Does effectiveness vary by severity? (KQ 2b)

Comparison and Outcome of Interest		Strength of Evidence[a]	Findings
Switch strategies: SGA switch versus SGA switch	Remission	Insufficient	One industry-supported secondary analysis found an insignificant trend toward difference in remission rates for those with severe depression, while a second government-funded secondary analysis found that having mild/moderate versus severe depression did not modify responses to different SGAs.

KQ = Key Question; SGA = second-generation antidepressant; SOE = strength of evidence; vs. = versus
[a]SOE grades (high, moderate, low, or insufficient) are based on methods guidance for the AHRQ EPC program; outcomes for which we have no studies are designated no evidence.

Findings in Relationship to What Is Already Known

Our findings are consistent with several prior systematic reviews and meta-analyses that compared SGAs with nonpharmacological interventions. Most of these reviews, however, included populations that were not eligible for our review, such as patients with minor depression, bipolar disorder, or dysthymia.

For psychological treatments, one meta-analysis found that serotonin-specific reuptake inhibitors (SSRIs) were more effective than psychotherapy in treating patients with depressive

disorders; however, this effect was small and potentially clinically insignificant.[145] Another meta-analysis found that SGAs and psychotherapy have equivalent efficacy in the short term after 6 to 26 weeks of treatment.[42] Our finding that SGA monotherapy, CBT, interpersonal therapy, and PSYD may all have equivalent effects in the short-term treatment of depressed patients is consistent with those results.

Our results are also consistent with the recommendations of both the American Psychiatric Association[20] and the U.S. Department of Veterans Affairs/Department of Defense.[146] These two groups consider both pharmacotherapy and psychotherapy to be appropriate individual first-step treatments for mild to moderate MDD. Furthermore, they state that pharmacotherapy plus psychotherapy may be a useful initial treatment for patients with moderate to severe MDD and for those with MDD and comorbid conditions. Although our results are consistent with the recommendations from these two entities, a case could be made for preferring psychological interventions as the first-step treatment for patients with mild to moderate MDD because psychological interventions have fewer to no side effects, and cognitive-behavioral interventions may have enduring effects that reduce subsequent risk.[147] Our results diverge from the APA and Department of Veterans Affairs/Department of Defense guidelines in that CBT had similar levels of effectiveness of symptomatic relief as SGAs, suggesting that there is no evidence-based reason to prefer SGAs over empirically supported psychological interventions. Again, this may be especially relevant given that the overall risk for adverse events or discontinuation of treatment because of adverse events, is lower for psychological therapies than with SGAs.

Several reviews have been done of CAM therapies for treating MDD patients; these include an APA Task Force Report, Clinical Guidelines from the Canadian Psychiatric Association, and a systematic review from the U.S. Department of Veterans Affairs.[50,51,148] Additionally, many reviews of individual CAM therapies have been published for the treatment of MDD,[55,144,149,150] including reviews by the Cochrane Collaboration.[48,151,152]

Although one systematic review of acupuncture concluded that it had efficacy comparable with that for antidepressant medications,[144] a Cochrane review[48] and reviews from the American Psychiatric Association, Canadian Network for Mood and Anxiety Treatments, and Department of Veteran Affairs agree that the evidence is insufficient to recommend acupuncture as monotherapy or combination therapy for treating MDD patients. Some reports recognize that risk of harms for acupuncture may be low. Nevertheless, most reports note that current trials often have high risk of bias. Similarly, we found few high-quality trials to support the use of acupuncture for MDD. Nevertheless, we found that a few RCTs, in addition to network meta-analysis, may indicate (a) similar effectiveness for acupuncture monotherapy compared with SGA and (b) better treatment response for a combination of acupuncture with SGA compared with only SGA. However, we concluded that the SOE for these associations was low due to the relative paucity of trials and high risk of bias among those trials we identified. It is also important to note that all trials of acupuncture we identified were conducted in China, where publication bias for trials of acupuncture continues to be problematic.[153,154]

Both the U.S. and Canadian reviews recommend omega-3 fatty acids as augmentation for treating patients with mild to moderate MDD, noting modest evidence of efficacy and low risks of harm. However, a well-done systematic review and meta-analysis comparing omega-3 fatty acids with placebo found only a small, non-significant benefit that was largely attributable to publication bias.[55] Currently, the Cochrane Collaboration is conducting a systematic review on its use for treatment of MDD.[152] Our network meta-analyses clearly favored treatment with SGAs over omega-3 fatty acids monotherapy.

Although the Canadian guidelines recommend the use of SAMe as monotherapy for mild to moderate MDD, the U.S. report calls for more studies to determine its efficacy.[50,51] Most studies of SAMe are limited to parenteral administration of the supplement, which appears to have better efficacy than a placebo.[155] However, few studies evaluate oral preparations, and little is known about optimal SAMe dosing.[149] We found only one trial to evaluate comparative effectiveness and concluded evidence was insufficient to make a recommendation for (or against) use of SAMe.

St. John's wort is perhaps the most commonly evaluated CAM therapy for MDD patients. Both the U.S. and Canadian guidelines recommend St. John's wort for first-step treatment of mild to moderate MDD, whereas there is less consensus on its use for severe MDD. A Cochrane review evaluating 18 RCTs comparing St. John's wort with placebo concluded there was superior efficacy for St. John's wort but noted high heterogeneity among trials. However, their analysis of 17 head-to-head RCTs comparing St. John's wort with both tricyclic antidepressants and SSRIs demonstrated similar treatment effectiveness for patients with mild to moderate MDD.[151] The Cochrane study authors concluded that *"...an attempt at treating mild to moderate major depression with hypericum...is clearly justified."* In contrast, although we found no difference in treatment outcomes between SGAs and St. John's wort, we concluded the SOE supporting these findings was low. Although our analyses used the same studies found in the Cochrane review, there are two important differences in our methods. First, we rated individual study quality using the Cochrane Risk of Bias tool,[75] which was not available to the Cochrane reviewers who instead used a combination of the Jadad and Internal Validity scales. While the Cochrane reviewers noted that *"...the majority of trials were of high quality...,"* we rated several trials as low quality, which were subsequently excluded from our primary analyses. Second, we noted that almost all trials of St. John's wort were conducted using low antidepressant doses,[68,69,156] which led us to decrease the SOE for all treatment outcomes. Although in sensitivity analyses we did not show a difference in outcomes between trials using low versus moderate antidepressant doses, no trial compared St. John's wort to fully adequate antidepressant doses, which might falsely bias our analyses towards concluding there were no treatment differences between the two agents.

Two additional differences between our conclusions and those of the Cochrane review are worth mentioning. First, we noted that participants in included trials had moderate to severe MDD according to reported baseline HAM-D scores. The definitions of depressive severity have varied, with limited empirical research available to define distinctions between mild, moderate, and severe.[69] Our analyses apply definitions of mild, moderate, and severe that compare HAM-D ranges to semistructured interviews and disease severity assessments;[69] these thresholds define our study population as moderate to severe rather than mild to moderate as previously reported. Second, in their review, the Cochrane authors noted that trials conducted in Germany tended to demonstrate more favorable results for St. John's wort compared with trials conducted outside of Germany. However, their analysis held for the placebo trials but not for the direct head-to-head comparisons. Likewise, we did not find any difference in outcomes between head-to-head studies conducted in Germany versus elsewhere. Therefore, we concluded there was no clear bias based on study country. In summary, we concluded that in patients with moderate to severe MDD, we did not show differences in treatment outcomes between SGAs and St. John's wort, but the SOE for these findings is low largely due to moderate to high risk of bias in many studies and comparisons using inadequately dosed antidepressants.

Numerous systematic reviews and meta-analyses have been done on exercise for depression.[49,63,64,157-161] These reviews have examined a variety of types of exercise, including walking, aerobic and nonaerobic forms of movement, and strength training, using randomized and nonrandomized designs and various comparison groups, including no treatment, wait-list controls, and active treatments. Overall, exercise has been found to have a small to moderate clinical benefit when compared with no treatment, wait-list, or placebo and comparable benefit when compared with other active treatments, including SGAs. Our findings are consistent with the recent Cochrane Review by Cooney et al.[49] that included a separate analysis of SGAs versus exercise and found that the SGA (sertraline) was no more effective than exercise for reducing depression. The Cooney et al. report included four studies—we included two in our review and excluded the other two; for the latter, one was excluded because the population was older adults with minor depression rather than MDD[162] and the other because the population was patients with coronary artery disease.[65]

Current literature suggests that depression severity is an important factor to consider when deciding to treat with an antidepressant. In particular, patients with higher severity MDD respond better to medication than those with lower severity depression,[22] possibly because those with low depressive severity respond well to a placebo arm (making it more difficult to detect a statistically significant difference in treatment response between drug and placebo). In any case, based on trials that met the eligibility criteria for our report, we could not draw any firm conclusions about whether depression severity influences the comparative benefits and harms of SGAs and psychological interventions or CAM treatments.

Applicability

The scope of this review was limited to trials that enrolled adult patients with MDD. We did not attempt to review literature on interventions for children with MDD or for patients with subthreshold depression, dysthymia, psychotic depression, or perinatal depression. Because of the serious methodological limitations of some trials, the degree of applicability of some of our findings to real-world settings might be compromised, grades of low or insufficient for SOE also reflect that problem.

The included trials covered populations with mild, moderate, and severe MDD. Most trial populations, however, excluded patients with medical comorbidities or suicidal ideas and behaviors; few trials included elderly patients. Furthermore, most trials were conducted in clinical settings. Results from samples of patients attending a clinic might not apply to members of the general community who suffer from MDD of the same type. Similarly, we did not find evidence to confirm or refute whether treatments are more or less efficacious for various subgroups: patients characterized by sex, race, or ethnicity or individuals with coexisting psychiatric conditions. The samples in many trials had some subjects with the aforementioned subgroup characteristics, even if the main focus was on a different population. For instance, the trials may have included individuals with a history of psychiatric comorbidities but did not report whether interventions were similarly efficacious (or not) for such individuals. Finally, many trials, particularly for CAM interventions, were conducted outside the United States. Whether and how differences in ethnic or cultural backgrounds and health systems affect the applicability of results to U.S. populations remains uninvestigated and unanswered. For example, most of the acupuncture trials were conducted in China, where acupuncture is commonplace, and the effects of acupuncture treatment expectancy may differ substantially between such populations and Western populations.[163]

With few exceptions, interventions in included trials were in line with clinical practice. Except for many CAM trials in which patients received SGA dosages at the lower end of the recommended range, prescribing patterns and doses in the SGA arms of our evidence base were consistent with clinical practice. Some newer SGAs such as desvenlafaxine, levomilnacipran, vilazodone, or vortioxetine, however, have never been compared with psychological or CAM treatments or exercise. Nevertheless, reliable evidence indicates that the comparative effectiveness of SGAs is similar.[33] Consequently, we believe that our findings are applicable across the class of SGAs.

As noted previously, detecting no statistically significant difference does not necessarily mean that the treatment options are equivalent. The studies involved were designed to test whether an outcome for one intervention was different from the outcome for another rather than to test equivalence, which would generally require a larger sample size. This point is especially relevant for those findings with a low SOE. Further, while comparative effectiveness at a group level did not show a difference between SGA and CBT, how best to tailor this information to an individual patient is still not clear. Indeed, other potentially relevant indicators (e.g., depressive severity, comorbid psychiatric illness) may favor one over another, but the current evidence base (as indicated in the KQ 1b and 2b findings) is quite limited.

The number and length of sessions of the various psychological interventions were generally consistent with clinical practice and likely represent an adequate course of treatment. As is generally the case when comparing the effectiveness of psychological treatments with other psychological interventions or other types of treatment, heterogeneity of the content and delivery of the identified intervention is problematic. Many of the psychological interventions in our evidence base provided broad descriptions of the type of intervention; others used a manualized protocol. Both of the included studies that used CBT or CT followed a manualized protocol.

Further, variability among the trials was high with respect to the degree to which treatment fidelity was assessed and adhered to. Type, training, and experience of the providers of the various interventions were also quite heterogeneous. Although clinician characteristics may be less problematic than the content of the intervention for understanding comparative benefits or harms, unlike the case with SGAs that are broadly equivalent and have standardized dosing, the cumulative effect of the various sources of heterogeneity within and across psychological interventions may limit the applicability of our findings. Clinician type, training, experience and degree of treatment fidelity are likely to be even less in routine clinical practice than in the studies included in this review. Along with psychotherapist availability, these are important factors for clinicians to consider when recommending psychological treatment and interventions.

For acupuncture, treatment protocols were so varied as to preclude definitive conclusions about any single acupuncture intervention. For these reasons, we find it difficult to recommend any single type of acupuncture, or acupuncture more generally, as a substitute for treatment with antidepressant medications.

For St. John's wort, use of standardized extracts may be broadly applicable with certain caveats. Although several different St. John's wort preparations were represented among the trials we found, many of the trials used St. John's wort doses that were consistent with current recommendations (i.e., 900 mg daily, standardized to 0.1 percent to 0.3 percent hypericin).[43,44,164] Furthermore, high quality, standardized St. John's wort extracts are now commonly available.

An important concern about the use of St. John's wort is its potential to interact with other medications. St. John's wort is well known to cause substantial changes in plasma concentrations of drugs metabolized by cytochrome P450 3A4, which includes SSRIs, tricyclic antidepressants,

and many drugs used to treat common conditions such as heart disease, hypertension, hypercholesterolemia, HIV, and many cancers.[61,165] Therefore, St. John's wort should not be recommended to patients taking any pharmaceutical medications without the advice of a medical provider or pharmacist with expertise in evaluating herb-drug interactions.

Doses in the exercise arms were within the dose range suggested for exercise programs for middle-age to older adults. For example, the guideline for depression from the National Institute of Health and Care Excellence recommends structured, supervised exercise three times per week.[36] However, the small numbers of trials that have examined dose-response of exercise for depression indicate that higher intensity and frequency of exercise may be more helpful in alleviating depression.[49] Although the two Blumenthal et al. trials, reported reasonable compliance rates for both the SGA and exercise groups, in clinical practice, particularly when exercise is prescribed in less structured formats, depressed patients may well have more difficulty in initiating exercise regimens or staying motivated to exercise, because depression is known to be associated with lower levels of physical activity.[166] Although our report had insufficient data to determine whether depression enhances quality of life, we did find that aerobic capacity increased significantly more among the exercise group. Because both of these trials targeted middle-age and older adults, the results cannot be generalized to younger age groups. Additionally, their generalizability to a typical primary care or psychiatric population of depressed adults is unclear because these trials only included patients free of medical comorbidities that would restrict their ability to follow the prescribed exercise regimens.

Most trials did not assess quality of life or functional capacity as outcomes. Conceivably, response to treatment and remission does also improve quality of life and functional capacity.

The lack of assessment of harms in many trials poses a serious threat to the applicability of findings to typical clinical settings or patient populations. The comparative balance of benefits and harms among treatment options is impossible to determine when harms are not assessed and reported reliably. In clinical trials of SGAs with close adverse events surveillance, up to 60 percent of patients experienced adverse events.[33] For some patients, these adverse effects were tolerable; for others, they led to discontinuation of treatment. In the body of evidence for this report, neither harms for SGAs nor harms for nonpharmacological treatments were assessed adequately. In particular, when studies comparing SGAs with psychotherapy alone or in combination with SGAs reported the occurrence of harms, they only infrequently considered potential harms that can specifically stem from psychotherapy (e.g., increased conflict with partners or negative consequences resulting from behavioral therapy). This limitation of our evidence base reflects a general lack of information about how to classify and measure potential harms that can result from psychotherapy.[167] For these reasons, we could not draw any conclusions about applicability.

Implications for Clinical and Policy Decisionmaking

Our systematic review of head-to-head trials detected no statistically significant differences in effectiveness between an SGA medication or CBT in treating MDD. These findings suggest that either approach can serve as a reasonable starting place for treatment of MDD. We caution, however, that it remains unknown whether the severity of depression should influence decisions about the initial treatment strategy.

Health care reform around the world reflects a trend toward integrative care as a remedy for the current, fragmented delivery of health and social services common in many health care systems. Given that both SGAs and psychotherapies can have equal merit in treating MDD,

locating clinicians who render mental health care in primary care settings needs to be part of this trend. Doing so would likely increase patient access to psychiatric consultation and therapy, and it would enhance coordination of care between primary care clinicians and mental health professionals. Further, we know that approximately 20 percent of patients do not fill their prescriptions for antidepressant medication; even if they start a course of treatment, they may discontinue early before receiving an adequate course.[168] Having access to nonpharmacological interventions in the primary care setting might enhance treatment adherence and improve treatment outcomes for patients with MDD. It may also have additional downstream effects in reducing the stigma associated with mental illness in general, empowering patients to address the symptoms and issues associated with not only depression but also other mental health–related concerns, and encouraging them to seek and maintain treatment more quickly at an earlier stage of their illness.

Related to this, access to psychotherapy should not be financially prohibitive. Some insurance plans in the United States charge different rates for psychotherapy and other mental health services than they do for generalized medical care. Decision- and policymakers need to make sure that fees associated with accessing these interventions do not make them unaffordable for patients that need and would benefit from these services the most.

Similarly, one great difficulty for CAM therapies, for both patients and providers, is how to pay for them. For most patients, their insurers do not cover CAM services. This lack of coverage is particularly vexing for patients and providers, especially when the weight of evidence addresses the efficacy of CAM treatment compared with placebo. In many of these instances, patients need to pay for these treatments out of pocket, which creates disparities in care by limiting access to proven treatments for patients who cannot manage those out-of-pocket costs.[169]

Although SOE is low, findings regarding the lack of statistically significant differences in effectiveness of SGAs and exercise, combined with the low adverse effects generally found in exercise trials, can provide clinicians with some indication as to how to guide their patients in clinical practice. In terms of clinical decisionmaking, the information in this review can be helpful to physicians because they can provide a summary of the available evidence base indicating the advantages and disadvantages of these options, and patients can identify which intervention they would prefer. Some options, such as medication and St. John's wort, would require close physician supervision and monitoring given potential side effects and drug interactions. Moreover, those patients who would like to maintain or start an exercise regimen in addition to undergoing SGA therapy can be encouraged to do so. The enhanced potential for increasing physical well-being as well as expanding social interactions may be an added incentive to encourage an exercise regimen.

Limitations of the Comparative Effectiveness Review Process

To find relevant studies, we employed an intensive search process in multiple electronic databases; we also conducted searches for grey literature. Because of time and monetary limitations, however, we limited eligible studies to those published in English, German, and Italian. Methods research indicates that such an approach can introduce language bias; in general, however, it may also lead to overestimates of the effectiveness of interventions.

For KQ 2, we extended eligibility criteria after we realized that we would not find sufficient evidence to answer this KQ. Despite re-reviewing more than 6,000 abstracts, we could still not

find reliable evidence to address the question about the best treatment option for patients who did not achieve remission during an initial treatment trial.

For harms, studies conducted in other patient populations (e.g., those with subthreshold depression or dysthymia) might have yielded useful information. Many studies using psychological or CAM therapies included populations suffering from any form of depression, not just MDD. In addition, studies with placebo or waiting list control groups could have provided important information about adverse effects of interventions. We lacked the resources to explore such a broad evidence base just to assess harms.

Because we dealt with study-level data, we could not reliably assess the impact of severity of MDD on the comparative benefits and harms of interventions. Such a question would best be addressed with individual patient data from trials and individual patient data meta-analyses.

If information in full-text articles was unclear or missing, we attempted to contact authors for clarification. The yield of this effort, however, was small. Despite multiple attempts to contact authors, few replied or were able to provide missing information.

Finally, publication bias and selective outcome reporting are potential limitations. Although we searched for grey and unpublished literature, the extent and impact of publication and reporting bias in this body of evidence is impossible to determine.

Limitations of the Evidence Base

Overall, several major limitations characterize this body of evidence. First, no reliable evidence was available assessing the effectiveness or risk of harms of many of our eligible interventions. Particularly for KQ 2 on populations who did not achieve response to an initial treatment attempt, we found no eligible switch trials directly comparing SGAs with CAM or exercise; neither did we find any eligible augmentation trials comparing SGAs with CAM or exercise. We also found no direct comparisons of switching strategies versus augmentation strategies. Likewise, the role of depressive severity as a moderator of the comparative effectiveness of both first- and second-step therapies has received very little planned, prospective study.

Second, even when evidence was available, the small number of trials and the small sample sizes posed considerable limitations. Much of the evidence base directly comparing treatments was powered to test whether one treatment was superior to the other. Failure to find such a difference is not equal to concluding that the interventions are equivalent. In addition, for some trials we had concerns about adequate dosing of SGAs. For example, three of eight trials compared St. John's wort to either fluoxetine 20 mg or sertraline 50 mg, the lowest recommended doses of these drugs. Considering that mean baseline depressive severity for most trials fell in the severe range (HAM-D scores 19 to 23), patients in the SGA arms were undertreated. The extent to which this affects the comparative benefits between SGAs and St. John's wort remains unclear.

Third, available evidence was frequently fraught with methodological shortcomings. Of the 44 trials meeting our eligibility criteria, we rated 16 as high risk of bias and only 4 as low risk of bias. Trials assessed as high risk of bias have significant flaws of various types (e.g., stemming from serious errors in design, conduct, or analysis) that may invalidate their results. Consequently, the evidence base for most critical outcomes was insufficient to draw conclusions. The SOE could be rated as low or moderate for only a few outcomes; the latter indicates reasonable confidence in the effect estimates from those trials.

Fourth, even when trials assessing the comparative effectiveness of interventions were available, they often did not assess harms or did not assess harms adequately. Of the 44 included trials, only one trial used an objective scale to assess harms. Most trials combined spontaneous patient-reported adverse events with a regular clinical examination by an investigator. Determining whether assessment methods were unbiased and adequate was often difficult. Rarely did authors report whether adverse events were prespecified and defined. Short trial durations and small sample sizes also limited the validity of adverse event assessment in many trials. No trials were designed to assess specific adverse events as primary outcomes.

Fifth, of the limited body of evidence, most trials were explanatory (i.e., designed to show if a treatment could work in ideal circumstances rather than in everyday practice) rather than pragmatic trials and provided information for the acute phase of treatment. These factors may well compromise the applicability of findings and do not inform management in the continuation or maintenance phases of treatment.

Sixth, few studies explored the role of treatment expectancy on outcomes. In a notable exception, an independent group of researchers reanalyzed the U.S. Hypericum Depression Trial.[92] In this three-arm study comparing sertraline, St. John's wort, and placebo, they concluded participant beliefs regarding treatment assignment were more strongly associated with clinical outcome than the actual treatment received,[170] a finding echoed in other studies of MDD.[171,172] Expectancy may play a larger role for CAM intervention studies conducted in countries where the treatment is commonly accepted, such as acupuncture in China or St. John's wort in Germany. Finally, it was not always clear how the diagnosis of MDD was ascertained in individual studies. Some studies used structured interviews based on DSM criteria, but others did not report the method of ascertainment. Finally, it was not always clear how the diagnosis of MDD was ascertained in individual studies. Some studies used structured interviews based on DSM criteria, but others did not report the method of ascertainment.

Research Gaps

Across all comparisons of interventions, major research gaps pertain to information about patient-centered outcomes, such as functional capacity and quality of life, and the comparative risk of harms. For patients and clinicians, balancing benefits and harms based on objective information is crucial. Lack of information about harms can lead to a biased knowledge base and the potential for decisions that cause more harm than good. Findings from the STAR*D study suggest that factors other than depression severity (e.g., comorbid medical disorders, employment status)[173] contribute significantly to the health-related quality of life of outpatients with MDD. A comprehensive assessment of quality of life outcomes is, therefore, paramount for informed decisions about treatment options.

We found no eligible studies that compared SGAs with behavior therapy or behavior modification, humanistic therapies, yoga, or mindfulness interventions. Given the wide use of these types of psychotherapies in clinical practice, further research into their comparative effectiveness with SGAs in treating MDD patients is desirable. For many psychotherapies and CAM therapies that have been evaluated against an SGA, the data were insufficient because trials did not report important outcomes, most notably quality of life and functional capacity. Future studies should assess remission, response to treatment, quality of life, and functional capacity using standardized measures to allow for more direct comparisons across studies using the same or similar SGAs and psychological interventions.

These same deficiencies in the literature extend to the comparative effectiveness of SGAs and both psychological and CAM interventions for treating MDD as a function of depression

severity. Only a single trial evaluating SAMe and no trials assessing psychological interventions or other CAM therapies were designed to address the question of whether depression severity affects the comparative effectiveness of SGAs as compared with these interventions.

Research comparing an SGA with exercise, either alone or in combination with an SGA, is also limited. We found only two trials comparing SGAs with exercise that met our criteria, and these both used aerobic exercise, in which individuals were assigned continuous walking or jogging that would maintain heart rate from 70 to 85 percent of their heart rate reserve. Missing from the literature were any studies meeting our criteria using other forms of exercise (e.g., strength training or mindful exercises such as yoga, tai chi, or qigong). Moreover, we found no studies in which an SGA was systematically compared with differing intensities and frequencies of exercise (this research could be helpful, because there is indication from non-SGA studies of better treatment outcomes with high-dose versus low-dose exercise regimens).[174] Changes in aerobic capacity were reported in both our included trials; more trials, however, should include standardized measures of quality of life and functional capacity. Having such data might then enable reviewers to compare results across trials. Trials that include a wider age range of participants would also be helpful in determining whether different types and intensities of exercise are more effective for patients of different ages; preferences and usefulness of various types and intensities of exercises may differ by sex or ethnic or cultural variables. Research should also investigate how baseline depression severity affects patient preferences, adherence, and outcomes of prescribing an SGA versus exercise or exercise-SGA combination.

One primary challenge for studies of CAM therapies is defining the proper dose of the therapy being tested. Although experts tend to agree about dosing of St. John's wort,[43,44,164] only scant evidence informs dosing regimens of SAMe, and dosing practices for omega-3 fatty acids differ widely. Future studies of natural products should be based on dosing regimens that are supported by investigations of their pharmacokinetic and dose-response properties. Similar problems exist for acupuncture dosing, but this particular issue is even more complex because of the heterogeneity of point selection, needle stimulation, session duration, and number of treatments for acupuncture interventions.

The limited amount of comparative intervention data addressing whether depressive severity moderates outcomes provides little guidance on how selection of treatment strategies might differ based on whether a depression is on the milder end of the spectrum compared with the more severe end. This question, raised by a number of systematic reviews,[22-24] remains without a clear answer.

Finally, beyond the two articles identified comparing switch and augmentation strategies employing a limited number of medication options or CT, the absence of relevant comparative data about which treatment options are most effective for those needing second-step treatment (about 70 percent of patients with MDD)[26,27] was striking. Further, no second-step therapy data at all exist that compare SGAs with CAM or exercise treatments. This void in the evidence base is a major one that will perplex and confound clinicians, patients, policymakers, and guideline-developers alike.

Conclusions

Available evidence indicates that SGAs and CBT do not differ significantly in effectiveness as first-step treatments for adult outpatients with mild to severe MDD. The SOE for this finding is moderate, which means that the body of evidence has some deficiencies, but we believe that the findings are likely to be stable as new studies emerge. Most comparisons of SGAs with other

treatment options also did not show statistically significant differences. Exceptions, however, are omega-3 fatty acids that appear to have lower effectiveness than SGAs, the combination of SGAs with acupuncture, and the combination of SGAs with interpersonal psychotherapy, which appear to have greater effectiveness than SGA monotherapy. These findings, however, have to be interpreted cautiously because of methodological limitations. Our confidence in these results was low or evidence was simply insufficient. We believe that future studies will have a substantial impact on results. In addition, populations with MDD are known to have high response rates to placebos. For many comparisons that are limited to single trials, determining whether similar treatment effects between SGAs and other interventions are based on similar effectiveness or high placebo response rates is impossible.[175]

Interventions other than SGAs usually have a lower risk for harms. One exception is St. John's wort, which is known to interact with many important medications and should not be taken without the supervision of a provider experienced in its use. It should be noted, however, that treatment side effects appear to be fewer with St. John's wort compared with SGAs. Some nonpharmacological interventions, however, require more personal engagement or costs than others, which could affect patient adherence.

The choice of the initial treatment of MDD should, therefore, consider patient preferences following a discussion of the advantages and disadvantages and the feasibility (e.g. costs, likely adherence) of each treatment option. Differences with respect to adverse events, personal engagement, and costs may be taken into consideration for the choice of a first-step treatment. Such shared and informed decisionmaking might enhance treatment adherence and improve treatment outcomes for patients with MDD, especially because treatment continuity is one of the main challenges in treating such patients.[176]

For second-step therapies, although evidence is limited, no clear benefit emerges to suggest either switching to a particular SGA or to CT or augmenting with a particular medication or CT. Available data suggest that switching to another SGA, switching to CT, or augmenting with a particular medication or cognitive therapy are all reasonable options. The more important decision appears to be simply to try a different evidence-based approach.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Publishing 2013.

2. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003 Jun 18;289(23):3095-105. PMID: 12813115.

3. Khan A, Sambunaris A, Edwards J, et al. Vilazodone in the treatment of major depressive disorder: efficacy across symptoms and severity of depression. Int Clin Psychopharmacol. 2014 Mar;29(2):86-92. PMID: 24247740.

4. Nemeroff CB. The burden of severe depression: a review of diagnostic challenges and treatment alternatives. J Psychiatr Res. 2007 Apr-Jun;41(3-4):189-206. PMID: 16870212.

5. Thase ME. Treatment of severe depression. J Clin Psychiatry. 2000;61 Suppl 1:17-25. PMID: 10703759.

6. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 2013 Nov;10(11):e1001547. PMID: 24223526.

7. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Geneva, Switzerland: Harvard School of Public Health on behalf of the World Health Organization and the World Bank 1996.

8. Fendrich M, Avci O, Johnson TP, et al. Depression, substance use and HIV risk in a probability sample of men who have sex with men. Addict Behav. 2013 Mar;38(3):1715-8. PMID: 23254224.

9. Silberbogen AK, Busby AK, Ulloa EW. Impact of Psychological Distress on Prostate Cancer Screening in U.S. Military Veterans. Am J Mens Health. 2013 Dec 20;8(5):399-408. PMID: 24362494.

10. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000 Jul 24;160(14):2101-7. PMID: 10904452.

11. McLaughlin KA. The public health impact of major depression: a call for interdisciplinary prevention efforts. Prev Sci. 2011 Dec;12(4):361-71. PMID: 21732121.

12. Farmer A, Korszun A, Owen MJ, et al. Medical disorders in people with recurrent depression. Br J Psychiatry. 2008 May;192(5):351-5. PMID: 18450658.

13. Chen YH, Lin HC. Increased risk of cancer subsequent to severe depression--a nationwide population-based study. J Affect Disord. 2011 Jun;131(1-3):200-6. PMID: 21242002.

14. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry. 2003 Dec;64(12):1465-75. PMID: 14728109.

15. Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: The National Academies Press 2001. http://www.nap.edu/openbook.php?record_id=10027.

16. Mojtabai R, Olfson M. National patterns in antidepressant treatment by psychiatrists and general medical providers: results from the national comorbidity survey replication. J Clin Psychiatry. 2008 Jul;69(7):1064-74. PMID: 18399725.

17. Gaynes BN, Rush AJ, Trivedi M, et al. A direct comparison of presenting characteristics of depressed outpatients from primary vs. specialty care settings: preliminary findings from the STAR*D clinical trial. Gen Hosp Psychiatry. 2005 Mar-Apr;27(2):87-96. PMID: 15763119.

18. Gaynes BN, Rush AJ, Trivedi MH, et al. Major depression symptoms in primary care and psychiatric care settings: a cross-sectional analysis. Ann Fam Med. 2007 Mar-Apr;5(2):126-34. PMID: 17389536.

19. Wang PS, Lane M, Olfson M, et al. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):629-40. PMID: 15939840.

20. American Psychiatric Association (APA). Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 3rd ed. Arlington, VA: American Psychiatric Association (APA); Oct 2010. http://www.guideline.gov/content.aspx?id=24158.

21. Qaseem A, Snow V, Denberg TD, et al. ACP clinical guidelines. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008;149(10):725. PMID: 2010112496. Corporate Author: Clinical Efficacy Assessment Subcommittee of American College of Physicians. Language: English. Entry Date: 20090123. Revision Date: 20090123. Publication Type: journal article.

22. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA. 2010 Jan 6;303(1):47-53. PMID: 20051569.

23. 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.

24. Kirsch I, Deacon BJ, Huedo-Medina TB, et al. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008 Feb;5(2):e45. PMID: 18303940.

25. Mitchell AJ, Rao S, Vaze A. Can general practitioners identify people with distress and mild depression? A meta-analysis of clinical accuracy. J Affect Disord. 2011 Apr;130(1-2):26-36. PMID: 20708274.

26. Gaynes BN, Rush AJ, Trivedi MH, et al. Primary versus specialty care outcomes for depressed outpatients managed with measurement-based care: results from STAR*D. J Gen Intern Med. 2008 May;23(5):551-60. PMID: 18247097.

27. Gaynes BN, Lux LJ, Lloyd SW, et al. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Reviews, No. 33. (Prepared by RTI International-University of North Carolina (RTI-UNC) Evidence-based Practice Center under Contract No. 290-02-0016I.). AHRQ Publication No. 11-EHC056-EF. Rockville, MD: Agency for Healthcare Research and Quality; Sep 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm. PMID: 22091472.

28. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006 Nov;163(11):1905-17. PMID: 17074942.

29. Gaynes BN, Warden D, Trivedi MH, et al. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr Serv. 2009 Nov;60(11):1439-45. PMID: 19880458.

30. Mojtabai R, Olfson M. National trends in long-term use of antidepressant medications: results from the US National Health and Nutrition Examination Survey. J Clin Psychiatry. 2014 Feb;75(2):169-77. PMID: 24345349.

31. Kupfer DJ, Perel JM, Pollock BG, et al. Fluvoxamine versus desipramine: comparative polysomnographic effects. Biol Psychiatry. 1991 Jan 1;29(1):23-40. PMID: 1900443.

32. Linde K, Schumann I, Meissner K, et al. Treatment of depressive disorders in primary care--protocol of a multiple treatment systematic review of randomized controlled trials. BMC Fam Pract. 2011;12:127. PMID: 22085705.

33. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med. 2011 Dec 6;155(11):772-85. PMID: 22147715.

34. Gartlehner G, Hansen RA, Morgan LC, et al. Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center, Contract No. 290-2007-10056-I.). AHRQ Publication No. 12-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm. PMID: 22299185.

35. Gartlehner G, Thieda P, Hansen RA, et al. Comparative risk for harms of second-generation antidepressants : a systematic review and meta-analysis. Drug Saf. 2008;31(10):851-65. PMID: 18759509.

36. Health NCCfM. National Institute for Health and Clinical Excellence: Guidance. In: Depression: The Treatment and Management of Depression in Adults (Updated Edition). Leicester (UK): British Psychological Society. Copyright (c) The British Psychological Society & The Royal College of Psychiatrists; 2010.

37. National Guideline Clearinghouse. Non-pharmaceutical management of depression in adults. A national clinical guideline. Rockville MD: Agency for Healthcare Research and Quality (AHRQ). http://www.guideline.gov/content.aspx?id=15596. Accessed 9/19/2014.

38. Gaynes BN, Dusetzina SB, Ellis AR, et al. Treating depression after initial treatment failure: directly comparing switch and augmenting strategies in STAR*D. J Clin Psychopharmacol. 2012 Feb;32(1):114-9. PMID: 22198447.

39. Cuijpers P, van Straten A, Andersson G, et al. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. J Consult Clin Psychol. 2008 Dec;76(6):909-22. PMID: 19045960.

40. Nieuwsma JA, Trivedi RB, McDuffie J, et al. Brief psychotherapy for depression: A systematic review and meta-analysis. Int J Psychiatry Med. 2012;43(2):129-51. PMID: 2012-17351-003. PMID: 22849036. First Author & Affiliation: Nieuwsma, Jason A.

41. Association AP. Recognition of Psychotherapy Effectiveness. 2012. http://www.apa.org/about/policy/resolution-psychotherapy.aspx. Accessed 2/25/15 2015.

42. Spielmans GI, Berman MI, Usitalo AN. Psychotherapy versus second-generation antidepressants in the treatment of depression: A meta-analysis. J Nerv Ment Dis. 2011;199(3):142-9. PMID: 21346483.

43. European Scientific Cooperative on Phytotherapy. E/S/C/O/P monographs : the scientific foundation for herbal medicinal products. Exeter, U.K.; Stuttgart, Germany; New York: European Scientific Cooperative on Phytotherapy; Thieme 2003.

44. Blumenthal M. Herbal Medicine: Expanded Commission E Monographs: Integrative Medicine Communications 2000. http://books.google.com/books?id=Wr9sAAAAMAAJ.

45. Butterweck V. St. John's Wort: Quality Issues and Active Compounds. In: Cooper R, Kronenberg F, eds. Botanical Medicine: From Bench to Bedside. Mary Ann Liebert; 2009:69-91. http://books.google.com/books?id=waYwAQAAMAAJ.

46. Maratos AS, Gold C, Wang X, et al. Music therapy for depression. Cochrane Database Syst Rev. 2008(1):CD004517. PMID: 18254052.

47. Jorm AF, Morgan AJ, Hetrick SE. Relaxation for depression. Cochrane Database Syst Rev. 2008(4):CD007142. PMID: 18843744.

48. Smith CA, Hay PP, Macpherson H. Acupuncture for depression. Cochrane Database Syst Rev. 2010(1):CD004046. PMID: 20091556.

49. Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. Cochrane Database Syst Rev. 2013;9:CD004366. PMID: 24026850.

50. Freeman MP, Fava M, Lake J, et al. Complementary and alternative medicine in major depressive disorder: the American Psychiatric Association Task Force report. J Clin Psychiatry. 2010 Jun;71(6):669-81. PMID: 20573326.

51. Ravindran AV, Lam RW, Filteau MJ, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. V. Complementary and alternative medicine treatments. J Affect Disord. 2009 Oct;117 Suppl 1:S54-64. PMID: 19666194.

52. Linde K, Berner MM, Kriston L. St John's wort for major depression. Cochrane Database Syst Rev. 2008(4):CD000448. PMID: 18843608.

53. Jorm AF, Morgan AJ, Hetrick SE. Relaxation for depression. Cochrane Database Syst Rev. 2008(4):CD007142. PMID: 18843744.

54. Balasubramaniam M, Telles S, Doraiswamy PM. Yoga on our minds: a systematic review of yoga for neuropsychiatric disorders. Front Psychiatry. 2012;3:117. PMID: 23355825.

55. Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. Mol Psychiatry. 2012 Dec;17(12):1272-82. PMID: 21931319.

56. Papakostas GI. Evidence for S-adenosyl-L-methionine (SAM-e) for the treatment of major depressive disorder. J Clin Psychiatry. 2009;70 Suppl 5:18-22. PMID: 19909689.

57. Freeman MP. Complementary and Alternative Medicine (CAM): considerations for the treatment of major depressive disorder. J Clin Psychiatry. 2009;70 Suppl 5:4-6. PMID: 19909686.

58. D'Silva S, Poscablo C, Habousha R, et al. Mind-body medicine therapies for a range of depression severity: A systematic review. Psychosomatics: Journal of Consultation and Liaison Psychiatry. 2012;53(5):407-23. PMID: 2012-24737-003. PMID: 22902090. First Author & Affiliation: D'Silva, Sahana.

59. Hawk C, Ndetan H, Evans MW, Jr. Potential role of complementary and alternative health care providers in chronic disease prevention and health promotion: an analysis of National Health Interview Survey data. Prev Med. 2012 Jan;54(1):18-22. PMID: 21777609.

60. Eisenberg DM, Cohen MH, Hrbek A, et al. Credentialing complementary and alternative medical providers. Ann Intern Med. 2002 Dec 17;137(12):965-73. PMID: 12484712.

61. Mueller SC, Majcher-Peszynska J, Uehleke B, et al. The extent of induction of CYP3A by St. John's wort varies among products and is linked to hyperforin dose. Eur J Clin Pharmacol. 2006 Jan;62(1):29-36. PMID: 16341856.

62. Kessler RC, Soukup J, Davis RB, et al. The use of complementary and alternative therapies to treat anxiety and depression in the United States. Am J Psychiatry. 2001 Feb;158(2):289-94. PMID: 11156813.

63. Rimer J, Dwan K, Lawlor DA, et al. Exercise for depression. Cochrane Database Syst Rev. 2012;7:CD004366. PMID: 22786489.

64. Bridle C, Spanjers K, Patel S, et al. Effect of exercise on depression severity in older people: Systematic review and meta-analysis of randomised controlled trials. Br J Psychiatry. 2012;201(3):180-5. PMID: 22945926.

65. Blumenthal JA, Sherwood A, Babyak MA, et al. Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease: results from the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) study. J Am Coll Cardiol. 2012 Sep 18;60(12):1053-63. PMID: 22858387.

66. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. PMID: 19622551.

67. AHRQ Methods for Effective Health Care. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.

68. Inventory of Depressive Symptomatology (IDS)/Quick Inventory of Depressive Symptomatology (QIDS). Table 4. Estimated comparisons of total scores. Pittsburgh, PA: University of Pittsburgh Epidemiology Data Center2010. http://www.ids-qids.org/index2.html#table4. Accessed April 20, 2015.

69. Zimmerman M, Martinez JH, Young D, et al. Severity classification on the Hamilton Depression Rating Scale. J Affect Disord. 2013 Sep 5;150(2):384-8. PMID: 23759278.

70. Cochrane Depression, Anxiety, and Neurosis Group. CCDAN Topic List: Intervention - Psychological therapies. 2013. http://ccdan.cochrane.org/sites/ccdan.cochrane.org/files/uploads/CCDAN%20topics%20list_psychological%20therapies%20for%20website.pdf. Accessed October 17, 2014.

71. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol. 2011 Apr;64(4):395-400. PMID: 21194891.

72. Wallace BC, Small K, Brodley CE, et al. Deploying an interactive machine learning system in an evidence-based practice center: abstrackr. Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium; 2012 Miami, Florida, USA. ACM; pp. 819-24.

73. Ioannidis JP, Evans SJ, Gotzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 2004 Nov 16;141(10):781-8. PMID: 15545678.

74. Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews AHRQ Publication No. 12-EHC047-EF. Rockville MD: Agency for Healthcare Research and Quality; March 2012. www.effectivehealthcare.ahrq.gov/. PMID: 22479713.

75. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. PMID: 22008217.

76. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27):iii-x, 1-173. PMID: 14499048.

77. Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009 Oct;62(10):1013-20. PMID: 19230606.

78. West SL, Gartlehner G, Mansfield AJ, et al. Comparative Effectiveness Review Methods: Clinical Heterogeneity. Methods Research Report. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center (EPC) under Contract No. 290-2007-10056-I.). AHRQ Publication No. 10-EHC070-EF. Rockville MD: Agency for Healthcare Research and Quality; September 2010. www.effectivehealthcare.ahrq.gov. PMID: 21433337.

79. Hong H, Carlin BP, Shamliyan TA, et al. Comparing Bayesian and frequentist approaches for multiple outcome mixed treatment comparisons. Med Decis Making. 2013 Jul;33(5):702-14. PMID: 23549384.

80. Jones B, Roger J, Lane PW, et al. Statistical approaches for conducting network meta-analysis in drug development. Pharm Stat. 2011 Nov-Dec;10(6):523-31. PMID: 22213533.

81. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess. 2005 Jul;9(26):1-134, iii-iv. PMID: 16014203.

82. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004 Oct 30;23(20):3105-24. PMID: 15449338.

83. Berkman ND, Lohr KN, Ansari M, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Prepared by the RTI-UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I). AHRQ Publication No. 13(14)-EHC130-EF. Rockville MD: Agency for Healthcare Research and Quality; November 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm. PMID: 24404627.

84. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions Methods Guide for Comparative Effectiveness Reviews. AHRQ Publication No. 11-EHC019-EF. Rockville MD: Agency for Healthcare Research and Quality; January 2011. PMID: 21433409.

85. Frank E, Cassano GB, Rucci P, et al. Predictors and moderators of time to remission of major depression with interpersonal psychotherapy and SSRI pharmacotherapy. Psychol Med. 2011 Jan;41(1):151-62. PMID: 20380782.

86. Salminen JK, Karlsson H, Hietala J, et al. Short-term psychodynamic psychotherapy and fluoxetine in major depressive disorder: a randomized comparative study. Psychother Psychosom. 2008;77(6):351-7. PMID: 18701831.

87. David D, Szentagotai A, Lupu V, et al. Rational emotive behavior therapy, cognitive therapy, and medication in the treatment of major depressive disorder: a randomized clinical trial, posttreatment outcomes, and six-month follow-up. J Clin Psychol. 2008 Jun;64(6):728-46. PMID: 18473339.

88. Raue PJ, Schulberg HC, Heo M, et al. Patients' depression treatment preferences and initiation, adherence, and outcome: a randomized primary care study. Psychiatr Serv. 2009 Mar;60(3):337-43. PMID: 19252046.

89. Blom MB, Jonker K, Dusseldorp E, et al. Combination treatment for acute depression is superior only when psychotherapy is added to medication. Psychother Psychosom. 2007;76(5):289-97. PMID: 17700049.

90. Kennedy SH, Konarski JZ, Segal ZV, et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry. 2007 May;164(5):778-88. PMID: 17475737.

91. Sun H, Zhao H, Ma C, et al. Effects of electroacupuncture on depression and the production of glial cell line-derived neurotrophic factor compared with fluoxetine: a randomized controlled pilot study. J Altern Complement Med. 2013 Sep;19(9):733-9. PMID: 23647408.

92. Davidson JRT, Gadde KM, Fairbank JA, et al. Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: a randomized controlled trial. J Am Med Assoc. 2002;287(14):1807-14.

93. Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older patients with major depression. Arch Intern Med. 1999 Oct 25;159(19):2349-56. PMID: 10547175.

94. Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom Med. 2007 Sep-Oct;69(7):587-96. PMID: 17846259.

95. McGrath CL, Kelley ME, Holtzheimer PE, et al. Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatry. 2013 Aug;70(8):821-9. PMID: 23760393.

96. Barber JP, Barrett MS, Gallop R, et al. Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial. J Clin Psychiatry. 2012 Jan;73(1):66-73. PMID: 22152401.

97. Dimidjian S, Hollon SD, Dobson KS, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol. 2006 Aug;74(4):658-70. PMID: 16881773.

98. Segal ZV, Kennedy S, Gemar M, et al. Cognitive reactivity to sad mood provocation and the prediction of depressive relapse. Arch Gen Psychiatry. 2006 Jul;63(7):749-55. PMID: 16818864.

99. DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch Gen Psychiatry. 2005 Apr;62(4):409-16. PMID: 15809408.

100. Miranda J, Chung JY, Green BL, et al. Treating depression in predominantly low-income young minority women: a randomized controlled trial. JAMA. 2003 Jul 2;290(1):57-65. PMID: 12837712.

101. Bastos AG, Guimaraes LS, Trentini CM. Neurocognitive changes in depressed patients in psychodynamic psychotherapy, therapy with fluoxetine and combination therapy. J Affect Disord. 2013 Dec;151(3):1066-75. PMID: 24103853.

102. Hegerl U, Hautzinger M, Mergl R, et al. Effects of pharmacotherapy and psychotherapy in depressed primary-care patients: a randomized, controlled trial including a patients' choice arm. Int J Neuropsychopharmacol. 2010;13(1):31-44. PMID: 19341510.

103. Menchetti M, Rucci P, Bortolotti B, et al. Moderators of remission with interpersonal counselling or drug treatment in primary care patients with depression: randomised controlled trial. Br J Psychiatry. 2014 Feb;204(2):144-50. PMID: 24311553.

104. Mischoulon D, Price LH, Carpenter LL, et al. A double-blind, randomized, placebo-controlled clinical trial of S-adenosyl-L-methionine (SAMe) versus escitalopram in major depressive disorder. J Clin Psychiatry. 2014 Dec 24. PMID: 24500245.

105. Qu SS, Huang Y, Zhang ZJ, et al. A 6-week randomized controlled trial with 4-week follow-up of acupuncture combined with paroxetine in patients with major depressive disorder. J Psychiatr Res. 2013 Jun;47(6):726-32. PMID: 23498306.

106. Gertsik L, Poland RE, Bresee C, et al. Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. J Clin Psychopharmacol. 2012 Feb;32(1):61-4. PMID: 22198441.

107. Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. Am J Psychiatry. 2007 May;164(5):739-52. PMID: 17475733.

108. Lam RW, Parikh SV, Ramasubbu R, et al. Effects of combined pharmacotherapy and psychotherapy for improving work functioning in major depressive disorder. Br J Psychiatry. 2013 Nov;203(5):358-65. PMID: 24029535.

109. Fava M, Alpert J, Nierenberg AA, et al. A double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. J Clin Psychopharmacol. 2005 Oct;25(5):441-7. PMID: 16160619.

110. Szegedi A, Kohnen R, Dienel A, et al. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. BMJ. 2005 Mar 5;330(7490):503. PMID: 15708844.

111. van Gurp G, Meterissian GB, Haiek LN, et al. St John's wort or sertraline? Randomized controlled trial in primary care. Can Fam Physician. 2002 May;48:905-12. PMID: 12053635.

112. Moreno RA, Teng CT, Almeida KM, et al. *Hypericum perforatum* versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample. Rev Bras Psiquiatr. 2006 Mar;28(1):29-32. PMID: 16612487.

113. Brenner R, Azbel V, Madhusoodanan S, et al. Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. Clin Ther. 2000 Apr;22(4):411-9. PMID: 10823363.

114. Schrader E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. Int Clin Psychopharmacol. 2000 Mar;15(2):61-8. PMID: 10759336.

115. Lenox-Smith AJ, Jiang Q. Venlafaxine extended release versus citalopram in patients with depression unresponsive to a selective serotonin reuptake inhibitor. Int Clin Psychopharmacol. 2008 May;23(3):113-9. PMID: 18408525.

116. Dekker JJ, Koelen JA, Van HL, et al. Speed of action: the relative efficacy of short psychodynamic supportive psychotherapy and pharmacotherapy in the first 8 weeks of a treatment algorithm for depression. J Affect Disord. 2008 Jul;109(1-2):183-8. PMID: 18061276.

117. Bjerkenstedt L, Edman GV, Alken RG, et al. Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. Eur Arch Psychiatry Clin Neurosci. 2005 Feb;255(1):40-7. PMID: 15538592.

118. Moradveisi L, Huibers MJ, Renner F, et al. Behavioural activation v. antidepressant medication for treating depression in Iran: randomised trial. Br J Psychiatry. 2013 Mar;202(3):204-11. PMID: 23391727.

119. Shamsaei F, Rahimi A, Zarabian MK, et al. Efficacy of pharmacotherapy and cognitive therapy, alone and in combination in major depressive disorder. Hong Kong J Psychiatr. 2008;18(2):76-80.

120. Jazayeri S, Tehrani-Doost M, Keshavarz SA, et al. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. Aust N Z J Psychiatry. 2008 Mar;42(3):192-8. PMID: 18247193.

121. Mynors-Wallis LM, Gath DH, Day A, et al. Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. BMJ. 2000 Jan 1;320(7226):26-30. PMID: 10617523.

122. Huang Y, Htut W, Li D, et al. Studies on the clinical observation and cerebral glucose metabolism in depression treated by electro-scalp acupuncture compared to fluoxetine. Int J Clin Acupunct. 2005;14(1):7-26. PMID: 0077160.

123. Zhang WJ, Yang XB, Zhong BL. Combination of acupuncture and fluoxetine for depression: a randomized, double-blind, sham-controlled trial. J Altern Complement Med. 2009 Aug;15(8):837-44. PMID: 19678773.

124. Song Y, Zhou D, Fan J, et al. Effects of electroacupuncture and fluoxetine on the density of GTP-binding-proteins in platelet membrane in patients with major depressive disorder. J Affect Disord. 2007 Mar;98(3):253-7. PMID: 16919758.

125. Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study. Pharmacopsychiatry. 2006 Mar;39(2):66-75. PMID: 16555167.

126. Gastpar M, Singer A, Zeller K. Efficacy and tolerability of hypericum extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. Pharmacopsychiatry. 2005 Mar;38(2):78-86. PMID: 15744631.

127. Behnke K, Jensen GS, Graubaum HJ, et al. Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression. Adv Ther. 2002 Jan-Feb;19(1):43-52. PMID: 12008860.

128. Harrer G, Schmidt U, Kuhn U, et al. Comparison of equivalence between the St. John's wort extract LoHyp-57 and fluoxetine. Arzneimittelforschung. 1999 Apr;49(4):289-96. PMID: 10337446.

129. Landenberger NAD. Self-concept and attributional style in the treatment of depression: ProQuest Information & Learning; 2002.

130. Hollon SD, DeRubeis RJ, Fawcett J, et al. Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial. JAMA Psychiatry. 2014 Oct 1;71(10):1157-64. PMID: 25142196.

131. Rucci P, Frank E, Scocco P, et al. Treatment-emergent suicidal ideation during 4 months of acute management of unipolar major depression with SSRI pharmacotherapy or interpersonal psychotherapy in a randomized clinical trial. Depress Anxiety. 2011 Apr;28(4):303-9. PMID: 21308882.

132. Kronstrom K, Salminen JK, Hietala J, et al. Does defense style or psychological mindedness predict treatement response in major depression? Depress Anxiety. 2009;26(7):689-95. PMID: 19496102.

133. Sava FA, Yates BT, Lupu V, et al. Cost-effectiveness and cost-utility of cognitive therapy, rational emotive behavioral therapy, and fluoxetine (Prozac) in treating depression: a randomized clinical trial. J Clin Psychol. 2009 Jan;65(1):36-52. PMID: 19051275.

134. Leykin Y, Amsterdam JD, DeRubeis RJ, et al. Progressive resistance to a selective serotonin reuptake inhibitor but not to cognitive therapy in the treatment of major depression. J Consult Clin Psychol. 2007 Apr;75(2):267-76. PMID: 17469884.

135. Chen JQ, Lin WR, Wang SX, et al. Acupuncture/electroacupuncture enhances antidepressant effect of seroxat: the symptom checklist-90 scores. Neural Regen Res. 2014;9(2):213-22.

136. Papakostas GI, Crawford CM, Scalia MJ, et al. Timing of clinical improvement and symptom resolution in the treatment of major depressive disorder. A replication of findings with the use of a double-blind, placebo-controlled trial of Hypericum perforatum versus fluoxetine. Neuropsychobiology. 2007;56(2-3):132-7. PMID: 18259086.

137. Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: Maintenance of therapeutic benefit. In: Monat A, Lazarus RS, Reevy G, eds. The Praeger handbook on stress and coping. Vol. 2. Westport, CT: Praeger Publishers/Greenwood Publishing Group; 2007:529-40. https://auth.lib.unc.edu/ezproxy_auth.php?url=http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2007-05754-014&site=ehost-live&scope=site.

138. Hoffman BM, Blumenthal JA, Babyak MA, et al. Exercise fails to improve neurocognition in depressed middle-aged and older adults. Med Sci Sports Exerc. 2008 Jul;40(7):1344-52. PMID: 18580416.

139. Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom Med. 2000 Sep-Oct;62(5):633-8. PMID: 11020092.

140. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med. 2006 Mar 23;354(12):1231-42. PMID: 16554525.

141. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med. 2006 Mar 23;354(12):1243-52. PMID: 16554526.

142. Rush AJ, Wisniewski SR, Warden D, et al. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. Arch Gen Psychiatry. 2008 Aug;65(8):870-80. PMID: 18678792.

143. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies. Draft Guidance. Rockville, MD: United States Department of Health and Human Services, Food and Drug Administration 2010.

144. Zhang ZJ, Chen HY, Yip KC, et al. The effectiveness and safety of acupuncture therapy in depressive disorders: systematic review and meta-analysis. J Affect Disord. 2010 Jul;124(1-2):9-21. PMID: 19632725.

145. Cuijpers P, van Straten A, van Oppen P, et al. Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? A meta-analysis of comparative studies. J Clin Psychiatry. 2008 Nov;69(11):1675-85; quiz 839-41. PMID: 18945396.

146. Department of Veteran Affairs, Department of Defense. VA/DoD clinical practice guideline for management of major depressive disorder (MDD). Washington (DC): Department of Veteran Affairs, Department of Defense; May 2009. http://www.healthquality.va.gov/mdd/mdd_full09_c.pdf.

147. Hollon SD, Stewart MO, Strunk D. Enduring effects for cognitive behavior therapy in the treatment of depression and anxiety. Annu Rev Psychol. 2006;57:285-315. PMID: 16318597.

148. Williams JW, Gierisch JM, McDuffie J, et al. An Overview of Complementary and Alternative Medicine Therapies for Anxiety and Depressive Disorders: Supplement to Efficacy of Complementary and Alternative Medicine Therapies for Posttraumatic Stress Disorder. Washington DC; Aug 2011.

149. Papakostas GI, Cassiello CF, Iovieno N. Folates and S-adenosylmethionine for major depressive disorder. Can J Psychiatry. 2012 Jul;57(7):406-13. PMID: 22762295.

150. Rahimi R, Nikfar S, Abdollahi M. Efficacy and tolerability of Hypericum perforatum in major depressive disorder in comparison with selective serotonin reuptake inhibitors: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2009 Feb 1;33(1):118-27. PMID: 19028540.

151. Linde K, Berner Michael M, Kriston L. St John's wort for major depression. Cochrane Database Syst Rev: John Wiley & Sons, Ltd; 2008.

152. Appleton KM, Perry R, Sallis H, et al. Omega-3 fatty acids for depression in adults (Protocol). Cochrane Database Syst Rev. 2014(5).

153. Vickers A, Goyal N, Harland R, et al. Do certain countries produce only positive results? A systematic review of controlled trials. Control Clin Trials. 1998 Apr;19(2):159-66. PMID: 9551280.

154. Zhang D, Freemantle N, Cheng KK. Are randomized trials conducted in China or India biased? A comparative empirical analysis. J Clin Epidemiol. 2011 Jan;64(1):90-5. PMID: 20554429.

155. Hardy ML, Coulter I, Morton SC, et al. S-adenosyl-L-methionine for treatment of depression, osteoarthritis, and liver disease. Evidence Report/Technology Assessment No. 64. AHRQ Publication No. 02-E034. Rockville, MD: Agency for Healthcare Quality and Research; August 2002. PMID: 12899148.

156. Hansen RA, Moore CG, Dusetzina SB, et al. Controlling for drug dose in systematic review and meta-analysis: A case study of the effect of antidepressant dose. Med Decis Making. 2009;29(1):91-103. PMID: 2009-03041-007. PMID: 19141788. First Author & Affiliation: Hansen, Richard A.

157. Robertson R, Robertson A, Jepson R, et al. Walking for depression or depressive symptoms: A systematic review and meta-analysis. Mental Health and Physical Activity. 2012;5(1):66-75.

158. Krogh J, Nordentoft M, Sterne JAC, et al. The effect of exercise in clinically depressed adults: Systematic review and meta-analysis of randomized controlled trials. J Clin Psychiatry. 2011;72(4):529-38. PMID: 21034688.

159. Schuch FB, Vasconcelos-Moreno MP, Fleck MP. The impact of exercise on quality of life within exercise and depression trials: A systematic review. Mental Health and Physical Activity. 2011;4(2):43-8.

160. Daley A. Exercise and depression: A review of reviews. J Clin Psychol Med Settings. 2008;15(2):140-7. PMID: 19104978.

161. Mura G, Moro MF, Patten SB, et al. Exercise as an add-on strategy for the treatment of major depressive disorder: a systematic review. CNS Spectr. 2014 Mar 3:1-13. PMID: 24589012.

162. Brenes GA, Williamson JD, Messier SP, et al. Treatment of minor depression in older adults: a pilot study comparing sertraline and exercise. Aging Ment Health. 2007 Jan;11(1):61-8. PMID: 17164159.

163. Linde K, Witt CM, Streng A, et al. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. Pain. 2007 Apr;128(3):264-71. PMID: 17257756.

164. Bradley PR, Association BHM. British Herbal Compendium: A Handbook of Scientific Information on Widely Used Plant Drugs: British Herbal Medicine Association 2006. http://books.google.com/books?id=lrUFBA AACAAJ.

165. Russo E, Scicchitano F, Whalley BJ, et al. Hypericum perforatum: pharmacokinetic, mechanism of action, tolerability, and clinical drug-drug interactions. Phytother Res. 2014 May;28(5):643-55. PMID: 23897801.

166. Goodwin RD. Association between physical activity and mental disorders among adults in the United States. Prev Med. 2003;36(6):698-703. PMID: 12744913

167. Linden M. How to define, find and classify side effects in psychotherapy: from unwanted events to adverse treatment reactions. Clin Psychol Psychother. 2013 Jul-Aug;20(4):286-96. PMID: 22253218.

168. Xing S, Dipaula BA, Lee HY, et al. Failure to fill electronically prescribed antidepressant medications: a retrospective study. Prim Care Companion CNS Disord. 2011;13(1)PMID: 21731832.

169. Wu C-H, Wang C-C, Tsai M-T, et al. Trend and Pattern of Herb and Supplement Use in the United States: Results from the 2002, 2007, and 2012 National Health Interview Surveys. Evid Based Complement Alternat Med. 2014;2014:7.

170. Chen JA, Papakostas GI, Youn SJ, et al. Association between patient beliefs regarding assigned treatment and clinical response: reanalysis of data from the Hypericum Depression Trial Study Group. J Clin Psychiatry. 2011 Dec;72(12):1669-76. PMID: 22053942.

171. Sotsky SM, Glass DR, Shea MT, et al. Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatry. 1991 Aug;148(8):997-1008. PMID: 1853989.

172. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol. 2009;19(1):34-40.

173. Daly EJ, Trivedi MH, Wisniewski SR, et al. Health-related quality of life in depression: a STAR*D report. Ann Clin Psychiatry. 2010 Feb;22(1):43-55. PMID: 20196982.

174. Trivedi MH, Greer TL, Church TS, et al. Exercise as an augmentation treatment for nonremitted major depressive disorder: A randomized, parallel dose comparison. J Clin Psychiatry. 2011;72(5):677-84.

175. Mancini M, Wade AG, Perugi G, et al. Impact of patient selection and study characteristics on signal detection in placebo-controlled trials with antidepressants. J Psychiatr Res. 2014;51:21-9. PMID: 24462042

176. Melartin TK, Rytsala HJ, Leskela US, et al. Continuity is the main challenge in treating major depressive disorder in psychiatric care. J Clin Psychiatry. 2005 Feb;66(2):220-7. PMID: 15705008.

Appendix A. Search Strategy

RTI MDD Search Strategy

Pubmed 02.05.2014

Search	Query	Items found
#1	Search ("Bupropion"[Mesh] OR "Bupropion"[tiab] OR 34911-55-2[rn])	3570
#2	Search ("Citalopram"[Mesh] OR "Citalopram"[tiab] OR 59729-33-8[rn])	5061
#3	Search ("Escitalopram"[tiab] OR 128196-01-0[rn])	4031
#4	Search ("O-desmethylvenlafaxine" [Supplementary Concept] OR Desvenlafaxine[tiab] OR 93413-62-8[rn])	234
#5	Search ("Fluoxetine"[Mesh] OR "Fluoxetine"[tiab] OR 54910-89-3[rn])	10911
#6	Search ("Fluvoxamine"[Mesh] OR "Fluvoxamine"[tiab] OR 54739-18-3[rn])	2551
#7	Search (("milnacipran"[Supplementary Concept] OR "Levomilnacipran"[tiab] OR 96847-54-0[rn]))	346
#8	Search ("mirtazapine"[Supplementary Concept] OR "mirtazapine"[tiab] OR 85650-52-8[rn])	1574
#9	Search ("nefazodone"[Supplementary Concept] OR "nefazodone"[tiab] OR 82752-99-6[rn])	706
#10	Search ("Paroxetine"[Mesh] OR "Paroxetine"[tiab] OR 61869-08-7[rn])	5220
#11	Search ("Sertraline"[Mesh] OR "Sertraline"[tiab] OR 79617-96-2[rn])	3732
#12	Search ("Trazodone"[Mesh] OR "Trazodone"[tiab] OR 19794-93-5[rn])	1685
#13	Search ("venlafaxine"[Supplementary Concept] OR "venlafaxine"[tiab] OR 93413-69-5[rn])	3124
#14	Search ("vilazodone"[Supplementary Concept] OR "vilazodone"[tiab] OR 163521-12-8[rn])	65
#15	Search ("vortioxetine"[Supplementary Concept] OR "vortioxetine"[tiab] OR 508233-74-7[rn])	50
#16	Search ("Antidepressive Agents, Second-Generation"[Mesh] OR "Antidepressive Agents, Second-Generation"[Pharmacological Action])	57579
#17	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)	67046
#18	Search ("Psychotherapy"[Mesh] OR psychotherap*[tiab])	156412
#19	Search (Acceptance and Commitment Therap*[tiab] OR Cognitive Therap*[tiab] OR Cognitive behavioral Therap*[tiab] OR interpersonal therap*[tiab] OR psychodynamic therap*[tiab] OR behavioral therap*[tiab])	8028
#20	Search (#18 OR #19)	158665
#21	Search "Hypericum"[Mesh] OR "Hypericum"[tiab] OR "St. Johns Wort"[tiab] OR "Saint Johns Wort"[tiab] OR "St. John's Wort"[tiab] OR "Saint John's Wort"[tiab] OR LI160[tiab] OR LI160[tiab] OR WS5572[tiab] OR WS5573[tiab] OR LoHyp-57[tiab]	2591
#22	Search "s adenosyl l methionine"[tiab] OR "s adenosylmethionine"[tiab] OR "S-Adenosylmethionine"[Mesh]	8814
#23	Search "Fatty Acids, Omega-3"[Mesh] OR (omega 3[tiab] AND fatty acid*[tiab]) OR fish oil[tiab] OR flax seed[tiab] OR borage seed[tiab] OR Borago[tiab] OR evening primrose[tiab] OR Oenothera[tiab] OR eicosapentaenoic acid[tiab] OR PUFA[tiab]	27732
#24	Search "Acupuncture"[Mesh] OR "Acupuncture Therapy"[Mesh] OR Acupuncture[tiab] OR Electroacupuncture[tiab]	20337
#25	Search "Yoga"[Mesh] OR yoga[tiab]	2387
#26	Search "Meditation"[Mesh] OR meditation[tiab] OR mindfulness[tiab]	4174
#27	Search ("Exercise"[Mesh] OR physical activit*[tiab] OR "physical exercise"[tiab])	159734
#28	Search (#22 OR #23 OR #24 OR #25 OR #26 OR #27)	221143
#29	Search ("Depressive Disorder, Major"[MeSH] OR "major depressive disorder"[tiab] OR "major depression"[tiab])	35489
#30	Search (#29 AND (#28 OR #20 OR #17))	7950
#31	Search (systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR "research synthesis"[tiab] OR "research	241160

Search	Query	Items found
	integration"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR "meta-analysis as topic"[mh] OR "Meta-Analysis"[pt] OR ("review"[tiab] AND ("rationale"[tiab] OR "evidence"[tiab]) AND review[pt]) OR "Systematic Review"[tiab] OR ("Review"[Publication Type] AND "systematic"[tiab])	
#32	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH] OR "Randomized Controlled Trial"[tiab] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	542163
#33	Search (("cohort studies"[MeSH] OR cohort stud*[tiab] OR cohort analy*[tiab] OR "Case-Control Studies"[Mesh] OR case control stud*[tiab] OR observational stud*[tiab] OR "observational study"[pt] OR ((longitudinal[tiab] OR retrospective[tiab] OR prospective[tiab]) AND (study[tiab] OR trial[tiab]))) AND ("Comparative Study"[pt] OR comparison[tiab] OR comparative[tiab]))	349594
#34	Search ("Controlled Clinical Trial"[pt] OR "Controlled Clinical Trials as Topic"[Mesh] OR controlled clinical trial*[tiab] OR controlled trial*[tiab] OR controlled stud*[tiab])	319105
#35	Search (#30 AND (#31 OR #32 OR #33 OR #34))	3642
#36	Search ("Animals"[Mesh] NOT "Humans"[Mesh])	3882887
#37	Search (#35 NOT #36)	3635
#38	Search ("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh]	1490657
#39	Search (#37 NOT #38)	3398
#40	Search #39 AND 1990:2014[dp] AND (english[la] OR german[la] OR italian[la])	3231

Addendum duloxetine 07.05.2014

Search	Query	Items found
#1	Search ("duloxetine" [Supplementary Concept] OR duloxetine[tiab])	1677
#2	Search ("Depressive Disorder, Major"[MeSH] OR "major depressive disorder"[tiab] OR "major depression"[tiab])	35518
#3	Search (#1 AND #2)	430
#4	Search ((systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR "research synthesis"[tiab] OR "research integration"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR "meta-analysis as topic"[mh] OR "Meta-Analysis"[pt] OR ("review"[tiab] AND ("rationale"[tiab] OR "evidence"[tiab]) AND review[pt]) OR "Systematic Review"[tiab] OR ("Review"[Publication Type] AND "systematic"[tiab]))	241577
#5	Search (("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH] OR "Randomized Controlled Trial"[tiab] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]))	542686
#6	Search ((("cohort studies"[MeSH] OR cohort stud*[tiab] OR cohort analy*[tiab] OR "Case-Control Studies"[Mesh] OR case control stud*[tiab] OR observational stud*[tiab] OR "observational study"[pt] OR ((longitudinal[tiab] OR retrospective[tiab] OR prospective[tiab]) AND (study[tiab] OR trial[tiab]))) AND ("Comparative Study"[pt] OR comparison[tiab] OR comparative[tiab])))	349872
#7	Search (("Controlled Clinical Trial"[pt] OR "Controlled Clinical Trials as Topic"[Mesh] OR controlled clinical trial*[tiab] OR controlled trial*[tiab] OR controlled stud*[tiab]))	319351
#8	Search (#3 AND (#7 OR #6 OR #5 OR #4))	234
#9	Search (("Animals"[Mesh] NOT "Humans"[Mesh]))	3884483
#10	Search (#8 NOT #9)	234
#11	Search (("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh])	1491426
#12	Search (#10 NOT #11)	234
#13	Search (#12 AND 1990:2014[dp] AND (english[la] OR german[la] OR italian[la]))	229

Cochrane Library 02.05.2014

ID	Search	Hits
#1	[mh Bupropion] or "Bupropion":ti,ab	934
#2	[mh Citalopram] or "Citalopram":ti,ab	1196
#3	Escitalopram:ti,ab	588
#4	Desvenlafaxine:ti,ab	71
#5	[mh Fluoxetine] or "Fluoxetine":ti,ab	2364
#6	[mh Fluvoxamine] or "Fluvoxamine":ti,ab	687
#7	Levomilnacipran:ti,ab	12
#8	mirtazapine:ti,ab	439
#9	nefazodone:ti,ab	194
#10	[mh Paroxetine] or "Paroxetine":ti,ab	1770
#11	[mh Sertraline] or "Sertraline":ti,ab	1350
#12	[mh Trazodone] or "Trazodone":ti,ab	335
#13	venlafaxine:ti,ab	989
#14	vilazodone:ti,ab	19
#15	vortioxetine:ti,ab	13
#16	[mh "Antidepressive Agents, Second-Generation"]	1230
#17	{or #1-#16}	9063
#18	[mh Psychotherapy] or psychotherap*:ti,ab	17066
#19	(Acceptance near/2 Commitment next Therap*):ti,ab or (Cognitive near/2 Therap*):ti,ab or ((interpersonal or psychodynamic or behavioral) next therap*):ti,ab	5015
#20	#18 or #19	19087
#21	[mh yoga] or yoga:ti,ab	688
#22	[mh meditation] or (meditation or mindfulness):ti,ab	1064
#23	[mh Acupuncture] or [mh "Acupuncture Therapy"] or (Acupuncture or Electroacupuncture):ti,ab	7130
#24	[mh Hypericum] or "Hypericum":ti,ab or (john* next wort):ti,ab or (LI160 or WS5572 or WS5573 or LoHyp-57):ti,ab	295
#25	("s adenosyl l methionine" or "s adenosylmethionine"):ti,ab or [mh S-Adenosylmethionine]	191
#26	[mh "fatty Acids, Omega-3"] or (omega-3 and fatty next acid*):ti,ab or ("fish oil" or "flax seed" or "borage seed" or Borago or "evening primrose" or Oenothera or "eicosapentaenoic acid" or PUFA):ti,ab	3661
#27	[mh Exercise] or (physical next (activit* or exercise)):ti,ab	18551
#28	{or #21-#27}	31146
#29	[mh "Depressive Disorder, Major"] or "major depressive disorder":ti,ab or (major next/1 depress*):ti,ab	6406
#30	#29 and (#17 or #20 or #28)	3544
#31	#30 Publication Date from 1990 to 2014	3460
#32	([mh infant] or [mh child] or [mh adolescent]) not [mh adult]	88056
#33	#31 not #32	2867
#34	#31 and (adult or adults):ti,ab	393
#35	#33 or #34	2945
#36	[mh animals] not [mh humans]	5655
#37	#35 not #36 in Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	2940
#38	(review:pt and systematic:ti,ab) or "systematic review"	37971
#39	meta-analysis:pt or (meta next analy*):ti,ab or metaanaly*:ti,ab or [mh Meta-Analysis] or [mh "Meta-Analysis as Topic"]	20924
#40	[mh "Randomized Controlled Trial"] or [mh "Randomized Controlled Trial as topic"] or "randomized controlled trial":pt or [mh "single-blind method"] or [mh "double-blind method"] or [mh "random allocation"] or (randomi?ed next controlled next "trial"):ti,ab	377221
#41	[mh "Controlled Clinical Trial"] or [mh "Controlled Clinical Trials as Topic"] or (controlled next/2 (trial or study)):ti,ab	149716
#42	([mh "cohort studies"] or (cohort next stud*):ti,ab or [mh "case-control studies"] or (case-control next stud*):ti,ab or (observational next stud*):ti,ab or "observational	51743

ID	Search	Hits
	study":pt or ((observational or longitudinal or retrospective) near/2 (study or trial)):ti,ab) and ("comparative study":pt or [mh "Comparative Study"] or comparison:ti,ab or comparative:ti,ab)	
#43	{or #38-#42}	458686
#44	#37 and #43 in Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	2000

Addendum duloxetine 07.05.2014

No.	Query	Results
#30	[mh "Depressive Disorder, Major"] or "major depressive disorder":ti,ab or (major next/1 depress*):ti,ab	6406
#31	#30 and "duloxetine":ti,ab	163
#32	#31 Publication Date from 1990 to 2014	163
#33	([mh infant] or [mh child] or [mh adolescent]) not [mh adult]	88056
#34	#32 not #33	143
#35	#32 and (adult or adults):ti,ab	29
#36	#34 or #35	149
#37	[mh animals] not [mh humans]	5655
#38	#36 not #37 in Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	149
#39	[mh "Randomized Controlled Trial"] or [mh "Randomized Controlled Trial as topic"] or "randomized controlled trial":pt or [mh "single-blind method"] or [mh "double-blind method"] or [mh "random allocation"] or (randomi?ed next controlled next "trial"):ti,ab	377221
#40	[mh "Controlled Clinical Trial"] or [mh "Controlled Clinical Trials as Topic"] or (controlled next/2 (trial or study)):ti,ab	149722
#41	#38 and (#39 or #40) in Trials	87
#42	#38 in Other Reviews	8
#43	#42 or #41	95

EMBASE 06.05.2014

No.	Query	Results
#1.1	'amfebutamone'/exp OR bupropion:tn,ab,ti OR '34911 55 2':rn	
#1.2	'citalopram'/exp OR citalopram:tn,ab,ti OR '59729 33 8':rn OR 'escitalopram'/exp OR escitalopram:tn,ab,ti OR '128196 01 0':rn	
#1.3	'desvenlafaxine'/exp OR desvenlafaxine:tn,ab,ti OR '93413 62 8':rn	
#1.4	'fluoxetine'/exp OR fluoxetine:tn,ab,ti OR '54910 89 3':rn	
#1.5	'fluvoxamine'/exp OR fluvoxamine:tn,ab,ti OR '54739 18 3':rn	
#1.6	'milnacipran'/exp OR levomilnacipran:tn,ab,ti OR '96847 54 0':rn	
#1.7	'mirtazapine'/exp OR mirtazapine:tn,ab,ti OR '85650 52 8':rn	
#1.8	'nefazodone'/exp OR nefazodone:tn,ab,ti OR '82752 99 6':rn	
#1.9	'paroxetine'/exp OR paroxetine:tn,ab,ti OR '61869 08 7':rn	
#1.10	'sertraline'/exp OR sertraline:tn,ab,ti OR '79617 96 2':rn	
#1.11	'trazodone'/exp OR trazodone:tn,ab,ti OR '19794 93 5':rn	
#1.12	'venlafaxine'/exp OR venlafaxine:tn,ab,ti OR '93413 69 5':rn	
#1.13	'vilazodone'/exp OR vilazodone:tn,ab,ti OR '163521 12 8':rn	
#1.14	'vortioxetine'/exp OR vortioxetine:tn,ab,ti OR '508233 74 7':rn	
#1.15	'antidepressant agent'/exp AND 'second generation':ab,ti	
#1.16	#1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9 OR #1.10 OR #1.11 OR #1.12 OR #1.13 OR #1.14 OR #1.15	87062
#1.17	'psychotherapy'/exp	187201
#1.18	((acceptance OR cognitive OR interpersonal OR psychodynamic OR behavioral) NEXT/3 (therapy OR therapies OR psychotherapy)):ab,ti	20374

No.	Query	Results
#1.19	#1.17 OR #1.18 AND 'treatment outcome'/exp	25169
#1.20	'hypericum'/exp OR hypericum:ab,ti OR (john* NEXT/1 wort):ab,ti OR li160:ab,ti OR ws5572:ab,ti OR ws5573:ab,ti OR 'lohyp 57':ab,ti	4193
#1.21	's adenosylmethionine'/exp OR 's adenosylmethionine' OR 's adenosyl l methionine':ab,ti OR 's adenosylmethionine':ab,ti	10557
#1.22	'omega 3 fatty acid'/exp OR ('omega 3':ab,ti AND acid*:ab,ti) OR 'fish oil':ab,ti OR 'flax seed':ab,ti OR 'borage seed':ab,ti OR borago:ab,ti OR 'evening primrose':ab,ti OR oenothera:ab,ti OR 'eicosapentaenoic acid':ab,ti OR pufa:ab,ti	34034
#1.23	'acupuncture'/exp OR acupuncture:ab,ti OR electroacupuncture:ab,ti	33369
#1.24	'yoga'/exp OR yoga:ab,ti	4138
#1.25	'meditation'/exp OR meditation:ab,ti OR mindfulness:ab,ti	6584
#1.26	'exercise'/exp	209232
#1.27	#1.20 OR #1.21 OR #1.22 OR #1.23 OR #1.24 OR #1.25 OR #1.26 AND 'treatment outcome'/exp	19807
#1.28	'major depression'/exp OR 'major depressive disorder':ab,ti OR (major NEXT/2 depress*):ab,ti	52013
#1.29	#1.28 AND (#1.27 OR #1.19 OR #1.16)	13000
#1.30	'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review':ab,ti OR (meta NEXT/1 analy*):ab,ti OR metaanaly*:ab,ti OR (review:it AND systematic:ab,ti) OR (systematic:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti OR review:ab,ti OR reviewed:ab,ti OR reviews:ab,ti)) OR 'research synthesis':ab,ti OR 'research integration':ab,ti OR (comprehensive*:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti)) OR (review:it AND review:ab,ti AND (rationale:ab,ti OR evidence:ab,ti))	287380
#1.31	'randomized controlled trial'/exp OR (randomi?ed NEXT/1 'controlled trial'):ab,ti OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomization'/exp OR 'random allocation':ab,ti OR (allocated NEXT/2 random*):ab,ti	441315
#1.32	'cohort analysis'/exp OR 'case control study'/exp OR 'observational study'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR (cohort NEXT/1 (stud* OR analy*)):ab,ti OR (observational OR 'case control') NEXT/1 stud* OR ((longitudinal OR retrospective OR prospective) NEXT/2 (trial OR study)):ab,ti AND ('comparative study'/exp OR comparative:ab,ti OR comparison:ab,ti)	149667
#1.33	'controlled clinical trial'/exp OR (controlled NEXT/2 (trial* OR stud*)):ab,ti	591400
#1.34	#1.29 AND (#1.30 OR #1.31 OR #1.32 OR #1.33)	
#1.35	'human'/exp	14753345
#1.36	#1.34 AND #1.35	4575
#1.37	'adult'/exp	5294678
#1.38	#1.36 AND #1.37	2399
#1.39	#1.38 AND [1990-2014]/py	2374
#1.40	#1.39 AND [english]/lim	2316
#1.41	#1.39 AND (german:la OR italian:la)	17
#1.42	#1.40 OR #1.41	2333
#1		2333
#2	#1 AND [embase]/lim	2232

Addendum duloxetine 07.05.2014

No.	Query	Results
#6	'randomized controlled trial'/exp OR (randomi?ed NEXT/1 'controlled trial'):ab,ti OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomization'/exp OR 'random allocation':ab,ti OR (allocated NEXT/2 random*):ab,ti	441315
#7	'cohort analysis'/exp OR 'case control study'/exp OR 'observational study'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR (cohort NEXT/1 (stud* OR analy*)):ab,ti OR (observational OR 'case control') NEXT/1 stud* OR ((longitudinal OR retrospective OR prospective) NEXT/2 (trial OR study)):ab,ti AND ('comparative study'/exp OR comparative:ab,ti OR comparison:ab,ti)	149667
#8	'controlled clinical trial'/exp OR (controlled NEXT/2 (trial* OR stud*)):ab,ti	591400
#9	#5 OR #6 OR #7 OR #8	1017694
#10	#4 AND #9	582
#11	#10 AND 'human'/exp AND 'adult'/exp	210
#12	#11 AND [1990-2014]/py AND [embase]/lim	205
#13	#12 AND ([english]/lim OR german:la OR italian:la)	205

CINAHL (via Ebsco) 02.05.2014

#	Query	Results
S1	(MH "Bupropion") OR "Bupropion"	1,072
S2	(MH "Citalopram") OR "Citalopram"	644
S3	"Escitalopram"	202
S4	(MH "Desvenlafaxine Succinate") OR TX Desvenlafaxine	49
S5	(MH "Fluoxetine+") OR "Fluoxetine"	1,144
S6	(MH "Fluvoxamine Maleate") OR "Fluvoxamine"	145
S7	"Levomilnacipran"	5
S8	(MH "Mirtazapine") OR "mirtazapine"	255
S9	(MH "Nefazodone") OR "nefazodone"	68
S10	(MH "Paroxetine") OR "Paroxetine"	732
S11	(MH "Sertraline Hydrochloride") OR "Sertraline"	643
S12	(MH "Trazodone") OR "Trazodone"	168
S13	(MH "Venlafaxine+") OR "venlafaxine"	605
S14	"vilazodone"	11
S15	"vortioxetine"	5
S16	(MH "Antidepressive Agents, Second Generation+")	2,806
S17	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	4,599
S18	(MH "Psychotherapy+") OR (TI psychotherap*) OR (AB psychotherap*)	86,97
S19	TI (("Acceptance and Commitment" OR cognitive OR behavioral OR psychodynamic OR interpersonal) N2 therap*) OR AB (("Acceptance and Commitment" OR cognitive OR behavioral OR psychodynamic OR interpersonal) N2 therap*)	4,172
S20	S18 OR S19	87,95
S21	(MH "Yoga+") OR (TI yoga) OR (AB yoga)	2,268
S22	(MH "Meditation") OR (TI (meditation OR mindfulness)) OR (AB (meditation OR mindfulness))	2,652
S23	(MH "St. John's Wort") OR "hypericum" OR (TI john* N2 wort) OR (AB john* N2 wort) OR (TI (LI160 OR WS5572 OR WS5573 OR LoHyp-57)) OR (AB (LI160 OR WS5572 OR WS5573 OR LoHyp-57))	932
S24	(MH "Fatty Acids, Omega-3+") OR (TI "omega 3" N1 fatty acid*) OR (AB "omega 3" N1 fatty acid*) OR (TI ("fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA)) OR (AB ("fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA))	4,996
S25	(MH "S-Adenosylmethionine") OR (TI ("s adenosyl l methionine" OR "s adenosylmethionine")) OR (AB ("s adenosyl l methionine" OR "s adenosylmethionine"))	204
S26	(MH "Acupuncture+") OR (TI (acupuncture OR electroacupuncture)) OR (AB (acupuncture OR electroacupuncture))	8,556
S27	(MH "Exercise+") OR TI (physical N1 (activit* OR exercise)) OR AB (physical N1 (activit* OR exercise))	65,646
S28	S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	83,353
S29	(MH "Depression+") AND (TX major N2 depress*)	3,393
S30	TI (major n2 depress* OR "major depressive disorder") OR AB (major n2 depress* OR "major depressive disorder")	3,998
S31	S29 OR S30	4,08
S32	S31 AND (S17 OR S20 OR S28)	1,115
S33	(MH "Animals") NOT (MH "Human")	24,505
S34	S32 NOT S33	1,114
S35	((MH "Infant") OR (MH "Child") OR (MH "Adolescence")) NOT (MH "Adult+")	221,397
S36	S34 NOT S35	1,012
S37	S36 AND (PY 1990-2014) AND (LA (english OR german Or italian))	1,003
S38	S37 NOT (PT (editorial OR letter OR commentary))	867

Addendum duloxetine 07.05.2014

#	Query	Results
S1	(MH "Duloxetine Hydrochloride") OR (TX Duloxetine)	378
S2	(MH "Depression+") AND (TX major N2 depress*)	3,397
S3	TI (major n2 depress* OR "major depressive disorder") OR AB (major n2 depress* OR "major depressive disorder")	4
S4	S2 OR S3	4,082
S5	S4 AND S1	51
S6	(MH "Animals") NOT (MH "Human")	24,582
S7	S5 NOT S6	51
S8	((MH "Infant") OR (MH "Child") OR (MH "Adolescence")) NOT (MH "Adult+")	221,684
S9	S7 NOT S8	51
S10	S9 AND (PY 1990-2014) AND (LA (english OR german Or italian))	51
S11	S10 NOT (PT (editorial OR letter OR commentary))	50

AMED (via Ovid) 02.05.2014

#	Search	Results
1	exp antidepressive agents/	272
2	Bupropion.mp.	15
3	Citalopram.mp.	9
4	Escitalopram.mp.	3
5	(Desvenlafaxine or O-desmethylvenlafaxine).mp.	0
6	Fluoxetine.mp.	50
7	Levomilnacipran.mp.	0
8	mirtazapine.mp.	6
9	(nefazodone or Paroxetine or Sertraline or Trazodone or venlafaxine or vilazodone or vortioxetine).mp.	69
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	363
11	exp psychotherapy/	8542
12	((acceptance or cognitive or interpersonal or psychodynamic or behavioral) adj3 (therap$ or psychotherap$)).mp.	1395
13	11 or 12	8895
14	exp fatty acids/ or exp fish oils/ or (omega 3 and acid*).mp. or (flax seed or borage seed or Borago or evening primrose or Oenothera or eicosapentaenoic acid or PUFA).mp.	640
15	exp hypericum/ or (hypericum or (john$ adj1 wort)).mp. or (LI160 or WS5572 or WS5573 or LoHyp-57).mp.	415
16	(S-Adenosylmethionine or s adenosyl l methionine).mp.	21
17	exp acupuncture/ or exp electroacupuncture/ or (acupuncture or electroacupuncture).mp.	9182
18	exp meditation/ or (meditation or mindfulness).mp.	658
19	exp Yoga/ or yoga.mp.	501
20	(physical adj1 (activit* or exercise)).mp. or exp Exercise/	9857
21	14 or 15 or 16 or 17 or 18 or 19 or 20	20984
22	exp depressive disorder/	890
23	((major adj2 depress$) or major depressive disorder).mp.	352
24	22 or 23	1126
25	10 or 13 or 21	29843
26	24 and 25	283
27	26	283
28	limit 27 to yr="1990 -Current"	282
29	(exp infant/ or exp child/ or exp adolescent/) not exp adult/	15352
30	28 not 29	269
31	28 and (adult or adults).ti,ab.	39
32	30 or 31	271

Addendum duloxetine 07.05.2014

#	Search	Results
1	duloxetine.mp.	22
2	exp depressive disorder/	894
3	((major adj2 depress$) or major depressive disorder).mp.	353
4	2 or 3	1131
5	1 and 4	5

PsycInfo (via Ebsco) 02.05.2014

#	Query	Results
S1	TX (Bupropion OR Citalopram OR Escitalopram OR O-desmethylvenlafaxine OR Desvenlafaxine OR Fluoxetine OR Fluvoxamine OR Levomilnacipran OR mirtazapine OR nefazodone OR Paroxetine OR Sertraline OR Trazodone OR venlafaxine OR vilazodone OR vortioxetine)	15,857
S2	DE "antidepressant drugs" AND TX (second generation)	144
S3	S1 OR S2	15,958
S4	(DE "acceptance and commitment therapy") or ((DE "cognitive therapy") or (DE "behavior therapy")) OR (DE psychotherapy)	64,196
S5	TI ((acceptance and commitment therap*) OR (cognitive N2 therap*) OR (behavior* therap) OR (interpersonal therap*) OR (psychodynamic therap*)) OR AB ((acceptance and commitment therap*) OR (cognitive N2 therap*) OR (behavior* therap) OR (interpersonal therap*) OR (psychodynamic therap*))	24,311
S6	S4 OR S5	78,648
S7	(DE acupuncture) OR (TX (acupuncture OR electroacupuncture))	1,717
S8	(DE meditation) OR (TX (meditation OR mindfulness))	8,986
S9	(DE hypericum perforatum) OR (TX (hypericum OR (john* N1 wort) OR LI160 OR WS5572 OR WS5573 LoHyp-57))	392
S10	(DE yoga) OR (TX yoga)	1,907
S11	TX ((omega-3 N1 fatty acid*) OR "fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA)	982
S12	TX ("s adenosyl l methionine" OR "s adenosylmethionine")	205
S13	DE exercise OR TI physical activit* OR AB physical activit*	30,086
S14	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	43,124
S15	DE ("major depressive disorder" OR "Major Depression") OR TI ("major depressive disorder" OR (Major N2 Depress*)) OR AB ("major depressive disorder" OR (Major N2 Depress*))	94,026
S16	S15 AND (S3 OR S6 OR S14)	13,953
S17	TI (controlled N2 (trial OR study)) OR AB (controlled N2 (trial OR study))	36,244
S18	TI (randomi*ed controlled trial) OR AB (randomi*ed controlled trial) OR TI (random* N4 (trial OR study)) OR AB (random* N4 (trial OR study))	39,503
S19	TI ("double-blind" OR (random* assigned) OR "single-blind") OR AB ("double-blind" OR (random* assigned) OR "single-blind")	42,931
S20	TI (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR AB (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR (comprehensive N3 (bibliographic OR literature)) OR ((TI "research integration") OR (AB "research integration")) OR ((TI "research synthesis") Or (AB "research synthesis")) OR ((TI metaanaly* OR meta-analy*) OR (AB metaanaly* OR meta-analy*)) OR (MR ("systematic review" OR "meta analysis"))	31,825
S21	((MR "longitudinal study" OR "retrospective study" OR "prospective study") OR (DE "cohort analysis") OR TI ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study))) OR AB ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study)))) AND (TI (comparative OR comparison) OR AB (comparative OR comparison))	10,731

#	Query	Results
S22	(S17 OR S18 OR S19 OR S20 OR S21) NOT ((ZZ "comment/reply") OR (ZZ "editorial") OR (ZZ "letter"))	113,102
S23	S16 AND S22	3,595
S24	((ZP "animal")) not ((ZP "human"))	279,088
S25	S23 NOT S24	3,586
S26	(((ZG "childhood (birth-12 yrs)") or (ZG "infancy (2-23 mo)")) or ((ZG "adolescence (13-17 yrs)"))) not ((ZG "adulthood (18 yrs & older)"))	396,672
S27	S25 NOT S26	3,4
S28	LA (english OR german OR italian)	3,441,047
S29	PY 1990-2014	2,451,294
S30	S27 AND S28 AND S29	3,172

Addendum duloxetine 07.05.2014

#	Query	Results
S1	DE ("major depressive disorder" OR "Major Depression") OR TI ("major depressive disorder" OR (Major N2 Depress*)) OR AB ("major depressive disorder" OR (Major N2 Depress*))	94,027
S2	S1 AND (TX duloxetine)	375
S3	TI (controlled N2 (trial OR study)) OR AB (controlled N2 (trial OR study))	36,244
S4	TI (randomi*ed controlled trial) OR AB (randomi*ed controlled trial) OR TI (random* N4 (trial OR study)) OR AB (random* N4 (trial OR study))	39,503
S5	TI ("double-blind" OR (random* assigned) OR "single-blind") OR AB ("double-blind" OR (random* assigned) OR "single-blind")	42,931
S6	TI (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR AB (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR (comprehensive N3 (bibliographic OR literature)) OR ((TI "research integration") OR (AB "research integration")) OR ((TI "research synthesis") Or (AB "research synthesis")) OR ((TI metaanaly* OR meta-analy*) OR (AB metaanaly* OR meta-analy*)) OR (MR ("systematic review" OR "meta analysis"))	31,825
S7	((MR "longitudinal study" OR "retrospective study" OR "prospective study") OR (DE "cohort analysis") OR TI ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study))) OR AB ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study)))) AND (TI (comparative OR comparison) OR AB (comparative OR comparison))	10,731
S8	(S3 OR S4 OR S5 OR S6 OR S7) NOT ((ZZ "comment/reply") OR (ZZ "editorial") OR (ZZ "letter"))	113,102
S9	S2 AND S8	161
S10	((ZP "animal")) not ((ZP "human"))	279,088
S11	S9 NOT S10	161
S12	(((ZG "childhood (birth-12 yrs)") or (ZG "infancy (2-23 mo)")) or ((ZG "adolescence (13-17 yrs)"))) not ((ZG "adulthood (18 yrs & older)"))	396,672
S13	S11 NOT S12	161
S14	LA (english OR german OR italian)	3,441,047
S15	PY 1990-2014	2,451,294
S16	S13 AND S14 AND S15	154

Pubmed 12 January 2015

Search	Query	Items found
#1	Search "Bupropion"[Mesh] OR "Bupropion"[tiab] OR 34911-55-2[rn]	3714
#2	Search "Citalopram"[Mesh] OR "Citalopram"[tiab] OR 59729-33-8[rn]	5305
#3	Search Escitalopram[tw] OR 128196-01-0[rn]	4250
#4	Search "O-desmethylvenlafaxine" [Supplementary Concept] OR Desvenlafaxine[tiab] OR 93413-62-8[rn]	255
#5	Search "Fluoxetine"[Mesh] OR "Fluoxetine"[tiab] OR 54910-89-3[rn]	11275
#6	Search "Fluvoxamine"[Mesh] OR "Fluvoxamine"[tiab] OR 54739-18-3[rn]	2609
#7	Search "milnacipran"[Supplementary Concept] OR "Levomilnacipran"[tiab] OR 96847-54-0[rn]	372
#8	Search "mirtazapine"[Supplementary Concept] OR "mirtazapine"[tiab] OR 85650-52-8[rn]	1650
#9	Search "nefazodone"[Supplementary Concept] OR "nefazodone"[tiab] OR 82752-99-6[rn]	715
#10	Search "Paroxetine"[Mesh] OR "Paroxetine"[tiab] OR 61869-08-7[rn]	5379
#11	Search "Sertraline"[Mesh] OR "Sertraline"[tiab] OR 79617-96-2[rn]	3875
#12	Search "Trazodone"[Mesh] OR "Trazodone"[tiab] OR 19794-93-5[rn]	1716
#13	Search "venlafaxine"[Supplementary Concept] OR "venlafaxine"[tiab] OR 93413-69-5[rn]	3290
#14	Search "vilazodone"[Supplementary Concept] OR "vilazodone"[tiab] OR 163521-12-8[rn]	83
#15	Search "vortioxetine"[Supplementary Concept] OR "vortioxetine"[tiab] OR 508233-74-7[rn]	75
#16	Search "duloxetine" [Supplementary Concept] OR duloxetine[tiab]	1778
#17	Search "Antidepressive Agents, Second-Generation"[Mesh] OR "Antidepressive Agents, Second-Generation"[Pharmacological Action]	58607
#18	Search #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	69934
#19	Search "Psychotherapy"[Mesh] OR psychotherap*[tiab]	160809
#20	Search Acceptance and Commitment Therap*[tiab] OR Cognitive Therap*[tiab] OR Cognitive behavioral Therap*[tiab] OR interpersonal therap*[tiab] OR psychodynamic therap*[tiab] OR behavioral therap*[tiab]	8733
#21	Search (#19 OR #20)	163324
#22	Search "Hypericum"[Mesh] OR Hypericum[tiab] OR St. Johns Wort[tiab] OR Saint Johns Wort[tiab] OR St. John's Wort[tiab] OR Saint John's Wort[tiab] OR LI160[tiab] OR WS5572[tiab] OR WS5573[tiab] OR LoHyp-57[tiab]	2688
#23	Search "s adenosyl l methionine"[tiab] OR "s adenosylmethionine"[tiab] OR "S-Adenosylmethionine"[Mesh]	9025
#24	Search "Fatty Acids, Omega-3"[Mesh] OR (omega 3[tiab] AND fatty acid*[tiab]) OR fish oil[tiab] OR flax seed[tiab] OR borage seed[tiab] OR Borago[tiab] OR evening primrose[tiab] OR Oenothera[tiab] OR eicosapentaenoic acid[tiab] OR PUFA[tiab]	29253
#25	Search "Acupuncture"[Mesh] OR "Acupuncture Therapy"[Mesh] OR Acupuncture[tiab] OR Electroacupuncture[tiab]	21423
#26	Search "Yoga"[Mesh] OR yoga[tiab]	2633
#27	Search "Meditation"[Mesh] OR meditation[tiab] OR mindfulness[tiab]	4674
#28	Search "Exercise"[Mesh] OR physical activit*[tiab] OR "physical exercise"[tiab]	169750
#29	Search #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	237070
#30	Search "Depressive Disorder, Major"[MeSH] OR "major depressive disorder"[tiab] OR "major depression"[tiab]	37436
#31	Search (#30 AND #18)	5363
#32	Search (#30 AND #21)	3258
#33	Search (#30 AND #29)	808
#34	Search (#31 OR #32 OR #33)	8749
#35	Search (systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR "research synthesis"[tiab] OR "research	265837

Search	Query	Items found
	integration"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR "meta-analysis as topic"[mh] OR "Meta-Analysis"[pt] OR ("review"[tiab] AND ("rationale"[tiab] OR "evidence"[tiab]) AND review[pt]) OR "Systematic Review"[tiab] OR ("Review"[Publication Type] AND "systematic"[tiab])	
#36	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH] OR "Randomized Controlled Trial"[tiab] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	565406
#37	Search (("cohort studies"[MeSH] OR cohort stud*[tiab] OR cohort analy*[tiab] OR "Case-Control Studies"[Mesh] OR case control stud*[tiab] OR observational stud*[tiab] OR "observational study"[pt] OR ((longitudinal[tiab] OR retrospective[tiab] OR prospective[tiab]) AND (study[tiab] OR trial[tiab]))) AND ("Comparative Study"[pt] OR comparison[tiab] OR comparative[tiab]))	363532
#38	Search ("Controlled Clinical Trial"[pt] OR "Controlled Clinical Trials as Topic"[Mesh] OR controlled clinical trial*[tiab] OR controlled trial*[tiab] OR controlled stud*[tiab])	334900
#39	Search (#34 AND (#35 OR #36 OR #37 OR #38))	4018
#40	Search "Animals"[Mesh] NOT "Humans"[Mesh]	3963556
#41	Search (#39 NOT #40)	4011
#42	Search ("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh]	1523966
#43	Search (#41 NOT #42)	3767
#44	Search #43 AND 2014:2015[dp] AND (english[la] OR german[la] OR italian[la])	202

Cochrane Library 12 January 2015

ID	Search	Hits
#1	[mh Bupropion] or Bupropion:ti,ab	990
#2	[mh Citalopram] or Citalopram:ti,ab	1238
#3	Escitalopram:ti,ab	655
#4	Desvenlafaxine:ti,ab	83
#5	[mh Fluoxetine] or Fluoxetine:ti,ab	2423
#6	[mh Fluvoxamine] or Fluvoxamine:ti,ab	693
#7	Levomilnacipran:ti,ab	15
#8	mirtazapine:ti,ab	457
#9	nefazodone:ti,ab	194
#10	[mh Paroxetine] or Paroxetine:ti,ab	1814
#11	[mh Sertraline] or sertraline:ti,ab	1415
#12	[mh Trazodone] or Trazodone:ti,ab	342
#13	venlafaxine:ti,ab	1030
#14	vilazodone:ti,ab	26
#15	vortioxetine:ti,ab	18
#16	duloxetine:ti,ab	541
#17	[mh "Antidepressive Agents, Second-Generation"]	1236
#18	{or #1-#17}	9842
#19	[mh Psychotherapy] or psychotherap*:ti,ab	17633
#20	(Acceptance near/2 Commitment next Therap*):ti,ab or (Cognitive near/2 Therap*):ti,ab or ((interpersonal or psychodynamic or behavioral) next therap*):ti,ab	5514
#21	#19 or #20	20047
#22	[mh yoga] or yoga:ti,ab	856
#23	[mh meditation] or (meditation or mindfulness):ti,ab	1296
#24	[mh Acupuncture] or [mh "Acupuncture Therapy"] or (Acupuncture or Electroacupuncture):ti,ab	7617
#25	[mh Hypericum] or "Hypericum":ti,ab or (john* next wort):ti,ab or (LI160 or WS5572 or WS5573 or LoHyp-57):ti,ab	302
#26	("s adenosyl l methionine" or "s adenosylmethionine"):ti,ab or [mh S-Adenosylmethionine]	202
#27	[mh "fatty Acids, Omega-3"] or (omega-3 and fatty next acid*):ti,ab or ("fish oil" or "flax	3983

ID	Search	Hits
	seed" or "borage seed" or Borago or "evening primrose" or Oenothera or "eicosapentaenoic acid" or PUFA):ti,ab	
#28	[mh Exercise] or (physical next (activit* or exercise)):ti,ab	19836
#29	{or #22-#28}	33596
#30	[mh "Depressive Disorder, Major"] or "major depressive disorder":ti,ab or (major next/1 depress*):ti,ab	6816
#31	#30 and (#18 or #21 or #29)	3847
#32	#31 Publication Year from 2014	119
#33	[mh animals] not [mh humans]	5683
#34	#32 not #33	119
#35	([mh infant] or [mh child] or [mh adolescent]) not [mh adult]	88719
#36	#34 not #35	119

Embase (embase.com) 13 January 2015

No.	Query	Results
#1	'amfebutamone'/exp OR bupropion:tn,ab,ti OR '34911 55 2':rn	14498
#2	'citalopram'/exp OR citalopram:tn,ab,ti OR '59729 33 8':rn	18173
#3	'escitalopram'/exp OR escitalopram:tn,ab,ti OR '128196 01 0':rn	7453
#4	'desvenlafaxine'/exp OR desvenlafaxine:tn,ab,ti OR '93413 62 8':rn	926
#5	'fluoxetine'/exp OR fluoxetine:tn,ab,ti OR '54910 89 3':rn	38642
#6	'fluvoxamine'/exp OR fluvoxamine:tn,ab,ti OR '54739 18 3':rn	11640
#7	'milnacipran'/exp OR levomilnacipran:tn,ab,ti OR '96847 54 0':rn	2006
#8	'mirtazapine'/exp OR mirtazapine:tn,ab,ti OR '85650 52 8':rn	9260
#9	'nefazodone'/exp OR nefazodone:tn,ab,ti OR '82752 99 6':rn	4885
#10	'paroxetine'/exp OR paroxetine:tn,ab,ti OR '61869 08 7':rn	23598
#11	'sertraline'/exp OR sertraline:tn,ab,ti OR '79617 96 2':rn	20413
#12	'trazodone'/exp OR trazodone:tn,ab,ti OR '19794 93 5':rn	10064
#13	'venlafaxine'/exp OR venlafaxine:tn,ab,ti OR '93413 69 5':rn	16550
#14	'vilazodone'/exp OR vilazodone:tn,ab,ti OR '163521 12 8':rn	264
#15	'vortioxetine'/exp OR vortioxetine:tn,ab,ti OR '508233 74 7':rn	231
#16	'duloxetine'/exp OR '116539 59 4':rn OR duloxetine:tn,ab,ti	7135
#17	'antidepressant agent'/exp AND 'second generation':ab,ti OR (antidep* NEAR/2 'second generation'):ab,ti	1393
#18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	93111
#19	'psychotherapy'/exp	193315
#20	((acceptance OR cognitive OR interpersonal OR psychodynamic OR behavioral) NEXT/3 (therapy OR therapies OR psychotherapy)):ab,ti	21899
#21	#19 OR #20	195814
#22	'hypericum'/exp OR hypericum:ab,ti OR (john* NEXT/1 wort):ab,ti OR li160:ab,ti OR ws5572:ab,ti OR ws5573:ab,ti OR 'lohyp 57':ab,ti	4330
#23	's adenosylmethionine'/exp OR 's adenosylmethionine' OR 's adenosyl l methionine':ab,ti OR 's adenosylmethionine':ab,ti	10883
#24	'omega 3 fatty acid'/exp OR ('omega 3':ab,ti AND acid*:ab,ti) OR 'fish oil':ab,ti OR 'flax seed':ab,ti OR 'borage seed':ab,ti OR borago:ab,ti OR 'evening primrose':ab,ti OR oenothera:ab,ti OR 'eicosapentaenoic acid':ab,ti OR pufa:ab,ti	35965
#25	'acupuncture'/exp OR acupuncture:ab,ti OR electroacupuncture:ab,ti	34890
#26	'yoga'/exp OR yoga:ab,ti	4566
#27	'meditation'/exp OR meditation:ab,ti OR mindfulness:ab,ti	7307
#28	'exercise'/exp OR (physical NEXT/2 (activit* OR exercis*)):ab,ti	284231
#29	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	374358
#30	'major depression'/exp OR 'major depressive disorder':ab,ti OR (major NEXT/2 depress*):ab,ti	55229
#31	#18 AND #30	12883

No.	Query	Results
#32	#21 AND #30	5686
#33	#29 AND #30	1555
#34	#31 OR #32 OR #33	17290
#35	'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review':ab,ti OR (meta NEXT/1 analy*):ab,ti OR metaanaly*:ab,ti OR (review:it AND systematic:ab,ti) OR (systematic:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti OR review:ab,ti OR reviewed:ab,ti OR reviews:ab,ti)) OR 'research synthesis':ab,ti OR 'research integration':ab,ti OR (comprehensive*:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti)) OR (review:it AND review:ab,ti AND (rationale:ab,ti OR evidence:ab,ti))	312865
#36	'randomized controlled trial'/exp OR (randomi?ed NEXT/1 'controlled trial'):ab,ti OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomization'/exp OR 'random allocation':ab,ti OR (allocated NEXT/2 random*):ab,ti	460334
#37	'cohort analysis'/exp OR 'case control study'/exp OR 'observational study'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR (cohort NEXT/1 (stud* OR analy*)):ab,ti OR (observational OR 'case control') NEXT/1 stud* OR ((longitudinal OR retrospective OR prospective) NEXT/2 (trial OR study)):ab,ti AND ('comparative study'/exp OR comparative:ab,ti OR comparison:ab,ti)	160923
#38	'controlled clinical trial'/exp OR (controlled NEXT/2 (trial* OR stud*)):ab,ti	618207
#39	#35 OR #36 OR #37 OR #38	1077437
#40	#34 AND #39	5782
#41	'animal'/exp NOT 'human'/exp	4405184
#42	#40 NOT #41	5779
#43	'groups by age'/exp NOT 'adult'/exp	5494792
#44	#42 NOT #43	2942
#45	#44 AND [2014-2015]/py	205
#46	#45 AND [english]/lim	204
#47	#45 AND (german:la OR italian:la)	0
#48	#46 OR #47	204
#49	#48 AND [embase]/lim	198

CINAHL Plus (Ebsco) 13 January 2015

#	Query	Results
S1	(MH "Bupropion") OR "Bupropion"	1,448
S2	(MH "Citalopram") OR "Citalopram"	1,094
S3	Escitalopram	397
S4	(MH "Desvenlafaxine Succinate") OR Desvenlafaxine	97
S5	(MH "Fluoxetine+") OR "Fluoxetine"	1,534
S6	(MH "Fluvoxamine Maleate") OR "Fluvoxamine"	207
S7	"Levomilnacipran"	11
S8	(MH "Mirtazapine") OR "mirtazapine"	363
S9	(MH "Nefazodone") OR "nefazodone"	82
S10	(MH "Paroxetine") OR "Paroxetine"	1,03
S11	(MH "Sertraline Hydrochloride") OR "Sertraline"	927
S12	(MH "Trazodone") OR "Trazodone"	234
S13	(MH "Venlafaxine+") OR "venlafaxine"	876
S14	"vilazodone"	25
S15	"vortioxetine"	17
S16	(MH "Duloxetine Hydrochloride") OR (TX Duloxetine)	1,305
S17	(MH "Antidepressive Agents, Second Generation+")	3,975
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	7,776
S19	(MH "Psychotherapy+") OR (TI psychotherap*) OR (AB psychotherap*)	117,68
S20	TI (("Acceptance and Commitment" OR cognitive OR behavioral OR psychodynamic	6,208

#	Query	Results
	OR interpersonal) N2 therap*) OR AB (("Acceptance and Commitment" OR cognitive OR behavioral OR psychodynamic OR interpersonal) N2 therap*)	
S21	S19 OR S20	119,031
S22	(MH "Yoga+") OR (TI yoga) OR (AB yoga)	4,665
S23	(MH "Meditation") OR (TI (meditation OR mindfulness)) OR (AB (meditation OR mindfulness))	4,231
S24	(MH "St. John's Wort") OR "hypericum" OR (TI john* N2 wort) OR (AB john* N2 wort) OR (TI (LI160 OR WS5572 OR WS5573 OR LoHyp-57)) OR (AB (LI160 OR WS5572 OR WS5573 OR LoHyp-57))	1,145
S25	(MH "Fatty Acids, Omega-3+") OR (TI "omega 3" N1 fatty acid*) OR (AB "omega 3" N1 fatty acid*) OR (TI ("fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA)) OR (AB ("fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA))	7,684
S26	(MH "S-Adenosylmethionine") OR (TI ("s adenosyl l methionine" OR "s adenosylmethionine")) OR (AB ("s adenosyl l methionine" OR "s adenosylmethionine"))	291
S27	(MH "Acupuncture+") OR (TI (acupuncture OR electroacupuncture)) OR (AB (acupuncture OR electroacupuncture))	11,43
S28	(MH "Exercise+") OR TI (physical N1 (activit* OR exercise)) OR AB (physical N1 (activit* OR exercise))	85,935
S29	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	112,416
S30	(MH "Depression") AND (TX major N2 depress*)	8,569
S31	TI (major N2 depress* OR "major depressive disorder") OR AB (major N2 depress* OR "major depressive disorder")	6,57
S32	S30 OR S31	9,83
S33	S18 AND S32	1,091
S34	S21 AND S32	1,482
S35	S29 AND S32	462
S36	S33 OR S34 OR S35	2,742
S37	(MH "Animals") NOT (MH "Human")	51,653
S38	S36 NOT S37	2,737
S39	((MH "Infant") OR (MH "Child") OR (MH "Adolescence")) NOT (MH "Adult+")	315,299
S40	S38 NOT S39	2,525
S41	S40 AND (LA (english OR german OR italian))	2,513
S42	S41 AND (PY 2014-2015)	136
S43	S42 NOT (PT (editorial OR letter OR commentary OR "case study"))	131

AMED (Ovid) 13 January 2015

#	Search	Results
1	exp antidepressive agents/	281
2	Bupropion.mp.	15
3	Citalopram.mp.	9
4	Escitalopram.mp.	3
5	(Desvenlafaxine or O-desmethylvenlafaxine).mp.	0
6	(Fluoxetine or Fluvoxamine).mp.	56
7	Levomilnacipran.mp.	0
8	mirtazapine.mp.	6
9	(nefazodone or Paroxetine or Sertraline or Trazodone or venlafaxine or vilazodone or vortioxetine or duloxetine).mp.	91
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	393
11	exp psychotherapy/	8680
12	((acceptance or cognitive or interpersonal or psychodynamic or behavioral) adj3 (therap$ or psychotherap$)).mp.	1443
13	11 or 12	9045

#	Search	Results
14	exp fatty acids/ or exp fish oils/ or (omega 3 and acid*).mp. or (flax seed or borage seed or Borago or evening primrose or Oenothera or eicosapentaenoic acid or PUFA).mp.	666
15	exp hypericum/ or (hypericum or (john$ adj1 wort)).mp. or (LI160 or WS5572 or WS5573 or LoHyp-57).mp.	420
16	(S-Adenosylmethionine or s adenosyl l methionine).mp.	21
17	exp acupuncture/ or exp electroacupuncture/ or (acupuncture or electroacupuncture).mp.	9406
18	exp meditation/ or (meditation or mindfulness).mp.	678
19	exp Yoga/ or yoga.mp.	521
20	(physical adj1 (activit* or exercise)).mp. or exp Exercise/	10153
21	14 or 15 or 16 or 17 or 18 or 19 or 20	21568
22	exp depressive disorder/	997
23	((major adj2 depress$) or major depressive disorder).mp.	360
24	22 or 23	1235
25	10 or 13 or 21	30590
26	24 and 25	306
27	exp animals/ not exp humans/	7987
28	26 not 27	287
29	(exp infant/ or exp child/ or exp adolescent/) not exp adult/	15990
30	28 not 29	272
31	limit 30 to yr="2014 -Current"	10

PsycINFO (Ebsco) 13 January 2015

#	Query	Results
S1	DE "Bupropion" OR TI Bupropion OR AB Bupropion	1,739
S2	DE "Citalopram" OR TI Citalopram OR AB Citalopram	2,213
S3	TX Escitalopram	1
S4	TX Desvenlafaxine	94
S5	DE "Fluoxetine" OR TI Fluoxetine OR AB Fluoxetine	5,746
S6	DE "Fluvoxamine" OR TI Fluvoxamine OR AB Fluvoxamine	1,479
S7	TX Levomilnacipran	11
S8	TX mirtazapine	995
S9	DE "Nefazodone" OR TI nefazodone OR AB nefazodone	457
S10	DE "Paroxetine" OR TI Paroxetine OR AB Paroxetine	2,924
S11	DE "Sertraline" OR TI Sertraline OR AB Sertraline	2,316
S12	DE "Trazodone" OR TI Trazodone OR AB Trazodone	784
S13	DE "Venlafaxine" OR TI venlafaxine OR AB venlafaxine	1,957
S14	TX vilazodone	23
S15	TX vortioxetine	24
S16	TX duloxetine	768
S17	DE "antidepressant drugs" AND TX (second generation)	155
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	16,934
S19	(DE "acceptance and commitment therapy") or ((DE "cognitive therapy") or (DE "behavior therapy")) OR (DE psychotherapy)	66,057
S20	TI ((acceptance and commitment therap*) OR (cognitive N2 therap*) OR (behavior* therap) OR (interpersonal therap*) OR (psychodynamic therap*)) OR AB ((acceptance and commitment therap*) OR (cognitive N2 therap*) OR (behavior* therap) OR (interpersonal therap*) OR (psychodynamic therap*))	25,883
S21	S19 OR S20	81,679
S22	(DE acupuncture) OR TI ((acupuncture OR electroacupuncture)) OR AB ((acupuncture OR electroacupuncture))	1,682
S23	(DE meditation) OR TI ((meditation OR mindfulness)) OR AB ((meditation OR mindfulness))	9,174

#	Query	Results
S24	(DE hypericum perforatum) OR TI ((hypericum OR (john* N1 wort) OR LI160 OR WS5572 OR WS5573 LoHyp-57)) OR AB ((hypericum OR (john* N1 wort) OR LI160 OR WS5572 OR WS5573 LoHyp-57))	399
S25	DE yoga) OR TI yoga OR AB yoga	1,72
S26	TX ((omega-3 N1 fatty acid*) OR "fish oil" OR "flax seed" OR "borage seed" OR Borago OR" evening primrose" OR Oenothera OR "eicosapentaenoic acid" OR PUFA)	1,06
S27	TX ("s adenosyl l methionine" OR "s adenosylmethionine")	218
S28	DE exercise OR TI (physical W1 (activit* OR exercis*)) OR AB (physical W1 (activit* OR exercis*))	31,426
S29	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	44,488
S30	DE ("major depressive disorder" OR "Major Depression") OR TI ("major depressive disorder" OR (Major N2 Depress*)) OR AB ("major depressive disorder" OR (Major N2 Depress*))	99,261
S31	S18 AND S30	7,216
S32	S21 AND S30	6,383
S33	S29 AND S30	2,047
S34	S31 OR S32 OR S33	14,918
S35	TI (controlled N2 (trial OR study)) OR AB (controlled N2 (trial OR study))	39,02
S36	TI (randomi*ed controlled trial) OR AB (randomi*ed controlled trial) OR TI (random* N4 (trial OR study)) OR AB (random* N4 (trial OR study))	43,179
S37	TI ("double-blind" OR (random* assigned) OR "single-blind") OR AB ("double-blind" OR (random* assigned) OR "single-blind")	45,025
S38	TI (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR AB (systematic N3 (bibliographic OR literature OR review# OR reviewed)) OR (comprehensive N3 (bibliographic OR literature)) OR ((TI "research integration") OR (AB "research integration")) OR ((TI "research synthesis") Or (AB "research synthesis")) OR ((TI metaanaly* OR meta-analy*) OR (AB metaanaly* OR meta-analy*)) OR (MR ("systematic review" OR "meta analysis"))	35,443
S39	((MR "longitudinal study" OR "retrospective study" OR "prospective study") OR (DE "cohort analysis") OR TI ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study))) OR AB ((cohort N1 (analy* OR stud*)) OR ((observational OR "case control") N1 stud*) OR ((longitudinal OR retrospective OR prospective) N2 (trial OR study)))) AND (TI (comparative OR comparison) OR AB (comparative OR comparison))	11,52
S40	S35 OR S36 OR S37 OR S38 OR S39	127,772
S41	S34 AND S40	4,196
S42	((ZZ "comment/reply") or (ZZ "editorial") or (ZZ "letter"))	150,398
S43	S41 NOT S42	3,957
S44	((ZP "animal")) not ((ZP "human"))	289,185
S45	S43 NOT S44	3,947
S46	(((ZG "childhood (birth-12 yrs)") or (ZG "infancy (2-23 mo)")) or ((ZG "adolescence (13-17 yrs)"))) not ((ZG "adulthood (18 yrs & older)"))	411,03
S47	S45 NOT S46	3,746
S48	LA (english OR german OR italian)	3,603,958
S49	S47 AND S48	3,619
S50	PY 2014-2015	155,082
S51	S49 AND S50	257

Grey Literature Search

ClinicalTrials.gov 04.06.2014

41 studies found for:

("major depressive disorder" OR "major depression") AND Bupropion   Adult, Senior Phase 2, 3, 4

170 studies found for:
("major depressive disorder" OR "major depression") AND Citalopram Adult, Senior Phase 2, 3, 4
170 studies found for:
("major depressive disorder" OR "major depression") AND Escitalopram Adult, Senior Phase 2, 3, 4
35 studies found for:
("major depressive disorder" OR "major depression") AND Desvenlafaxine Adult, Senior Phase 2, 3, 4
45 studies found for:
("major depressive disorder" OR "major depression") AND Fluoxetine Adult, Senior Phase 2, 3, 4
6 studies found for:
("major depressive disorder" OR "major depression") AND Fluvoxamine Adult, Senior Phase 2, 3, 4
7 studies found for:
("major depressive disorder" OR "major depression") AND Levomilnacipran Adult, Senior Phase 2, 3, 4
21 studies found for:
("major depressive disorder" OR "major depression") AND mirtazapine Adult, Senior Phase 2, 3, 4

Found no studies with search of: ("major depressive disorder" OR "major depression") AND nefazodone Adult,
        Senior Phase 2, 3, 4
61 studies found for:
("major depressive disorder" OR "major depression") AND Paroxetine Adult, Senior Phase 2, 3, 4
66 studies found for:
("major depressive disorder" OR "major depression") AND Sertraline Adult, Senior Phase 2, 3, 4
4 studies found for:
("major depressive disorder" OR "major depression") AND Trazodone Adult, Senior Phase 2, 3, 4
66 studies found for:
("major depressive disorder" OR "major depression") AND venlafaxine Adult, Senior Phase 2, 3, 4
13 studies found for:
("major depressive disorder" OR "major depression") AND vilazodone Adult, Senior Phase 2, 3, 4
24 studies found for:
("major depressive disorder" OR "major depression") AND vortioxetine Adult, Senior Phase 2, 3, 4
74 studies found for:
("major depressive disorder" OR "major depression") AND duloxetine Adult, Senior Phase 2, 3, 4
Document: GreyLiterature.enl

ICTRP 04.06.2014

342 records for 243 trials found for: major depress* AND antidepress*
Document: ICTRP-040614.xlsx

Drugs@FDA 02.06.2014

Levomilnacipran:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=204168&DrugName=FETZIMA&ActiveIngred=LEVOMILNACIPRAN%20HYDROCHLORIDE&SponsorApplicant=FOREST%20LABS%20INC&ProductMktStatus=1&goto=Search.DrugDetails
Vilazodone:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=022567&DrugName=VIIBRYD&ActiveIngred=VILAZODONE%20HYDROCHLORIDE&SponsorApplicant=FOREST%20LABS%20INC&ProductMktStatus=1&goto=Search.DrugDetails
Vortioxetine:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=204447&DrugName=BRINTELLIX&ActiveIngred=VORTIOXETINE%20HYDROBROMIDE&SponsorApplicant=TAKEDA%20PHARMS%20USA&ProductMktStatus=1&goto=Search.DrugDetails
Folder: FDA

European Medicines Agency 02.06.2014

Levomilnacipran: 0
Vilazodone: 0

Vortioxetine:
http://www.ema.europa.eu:80/ema/index.jsp?curl=pages/medicines/human/medicines/002717/human_med_001714.jsp&mid=WC0b01ac058001d124
Folder: EMA

National Institute of Mental Health Web site 11.06.2014
Search Terms: "major depression", "major depressive disorder"
Folder: NIMH

American Psychological Association 11.06.2014
Search terms, "major depressive disorder", major depression"
Folder: APA

Scopus 16.06.2014
(TITLE-ABS-KEY({major depressive disorder} OR {major depression}) OR KEY({disorder, major depressive})) AND (TITLE-ABS-KEY((bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR levomilnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine) OR ("Acceptance and Commitment Therapy" OR "Cognitive Therapy" OR "Cognitive behavioral Therapy" OR "interpersonal therapy" OR "psychodynamic therapy" OR "behavioral therapy") OR (hypericum OR "St. Johns Wort" OR "Saint Johns Wort" OR "St. John's Wort" OR "Saint John's Wort") OR ("s adenosyl l methionine" OR "S-Adenosylmethionine") OR ("omega 3") OR (acupuncture OR electroacupuncture) OR (yoga OR meditation OR mindfulness) OR ("physical activity" OR "physical exercise")) OR KEY(psychotherapy)) AND (TITLE-ABS-KEY(adult*)) AND (DOCTYPE(cp))

162 document results

Document: GreyLiterature.enl

Web of Science Conference Proceedings Citation Index- Science 16.06 2014

Set	Results	Search
		Indexes=CPCI-S Timespan=All years
# 1	3,944	TOPIC: ("major depressive disorder" OR "major depression")
		Indexes=CPCI-S Timespan=All years
# 2	4,014	TOPIC: (bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR levomilnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine)
		Indexes=CPCI-S Timespan=1990-2014
# 3	628	TOPIC: ("Acceptance and Commitment Therapy" OR "Cognitive Therapy" OR "Cognitive behavioral Therapy" OR "interpersonal therapy" OR "psychodynamic therapy" OR "behavioral therapy")
		Indexes=CPCI-S Timespan=1990-2014
# 4	404	TOPIC: (hypericum OR "St. Johns Wort" OR "Saint Johns Wort" OR "St. John's Wort" OR "Saint John's Wort")
		Indexes=CPCI-S Timespan=1990-2014
# 5	456	TOPIC: ("s adenosyl l methionine" OR "S-Adenosylmethionine")
		Indexes=CPCI-S Timespan=1990-2014
# 6	1,749	TOPIC: ("omega 3")
		Indexes=CPCI-S Timespan=1990-2014
# 7	1,068	TOPIC: (acupuncture OR electroacupuncture)
		Indexes=CPCI-S Timespan=1990-2014
# 8	517	TOPIC: (yoga OR meditation OR mindfulness)
		Indexes=CPCI-S Timespan=1990-2014
# 9	6,836	TOPIC: ("physical activity" OR "physical exercise")
		Indexes=CPCI-S Timespan=1990-2014
# 10	15,492	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
		Indexes=CPCI-S Timespan=1990-2014
# 11	874	#10 AND #1
		Indexes=CPCI-S Timespan=1990-2014
		Refined by: TOPIC: (adult*)
# 12	55	#10 AND #1

Document: GreyLiterature.enl

Appendix B. Cochrane Depression, Anxiety and Neurosis Group (CCDAN) Topic List: Intervention – Psychological Therapies[2]

- **Behavior therapy / behavior modification**
  - o Activity scheduling
  - o Assertiveness training [CINAHL]
  - o Aversion therapy [APA]
    - ▪ Covert sensitization [APA]
  - o Behavior contracting [CINAHL]
  - o Behavior modification
  - o Biofeedback, psychology [MeSH]
    - ▪ Feedback, sensory [MeSH]
  - o Contingency management [CINAHL]
  - o Conversion therapy [APA]
  - o Distraction therapy
  - o Exposure therapy (APA)
    - ▪ Abreaction therapy
    - ▪ Sensitivity training
    - ▪ Systematic desensitization therapy (APA)
      - • Eye movement desensitization reprocessing [MeSH]
    - ▪ Implosive therapy [APA, MeSH]
  - o Pleasant events
  - o Psychoeducation
  - o Problem-focused
  - o Reciprocal inhibition therapy (APA)
  - o Relaxation techniques [CINAHL]
  - o Autogenic training
    - ▪ Distraction [CINAHL]
    - ▪ Guided imagery [CINAHL]
  - o Response cost (APA)
  - o Sleep phase chronotherapy [MeSH]
  - o Social skills training
    - ▪ Social effectiveness
- **Cognitive behavioral therapy [APA]**
  - o Problem solving
  - o Rational emotive therapy
  - o Reality therapy
  - o Restructuring
  - o Role play
  - o Schemas

---

[2] Cochrane Depression, Anxiety, and Neurosis Group. CCDAN Topic List: Intervention - Psychological therapies. 2013 http://ccdan.cochrane.org/sites/ccdan.cochrane.org/files/uploads/CCDAN%20topics%20list_psychological%20therapies%20for%20website.pdf. Accessed October 17, 2014.

- o Self-control
- o Stress management
- **Third wave cognitive behavioral therapies**
  - o Acceptance and commitment therapy (ACT)
  - o Behavioral activation
  - o Cognitive behavioral analysis system of psychotherapy (CBASP)
  - o Compassion-focused
  - o Dialectical behavior therapy (APA)
  - o Diffusion
  - o Functional analytic psychotherapy (FAP)
  - o Metacognitive therapy
  - o Mind training
  - o Mindfulness
- **Psychodynamic therapies**
  - o Brief psychotherapy
  - o Countertransference
  - o Freudian
  - o Group therapy
    - ▪ Balint group therapy
  - o Insight oriented therapy
  - o Jungian
  - o Kleinian
  - o Object relations
  - o Person centred therapy, client-centred therapy
  - o Psychoanalytic therapy
    - ▪ Alderian therapy
    - ▪ Dream analysis
    - ▪ Free association
    - ▪ Self analysis
  - o Short-term psychotherapy
  - o Transference
- **Humanistic therapies**
  - o Existential therapy
  - o Experiential therapy
    - ▪ Process-experiential
    - ▪ Gestalt therapy
  - o Expressive therapy
  - o Griefwork
  - o Rogerian
  - o Non-directive therapy
  - o Supportive therapy
  - o Transactional analysis
- **Integrative therapies**
  - o Cognitive analytical therapy
  - o Counselling
  - o Eclectic therapy

- o Interpersonal therapy
  - ▪ Psychodynamic interpersonal therapy
- o Multimodal
- o Transtheoretical
- **Systemic therapies**
  - o Conjoint therapy
    - ▪ Couples, marital or relationship therapy
      - • Emotion focused therapy
    - ▪ Family therapy
  - o Integrative behavioral couple therapy (IBCT)
  - o Narrative therapy
  - o Personal construct
  - o Socioenvironmental therapy
    - ▪ Milieu therapy
    - ▪ Therapeutic community
  - o Solution focused brief therapy
- **Other psychologically-oriented interventions**
  - o Acting out
  - o Age regression therapy
  - o Art therapy
  - o Bibliotherapy
  - o Catharsis
  - o Colour therapy
  - o Crisis intervention
  - o Dance therapy
  - o Drama therapy
  - o Emotional freedom techniqueso hypnotherapy
    - ▪ Autosuggestion
    - ▪ Neuro-linguistic programming (NLP)
    - ▪ Persuasion
  - o Meditation [CINAHL]
  - o Morita therapy
  - o Music therapy
  - o Play therapy
  - o Primal therapy
  - o Psychodrama
  - o Reminiscence therapy
  - o Sex therapy

Appendix C. Studies Excluded at the Full-Text Review Stage

Exclude Code	Exclude Reason
X1	Ineligible publication type
X2	Ineligible population(s)
X3	Ineligible or no intervention(s)
X4	Ineligible study design
X5	Ineligible or no comparison(s)
X6	Ineligible outcome(s)
X7	Does not answer a Key Question of the review
X8	Mixed treatment comparisons
X9	Systematic review without relevant meta-analysis
X10	Abstract only available

1. St. John's wort ineffective for major depression. J Psychosoc Nurs Ment Health Serv. 2001;39(7):9-.

2. Research notebook. Study shows St. John's wort ineffective for major depression. FDA Consum. 2002;36(3):8-.

3. Treating late-life depression: pharmacotherapy or psychotherapy? Brown University Geriatric Psychopharmacology Update. 2006;10(12):3-4.

4. Paroxetine plus psychotherapy for major depression in the elderly. Brown University Psychopharmacology Update. 2006;17(8):4-5.

5. Paroxetine found to maintain quality of life in elderly patients with depression. Brown University Geriatric Psychopharmacology Update. 2007;11(11):1.

6. Augmenting standard antidepressant treatment may help recovery in elderly. Brown University Geriatric Psychopharmacology Update. 2007;11(8):1.

7. . Cost effectiveness of therapy and fluoxetine for MDD in Romania... major depressive disorder. Brown University Psychopharmacology Update. 2009;20(4):4-.

8. Better response and remission with mirtazapine for MD... major depression. Brown University Psychopharmacology Update. 2010;21(10):3-4. PMID: 2010780944. Language: English. Entry Date: 20101008. Revision Date: 20140103. Publication Type: journal article. Journal Subset: Biomedical.

9. Omega-3 effective in treating major depression - but only in absence of anxiety. Canadian Nursing Home. 2010;21(3):26-.

10. [Therapy of moderately severe depressions in daily practice: first patient care research study reinforces clinical data]. MMW Fortschr Med. 2011 Oct 13;153(41):38-9. Epub: 2011/11/04. PMID: 22046838.

11. A Double-Blind, Paroxetine- and Placebo-Controlled Study of 50 mg/Day and 100 mg/Day of EB-1010 Among Outpatients With Major Depressive Disorder Who Have Responded Inadequately to Prior Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (Triple Reuptake Inhibitor Anti-Depressant Effects - TRIADE Study) [NCT01318434]. Clinicaltrials.gov [www.clinicaltrials.gov]. 2011PMID: CN-00850845.

12. Mittelschwere und schwere depression: langzeitbehandlung mit hypericum-extrakt WS 5570 gleich wirksam wie paroxetin. Schweiz Z Ganzheits Medizin. 2008 May;20(4):198-9. PMID: 0110887.

13. Abdallah CG, Niciu MJ, Fenton LR, et al. Decreased occipital cortical glutamate levels in response to successful cognitive-behavioral therapy and pharmacotherapy for major depressive disorder. Psychother Psychosom. 2014;83(5):298-307. PMID: 2012707226. Language: English. Entry Date: In Process. Revision Date: 20140912. Publication Type: journal article. Journal Subset: Biomedical.

14. Abt KL. The effects of a group exercise intervention in the adjunctive treatment of depression. US: ProQuest Information & Learning; 2006.

15. Agid O, Lerer B. Algorithm-based treatment of major depression in an outpatient clinic: Clinical correlates of response to a specific serotonin reuptake inhibitor and to triiodothyronine augmentation. Int J Neuropsychopharmacol. 2003;6(1):41-9.

16. Alexopoulos GS, Canuso CM, Gharabawi GM, et al. Placebo-controlled study of relapse prevention with risperidone augmentation in older patients with resistant depression. Am J Geriatr Psychiatry. 2008 Jan;16(1):21-30. Epub: 2007/10/12. PMID: 17928573.

17. Alper BS. Evidence-based medicine. St. John's wort may be as effective as standard antidepressants--and more tolerable--for major depression. Clinical Advisor for Nurse Practitioners. 2009;12(2):84-. PMID: 2010218029. Language: English. Entry Date: 20090410. Revision Date: 20090410. Publication Type: journal article.

18.   Anghelescu IG, Kohnen R, Szegedi A, et al. Comparison of Hypericum extract WS 5570 and paroxetine in ongoing treatment after recovery from an episode of moderate to severe depression: results from a randomized multicenter study. Pharmacopsychiatry. 2006 Nov;39(6):213-9. Epub: 2006/11/25. PMID: 17124643.

19.   Appelberg BG, Syvälahti EK, Koskinen TE, et al. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. J Clin Psychiatry. 2001;62(6):448-52. PMID: CN-00349570.

20.   Appelhof BC, Brouwer JP, van Dyck R, et al. Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. J Clin Endocrinol Metab. 2004 Dec;89(12):6271-6. Epub: 2004/12/08. PMID: 15579788.

21.   Arnow BA, Blasey C, Manber R, et al. Dropouts versus completers among chronically depressed outpatients. J Affect Disord. 2007 Jan;97(1-3):197-202. Epub: 2006/07/22. PMID: 16857266.

22.   Arnow BA, Steidtmann D, Blasey C, et al. The relationship between the therapeutic alliance and treatment outcome in two distinct psychotherapies for chronic depression. J Consult Clin Psychol. 2013;81(4):627-38. PMID: 2013-01524-001. PMID: 23339536. First Author & Affiliation: Arnow, Bruce A.

23.   Ashouri A, Atef-Vahid MK, Gharaee B, et al. Effectiveness of meta-cognitive and cognitive-behavioral therapy in patients with major depressive disorder. Iranian Journal of Psychiatry and Behavioral Sciences. 2013;7(2):24-34.

24.   Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: Maintenance of therapeutic benefit. In: Monat A, Lazarus RS, Reevy G, eds. The Praeger handbook on stress and coping. Vol. 2. Westport, CT: Praeger Publishers/Greenwood Publishing Group; 2007:529-40.

25.   Bagby RM, Quilty LC, Segal ZV, et al. Personality and differential treatment response in major depression: a randomized controlled trial comparing cognitive-behavioural therapy and pharmacotherapy. Can J Psychiatry. 2008 Jun;53(6):361-70. Epub: 2008/07/12. PMID: 18616856.

26.   Baldomero EB, Ubago JG, Cercós CL, et al. Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. Depress Anxiety. 2005;22(2):68-76. PMID: 2005-15269-004. PMID: 16094658. First Author & Affiliation: Baldomero, E. Baca.

27.   Ballesteros J, Callado LF, Gutierrez M. An independent meta-analysis using summary data for clinical response, remission, and discontinuation for any reason from the 6 pivotal phase III randomized clinical trials of duloxetine in major depressive disorder. J Clin Psychopharmacol. 2007 Apr;27(2):219-21. Epub: 2007/04/07. PMID: 17414254.

28.   Bauer M, Bschor T, Kunz D, et al. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am J Psychiatry. 2000;157(9):1429-35.

29.   Bauer M, Pretorius HW, Constant EL, et al. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. J Clin Psychiatry. 2009 Apr;70(4):540-9. Epub: 2009/04/11. PMID: 19358791.

30.   Baumann P, Nil R, Souche A, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: A clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol. 1996;16(4):307-14. PMID: 1996-05541-004. PMID: 8835706. Partial author list. First Author & Affiliation: Baumann, Pierre.

31.   Bell AC, D'Zurilla TJ. Problem-solving therapy for depression: a meta-analysis. Clin Psychol Rev. 2009 Jun;29(4):348-53. Epub: 2009/03/21. PMID: 19299058.

32.   Benazzi F. Fluoxetine and olanzapine for resistant depression. Am J Psychiatry. 2002 Jan;159(1):155-6. Epub: 2002/01/05. PMID: 11772722.

33.   Benvenuti A, Rucci P, Miniati M, et al. Treatment-emergent mania/hypomania in unipolar patients. Bipolar Disord. 2008 Sep;10(6):726-32. Epub: 2008/10/08. PMID: 18837867.

34.   Berman RM, Darnell AM, Miller HL, et al. Effect of pindolol in hastening response to fluoxetine in the treatment of major depression: a double-blind, placebo-controlled trial. Am J Psychiatry. 1997 Jan;154(1):37-43. Epub: 1997/01/01. PMID: 8988956.

35.   Berman RM, Fava M, Thase ME, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr. 2009 Apr;14(4):197-206. Epub: 2009/05/02. PMID: 19407731.

36.   Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007 Jun;68(6):843-53. Epub: 2007/06/27. PMID: 17592907.

37.   Bhar SS, Gelfand LA, Schmid SP, et al. Sequence of improvement in depressive symptoms across cognitive therapy and pharmacotherapy. J Affect Disord. 2008 Sep;110(1-2):161-6. Epub: 2008/02/16. PMID: 18276017.

38.   Bhattacharya R, Kelley G, Bhattacharjee S. Long-term follow-up effects of computerized or internet-based cognitive behavioral therapy for depression and anxiety: A metaanalysis. Value Health. 2012;15(4):A82.

39. Bisserbe JC, Boyer P, Souetre E, et al. A Six Month Sertraline Fluoxetine Comparative Study in Depressed Outpatients: Outcome and Costs CONFERENCE ABSTRACT. XXth Collegium Internationale Neuro-psychopharmacologicum. Melbourne, Australia. 23rd-27th June, 1996. 1996PMID: CN-00278847.

40. Blackburn IM, Bishop S, Glen AI, et al. The efficacy of cognitive therapy in depression: a treatment trial using cognitive therapy and pharmacotherapy, each alone and in combination. Br J Psychiatry. 1981 Sep;139:181-9. Epub: 1981/09/01. PMID: 7317698.

41. Blackburn IM, Moore RG. Controlled acute and follow-up trial of cognitive therapy and pharmacotherapy in out-patients with recurrent depression. Br J Psychiatry. 1997 Oct;171:328-34. Epub: 1997/11/28. PMID: 9373420.

42. Blitzer LE, Atchison-Nevel DJ, Kenny MC. Using acupuncture to treat major depressive disorder: a pilot investigation. Clinical Acupuncture & Oriental Medicine. 2003;4(4):144-7. PMID: 2004075709. Language: English. Entry Date: 20040514. Revision Date: 20091218. Publication Type: journal article.

43. Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. Mol Psychiatry. 2012 Dec;17(12):1272-82. Epub: 2011/09/21. PMID: 21931319.

44. Blom MB, Hoek HW, Spinhoven P, et al. Treatment of depression in patients from ethnic minority groups in the Netherlands. Transcult Psychiatry. 2010 Jul;47(3):473-90. Epub: 2010/08/07. PMID: 20688800.

45. Blom MBJ, Spinhoven P, Hoffman T, et al. Severity and duration of depression, not personality factors, predict short term outcome in the treatment of major depression. J Affect Disord. 2007;104(1-3):119-26.

46. Bobo WV, Chen H, Trivedi MH, et al. Randomized comparison of selective serotonin reuptake inhibitor (escitalopram) monotherapy and antidepressant combination pharmacotherapy for major depressive disorder with melancholic features: a CO-MED report. J Affect Disord. 2011 Oct;133(3):467-76. Epub: 2011/05/24. PMID: 21601287.

47. Bobo WV, Shelton RC. Fluoxetine and olanzapine combination therapy in treatment-resistant major depression: review of efficacy and safety data. Expert Opin Pharmacother. 2009 Sep;10(13):2145-59. Epub: 2009/07/31. PMID: 19640209.

48. Bolton PG, Fergusson KJ, Parker SM, et al. Randomised controlled trial of cognitive-behavioural therapy and routine GP care for major depression. Med J Aust. 2001 Jul 16;175(2):118-9. Epub: 2001/09/15. PMID: 11556412.

49. Bone K. St. John's Wort and depression: Avoiding drug interactions. Townsend Letter for Doctors and Patients. 2007;282:45-8. PMID: 0094709.

50. Bortolotti B, Menchetti M, Bellini F, et al. Psychological interventions for major depression in primary care: a meta-analytic review of randomized controlled trials. Gen Hosp Psychiatry. 2008 Jul-Aug;30(4):293-302. Epub: 2008/07/01. PMID: 18585531.

51. Bosmans JE, van Schaik DJ, Heymans MW, et al. Cost-effectiveness of interpersonal psychotherapy for elderly primary care patients with major depression. Int J Technol Assess Health Care. 2007 Fall;23(4):480-7. Epub: 2007/10/17. PMID: 17937837.

52. Bosscher RJ. Running and mixed physical exercises with depressed psychiatric patients. Int J Sport Psychol. 1993;24(2):170-84. PMID: 1994-06914-001. First Author & Affiliation: Bosscher, Rudolf J.

53. Braun SR, Gregor B, Tran US. Comparing bona fide psychotherapies of depression in adults with two meta-analytical approaches. PLoS One. 2013;8(6)PMID: 2013-25847-001. First Author & Affiliation: Braun, Sarah R.

54. Brenner R, Madhusoodanan S, Pawlowska M. Efficacy of continuation treatment with Hypericum perforatum in depression. J Clin Psychiatry. 2002;63(5)PMID: 2002-13479-018. PMID: 12019675. First Author & Affiliation: Brenner, Ronald.

55. Brody A, Saxena S, Stoessel P, et al. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy. Arch Gen Psychiatry. 2001 Jul;58(7):631-40. PMID: 0028127.

56. Brosse A, Sheets E, Lett H, et al. Exercise and the treatment of clinical depression in adults: recent findings and future directions. Sports Medicine (Auckland). 2002;32(12):741-60. PMID: 0043625.

57. Brown WA, Harrison W. Are patients who are intolerant to one SSRI intolerant to another? Psychopharmacol Bull. 1992;28(3):253-6. Epub: 1992/01/01. PMID: 1480728.

58. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? J Clin Psychiatry. 1995 Jan;56(1):30-4. Epub: 1995/01/01. PMID: 7836337.

59. Bulmash E, Harkness KL, Stewart JG, et al. Personality, stressful life events, and treatment response in major depression. J Consult Clin Psychol. 2009 Dec;77(6):1067-77. Epub: 2009/12/09. PMID: 19968383.

60. Buysse DJ, Kupfer DJ, Cherry C, et al. Effects of prior fluoxetine treatment on EEG sleep in women with recurrent depression. Neuropsychopharmacology. 1999 Aug;21(2):258-67. Epub: 1999/08/05. PMID: 10432474.

61. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of mirtazapine augmentation for refractory major depression: preliminary findings. 52nd Institute on Psychiatric Services; 2000 October 25-29th; Philadelphia, PA. 2000PMID: CN-00320610.

62.   Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry. 2002 Jan 15;51(2):183-8. Epub: 2002/02/02. PMID: 11822997.

63.   Carta MG, Hardoy MC, Pilu A, et al. Improving physical quality of life with group physical activity in the adjunctive treatment of major depressive disorder. Clin Pract Epidemiol Ment Health. 2008;4PMID: 2008-15806-001. First Author & Affiliation: Carta, Mauro Giovanni.

64.   Carvalho AF, Berk M, Hyphantis TN, et al. The integrative management of treatment-resistant depression: a comprehensive review and perspectives. Psychother Psychosom. 2014;83(2):70-88. Epub: 2014/01/25. PMID: 24458008.

65.   Casacalenda N, Perry JC, Looper K. Remission in major depressive disorder: a comparison of pharmacotherapy, psychotherapy, and control conditions. Am J Psychiatry. 2002 Aug;159(8):1354-60. Epub: 2002/08/03. PMID: 12153828.

66.   Chalder M, Wiles NJ, Campbell J, et al. Facilitated physical activity as a treatment for depressed adults: Randomised controlled trial. BMJ: British Medical Journal. 2012;344(7860)PMID: 2012-15758-001. First Author & Affiliation: Chalder, Melanie.

67.   Chen J, Gao K, Kemp DE. Second-generation antipsychotics in major depressive disorder: update and clinical perspective. Curr Opin Psychiatry. 2011 Jan;24(1):10-7. Epub: 2010/11/20. PMID: 21088586.

68.   Chiesa A, Serretti A. L'utilità delle meditazioni basate sulla consapevolezza per i disturbi psichiatrici: Una review sistematica. Psichiatria e Psicoterapia. 2009;28(2):93-110. PMID: 2009-17997-001. First Author & Affiliation: Chiesa, Alberto. Translated Title: Usefulness of mindfulness meditations for psychiatric disorders: A systematic review.. Other Journal Titles: Psichiatria e Psicoterapia Analitica. Release Date: 20110110. Publication Type: Journal, (0100).

69.   Chiesa A, Serretti A. Mindfulness based cognitive therapy for psychiatric disorders: a systematic review and meta-analysis. Psychiatry Res. 2011 May 30;187(3):441-53. Epub: 2010/09/18. PMID: 20846726.

70.   Cody RA, Drysdale K. The effects of psychotherapy on reducing depression in residential aged care: A meta-analytic review. Clinical Gerontologist: The Journal of Aging and Mental Health. 2013;36(1):46-69. PMID: 2012-35079-004. First Author & Affiliation: Cody, Robyn Ann.

71.   Coelho HF, Canter PH, Ernst E. Mindfulness-based cognitive therapy: evaluating current evidence and informing future research. J Consult Clin Psychol. 2007 Dec;75(6):1000-5. Epub: 2007/12/19. PMID: 18085916.

72.   Combs K, Smith PJ, Sherwood A, et al. Impact of sleep complaints and depression outcomes among participants in the standard medical intervention and long-term exercise study of exercise and pharmacotherapy for depression. J Nerv Ment Dis. 2014 Feb;202(2):167-71. Epub: 2014/01/29. PMID: 24469530.

73.   Coon DW, DeVries HM, Gallagher-Thompson D. COGNITIVE BEHAVIORAL THERAPY WITH SUICIDAL OLDER ADULTS. Behav Cogn Psychother. 2004;32(04):481-93.

74.   Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. Cochrane Database Syst Rev. 2013;9:CD004366. Epub: 2013/09/13. PMID: 24026850.

75.   Cornwall PL, Jenaway A, Garland A, et al. Cogntive therapy for major depression in partial remission: preliminary findings. 9th Congress of the Association of European Psychiatrists. Copenhagen, Denmark. 20-24th September 1998. 1998PMID: CN-00279581.

76.   Corya SA, Williamson D, Sanger TM, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. Depress Anxiety. 2006;23(6):364-72. Epub: 2006/05/20. PMID: 16710853.

77.   Crawford AA, Lewis S, Nutt D, et al. Adverse effects from antidepressant treatment: Randomised controlled trial of 601 depressed individuals. Psychopharmacology (Berl). 2014;231(15):2921-31. PMID: 2014-30312-002.

78.   Cuijpers P, de Beurs DP, van Spijker BAJ, et al. The effects of psychotherapy for adult depression on suicidality and hopelessness: A systematic review and meta-analysis. J Affect Disord. 2013;144(3):183-90. PMID: 2012-20095-001. PMID: 22832172. First Author & Affiliation: Cuijpers, Pim.

79.   Cuijpers P, Dekker J, Hollon SD, et al. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis. J Clin Psychiatry. 2009 Sep;70(9):1219-29. Epub: 2009/10/13. PMID: 19818243.

80.   Cuijpers P, Reynolds CF, III, Donker T, et al. Personalized treatment of adult depression: Medication, psychotherapy, or both? A systematic review. Depress Anxiety. 2012;29(10):855-64. PMID: 2012-26844-004. PMID: 22815247. First Author & Affiliation: Cuijpers, Pim.

81.   Cuijpers P, Sijbrandij M, Koole SL, et al. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. World Psychiatry. 2014 Feb;13(1):56-67. Epub: 2014/02/06. PMID: 24497254.

82.   Cuijpers P, Straten A, Schuurmans J, et al. Psychotherapy for chronic major depression and dysthymia: a meta-analysis (Structured abstract). Clin Psychol Rev. 2009;30(1):51-62. PMID: DARE-12009108768.

83.	Cuijpers P, Straten A, Warmerdam L. Behavioral activation treatments of depression: a meta-analysis (Structured abstract). Clin Psychol Rev. 2007;27(3):318-26. PMID: DARE-12007001174.

84.	Cuijpers P, van Straten A, Hollon SD, et al. The contribution of active medication to combined treatments of psychotherapy and pharmacotherapy for adult depression: A meta-analysis. Acta Psychiatr Scand. 2010;121(6):415-23. PMID: 2010-09276-003. PMID: 19922522. First Author & Affiliation: Cuijpers, P.

85.	Cuijpers P, van Straten A, Smit F, et al. Is psychotherapy for depression equally effective in younger and older adults? A meta-regression analysis. Int Psychogeriatr. 2009;21(1):16-24. PMID: 2009-02458-005. PMID: 19040783. First Author & Affiliation: Cuijpers, Pirn.

86.	Cuijpers P, van Straten A, van Oppen P, et al. Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? A meta-analysis of comparative studies. J Clin Psychiatry. 2008 Nov;69(11):1675-85; quiz 839-41. Epub: 2008/10/24. PMID: 18945396.

87.	Cuijpers P, van Straten A, van Oppen P, et al. Comparing psychotherapy and pharmacotherapy for adult depression: adjusting for differential dropout rates. J Clin Psychiatry. 2010 Sep;71(9):1246. Epub: 2010/10/07. PMID: 20923628.

88.	Cuijpers P, van Straten A, Warmerdam L, et al. Psychological treatment of depression: A meta-analytic database of randomized studies. BMC Psychiatry. 2008;8PMID: 2008-10088-001. PMID: 18485191. First Author & Affiliation: Cuijpers, Pim.

89.	Cuijpers P, van Straten A, Warmerdam L, et al. Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: a meta-analysis. Depress Anxiety. 2009;26(3):279-88. Epub: 2008/11/26. PMID: 19031487.

90.	Curran S, Rampat R, Spencer R, et al. Paroxetine for the treatment of old age depression: A systematic review. Eur Neuropsychopharmacol. 2009;19:S403-S4.

91.	Daley A. Exercise and depression: A review of reviews. J Clin Psychol Med Settings. 2008;15(2):140-7. PMID: 19104978.

92.	Dannlowski U, Baune BT, Bockermann I, et al. Adjunctive antidepressant treatment with quetiapine in agitated depression: Positive effects on symptom reduction, psychopathology and remission rates. Human Psychopharmacology. 2008;23(7):587-93.

93.	Davis AS. A meta-analysis of the efficacy of cognitive therapy, pharmacotherapy, and the combination of cognitive therapy and pharmacotherapy in the treatment of depession. US: ProQuest Information & Learning; 1991.

94.	de Graaf LE, Gerhards SAH, Arntz A, et al. One-year follow-up results of unsupported online computerized cognitive behavioural therapy for depression in primary care: A randomized trial. J Behav Ther Exp Psychiatry. 2011;42(1):89-95. PMID: 2010-26707-013. PMID: 20723885. First Author & Affiliation: de Graaf, L. E.

95.	de Jonghe F, Hendricksen M, van Aalst G, et al. Psychotherapy alone and combined with pharmacotherapy in the treatment of depression. Br J Psychiatry. 2004 Jul;185:37-45. Epub: 2004/07/03. PMID: 15231554.

96.	de Jonghe F, Kool S, van Aalst G, et al. Combining psychotherapy and antidepressants in the treatment of depression. J Affect Disord. 2001 May;64(2-3):217-29. Epub: 2001/04/21. PMID: 11313088.

97.	De Jong-Meyer R, Hautzinger M, Rudolf GAE, et al. Outcome prediction and longitudinal analyses of endogenously depressed patients treated with combined psychological and antidepressant therapies. Zeitschrift fur Klinische Psychologie. 1996;25(2):110-29.

98.	de la Cerda P, Cervello E, Cocca A, et al. Effect of an aerobic training program as complementary therapy in patients with moderate depression. Percept Mot Skills. 2011 Jun;112(3):761-9. Epub: 2011/08/23. PMID: 21853765.

99.	De Maat S, Dekker J, Schoevers R, et al. Relative efficacy of psychotherapy and pharmacotherapy in the treatment of depression: A meta-analysis. Psychotherapy Research. 2006;16(5):562-72. PMID: 2006-21953-005. First Author & Affiliation: De Maat, Saskia.

100.	de Maat S, Dekker J, Schoevers R, et al. Short psychodynamic supportive psychotherapy, antidepressants, and their combination in the treatment of major depression: a mega-analysis based on three randomized clinical trials. Depress Anxiety. 2008;25(7):565-74. Epub: 2007/06/09. PMID: 17557313.

101.	de Mello MF, de Jesus Mari J, Bacaltchuk J, et al. A systematic review of research findings on the efficacy of interpersonal therapy for depressive disorders. Eur Arch Psychiatry Clin Neurosci. 2005 Apr;255(2):75-82. Epub: 2005/04/07. PMID: 15812600.

102.	DeBattista C, Doghramji K, Menza MA, et al. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: A preliminary double-blind, placebo-controlled study. J Clin Psychiatry. 2003;64(9):1057-64.

103.	DeBattista C, Solvason HB, Poirier J, et al. A prospective trial of bupropion SR augmentation of partial and non-responders to serotonergic antidepressants. J Clin Psychopharmacol. 2003 Feb;23(1):27-30. Epub: 2003/01/25. PMID: 12544372.

104. Den Boer PCAM, Wiersma D, Ten Vaarwerk I, et al. Cognitive self-therapy for chronic depression and anxiety: A multi-centre randomized controlled study. Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences. 2007;37(3):329-39. PMID: 2007-03729-003. First Author & Affiliation: Den Boer, Peter C. A. M.

105. Denton WH, Carmody TJ, Rush AJ, et al. Dyadic discord at baseline is associated with lack of remission in the acute treatment of chronic depression. Psychol Med. 2010 Mar;40(3):415-24. Epub: 2009/07/18. PMID: 19607755.

106. DeRubeis RJ, Evans MD, Hollon SD, et al. How does cognitive therapy work? Cognitive change and symptom change in cognitive therapy and pharmacotherapy for depression. J Consult Clin Psychol. 1990 Dec;58(6):862-9. Epub: 1990/12/01. PMID: 2292637.

107. DeRubeis RJ, Gelfand LA, Tang TZ, et al. Medications versus cognitive behavior therapy for severely depressed outpatients: Mega-analysis of four randomized comparisons. The American Journal of Psychiatry. 1999;156(7):1007-13. PMID: 1999-03084-003. PMID: 10401443. First Author & Affiliation: DeRubeis, Robert J.

108. Dew MA, Whyte EM, Lenze EJ, et al. Recovery from major depression in older adults receiving augmentation of antidepressant pharmacotherapy. Am J Psychiatry. 2007;164(6):892-9. PMID: 2009673818. Language: English. Entry Date: 20071012. Revision Date: 20091218. Publication Type: journal article.

109. Dhillon S, Yang LPH, Curran MP. Spotlight on bupropion in major depressive disorder. CNS Drugs. 2008;22(7):613-7. PMID: 2008-08817-006. PMID: 18547129. First Author & Affiliation: Dhillon, Sohita.

110. Dias M, Vellarde G, Olej B. Effects of electroacupuncture on stress-related symptoms in medical students: A randomised placebo-controlled study. Acupunct Med. 2014 Feb;32(1):4-11. PMID: 0175473.

111. Dombrovski AY, Lenze EJ, Dew MA, et al. Maintenance treatment for old-age depression preserves health-related quality of life: a randomized, controlled trial of paroxetine and interpersonal psychotherapy. J Am Geriatr Soc. 2007 Sep;55(9):1325-32. Epub: 2007/09/05. PMID: 17767673.

112. Dording CM, Mischoulon D, Shyu I, et al. SAMe and sexual functioning. Eur Psychiatry. 2012 Aug;27(6):451-4. Epub: 2011/03/15. PMID: 21398094.

113. Doree JP, Des Rosiers J, Lew V, et al. Quetiapine augmentation of treatment-resistant depression: A comparison with lithium. Curr Med Res Opin. 2007;23(2):333-41.

114. Dozois DJ, Bieling PJ, Patelis-Siotis I, et al. Changes in self-schema structure in cognitive therapy for major depressive disorder: a randomized clinical trial. J Consult Clin Psychol. 2009 Dec;77(6):1078-88. Epub: 2009/12/09. PMID: 19968384.

115. Dozois DJA, Bieling PJ, Evraire LE, et al. Changes in Core Beliefs (Early Maladaptive Schemas) and Self-Representation in Cognitive Therapy and Pharmacotherapy for Depression. Int J Cogn Ther. 2014;7(3):217-34. PMID: 2012744839. Language: English. Entry Date: 20141017. Revision Date: 20141024. Publication Type: journal article.

116. Dunlop BW, Crits-Christoph P, Evans DL, et al. Coadministration of modafinil and a selective serotonin reuptake inhibitor from the initiation of treatment of major depressive disorder with fatigue and sleepiness: A double-blind, placebo-controlled study. J Clin Psychopharmacol. 2007;27(6):614-9.

117. Dunlop BW, Kelley ME, Mletzko TC, et al. Depression beliefs, treatment preference, and outcomes in a randomized trial for major depressive disorder. J Psychiatr Res. 2012 Mar;46(3):375-81. Epub: 2011/11/29. PMID: 22118808.

118. Dunner DL, Amsterdam JD, Shelton RC, et al. Efficacy and tolerability of adjunctive ziprasidone in treatment-resistant depression: a randomized, open-label, pilot study. J Clin Psychiatry. 2007 Jul;68(7):1071-7. Epub: 2007/08/10. PMID: 17685744.

119. Eisendrath SJ, Gillung E, Delucchi K, et al. A preliminary study: Efficacy of mindfulness-based cognitive therapy versus sertraline as first-line treatments for major depressive disorder. Mindfulness. 2014PMID: 2014-03529-001. Publication Status: Online First Posting. First Author & Affiliation: Eisendrath, Stuart J.. Release Date: 20140203. Publication Type: Journal, (0100).

120. Ekers D, Richards D, Gilbody S. A meta-analysis of randomized trials of behavioural treatment of depression. Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences. 2008;38(5):611-23. PMID: 2008-05402-002. First Author & Affiliation: Ekers, D.

121. Ekselius L, von Knorring L. Effect on sexual function of long-term treatment with selective serotonin reuptake inhibitors in depressed patients treated in primary care. J Clin Psychopharmacol. 2001 Apr;21(2):154-60. Epub: 2001/03/29. PMID: 11270911.

122. El-Khalili N, Joyce M, Atkinson S, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: A multicentre, randomized, double-blind, placebo-controlled study. Int J Neuropsychopharmacol. 2010;13(7):917-32.

123. Eriksson E. Cognitive behavioural therapy for treatment-resistant depression. Lancet. 2013 May 25;381(9880):1814-5. PMID: 0169677.

124. Eriksson S, Gard G. Physical exercise and depression. Phys Ther Rev. 2011 Aug;16(4):261-8. PMID: 0148106.

125. Ernst E, Lee MS, Choi T-Y. Acupuncture for depression?: A systematic review of systematic reviews. Eval Health Prof. 2011;34(4):403-12. PMID: 2011-29673-001. First Author & Affiliation: Ernst, E.

126. Fang Y, Yuan C, Xu Y, et al. A pilot study of the efficacy and safety of paroxetine augmented with risperidone, valproate, buspirone, trazodone, or thyroid hormone in adult Chinese patients with treatment-resistant major depression. J Clin Psychopharmacol. 2011 Oct;31(5):638-42. Epub: 2011/08/27. PMID: 21869688.

127. Farabaugh A, Alpert J, Wisniewski SR, et al. Cognitive therapy for anxious depression in STAR(*) D: what have we learned? J Affect Disord. 2012 Dec 15;142(1-3):213-8. Epub: 2012/08/11. PMID: 22877961.

128. Fava GA, Rafanelli C, Grandi S, et al. Prevention of recurrent depression with cognitive behavioral therapy: preliminary findings. Arch Gen Psychiatry. 1998 Sep;55(9):816-20. Epub: 1998/09/15. PMID: 9736008.

129. Fava GA, Ruini C, Rafanelli C, et al. Cognitive behavior approach to loss of clinical effect during long-term antidepressant treatment: a pilot study. Am J Psychiatry. 2002 Dec;159(12):2094-5. Epub: 2002/11/27. PMID: 12450962.

130. Fava M, Alpert J, Nierenberg A, et al. Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. J Clin Psychopharmacol. 2002 Aug;22(4):379-87. Epub: 2002/08/13. PMID: 12172337.

131. Fava M, Rosenbaum JF, McGrath PJ, et al. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry. 1994 Sep;151(9):1372-4. Epub: 1994/09/01. PMID: 8067495.

132. Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry. 2008 Mar;165(3):342-51. Epub: 2008/01/04. PMID: 18172020.

133. Feldman G, Harley R, Kerrigan M, et al. Change in emotional processing during a dialectical behavior therapy-based skills group for major depressive disorder. Behav Res Ther. 2009 Apr;47(4):316-21. Epub: 2009/02/24. PMID: 19232571.

134. Feng CY, Chu H, Chen CH, et al. The effect of cognitive behavioral group therapy for depression: A meta-analysis 2000–2010. Worldviews Evid Based Nurs. 2012;9(1):2-17. PMID: 2012-03102-002. PMID: 22221447. First Author & Affiliation: Feng, Chiueng-Yi.

135. Finch EJL, Katona CLE. Lithium augmentation in the treatment of refractory depression in old age. Int J Geriatr Psychiatry. 1989;4(1):41-6.

136. Fjorback LO, Arendt M, Ørnbøl E, et al. Mindfulness-Based Stress Reduction and Mindfulness-Based Cognitive Therapy—A systematic review of randomized controlled trials. Acta Psychiatr Scand. 2011;124(2):102-19. PMID: 2011-14452-003. PMID: 21534932. First Author & Affiliation: Fjorback, L. O.

137. Fleurence R, Williamson R, Jing Y, et al. A systematic review of augmentation strategies for patients with major depressive disorder. Psychopharmacol Bull. 2009;42(3):57-90. Epub: 2009/09/16. PMID: 19752841.

138. Flint AJ, Rifat SL. The effect of sequential antidepressant treatment on geriatric depression. J Affect Disord. 1996 Jan 22;36(3-4):95-105. Epub: 1996/01/22. PMID: 8821312.

139. Forest L. Two-Week Double-Blind Placebo-Controlled Study of Escitalopram in the Treatment of Severe Major Depression [SCT-MD-26]. Forest Laboratories - Clinical Study Register [www.forestclinicaltrials.com]. 2002PMID: CN-00766939.

140. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA. 2010 Jan 6;303(1):47-53. Epub: 2010/01/07. PMID: 20051569.

141. Fournier JC, DeRubeis RJ, Hollon SD, et al. Differential change in specific depressive symptoms during antidepressant medication or cognitive therapy. Behav Res Ther. 2013;51(7):392-8. PMID: 2013-19059-010. PMID: 23644038. First Author & Affiliation: Fournier, Jay C.

142. Fournier JC, DeRubeis RJ, Shelton RC, et al. Prediction of response to medication and cognitive therapy in the treatment of moderate to severe depression. J Consult Clin Psychol. 2009 Aug;77(4):775-87. Epub: 2009/07/29. PMID: 19634969.

143. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry. 2006 Dec;67(12):1954-67. Epub: 2006/12/30. PMID: 17194275.

144. Freeman MP, Mischoulon D, Tedeschini E, et al. Complementary and alternative medicine for major depressive disorder: a meta-analysis of patient characteristics, placebo-response rates, and treatment outcomes relative to standard antidepressants (Provisional abstract). J Clin Psychiatry. 2010;71(6):682-8. PMID: DARE-12010004817.

145. Freeman MP, Rapaport MH. Omega-3 fatty acids and depression: from cellular mechanisms to clinical care. J Clin Psychiatry. 2011 Feb;72(2):258-9. Epub: 2011/03/09. PMID: 21382308.

146. Friede M, Henneicke von Zepelin HH, Freudenstein J. Differential therapy of mild to moderate depressive episodes (ICD-10 F 32.0; F 32.1) with St. John's wort. Pharmacopsychiatry. 2001;34(Suppl1):S38-S41. PMID: 2001-11122-006. First Author & Affiliation: Friede, Michael.

147.	Gahlsdorf T, Krause R, Beal M. Efficacy of St John's Wort for treating mild to moderate depression. Complementary Health Practice Review. 2007 Oct;12(3):184-95. PMID: 0105158.

148.	Gangadhar BN, Naveen GH, Rao MG, et al. Positive antidepressant effects of generic yoga in depressive out-patients: A comparative study. Indian J Psychiatry. 2013;55(7):S369-S73.

149.	Garakani A, Martinez JM, Marcus S, et al. A randomized, double-blind, and placebo-controlled trial of quetiapine augmentation of fluoxetine in major depressive disorder. Int Clin Psychopharmacol. 2008 Sep;23(5):269-75. Epub: 2008/08/16. PMID: 18703936.

150.	Gartlehner G, Thieda P, Hansen RA, et al. Comparative risk for harms of second-generation antidepressants : a systematic review and meta-analysis. Drug Saf. 2008;31(10):851-65. Epub: 2008/09/02. PMID: 18759509.

151.	Gilbert G. Adults with both anxiety and depression respond poorly to treatment. J Natl Med Assoc. 2008;100(7):870-1.

152.	Gloaguen V, Cottraux J, Cucherat M, et al. A meta-analysis of the effects of cognitive therapy in depressed patients. J Affect Disord. 1998 Apr;49(1):59-72. Epub: 1998/05/09. PMID: 9574861.

153.	Goldstein CN, Topel ME, Zajecka JM. Second generation antipsychotic medications in the treatment of affective disorders. In: Schwartz TL, Megna J, Topel ME, eds. Antipsychotic drugs: Pharmacology, side effects and abuse prevention. Hauppauge, NY US: Nova Biomedical Books; 2013:9-31.

154.	Gould R, Coulson M, Howard R. Cognitive behavioral therapy for depression in older people: A meta-analysis and meta-regression of randomized controlled trials. Journal - American Geriatrics Society. 2012 Oct;60(10):1817-30. PMID: 0161072.

155.	Green BL, Krupnick JL, Chung J, et al. Impact of PTSD comorbidity on one-year outcomes in a depression trial. J Clin Psychol. 2006 Jul;62(7):815-35. Epub: 2006/05/17. PMID: 16703602.

156.	Greenlee A, Karp JF, Dew MA, et al. Anxiety impairs depression remission in partial responders during extended treatment in late-life. Depress Anxiety. 2010 May;27(5):451-6. Epub: 2010/02/27. PMID: 20186975.

157.	Grobler AC, Matthews G, Molenberghs G. The impact of missing data on clinical trials: a re-analysis of a placebo controlled trial of Hypericum perforatum (St Johns wort) and sertraline in major depressive disorder. Psychopharmacology (Berl). 2013 Nov 15Epub: 2013/11/16. PMID: 24232445.

158.	Grobler AC, Matthews G, Molenberghs G. The impact of missing data on clinical trials: a re-analysis of a placebo controlled trial of Hypericum perforatum (St Johns wort) and sertraline in major depressive disorder. Psychopharmacology (Berl). 2014 May;231(9):1987-99. Epub: 2013/11/16. PMID: 24232445.

159.	Grosso G, Pajak A, Marventano S, et al. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. PLoS One. 2014;9(5):e96905. Epub: 2014/05/09. PMID: 24805797.

160.	Güemes I, Guillén V, Ballesteros J. Psychotherapy versus drug therapy in depression in outpatient care. Actas Españolas de Psiquiatría. 2008;36(5):299-306. PMID: 2008-16648-007. PMID: 18523896. First Author & Affiliation: Güemes, I.

161.	Gulrez G, Badyal DK, Deswal RS, et al. Bupropion as an augmenting agent in patients of depression with partial response. Basic Clin Pharmacol Toxicol. 2012 Mar;110(3):227-30. Epub: 2011/09/08. PMID: 21895979.

162.	Haeffel G. CBT self-help that harms. Human Givens. 2010;17(2):8. PMID: 0133238.

163.	Han C, Wang SM, Seo HJ, et al. Aripiprazole augmentation, antidepressant combination or switching therapy in patients with major depressive disorder who are partial- or non-responsive to current antidepressants: A multi-center, naturalistic study. J Psychiatr Res. 2014;49(1):75-82.

164.	Harkness KL, Bagby RM, Kennedy SH. Childhood maltreatment and differential treatment response and recurrence in adult major depressive disorder. J Consult Clin Psychol. 2012 Jun;80(3):342-53. Epub: 2012/03/21. PMID: 22428942.

165.	Hecht H, van Calker D. [Evidence-based psychotherapy of depressive disorders: acute therapy and maintenance therapy]. Psychother Psychosom Med Psychol. 2008 Aug;58(8):326-34; quiz 35-8. Epub: 2008/07/16. PMID: 18626847.

166.	Herman S, Blumenthal JA, Babyak M, et al. Exercise therapy for depression in middle-aged and older adults: predictors of early dropout and treatment failure. Health Psychol. 2002 Nov;21(6):553-63. Epub: 2002/11/16. PMID: 12433007.

167.	Hermens ML, van Hout HP, Terluin B, et al. Clinical effectiveness of usual care with or without antidepressant medication for primary care patients with minor or mild-major depression: a randomized equivalence trial. BMC Med. 2007;5:36. Epub: 2007/12/11. PMID: 18067659.

168.	Hinrichsen GA. Treating older adults with interpersonal psychotherapy for depression. J Clin Psychol. 1999;55(8):949-60.

169.	Hirschfeld RM, Dunner DL, Keitner G, et al. Does psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone, psychotherapy, and their combination. Biol Psychiatry. 2002 Jan 15;51(2):123-33. Epub: 2002/02/02. PMID: 11822991.

170. Hirvonen J, Hietala J, Kajander J, et al. Effects of antidepressant drug treatment and psychotherapy on striatal and thalamic dopamine D2/3 receptors in major depressive disorder studied with [11C]raclopride PET. J Psychopharmacol. 2011 Oct;25(10):1329-36. Epub: 2010/09/11. PMID: 20829308.

171. Hoffman BM, Babyak MA, Craighead WE, et al. Exercise and pharmacotherapy in patients with major depression: one-year follow-up of the SMILE study. Psychosom Med. 2011 Feb-Mar;73(2):127-33. Epub: 2010/12/15. PMID: 21148807.

172. Hofmann SG, Sawyer AT, Witt AA, et al. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. J Consult Clin Psychol. 2010 Apr;78(2):169-83. Epub: 2010/03/31. PMID: 20350028.

173. Høifødt RS, Strøm C, Kolstrup N, et al. Effectiveness of cognitive behavioural therapy in primary health care: A review. Fam Pract. 2011;28(5):489-504. PMID: 2011-24876-005. PMID: 21555339. First Author & Affiliation: Høifødt, Ragnhild Sørensen.

174. Hollon SD, DeRubeis RJ, Fawcett J, et al. Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial. JAMA Psychiatry. 2014 Oct 1;71(10):1157-64. Epub: 2014/08/22. PMID: 25142196.

175. Hollon SD, Jarrett RB, Nierenberg AA, et al. Psychotherapy and medication in the treatment of adult and geriatric depression: Which monotherapy or combined treatment? J Clin Psychiatry. 2005;66(4):455-68.

176. Hsiao FH, Jow GM, Lai YM, et al. The long-term effects of psychotherapy added to pharmacotherapy on morning to evening diurnal cortisol patterns in outpatients with major depression. Psychother Psychosom. 2011;80(3):166-72. Epub: 2011/03/11. PMID: 21389753.

177. Huibers MJ, van Breukelen G, Roelofs J, et al. Predicting response to cognitive therapy and interpersonal therapy, with or without antidepressant medication, for major depression: a pragmatic trial in routine practice. J Affect Disord. 2014 Jan;152-154:146-54. Epub: 2013/09/26. PMID: 24060588.

178. Ilhan Yargic L, Corapcioglu A, Kocabasoglu N, et al. A prospective randomized single-blind, multicenter trial comparing the efficacy and safety of paroxetine with and without quetiapine therapy in depression associated with anxiety. Int J Psychiatry Clin Pract. 2004;8(4):205-11.

179. Jakobsen JC, Hansen JL, Simonsen E, et al. The effect of adding psychodynamic therapy to antidepressants in patients with major depressive disorder. A systematic review of randomized clinical trials with meta-analyses and trial sequential analyses (Provisional abstract). Database of Abstracts of Reviews of Effects. 2012(4):4-14. PMID: DARE-12012011865.

180. Jakobsen JC, Hansen JL, Simonsen S, et al. Effects of cognitive therapy versus interpersonal psychotherapy in patients with major depressive disorder: a systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. Psychol Med. 2012 Jul;42(7):1343-57. Epub: 2011/11/05. PMID: 22051174.

181. Jakobsen JC, Hansen JL, Storebo OJ, et al. The effects of cognitive therapy versus 'treatment as usual' in patients with major depressive disorder. PLoS One. 2011;6(8)PMID: CN-00894260.

182. Jarrett RB, Minhajuddin A, Gershenfeld H, et al. Preventing depressive relapse and recurrence in higher-risk cognitive therapy responders: a randomized trial of continuation phase cognitive therapy, fluoxetine, or matched pill placebo. JAMA Psychiatry. 2013 Nov;70(11):1152-60. Epub: 2013/09/06. PMID: 24005123.

183. Jarrett RB, Thase ME. Comparative efficacy and durability of continuation phase cognitive therapy for preventing recurrent depression: design of a double-blinded, fluoxetine- and pill placebo-controlled, randomized trial with 2-year follow-up. Contemp Clin Trials. 2010 Jul;31(4):355-77. Epub: 2010/05/11. PMID: 20451668.

184. Jha MK, Minhajuddin A, Thase ME, et al. Improvement in self-reported quality of life with cognitive therapy for recurrent major depressive disorder. J Affect Disord. 2014;167:37-43. PMID: 2012667650. Language: English. Entry Date: In Process. Revision Date: 20140808. Publication Type: journal article. Journal Subset: Biomedical.

185. Joyce AS, O'Kelly JG, Ogrodniczuk JS, et al. A naturalistic trial of brief psychodynamic therapy for recurrent major depression. Psychodyn Psychiatry. 2012 Dec;40(4):645-71. Epub: 2012/12/12. PMID: 23216401.

186. Kaltenthaler E, Parry G, Beverley C. Computerized Cognitive Behaviour Therapy: A Systematic Review. Behav Cogn Psychother. 2004;32(1):31-55. PMID: 2004-12191-003. First Author & Affiliation: Kaltenthaler, Eva.

187. Kamatrh J. A Randomized, Double-Blind Placebo-controlled Study Evaluating the Efficacy of Omega 3 Fatty Acid Augmentation of Desvenlafaxine for the Treatment of Major Depressive Disorder in Patients With Medical Illness. Http://clinicaltrials.gov/show/NCT01803711. 2013PMID: CN-00974608.

188. Karlsson H, Hirvonen J, Salminen J, et al. Increased serotonin receptor 1A binding in major depressive disorder after psychotherapy, but not after SSRI pharmacotherapy, is related to improved social functioning capacity. Psychother Psychosom. 2013;82(4):260-1. Epub: 2013/06/06. PMID: 23736831.

189. Karyotaki E, Smit Y, Cuijpers P, et al. The long-term efficacy of psychotherapy, alone or in combination with antidepressants, in the treatment of adult major depression (Structured abstract). Health Technology Assessment Database. 2014(4)PMID: HTA-32014001117.

190. Kasper S, Gastpar M, Moller HJ, et al. Better tolerability of St. John's wort extract WS 5570 compared to treatment with SSRIs: a reanalysis of data from controlled clinical trials in acute major depression. Int Clin Psychopharmacol. 2010 Jul;25(4):204-13. Epub: 2010/06/24. PMID: 20568656.

191. Katon W, Robinson P, Von Korff M, et al. A multifaceted intervention to improve treatment of depression in primary care. Arch Gen Psychiatry. 1996 Oct;53(10):924-32. Epub: 1996/10/01. PMID: 8857869.

192. Katona C. New antidepressants for older people: a critical review of the evidence base. Encephale. 2008 Apr;34 Suppl 2:S71-S6. Epub: 2008/08/05. PMID: 18675006.

193. Katz T, Fisher P, Katz A, et al. The feasibility of a randomised, placebo-controlled clinical trial of homeopathic treatment of depression in general practice. Homeopathy. 2005;94(3):145-52. PMID: CN-00523588.

194. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med. 2000 May 18;342(20):1462-70. Epub: 2000/05/18. PMID: 10816183.

195. Kennedy SH, Segal ZV, Cohen NL, et al. Lithium carbonate versus cognitive therapy as sequential combination treatment strategies in partial responders to antidepressant medication: an exploratory trial. J Clin Psychiatry. 2003 Apr;64(4):439-44. Epub: 2003/04/29. PMID: 12716247.

196. Kessler D, Lewis G, Kaur S, et al. Therapist-delivered internet psychotherapy for depression in primary care: A randomised controlled trial. The Lancet. 2009;374(9690):628-34. PMID: 2009-18405-013. First Author & Affiliation: Kessler, David.

197. Khazaie H, Rezaie L, Rezaei Payam N, et al. Antidepressant-induced sexual dysfunction during treatment with fluoxetine, sertraline and trazodone; a randomized controlled trial. Gen Hosp Psychiatry. 2014 Oct 30Epub: 2014/12/04. PMID: 25467077.

198. Kingston T, Dooley B, Bates A, et al. Mindfulness-based cognitive therapy for residual depressive symptoms. Psychol Psychother. 2007 Jun;80(Pt 2):193-203. Epub: 2007/05/31. PMID: 17535594.

199. Klainin-Yobas P, Cho MAA, Creedy D. Efficacy of mindfulness-based interventions on depressive symptoms among people with mental disorders: A meta-analysis. Int J Nurs Stud. 2012;49(1):109-21. PMID: 2012-01598-015. PMID: 21963234. First Author & Affiliation: Klainin-Yobas, Piyanee.

200. Kloiber S. Acupuncture for the treatment of major depressive disorder: A randomized controlled trial. Deutsche zeitschrift fur akupunktur. 2013;54(3):35-6. PMID: CN-00850910.

201. Kocsis JH, Gelenberg AJ, Rothbaum BO, et al. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: the REVAMP Trial. Arch Gen Psychiatry. 2009 Nov;66(11):1178-88. Epub: 2009/11/04. PMID: 19884606.

202. Kocsis JH, Leon AC, Markowitz JC, et al. Patient preference as a moderator of outcome for chronic forms of major depressive disorder treated with nefazodone, cognitive behavioral analysis system of psychotherapy, or their combination. J Clin Psychiatry. 2009 Mar;70(3):354-61. Epub: 2009/02/05. PMID: 19192474.

203. Kocsis JH, Rush AJ, Markowitz JC, et al. Continuation treatment of chronic depression: a comparison of nefazodone, cognitive behavioral analysis system of psychotherapy, and their combination. Psychopharmacol Bull. 2003;37(4):73-87. Epub: 2004/05/08. PMID: 15131518.

204. Komossa K, Depping AM, Gaudchau A, et al. Second-generation antipsychotics for major depressive disorder and dysthymia. Cochrane Database Syst Rev. 2010(12):CD008121. Epub: 2010/12/15. PMID: 21154393.

205. Kramer U, de Roten Y, Perry JC, et al. Change in defense mechanisms and coping patterns during the course of 2-year-long psychotherapy and psychoanalysis for recurrent depression: a pilot study of a randomized controlled trial. J Nerv Ment Dis. 2013 Jul;201(7):614-20. Epub: 2013/07/03. PMID: 23817160.

206. Krishna M, Jauhari A, Lepping P, et al. Is group psychotherapy effective in older adults with depression? A systematic review. Int J Geriatr Psychiatry. 2011;26(4):331-40. PMID: 2011-07526-001. PMID: 20973096. First Author & Affiliation: Krishna, Murali.

207. Kriston L, von Wolff A, Westphal A, et al. EFFICACY AND ACCEPTABILITY OF ACUTE TREATMENTS FOR PERSISTENT DEPRESSIVE DISORDER: A NETWORK META-ANALYSIS. Depress Anxiety. 2014 Jan 21Epub: 2014/01/23. PMID: 24448972.

208. Krogh J, Nordentoft M, Sterne JAC, et al. The effect of exercise in clinically depressed adults: Systematic review and meta-analysis of randomized controlled trials. J Clin Psychiatry. 2011;72(4):529-38. PMID: 21034688.

209. Krogh J, Rostrup E, Thomsen C, et al. The effect of exercise on hippocampal volume and neurotrophines in patients with major depression--a randomized clinical trial. J Affect Disord. 2014 Aug;165:24-30. Epub: 2014/06/03. PMID: 24882173.

210. Kronstrom K, Salminen JK, Hietala J, et al. Personality traits and recovery from major depressive disorder. Nord J Psychiatry. 2011 Feb;65(1):52-7. Epub: 2010/05/27. PMID: 20500120.

211. Kruisdijk FR, Hendriksen IJ, Tak EC, et al. Effect of running therapy on depression (EFFORT-D). Design of a randomised controlled trial in adult patients [ISRCTN 1894]. BMC Public Health. 2012;12:50. Epub: 2012/01/21. PMID: 22260713.

212.   Lafferman J, Solomon K, Ruskin P. Lithium augmentation for treatment-resistant depression in the elderly. J Geriatr Psychiatry Neurol. 1988 Jan;1(1):49-52. Epub: 1988/01/01. PMID: 3150926.

213.   Laidlaw K, Davidson K, Toner H, et al. A randomised controlled trial of cognitive behaviour therapy vs treatment as usual in the treatment of mild to moderate late life depression. Int J Geriatr Psychiatry. 2008 Aug;23(8):843-50. Epub: 2008/03/04. PMID: 18311844.

214.   Lam RW, Kennedy SH. Evidence-based strategies for achieving and sustaining full remission in depression: focus on metaanalyses. Can J Psychiatry. 2004 Mar;49(3 Suppl 1):17S-26S. Epub: 2004/05/19. PMID: 15147033.

215.   Lampe L, Coulston CM, Berk L. Psychological management of unipolar depression. Acta Psychiatr Scand Suppl. 2013(443):24-37. Epub: 2013/04/23. PMID: 23586874.

216.   Landén M, Björling G, Agren H, et al. A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J Clin Psychiatry. 1998;59(12):664-8. PMID: CN-00159171.

217.   Lavretsky H. Combination of methylpehnidate with citalopram is superior to either drug alone in improving clinical and cognitive outcomes in geriatric depression. Neuropsychopharmacology. 2013;38:S90.

218.   Lavretsky H, Alstein LL, Olmstead RE, et al. Complementary use of tai chi chih augments escitalopram treatment of geriatric depression: a randomized controlled trial. Am J Geriatr Psychiatry. 2011 Oct;19(10):839-50. Epub: 2011/03/02. PMID: 21358389.

219.   Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: Systematic review and meta-regression analysis of randomised controlled trials. BMJ: British Medical Journal. 2001;322(7289):763-6. PMID: 2001-17117-001. First Author & Affiliation: Lawlor, Debbie A.

220.   Leo RJ, Ligot JSA, Jr. A systematic review of randomized controlled trials of acupuncture in the treatment of depression. J Affect Disord. 2007;97(1-3):13-22. PMID: 2006-23532-003. PMID: 16899301. First Author & Affiliation: Leo, Raphael J.

221.   Lesperance F, Frasure-Smith N, St-Andre E, et al. The efficacy of omega-3 supplementation for major depression: a randomized controlled trial. J Clin Psychiatry. 2011 Aug;72(8):1054-62. Epub: 2010/06/30. PMID: 20584525.

222.   Lester H, Gilbody S. Choosing a second generation antidepressant for treatment of major depressive disorder. BMJ. 2012;344:e1014. Epub: 2012/02/16. PMID: 22334542.

223.   Lewis AJ, Dennerstein M, Gibbs PM. Short-term psychodynamic psychotherapy: Review of recent process and outcome studies. Aust N Z J Psychiatry. 2008;42(6):445-55. PMID: 2008-12696-002. PMID: 18465371. First Author & Affiliation: Lewis, Andrew J.

224.   Lin C-H, Lin S-H, Jang F-L. Adjunctive low-dose aripiprazole with standard-dose sertraline in treating fresh major depressive disorder. J Clin Psychopharmacol. 2011;31(5):563-8. PMID: 2011-19925-003. PMID: 21869699. First Author & Affiliation: Lin, Chien-Ho.

225.   Ludman EJ, Simon GE, Tutty S, et al. A randomized trial of telephone psychotherapy and pharmacotherapy for depression: continuation and durability of effects. J Consult Clin Psychol. 2007 Apr;75(2):257-66. Epub: 2007/05/02. PMID: 17469883.

226.   Lynch TR, Morse JQ, Mendelson T, et al. Dialectical behavior therapy for depressed older adults: A randomized pilot study. The American Journal of Geriatric Psychiatry. 2003;11(1):33-45. PMID: 2003-01261-008. PMID: 12527538. First Author & Affiliation: Lynch, Thomas R.

227.   Lyons Z, van dWG, Shen Z, et al. Acupuncture and Chinese herbs as treatments for depression: An Australian pilot study. Complement Ther Clin Pract. 2012 Nov;18(4):216-20. PMID: 0165371.

228.   Ma SH, Teasdale JD. Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects. J Consult Clin Psychol. 2004 Feb;72(1):31-40. Epub: 2004/02/06. PMID: 14756612.

229.   Malik ML, Beutler LE, Alimohamed S, et al. Are all cognitive therapies alike? A comparison of cognitive and noncognitive therapy process and implications for the application of empirically supported treatments. J Consult Clin Psychol. 2003 Feb;71(1):150-8. Epub: 2003/02/27. PMID: 12602435.

230.   Manber R, Arnow B, Blasey C, et al. Patient's therapeutic skill acquisition and response to psychotherapy, alone or in combination with medication. Psychol Med. 2003 May;33(4):693-702. Epub: 2003/06/06. PMID: 12785471.

231.   Manber R, Edinger JD, Gress JL, et al. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. Sleep. 2008 Apr;31(4):489-95. Epub: 2008/05/07. PMID: 18457236.

232.   Manber R, Rush AJ, Thase ME, et al. The effects of psychotherapy, nefazodone, and their combination on subjective assessment of disturbed sleep in chronic depression. Sleep. 2003 Mar 15;26(2):130-6. Epub: 2003/04/10. PMID: 12683470.

233.   Maron E, Eller T, Vasar V, et al. Effects of bupropion augmentation in escitalopram-resistant patients with major depressive disorder: An open-label, naturalistic study. J Clin Psychiatry. 2009;70(7):1054-6.

234.	Martin S. A randomised controlled trial of cognitive therapy versus anti-depressants for major depression with sequential SPECT scanning to measure changes in cerebral blood flow with treatment. National Research Register. 1999PMID: CN-00712826.

235.	Martin SD, Martin E, Rai SS, et al. Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride: preliminary findings. Arch Gen Psychiatry. 2001 Jul;58(7):641-8. Epub: 2001/07/31. PMID: 11448369.

236.	Martiny K, Lunde M, Bech P, et al. A short-term double-blind randomized controlled pilot trial with active or placebo pindolol in patients treated with venlafaxine for major depression. Nord J Psychiatry. 2012 Jun;66(3):147-54. Epub: 2012/03/31. PMID: 22458638.

237.	Mather AS, Rodriguez C, Guthrie MF, et al. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder: Randomised controlled trial. Br J Psychiatry. 2002;180(5):411-5. PMID: 2002-13169-003. First Author & Affiliation: Mather, Anne S.

238.	Matreja PS, Badyal DK, Deswal RS, et al. Efficacy and safety of add on low-dose mirtazapine in depression. Indian J Pharmacol. 2012;44(2):173-7.

239.	Mazzucchelli T, Kane R, Rees C. Behavioral activation treatments for depression in adults: A meta-analysis and review. Clinical Psychology: Science and Practice. 2009;16(4):383-411. PMID: 2009-20281-001. First Author & Affiliation: Mazzucchelli, Trevor.

240.	McBride C, Segal Z, Kennedy S, et al. Changes in autobiographical memory specificity following cognitive behavior therapy and pharmacotherapy for major depression. Psychopathology. 2007;40(3):147-52. Epub: 2007/02/24. PMID: 17318006.

241.	McIntyre A, Gendron A, McIntyre A. Quetiapine adjunct to selective serotonin reuptake inhibitors or venlafaxine in patients with major depression, comorbid anxiety, and residual depressive symptoms: a randomized, placebo-controlled pilot study. Depress Anxiety. 2007;24(7):487-94. Epub: 2006/12/21. PMID: 17177199.

242.	McPherson S, Cairns P, Carlyle J, et al. The effectiveness of psychological treatments for treatment-resistant depression: a systematic review. Acta Psychiatr Scand. 2005 May;111(5):331-40. Epub: 2005/04/12. PMID: 15819726.

243.	Mehta P, Sharma M. Yoga as a complementary therapy for clinical depression. Complementary Health Practice Review. 2010;15(3):156-70. PMID: 2010-25846-004. First Author & Affiliation: Mehta, Purvi.

244.	Mergl R, Henkel V, Allgaier A-K, et al. Are treatment preferences relevant in response to serotonergic antidepressants and cognitive-behavioral therapy in depressed primary care patients? Results from a randomized controlled trial including a patients' choice arm. Psychother Psychosom. 2010;80(1):39-47. PMID: 2010-26489-005. PMID: 20975325. First Author & Affiliation: Mergl, Roland.

245.	Minelli A, Zambello F, Vaona A. Efficacia della psicoterapia cognitivo-comportamentale associata a terapia psicofarmacologica nella depressione. Revisione della letteratura metanalitica. Rivista di Psichiatria. 2011;46(1):18-23. PMID: 2011-05487-002. PMID: 21446108. First Author & Affiliation: Minelli, Alessandra.

246.	Miniati M, Rucci P, Frank E, et al. Sensitivity to change and predictive validity of the MOODS-SR questionnaire, last-month version. Psychother Psychosom. 2009;78(2):116-24. Epub: 2009/02/17. PMID: 19218830.

247.	Miranda J, Green BL, Krupnick JL, et al. One-year outcomes of a randomized clinical trial treating depression in low-income minority women. J Consult Clin Psychol. 2006;74(1):99-111. PMID: 2006-03253-010. PMID: 16551147. First Author & Affiliation: Miranda, Jeanne.

248.	Miser WF. Exercise as an effective treatment option for major depression in older adults. J Fam Pract. 2000 Feb;49(2):109-10. Epub: 2000/03/16. PMID: 10718684.

249.	Mohr DC, Carmody T, Erickson L, et al. Telephone-administered cognitive behavioral therapy for veterans served by community-based outpatient clinics. J Consult Clin Psychol. 2011 Apr;79(2):261-5. Epub: 2011/02/09. PMID: 21299274.

250.	Molenaar PJ, Dekker J, Van R, et al. Does adding psychotherapy to pharmacotherapy improve social functioning in the treatment of outpatient depression? Depress Anxiety. 2007;24(8):553-62. PMID: 2007-19727-004. PMID: 17131302. First Author & Affiliation: Molenaar, Pieter J.

251.	Moller H. Johanniskraut in der primar-arztlichen Therapie: Hypericum als fester Bestandteil in der Therapie von Depressionen. Schweiz Z Ganzheits Medizin. 2004 Nov;16(7-8):391-2. PMID: 0082428.

252.	Moore RG, Blackburn IM. Cognitive therapy in the treatment of non-responders to antidepressant medication: A controlled pilot study. Behav Cogn Psychother. 1997;25(3):251-9. PMID: CN-00185392.

253.	Moradveisi L, Huibers M, Renner F, et al. The influence of patients' preference/attitude towards psychotherapy and antidepressant medication on the treatment of major depressive disorder. J Behav Ther Exp Psychiatry. 2014;45(1):170-7.

254. Mota-Pereira J, Silverio J, Carvalho S, et al. Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. J Psychiatr Res. 2011 Aug;45(8):1005-11. Epub: 2011/03/08. PMID: 21377690.

255. Mozaffari-Khosravi H, Yassini-Ardakani M, Karamati M, et al. Eicosapentaenoic acid versus docosahexaenoic acid in mild-to-moderate depression: A randomized, double-blind, placebo-controlled trial. Eur Neuropsychopharmacol. 2013;23(7):636-44. PMID: 2012-22973-001. PMID: 22910528. First Author & Affiliation: Mozaffari-Khosravi, Hassan.

256. Mukaino Y, Park J, White A, et al. The effectiveness of acupuncture for depression - a systematic review of randomised controlled trials. Acupunct Med. 2005 Jun;23(2):70-6. PMID: 0075492.

257. Mulrow CD, Williams JW, Jr., Trivedi M, et al. Treatment of depression--newer pharmacotherapies. Psychopharmacol Bull. 1998;34(4):409-795. Epub: 1999/10/08. PMID: 10513454.

258. Mura G, Moro MF, Patten SB, et al. Exercise as an add-on strategy for the treatment of major depressive disorder: a systematic review. CNS Spectr. 2014 Mar 3:1-13. Epub: 2014/03/05. PMID: 24589012.

259. Mynors-Wallis L. Problem-solving treatment: evidence for effectiveness and feasibility in primary care. Int J Psychiatry Med. 1996;26(3):249-62. Epub: 1996/01/01. PMID: 8976466.

260. Nelson JC. S-adenosyl methionine (SAMe) augmentation in major depressive disorder. Am J Psychiatry. 2010 Aug;167(8):889-91. Epub: 2010/08/10. PMID: 20693465.

261. Nelson MK. Meta-analysis: Hypnotherapy/cognitive-behavioral therapy and its efficacy on depression compared to pharmacotherapy. US: ProQuest Information & Learning; 2002.

262. Nemeroff CB, Amchin J. Placebo-controlled trial of the efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. 11th European College of Neuropsychopharmacology Congress. Paris, France. 31st October 4th November 1998. 1998PMID: CN-00283230.

263. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry. 2002 Mar;159(3):477-9. Epub: 2002/03/01. PMID: 11870016.

264. Newhouse PA. Use of serotonin selective reuptake inhibitors in geriatric depression. J Clin Psychiatry. 1996;57 Suppl 5:12-22. Epub: 1996/01/01. PMID: 8647788.

265. Nieuwsma JA, Trivedi RB, McDuffie J, et al. Brief psychotherapy for depression: A systematic review and meta-analysis. Int J Psychiatry Med. 2012;43(2):129-51. PMID: 2012-17351-003. PMID: 22849036. First Author & Affiliation: Nieuwsma, Jason A.

266. Ninan PT, Rush AJ, Crits-Christoph P, et al. Symptomatic and syndromal anxiety in chronic forms of major depression: effect of nefazodone, cognitive behavioral analysis system of psychotherapy, and their combination. J Clin Psychiatry. 2002 May;63(5):434-41. Epub: 2002/05/25. PMID: 12025827.

267. Oeland A-M, Laessoe U, Olesen AV, et al. Impact of exercise on patients with depression and anxiety. Nordic Journal of Psychiatry. 2010;64(3):210-7. PMID: 2010-09396-010. PMID: 20100135. First Author & Affiliation: Oeland, Anne-Marie.

268. Onder E, Tural U. Faster response in depressive patients treated with fluoxetine alone than in combination with buspirone. J Affect Disord. 2003 Sep;76(1-3):223-7. Epub: 2003/08/29. PMID: 12943952.

269. Otto M, Wisniewski S. CBT for treatment resistant depression. Lancet. 2013 Feb 2;381(9864):352-3. PMID: 0165503.

270. Pae CU, Patkar AA, Jun TY, et al. Aripiprazole augmentation for treatment of patients with inadequate antidepressants response. Depress Anxiety. 2007;24(7):522-6.

271. 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. Epub: 2004/07/09. PMID: 15237083.

272. Papakostas GI, Cassiello CF, Iovieno N. Folates and S-adenosylmethionine for major depressive disorder. Can J Psychiatry. 2012 Jul;57(7):406-13. Epub: 2012/07/06. PMID: 22762295.

273. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. Biol Psychiatry. 2008 Apr 1;63(7):699-704. Epub: 2007/10/09. PMID: 17919460.

274. Papakostas GI, Mischoulon D, Shyu I, et al. S-adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. Am J Psychiatry. 2010 Aug;167(8):942-8. Epub: 2010/07/03. PMID: 20595412.

275. Papakostas GI, Petersen TJ, Kinrys G, et al. Aripiprazole augmentation of selective serotonin reuptake inhibitors for treatment-resistant major depressive disorder. J Clin Psychiatry. 2005;66(10):1326-30.

276. Parker G, Brotchie H, Parker K. Is combination olanzapine and antidepressant medication associated with a more rapid response trajectory than antidepressant alone? Am J Psychiatry. 2005;162(4):796-8.

277. Parker G, Paterson A, Blanch B. Suggested early onset of true action of antidepressant drugs may be artefactual: a heuristic study. Int Clin Psychopharmacol. 2013 Jan;28(1):29-32. Epub: 2012/12/13. PMID: 23232755.

278. Parker G, Roy K, Wilhelm K, et al. Assessing the comparative effectiveness of antidepressant therapies: a prospective clinical practice study. J Clin Psychiatry. 2001 Feb;62(2):117-25. Epub: 2001/03/15. PMID: 11247097.

279. Patkar AA, Masand PS, Pae CU, et al. A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. J Clin Psychopharmacol. 2006;26(6):653-6.

280. Paykel ES, Scott J, Cornwall PL, et al. Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. Psychol Med. 2005 Jan;35(1):59-68. Epub: 2005/04/22. PMID: 15842029.

281. Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy: a controlled trial. Arch Gen Psychiatry. 1999 Sep;56(9):829-35. Epub: 2003/07/30. PMID: 12884889.

282. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. Arch Gen Psychiatry. 2002 Oct;59(10):913-9. Epub: 2002/10/09. PMID: 12365878.

283. Pereira D, de QB, Miranda A, et al. Effects of physical exercise on plasma levels of brain-derived neurotrophic factor and depressive symptoms in elderly women-a randomized clinical trial. Arch Phys Med Rehabil. 2013 Aug;94(8):1443-50. PMID: 0170573.

284. Perez V, Puiigdemont D, Gilaberte I, et al. Augmentation of fluoxetine's antidepressant action by pindolol: analysis of clinical, pharmacokinetic, and methodologic factors. J Clin Psychopharmacol. 2001 Feb;21(1):36-45. Epub: 2001/02/24. PMID: 11199945.

285. Perez V, Soler J, Puigdemont D, et al. A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Grup de Recerca en Trastorns Afectius. Arch Gen Psychiatry. 1999 Apr;56(4):375-9. Epub: 1999/04/10. PMID: 10197835.

286. Perlis RH, Alpert J, Nierenberg AA, et al. Clinical and sociodemographic predictors of response to augmentation, or dose increase among depressed outpatients resistant to fluoxetine 20 mg/day. Acta Psychiatr Scand. 2003 Dec;108(6):432-8. Epub: 2003/11/18. PMID: 14616224.

287. Perlis RH, Nierenberg AA, Alpert JE, et al. Effects of adding cognitive therapy to fluoxetine dose increase on risk of relapse and residual depressive symptoms in continuation treatment of major depressive disorder. J Clin Psychopharmacol. 2002 Oct;22(5):474-80. Epub: 2002/09/28. PMID: 12352270.

288. Perry EB, Berman RM, Sanacora G, et al. Pindolol augmentation in depressed patients resistant to selective serotonin reuptake inhibitors: a double-blind, randomized, controlled trial. J Clin Psychiatry. 2004 Feb;65(2):238-43. Epub: 2004/03/09. PMID: 15003079.

289. Petersen T, Harley R, Papakostas GI, et al. Continuation cognitive-behavioural therapy maintains attributional style improvement in depressed patients responding acutely to fluoxetine. Psychol Med. 2004 Apr;34(3):555-61. Epub: 2004/07/21. PMID: 15259840.

290. Peterson TJ, Feldman G, Harley R, et al. Extreme response style in recurrent and chronically depressed patients: change with antidepressant administration and stability during continuation treatment. J Consult Clin Psychol. 2007 Feb;75(1):145-53. Epub: 2007/02/14. PMID: 17295573.

291. Pfaff JJ, Alfonso H, Newton RU, et al. ACTIVEDEP: a randomised, controlled trial of a home-based exercise intervention to alleviate depression in middle-aged and older adults. Br J Sports Med. 2014 Feb;48(3):226-32. Epub: 2013/07/09. PMID: 23833045.

292. Pilkington K, Kirkwood G, Rampes H, et al. Yoga for depression: The research evidence. J Affect Disord. 2005;89(1-3):13-24. PMID: 2006-00510-002. PMID: 16185770. First Author & Affiliation: Pilkington, Karen.

293. Pinquart M, Duberstein PR, Lyness JM. Treatments for later-life depressive conditions: a meta-analytic comparison of pharmacotherapy and psychotherapy. Am J Psychiatry. 2006 Sep;163(9):1493-501. Epub: 2006/09/02. PMID: 16946172.

294. Pinquart M, Duberstein PR, Lyness JM. Effects of pharmacotherapy and psychotherapy in late-life depression. Brown University Psychopharmacology Update. 2006;17(12):1. PMID: 2009361051. Language: English. Entry Date: 20080125. Publication Type: journal article. Journal Subset: Biomedical.

295. Posternak M, Novak S, Stern R, et al. A pilot effectiveness study: placebo-controlled trial of adjunctive L-triiodothyronine (T3) used to accelerate and potentiate the antidepressant response. Int J Neuropsychopharmacol. 2008 Feb;11(1):15-25. Epub: 2007/03/14. PMID: 17352847.

296. Potter C. Depression - psychosoziale Selbsttotung: Selbstbehauptungsstorungen als Ausdruck einer tiefen Identitatskrise durch Adapttion falscher Verhaltensmuster. Naturheilkunde. 2006;2006(5):22-4. PMID: 0093045.

297. Proudfoot J, Goldberg D, Mann A, et al. Computerized, interactive, multimedia cognitive-behavioural program for anxiety and depression in general practice. Psychol Med. 2003 Feb;33(2):217-27. Epub: 2003/03/08. PMID: 12622301.

298. Proudfoot J, Ryden C, Everitt B, et al. Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: Randomised controlled trial. Br J Psychiatry. 2004;185(1):46-54. PMID: 2004-16407-010. First Author & Affiliation: Proudfoot, Judith.

299. Quilty LC, De Fruyt F, Rolland JP, et al. Dimensional personality traits and treatment outcome in patients with major depressive disorder. J Affect Disord. 2008 Jun;108(3):241-50. Epub: 2007/12/11. PMID: 18067975.

300. Quilty LC, Dozois DJA, Lobo DSS, et al. Cognitive Structure and Processing During Cognitive Behavioral Therapy vs. Pharmacotherapy for Depression. Int J Cogn Ther. 2014;7(3):235-50. PMID: 2012744840. Language: English. Entry Date: 20141017. Revision Date: 20141024. Publication Type: journal article.

301. Rafanelli C, Ruini C, Belaise C, et al. Approccio cognitivo comportamentale alla perdita di efficacia durante la terapia di mantenimento con antidepressivi. Rivista di Psichiatria. 2003;38(5):259-62. PMID: 2003-10067-004. First Author & Affiliation: Rafanelli, Chiara.

302. Rahimi R, Nikfar S, Abdollahi M. Efficacy and tolerability of Hypericum perforatum in major depressive disorder in comparison with selective serotonin reuptake inhibitors: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2009 Feb 1;33(1):118-27. Epub: 2008/11/26. PMID: 19028540.

303. Rapaport MH, Gharabawi GM, Canuso CM, et al. Corrigendum: Effects of Risperidone Augmentation in Patients with Treatment-Resistant Depression: Results of Open-Label Treatment Followed by Double-Blind Continuation. Neuropsychopharmacology. 2006;31(11)PMID: 2006-20317-023. First Author & Affiliation: Rapaport, Mark Hyman.

304. Ravindran AV, Kennedy SH, O'Donovan MC, et al. Osmotic-release oral system methylphenidate augmentation of antidepressant monotherapy in major depressive disorder: Results of a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2008;69(1):87-94.

305. Reeves H, Batra S, May RS, et al. Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: A randomized, double-blind, placebo-controlled pilot study. J Clin Psychiatry. 2008;69(8):1228-36.

306. Rethorst CD, Wipfli BM, Landers DM. The antidepressive effects of exercise: A meta-analysis of randomized trials. Sports Med. 2009;39(6):491-511. PMID: 2009-08145-001. PMID: 19453207. First Author & Affiliation: Rethorst, Chad D.

307. Reynolds CF, III, Dew MA, Martire LM, et al. Treating depression to remission in older adults: A controlled evaluation of combined escitalopram with interpersonal psychotherapy versus escitalopram with depression care management. Int J Geriatr Psychiatry. 2010;25(11):1134-41. PMID: 2010-23017-006. PMID: 20957693. First Author & Affiliation: Reynolds, Charles F. III.

308. Robertson R, Robertson A, Jepson R, et al. Walking for depression or depressive symptoms: A systematic review and meta-analysis. Mental Health and Physical Activity. 2012;5(1):66-75.

309. Röder C, Schaefer M, Leucht S. Meta-Analyse zu Wirksamkeit und Verträglichkeit der Behandlung der leichten und mittelschweren Depression mit Johanniskraut. Fortschritte der Neurologie, Psychiatrie. 2004;72(6):330-43. PMID: 2004-15951-002. First Author & Affiliation: Röder, Claudia.

310. Roshanaei-Moghaddam B, Pauly MC, Atkins DC, et al. Relative effects of CBT and pharmacotherapy in depression versus anxiety: is medication somewhat better for depression, and CBT somewhat better for anxiety? Depress Anxiety. 2011 Jul;28(7):560-7. Epub: 2011/05/25. PMID: 21608087.

311. Ruhe HG, Huyser J, Swinkels JA, et al. Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. J Clin Psychiatry. 2006 Dec;67(12):1836-55. Epub: 2006/12/30. PMID: 17194261.

312. Rush AJ. Combining antidepressant medications: a good idea? Am J Psychiatry. 2010 Mar;167(3):241-3. Epub: 2010/03/03. PMID: 20194484.

313. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control Clin Trials. 2004 Feb;25(1):119-42. Epub: 2004/04/06. PMID: 15061154.

314. Rush AJ, Trivedi MH, Carmody TJ, et al. Self-reported depressive symptom measures: Sensitivity to detecting change in a randomized, controlled trial of chronically depressed, nonpsychotic outpatients. Neuropsychopharmacology. 2005;30(2):405-16.

315. Rush AJ, Wisniewski SR, Warden D, et al. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. Arch Gen Psychiatry. 2008 Aug;65(8):870-80. Epub: 2008/08/06. PMID: 18678792.

316. Rutherford B, Sneed J, Miyazaki M, et al. An open trial of aripiprazole augmentation for SSRI non-remitters with late-life depression. Int J Geriatr Psychiatry. 2007;22(10):986-91.

317. Saiz-Ruiz J, Ibaez A, Diaz-Marsa M, et al. Efficacy of venlafaxine in major depression resistant to selective serotonin reuptake inhibitors. Prog Neuropsychopharmacol Biol Psychiatry. 2002;26(6):1129-34.

318. Samad Z, Brealey S, Gilbody S. The effectiveness of behavioural therapy for the treatment of depression in older adults: A meta-analysis. Int J Geriatr Psychiatry. 2011;26(12):1211-20. PMID: 2012-11062-001. PMID: 21308789. First Author & Affiliation: Samad, Zara.

319. Sarris J, Fava M, Schweitzer I, et al. St John's wort (Hypericum perforatum) versus sertraline and placebo in major depressive disorder: continuation data from a 26-week RCT. Pharmacopsychiatry. 2012 Nov;45(7):275-8. Epub: 2012/05/18. PMID: 22592504.

320.	Sarris J, Schoendorfer N, Kavanagh DJ. Major depressive disorder and nutritional medicine: a review of monotherapies and adjuvant treatments. Nutr Rev. 2009 Mar;67(3):125-31. Epub: 2009/02/26. PMID: 19239627.

321.	Schaefer KL. Residual symptoms after treatment of chronic depression: A comparison across treatment modalities. US: ProQuest Information & Learning; 2008.

322.	Schatzberg AF, Rush AJ, Arnow BA, et al. Chronic depression: medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. Arch Gen Psychiatry. 2005 May;62(5):513-20. Epub: 2005/05/04. PMID: 15867104.

323.	Schuch FB, Vasconcelos-Moreno MP, Fleck MP. The impact of exercise on quality of life within exercise and depression trials: A systematic review. Mental Health and Physical Activity. 2011;4(2):43-8.

324.	Schwartz TL, Nasra GS, Chilton M, et al. Aripiprazole augmentation of selective serotonin or serotonin norepinephrine reuptake inhibitors in the treatment of major depressive disorder. Primary Psychiatry. 2007;14(1):67-9.

325.	Scott C, Tacchi MJ, Jones R, et al. Acute and one-year outcome of a randomised controlled trial of brief cognitive therapy for major depressive disorder in primary care. Br J Psychiatry. 1997 Aug;171:131-4. Epub: 1997/08/01. PMID: 9337947.

326.	Scott J, Palmer S, Paykel E, et al. Use of cognitive therapy for relapse prevention in chronic depression. Cost-effectiveness study. Br J Psychiatry. 2003 Mar;182:221-7. Epub: 2003/03/04. PMID: 12611785.

327.	Scott J, Teasdale JD, Paykel ES, et al. Effects of cognitive therapy on psychological symptoms and social functioning in residual depression. Br J Psychiatry. 2000 Nov;177:440-6. Epub: 2000/11/04. PMID: 11059998.

328.	Segal Z, Vincent P, Levitt A. Efficacy of combined, sequential and crossover psychotherapy and pharmacotherapy in improving outcomes in depression. J Psychiatry Neurosci. 2002 Jul;27(4):281-90. Epub: 2002/08/15. PMID: 12174737.

329.	Seo HJ, Jung YE, Woo YS, et al. Effect of augmented atypical antipsychotics on weight change in patients with major depressive disorder in a naturalistic setting. Hum Psychopharmacol. 2009 Mar;24(2):135-43. Epub: 2009/01/22. PMID: 19156709.

330.	Serfaty MA, Haworth D, Blanchard M, et al. Clinical effectiveness of individual cognitive behavioral therapy for depressed older people in primary care: a randomized controlled trial. Arch Gen Psychiatry. 2009 Dec;66(12):1332-40. Epub: 2009/12/10. PMID: 19996038.

331.	Sharma VK, Das S, Mondal S, et al. Effect of Sahaj Yoga on neuro-cognitive functions in patients suffering from major depression. Indian J Physiol Pharmacol. 2006 Oct-Dec;50(4):375-83. Epub: 2007/04/04. PMID: 17402267.

332.	Sharma VK, Das S, Mondal S, et al. Effect of Sahaj Yoga on depressive disorders. Indian J Physiol Pharmacol. 2005 Oct-Dec;49(4):462-8. Epub: 2006/04/04. PMID: 16579401.

333.	Shelton RC, Papakostas GI. Augmentation of antidepressants with atypical antipsychotics for treatment-resistant major depressive disorder. Acta Psychiatr Scand. 2008 Apr;117(4):253-9. Epub: 2008/01/15. PMID: 18190674.

334.	Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry. 2001 Jan;158(1):131-4. Epub: 2001/01/04. PMID: 11136647.

335.	Shimodera S, Watanabe N, Furukawa TA, et al. Change in quality of life after brief behavioral therapy for insomnia in concurrent depression: analysis of the effects of a randomized controlled trial. J Clin Sleep Med. 2014;10(4):433-9. Epub: 2014/04/16. PMID: 24733990.

336.	Shirazi MM. St. John's wort doesn't help with major depression. Tufts University Health & Nutrition Letter. 2001;19(4):2-.

337.	Siddique J, Chung JY, Brown CH, et al. Comparative effectiveness of medication versus cognitive-behavioral therapy in a randomized controlled trial of low-income young minority women with depression. J Consult Clin Psychol. 2012 Dec;80(6):995-1006. Epub: 2012/10/24. PMID: 23088620.

338.	Sikorski C, Luppa M, Kersting A, et al. Effektivität computer- und internetgestützter kognitiver Verhaitenstherapie bei Depression: Ein systematischer Literaturüberblick. Psychiatr Prax. 2011;38(2):61-8. PMID: 2011-08849-003. PMID: 20972949. First Author & Affiliation: Sikorski, Claudia.

339.	Simon JS, Nemeroff CB. Aripiprazole augmentation of antidepressants for the treatment of partially responding and nonresponding patients with major depressive disorder. J Clin Psychiatry. 2005 Oct;66(10):1216-20. Epub: 2005/11/02. PMID: 16259533.

340.	Singh NA, Stavrinos TM, Scarbek Y, et al. A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. J Gerontol A Biol Sci Med Sci. 2005 Jun;60(6):768-76. Epub: 2005/06/29. PMID: 15983181.

341.	Sjosten N, Kivela SL. The effects of physical exercise on depressive symptoms among the aged: a systematic review. Int J Geriatr Psychiatry. 2006 May;21(5):410-8. Epub: 2006/05/06. PMID: 16676285.

342.	Smith A, Jainer AK, Bennet C. Sertraline for recurrent major depression. Am J Psychiatry. 2005 May;162(5):1025-6. Epub: 2005/05/03. PMID: 15863821.

343.	Sokolski KN. Adjunctive aripiprazole for bupropion-resistant major depression. Ann Pharmacother. 2008;42(7-8):1124-9. PMID: 2010001602. Language: English. Entry Date: 20080926. Publication Type: journal article.

344. Sokolski KN, Conney JC, Brown BJ, et al. Once-daily high-dose pindolol for SSRI-refractory depression. Psychiatry Res. 2004 Feb 15;125(2):81-6. Epub: 2004/03/10. PMID: 15006431.

345. Spek V, Cuijpers P, Nyklíček I, et al. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: A meta-analysis. Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences. 2007;37(3):319-28. PMID: 2007-03729-002. First Author & Affiliation: Spek, Viola.

346. Spielmans GI, Berman MI, Linardatos E, et al. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. PLoS Med. 2013;10(3):e1001403. Epub: 2013/04/05. PMID: 23554581.

347. Spielmans GI, Berman MI, Usitalo AN. Psychotherapy versus second-generation antidepressants in the treatment of depression: A meta-analysis. J Nerv Ment Dis. 2011;199(3):142-9. PMID: 21346483.

348. Spijker J, van Straten A, Bockting CL, et al. Psychotherapy, antidepressants, and their combination for chronic major depressive disorder: a systematic review. Can J Psychiatry. 2013 Jul;58(7):386-92. Epub: 2013/07/23. PMID: 23870720.

349. Steffens DC, Doraiswamy PM, McQuoid DR. Bupropion SR in the naturalistic treatment of elderly patients with major depression. Int J Geriatr Psychiatry. 2001;16(9):862-5.

350. Steidtmann D, Manber R, Arnow BA, et al. Patient treatment preference as a predictor of response and attrition in treatment for chronic depression. Depress Anxiety. 2012;29(10):896-905.

351. Stevinson C. Negative result for St John's wort in major depression. Focus on Alternative and Complementary Therapies. 2001 Sep;6(3):196-7. PMID: 0029317.

352. Stich FA. A meta-analysis of physical exercise as a treatment for symptoms of anxiety and depression. US: ProQuest Information & Learning; 1999.

353. Sturmey P. Behavioral activation is an evidence-based treatment for depression. Behav Modif. 2009;33(6):818-29. PMID: 2009-22984-006. PMID: 19933444. First Author & Affiliation: Sturmey, Peter.

354. Tadic A, Gorbulev S, Dahmen N, et al. Rationale and design of the randomised clinical trial comparing early medication change (EMC) strategy with treatment as usual (TAU) in patients with Major Depressive Disorder - the EMC trial. Trials. 2010;11.

355. Taneja C, Papakostas GI, Jing Y, et al. Cost-effectiveness of adjunctive therapy with atypical antipsychotics for acute treatment of major depressive disorder. Ann Pharmacother. 2012;46(5):642-9. PMID: 2011549176. Language: English. Entry Date: 20130614. Revision Date: 20130614. Publication Type: journal article.

356. Teasdale JD, Moore RG, Hayhurst H, et al. Metacognitive awareness and prevention of relapse in depression: empirical evidence. J Consult Clin Psychol. 2002 Apr;70(2):275-87. Epub: 2002/04/16. PMID: 11952186.

357. Thase ME, Friedman ES, Fasiczka AL, et al. Treatment of men with major depression: a comparison of sequential cohorts treated with either cognitive-behavioral therapy or newer generation antidepressants. J Clin Psychiatry. 2000 Jul;61(7):466-72. Epub: 2000/08/11. PMID: 10937603.

358. Thase ME, Greenhouse JB, Frank E, et al. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. Arch Gen Psychiatry. 1997 Nov;54(11):1009-15. Epub: 1997/11/21. PMID: 9366657.

359. Thase ME, Rush AJ, Manber R, et al. Differential effects of nefazodone and cognitive behavioral analysis system of psychotherapy on insomnia associated with chronic forms of major depression. J Clin Psychiatry. 2002 Jun;63(6):493-500. Epub: 2002/06/29. PMID: 12088160.

360. Thomas P, Bordet R, Alexandre JY, et al. Pindolol addition shorten delay of action of paroxetine in major depression: a double blind controlled trial. 10th European College of Neuropsychopharmacology Congress. Vienna, Austria. 13th 17th September. 1997PMID: CN-00285037.

361. Trivedi MH, Greer TL, Church TS, et al. Exercise as an augmentation treatment for nonremitted major depressive disorder: A randomized, parallel dose comparison. J Clin Psychiatry. 2011;72(5):677-84.

362. Trivedi MH, Greer TL, Grannemann BD, et al. Exercise as an augmentation strategy for treatment of major depression. J Psychiatr Pract. 2006;12(4):205-13. PMID: 2009256065. Language: English. Entry Date: 20070105. Revision Date: 20091218. Publication Type: journal article.

363. Tsang HWH, Chan EP, Cheung WM. Effects of mindful and non mindful exercises on people with depression: A systematic review. Br J Clin Psychol. 2008;47(3):303-22. PMID: 2009-01053-005. First Author & Affiliation: Tsang, Hector W. H.

364. Turner P, Kantaria R, Young AH. A systematic review and meta-analysis of the evidence base for add-on treatment for patients with major depressive disorder who have not responded to antidepressant treatment: a European perspective. J Psychopharmacol. 2014 Feb;28(2):85-98. Epub: 2013/10/11. PMID: 24108407.

365. van Hees ML, Rotter T, Ellermann T, et al. The effectiveness of individual interpersonal psychotherapy as a treatment for major depressive disorder in adult outpatients: a systematic review. BMC Psychiatry. 2013;13:22. Epub: 2013/01/15. PMID: 23312024.

366. van Schaik A, van Marwijk H, Ader H, et al. Interpersonal psychotherapy for elderly patients in primary care. Am J Geriatr Psychiatry. 2006 Sep;14(9):777-86. Epub: 2006/09/01. PMID: 16943174.

367. Vis PM, Baardewijk M, Einarson TR. Duloxetine and venlafaxine-XR in the treatment of major depressive disorder: a meta-analysis of randomized clinical trials (Structured abstract). Ann Pharmacother. 2005;39(11):1798-807. PMID: DARE-12005002025.

368. Vitiello B, Shader RI, Parker CB, et al. Hyperforin plasma level as a marker of treatment adherence in the National Institutes of Health Hypericum Depression Trial. J Clin Psychopharmacol. 2005 Jun;25(3):243-9. Epub: 2005/05/07. PMID: 15876903.

369. Vittengl JR, Clark LA, Dunn TW, et al. Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. J Consult Clin Psychol. 2007 Jun;75(3):475-88. Epub: 2007/06/15. PMID: 17563164.

370. Wagner JJ. A meta-analysis/literature review comparing the effectiveness of SSRI antidepressants, cognitive behavioral therapy, and placebo for the treatment of depression. US: ProQuest Information & Learning; 2005.

371. Ward EC. Examining differential treatment effects for depression in racial and ethnic minority women: A qualitative systematic review. J Natl Med Assoc. 2007;99(3):265-74. PMID: 2007-03731-005. PMID: 17393951. First Author & Affiliation: Ward, Earlise C.

372. Warden D, Trivedi MH, Carmody T, et al. Adherence to Antidepressant Combinations and Monotherapy for Major Depressive Disorder: A CO-MED Report of Measurement-Based Care. J Psychiatr Pract. 2014 Mar;20(2):118-32. Epub: 2014/03/19. PMID: 24638046.

373. Watanabe N. Cost-effectiveness of brief behavioral therapy for insomnia comorbid with depression: Analysis of a randomized controlled trial. Psychosom Med. 2014;76(3):A-90. PMID: CN-01010647.

374. Watkins ER, Mullan E, Wingrove J, et al. Rumination-focused cognitive-behavioural therapy for residual depression: phase II randomised controlled trial. Br J Psychiatry. 2011 Oct;199(4):317-22. Epub: 2011/07/23. PMID: 21778171.

375. Weisler R, McIntyre RS, Bauer M. Extended-release quetiapine fumarate in the treatment of patients with major depressive disorder: adjunct therapy. Expert Rev Neurother. 2013 Nov;13(11):1183-200. Epub: 2013/11/02. PMID: 24175721.

376. Whiskey E, Werneke U, Taylor D. A systematic review and meta-analyis of Hypericum perforatum in depression: A comprehensive clinical review. Int Clin Psychopharmacol. 2001;16(5):239-52. PMID: 2001-18595-001. PMID: 11552767. First Author & Affiliation: Whiskey, E.. Release Date: 20010919. Publication Type: Journal, (0100).

377. Whyte EM, Basinski J, Farhi P, et al. Geriatric depression treatment in nonresponders to selective serotonin reuptake inhibitors. J Clin Psychiatry. 2004 Dec;65(12):1634-41. Epub: 2005/01/12. PMID: 15641868.

378. Wiles N, Thomas L, Abel A, et al. Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: Results of the CoBalT randomised controlled trial. Lancet. 2013 Feb 2;381(9864):375-84. PMID: 0165506.

379. Wilkinson P, Alder N, Juszczak E, et al. A pilot randomised controlled trial of a brief cognitive behavioural group intervention to reduce recurrence rates in late life depression. Int J Geriatr Psychiatry. 2009 Jan;24(1):68-75. Epub: 2008/07/11. PMID: 18615497.

380. Williams A-l, Katz D, Ali A, et al. Do essential fatty acids have a role in the treatment of depression? J Affect Disord. 2006;93(1-3):117-23. PMID: 2006-07896-014. PMID: 16650900. First Author & Affiliation: Williams, Anna-leila.

381. Wisniewski SR, Chen CC, Kim E, et al. Global benefit-risk analysis of adjunctive aripiprazole in the treatment of patients with major depressive disorder. Pharmacoepidemiol Drug Saf. 2009 Oct;18(10):965-72. Epub: 2009/08/08. PMID: 19662630.

382. Wu J, Yeung AS, Schnyer R, et al. Acupuncture for depression: a review of clinical applications. Can J Psychiatry. 2012 Jul;57(7):397-405. Epub: 2012/07/06. PMID: 22762294.

383. Xiao L. A Double-blind, Active-controlled, Randomized Study Comparing Mirtazapine Combined With Paroxetine or Paroxetine Monotherapy in Patients With Major Depressive Patients Without Early Improvement in the First 2 Weeks [NCT01458626]. Clinicaltrials.gov [www.clinicaltrials.gov]. 2011PMID: CN-00852533.

384. Xie F, Despiegel N, Danchenko N, et al. Cost effectiveness analysis of escitalopram compared to venlafaxine and fluvoxamine in treatment of major depressive disorder (Structured abstract). Int J Psychiatry Clin Pract. 2009;13(1):59-69. PMID: NHSEED-22009101046.

385. Yeung WF, Chung KF, Tso KC, et al. Electroacupuncture for residual insomnia associated with major depressive disorder: a randomized controlled trial. Sleep. 2011 Jun;34(6):807-15. Epub: 2011/06/02. PMID: 21629370.

386. Zajecka J, Dunner DL, Gelenberg AJ, et al. Sexual function and satisfaction in the treatment of chronic major depression with nefazodone, psychotherapy, and their combination. J Clin Psychiatry. 2002 Aug;63(8):709-16. Epub: 2002/08/29. PMID: 12197452.

387. Zhang ZJ, Chen HY, Yip KC, et al. The effectiveness and safety of acupuncture therapy in depressive disorders: systematic review and meta-analysis. J Affect Disord. 2010 Jul;124(1-2):9-21. Epub: 2009/07/28. PMID: 19632725.

388.   Zhang ZJ, Ng R, Man SC, et al. Dense cranial electroacupuncture stimulation for major depressive disorder-A single-blind, randomized, controlled study. PLoS One. 2012;7(1).

389.   Zilcha-Mano S, Dinger U, McCarthy KS, et al. Changes in well-being and quality of life in a randomized trial comparing dynamic psychotherapy and pharmacotherapy for major depressive disorder. J Affect Disord. 2014 Jan;152-154:538-42. Epub: 2013/11/02. PMID: 24176534.

390.   Zu S, Xiang YT, Liu J, et al. A comparison of cognitive-behavioral therapy, antidepressants, their combination and standard treatment for Chinese patients with moderate-severe major depressive disorders. J Affect Disord. 2014;152-154(1):262-7.

Appendix D. Risk of Bias Evaluations

Table D1. Risk of bias domains and ratings

Author, Year Trial Name	Randomi-zation method adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome asse-ssors masked?	Care providers masked?	Patients masked?	Low overall (i.e., <20%) attrition?	Low differential (i.e., <15%) attrition?	Use Intention-to-treat analyses?	Appropriate method of handling dropouts in analyses used?	Comprehensive (not selective) reporting of outcomes?	Risk of Bias
Barber et al., 2012[1]	Yes	NR	No	Unclear	No	No	No	No	Yes	Yes	Yes	Medium
Bastos et al., 2013[2]	NR	NR	Yes	Yes	No	No	No	No	Yes	Yes	No	Medium
Behnke et al., 2002[3]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	NR	Unclear	Medium
Bjerkenstedt et al., 2005[4]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Blom et al., 2007[5]	NR	NR	Yes	Yes	Unclear	Unclear	No	Yes	Unclear	Unclear	Yes	Medium[a]
Blumenthal et al., 1999[6] Babyak et al., 2000[7]	Unclear	Unclear	Unclear	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Medium
Blumenthal et al, 2007[8] Hoffman et al., 2008[9]	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Medium
Brenner et al., 2000[10]	NR	NR	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	High[b]
David et al., 2008[11] Sava et al., 2009[12]	NR	NR	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Medium
Davidson et al., 2002[13]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Medium
Dekker et al., 2008[14]	NR	NR	Yes	NR	No	No	No	Yes	Yes	Yes	Yes	Medium[c]
DeRubeis et al., 2005[15] Landenberger et al., 2002[31] Leykin et al., 2007[16]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Medium[d]

Table D1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Randomization method adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care providers masked?	Patients masked?	Low overall (i.e., <20%) attrition?	Low differential (i.e., <15%) attrition?	Use Intention-to-treat analyses?	Appropriate method of handling dropouts in analyses used?	Comprehensive (not selective) reporting of outcomes?	Risk of Bias
Dimidjian et al., 2006[17]	Yes	NR	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Medium
Fava et al., 2005[18] Papakostas et al., 2007[19]	NR	NR	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Frank et al., 2011[20] Rucci, 2011[21]	NR	NR	No	Unclear	No	No	No	Yes	Yes	Yes	No	High
Gastpar et al., 2005[22]	Yes	Unclear	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Yes	Medium
Gastpar et al., 2006[23]	Yes	Unclear	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Low
Gertsik et al., 2012[24]	NR	NR	Yes	NR	NR	Yes	No	No	No	NR	Yes	High
Harrer et al., 1999[25]	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	No	NR	Unclear	Medium
Hegerl et al., 2010[26]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	High[e]
Huang et al., 2005[27]	Unclear	Unclear	Unclear	Unclear	No	No	Yes	Yes	No	No	Yes	Medium
Jazayeri et al., 2008[28]	NR	NR	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	High
Kennedy et al., 2007[29]	NR	NR	No	NR	No	No	No	Yes	No	NR	Yes	High
Lam et al., 2013[30]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Low
Lenox-Smith and Jiang, 2008[32]	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
McGrath et al., 2013[33]	Yes	Yes	No	Yes	No	No	No	Yes	No	NR	Yes	High

D-2

Table D1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Randomization Method Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Outcome Assessors Masked?	Care Providers Masked?	Patients Masked?	Low Overall (i.e., <20%) Attrition?	Low Differential (i.e., <15%) Attrition?	Use Intention-to-Treat Analyses?	Appropriate Method of Handling Dropouts in Analyses Used?	Comprehensive (not selective) reporting of outcomes?	Risk of Bias
Menchetti et al., 2014[34]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Medium
Miranda et al., 2003[35] WECare	Yes	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Medium
Mischoulon et al., 2014[36]	Yes	NR	NR	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Moradveisi et al., 2013[37]	Yes	NR	Yes	Yes	No	No	No	No	Yes	Yes	Yes	High[†]
Moreno et al., 2006[38]	Unclear	Unclear	No	Unclear	Yes	Yes	Yes	Yes	No	Yes	No	High
Mynors-Wallis et al., 2000[39]	Unclear	Unclear	Yes	Yes	No	No	No	No	Unclear	Unclear	No	Medium
Qu et al., 2013[40] Chen et al., 2014[41]	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	No	NR	Yes	Medium
Raue et al., 2009[42]	NR	NR	NR	NR	No	No	Yes	NR	NR	NR	No	High
Salminen et al., 2008[43] Kronstrom et al., 2009[44]	NR	NR	Yes	NR	No	No	No	Yes	Yes	NR	Yes	Medium
Schrader et al., 2000[45]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Medium
Segal et al., 2006[46]	NR	NR	Yes	NR	No	No	No	No	No	NR	Yes	High
Shamsaei et al., 2008[47]	Yes	NR	Yes	No	No	No	NR	NR	NR	NR	Yes	High
Song et al., 2007[48]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NR	Unclear	No	High
Sun et al., 2013[49]	Yes	Yes	Unclear	Unclear	No	Yes	Yes	Yes	Yes	No	Yes	High

D-3

Table D1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Randomi-zation Method Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Outcome Asse-ssors Masked?	Care Providers Masked?	Patients Masked?	Low Overall (i.e., <20%) Attrition?	Low Differential (i.e., <15%) Attrition?	Use Intention-to-Treat Analyses?	Appropriate Method of Handling Dropouts in Analyses Used?	Comprehen sive (not selective) reporting of outcomes?	Risk of Bias
Szegedi et al., 2005[50]	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Yes	No	Yes	Medium
Thase et al., 2007[51] Rush et al., 2006[52] Trivedi et al., 2006[53] STAR*D	Yes	Yes	Yes	Yes	No	No	No	Unclear	Yes	Yes	Yes	Medium
van Gurp et al., 2002[54]	Yes	NR	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Medium
Zhang et al., 2009[55]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Medium

[a] Study rated high risk of bias for overall discontinuation outcomes.

[b] Study rated medium risk of bias for response and remission outcomes.

[c] Study rated high risk of bias for overall discontinuation outcomes.

[d] Study rated high risk of bias for change in HAM-D outcome.

[e] Study rated medium risk of bias for response and remission outcomes.

[f] Study rated medium for overall discontinuation and discontinuation due to adverse events outcomes.

Appendix D References

1.   Barber JP, Barrett MS, Gallop R, et al. Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial. J Clin Psychiatry. 2012 Jan;73(1):66-73. Epub: 2011/12/14. PMID: 22152401.

2.   Bastos AG, Guimaraes LS, Trentini CM. Neurocognitive changes in depressed patients in psychodynamic psychotherapy, therapy with fluoxetine and combination therapy. J Affect Disord. 2013 Dec;151(3):1066-75. PMID: 24103853.

3.   Behnke K, Jensen GS, Graubaum HJ, et al. Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression. Adv Ther. 2002 Jan-Feb;19(1):43-52. Epub: 2002/05/15. PMID: 12008860.

4.   Bjerkenstedt L, Edman GV, Alken RG, et al. Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. Eur Arch Psychiatry Clin Neurosci. 2005 Feb;255(1):40-7. Epub: 2004/11/13. PMID: 15538592.

5.   Blom MB, Jonker K, Dusseldorp E, et al. Combination treatment for acute depression is superior only when psychotherapy is added to medication. Psychother Psychosom. 2007;76(5):289-97. Epub: 2007/08/19. PMID: 17700049.

6.   Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older patients with major depression. Arch Intern Med. 1999 Oct 25;159(19):2349-56. Epub: 1999/11/05. PMID: 10547175.

7.   Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom Med. 2000 Sep-Oct;62(5):633-8. Epub: 2000/10/06. PMID: 11020092.

8.   Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom Med. 2007 Sep-Oct;69(7):587-96. Epub: 2007/09/12. PMID: 17846259.

9.   Hoffman BM, Blumenthal JA, Babyak MA, et al. Exercise fails to improve neurocognition in depressed middle-aged and older adults. Med Sci Sports Exerc. 2008 Jul;40(7):1344-52. Epub: 2008/06/27. PMID: 18580416.

10.   Brenner R, Azbel V, Madhusoodanan S, et al. Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. Clin Ther. 2000 Apr;22(4):411-9. PMID: 10823363.

11.   David D, Szentagotai A, Lupu V, et al. Rational emotive behavior therapy, cognitive therapy, and medication in the treatment of major depressive disorder: a randomized clinical trial, posttreatment outcomes, and six-month follow-up. J Clin Psychol. 2008 Jun;64(6):728-46. Epub: 2008/05/14. PMID: 18473339.

12.   Sava FA, Yates BT, Lupu V, et al. Cost-effectiveness and cost-utility of cognitive therapy, rational emotive behavioral therapy, and fluoxetine (Prozac) in treating depression: a randomized clinical trial. J Clin Psychol. 2009 Jan;65(1):36-52. Epub: 2008/12/04. PMID: 19051275.

13.   Davidson JRT, Gadde KM, Fairbank JA, et al. Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: a randomized controlled trial. J Am Med Assoc. 2002;287(14):1807-14.

14.   Dekker JJ, Koelen JA, Van HL, et al. Speed of action: the relative efficacy of short psychodynamic supportive psychotherapy and pharmacotherapy in the first 8 weeks of a treatment algorithm for depression. J Affect Disord. 2008 Jul;109(1-2):183-8. Epub: 2007/12/07. PMID: 18061276.

15.   DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch Gen Psychiatry. 2005 Apr;62(4):409-16. Epub: 2005/04/06. PMID: 15809408.

16.   Leykin Y, Amsterdam JD, DeRubeis RJ, et al. Progressive resistance to a selective serotonin reuptake inhibitor but not to cognitive therapy in the treatment of major depression. J Consult Clin Psychol. 2007 Apr;75(2):267-76. Epub: 2007/05/02. PMID: 17469884.

17.   Dimidjian S, Hollon SD, Dobson KS, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol. 2006 Aug;74(4):658-70. Epub: 2006/08/03. PMID: 16881773.

18.   Fava M, Alpert J, Nierenberg AA, et al. A double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. J Clin Psychopharmacol. 2005 Oct;25(5):441-7. Epub: 2005/09/15. PMID: 16160619.

19.   Papakostas GI, Crawford CM, Scalia MJ, et al. Timing of clinical improvement and symptom resolution in the treatment of major depressive disorder. A replication of findings with the use of a double-blind, placebo-controlled trial of Hypericum perforatum versus fluoxetine. Neuropsychobiology. 2007;56(2-3):132-7. Epub: 2008/02/09. PMID: 18259086.

20.   Frank E, Cassano GB, Rucci P, et al. Predictors and moderators of time to remission of major depression with interpersonal psychotherapy and SSRI pharmacotherapy. Psychol Med. 2011 Jan;41(1):151-62. Epub: 2010/04/13. PMID: 20380782.

21.   Rucci P, Frank E, Scocco P, et al. Treatment-emergent suicidal ideation during 4 months of acute management of unipolar major depression with SSRI pharmacotherapy or interpersonal psychotherapy in a randomized clinical trial. Depress Anxiety. 2011 Apr;28(4):303-9. Epub: 2011/02/11. PMID: 21308882.

22.   Gastpar M, Singer A, Zeller K. Efficacy and tolerability of hypericum extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. Pharmacopsychiatry. 2005 Mar;38(2):78-86. PMID: 15744631.

23.   Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study. Pharmacopsychiatry. 2006 Mar;39(2):66-75. Epub: 2006/03/24. PMID: 16555167.

24.   Gertsik L, Poland RE, Bresee C, et al. Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. J Clin Psychopharmacol. 2012 Feb;32(1):61-4. Epub: 2011/12/27. PMID: 22198441.

25.   Harrer G, Schmidt U, Kuhn U, et al. Comparison of equivalence between the St. John's wort extract LoHyp-57 and fluoxetine. Arzneimittelforschung. 1999 Apr;49(4):289-96. Epub: 1999/05/25. PMID: 10337446.

26.   Hegerl U, Hautzinger M, Mergl R, et al. Effects of pharmacotherapy and psychotherapy in depressed primary-care patients: a randomized, controlled trial including a patients' choice arm. Int J Neuropsychopharmacol. 2010;13(1):31-44. PMID: 19341510.

27.   Huang Y, Htut W, Li D, et al. Studies on the clinical observation and cerebral glucose metabolism in depression treated by electro-scalp acupuncture compared to fluoxetine. Int J Clin Acupunct. 2005;14(1):7-26. PMID: 0077160.

28.   Jazayeri S, Tehrani-Doost M, Keshavarz SA, et al. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. Aust N Z J Psychiatry. 2008 Mar;42(3):192-8. Epub: 2008/02/06. PMID: 18247193.

29.   Kennedy SH, Konarski JZ, Segal ZV, et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry. 2007 May;164(5):778-88. Epub: 2007/05/04. PMID: 17475737.

30.   Lam RW, Parikh SV, Ramasubbu R, et al. Effects of combined pharmacotherapy and psychotherapy for improving work functioning in major depressive disorder. Br J Psychiatry. 2013 Nov;203(5):358-65. PMID: 24029535.

31.   Landenberger NAD. Self-concept and attributional style in the treatment of depression: ProQuest Information & Learning; 2002.

32.   Lenox-Smith AJ, Jiang Q. Venlafaxine extended release versus citalopram in patients with depression unresponsive to a selective serotonin reuptake inhibitor. Int Clin Psychopharmacol. 2008 May;23(3):113-9. Epub: 2008/04/15. PMID: 18408525.

33.   McGrath CL, Kelley ME, Holtzheimer PE, et al. Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatry. 2013 Aug;70(8):821-9. Epub: 2013/06/14. PMID: 23760393.

34.   Menchetti M, Rucci P, Bortolotti B, et al. Moderators of remission with interpersonal counselling or drug treatment in primary care patients with depression: randomised controlled trial. Br J Psychiatry. 2014 Feb;204(2):144-50. PMID: 24311553.

35.   Miranda J, Chung JY, Green BL, et al. Treating depression in predominantly low-income young minority women: a randomized controlled trial. JAMA. 2003 Jul 2;290(1):57-65. Epub: 2003/07/03. PMID: 12837712.

36.   Mischoulon D, Price LH, Carpenter LL, et al. A double-blind, randomized, placebo-controlled clinical trial of S-adenosyl-L-methionine (SAMe) versus escitalopram in major depressive disorder. J Clin Psychiatry. 2014 Dec 24. Epub: 2014/02/07. PMID: 24500245.

37.   Moradveisi L, Huibers MJ, Renner F, et al. Behavioural activation v. antidepressant medication for treating depression in Iran: randomised trial. Br J Psychiatry. 2013 Mar;202(3):204-11. Epub: 2013/02/09. PMID: 23391727.

38.   Moreno RA, Teng CT, Almeida KM, et al. *Hypericum perforatum* versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample. Rev Bras Psiquiatr. 2006 Mar;28(1):29-32. PMID: 16612487.

39.   Mynors-Wallis LM, Gath DH, Day A, et al. Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. BMJ. 2000 Jan 1;320(7226):26-30. Epub: 2000/01/05. PMID: 10617523.

40.   Qu SS, Huang Y, Zhang ZJ, et al. A 6-week randomized controlled trial with 4-week follow-up of acupuncture combined with paroxetine in patients with major depressive disorder. J Psychiatr Res. 2013 Jun;47(6):726-32. Epub: 2013/03/19. PMID: 23498306.

41.   Chen JQ, Lin WR, Wang SX, et al. Acupuncture/electroacupuncture enhances antidepressant effect of seroxat: the symptom checklist-90 scores. Neural Regen Res. 2014;9(2):213-22.

42.   Raue PJ, Schulberg HC, Heo M, et al. Patients' depression treatment preferences and initiation, adherence, and outcome: a randomized primary care study. Psychiatr Serv. 2009 Mar;60(3):337-43. Epub: 2009/03/03. PMID: 19252046.

43.   Salminen JK, Karlsson H, Hietala J, et al. Short-term psychodynamic psychotherapy and fluoxetine in major depressive disorder: a randomized comparative study. Psychother Psychosom. 2008;77(6):351-7. Epub: 2008/08/15. PMID: 18701831.

44.   Kronstrom K, Salminen JK, Hietala J, et al. Does defense style or psychological mindedness predict treatement response in major depression? Depress Anxiety. 2009;26(7):689-95. Epub: 2009/06/06. PMID: 19496102.

45.   Schrader E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. Int Clin Psychopharmacol. 2000 Mar;15(2):61-8. PMID: 10759336.

46.   Segal ZV, Kennedy S, Gemar M, et al. Cognitive reactivity to sad mood provocation and the prediction of depressive relapse. Arch Gen Psychiatry. 2006 Jul;63(7):749-55. Epub: 2006/07/05. PMID: 16818864.

47.   Shamsaei F, Rahimi A, Zarabian MK, et al. Efficacy of pharmacotherapy and cognitive therapy, alone and in combination in major depressive disorder. Hong Kong J Psychiatr. 2008;18(2):76-80.

48.   Song Y, Zhou D, Fan J, et al. Effects of electroacupuncture and fluoxetine on the density of GTP-binding-proteins in platelet membrane in patients with major depressive disorder. J Affect Disord. 2007 Mar;98(3):253-7. Epub: 2006/08/22. PMID: 16919758.

49.   Sun H, Zhao H, Ma C, et al. Effects of electroacupuncture on depression and the production of glial cell line-derived neurotrophic factor compared with fluoxetine: a randomized controlled pilot study. J Altern Complement Med. 2013 Sep;19(9):733-9. PMID: 23647408.

50. Szegedi A, Kohnen R, Dienel A, et al. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. BMJ. 2005 Mar 5;330(7490):503. Epub: 2005/02/15. PMID: 15708844.

51. Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. Am J Psychiatry. 2007 May;164(5):739-52. Epub: 2007/05/04. PMID: 17475733.

52. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med. 2006 Mar 23;354(12):1231-42. Epub: 2006/03/24. PMID: 16554525.

53. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med. 2006 Mar 23;354(12):1243-52. Epub: 2006/03/24. PMID: 16554526.

54. van Gurp G, Meterissian GB, Haiek LN, et al. St John's wort or sertraline? Randomized controlled trial in primary care. Can Fam Physician. 2002 May;48:905-12. Epub: 2002/06/11. PMID: 12053635.

55. Zhang WJ, Yang XB, Zhong BL. Combination of acupuncture and fluoxetine for depression: a randomized, double-blind, sham-controlled trial. J Altern Complement Med. 2009 Aug;15(8):837-44. Epub: 2009/08/15. PMID: 19678773.

Appendix E. Summary of Findings Tables

Table E1. Benefits and risks of second-generation antidepressants compared with cognitive behavioral therapy monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with CBT monotherapy*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response Assessed with: HAM-D Followup: range 8 to 16 weeks	46 per 100	41 per 100 (35 to 49)	RR, 0.91 (0.77 to 1.07)	660 (5 trials[1-5])	Moderate[b]	Comparisons limited to fluoxetine, fluvoxamine, paroxetine, or sertraline and CBT, CT, PST, or REBT. Sensitivity analysis with 3 additional trials (rated high risk of bias)[6-8] did not change the statistical significance of the results (RR, 1.03; 95% CI, 0.92 to 1.15).
Remission Assessed with: HAM-D Followup: range 12 to 16 weeks	48 per 100	47 per 100 (35 to 63)	RR, 0.98 (0.73 to 1.32)	432 (3 trials[1,4,5])	Low[b,c]	Comparisons limited to fluoxetine, fluvoxamine, or paroxetine and CBT, CT, PST, or REBT. Sensitivity analysis with 3 additional trials (rated high risk of bias)[6-8] did not change the statistical significance of the results (RR, 1.08; 95% CI, 0.90 to 1.30).
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity Assessed with: Social Adjustment Scale Followup: mean 12 weeks	Mean scores were within 0.3 points between groups and CIs overlapped.	Mean scores were within 0.3 points between groups and CIs overlapped.	Not estimable	116 (1 study[4])	Low[d,e]	Comparison limited to fluvoxamine or paroxetine and PST.
Suicidal ideas or behaviors	2 per 100	2 per 100 (0 to 9)	RR, 0.85 (0.18 to	373 (3	Insufficient[g] [,h]	None

Followup: range 8 to 16 weeks	3.91) trials[2,3,5,9])[†]

Table E1. Benefits and risks of second-generation antidepressants compared with cognitive behavioral therapy monotherapy (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with CBT monotherapy*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Serious adverse events Followup: range 8 to 10 weeks	NA	NA	RR, 5.32 (0.3 to 95.0)	228 (2 trials[2,3,9])[f]	Insufficent[g,i,j]	None
Overall risk for overall adverse events: Followup: mean 13 weeks	1 per 100	16 per 100 (2 to 100)	RR, 17.84 (2.32 to 137.4)	170 (1 trial[l])	Insufficient[k,l]	Results for SGAs appear to substantially underestimate the risk of adverse events. A comprehensive systematic assessments of the risk of harms for SGAs reported that, on average, 60 percent of patients treated with SGAs experience at least one adverse event during the course of treatment.
Overall discontinuation Followup: range 8 to 14 weeks	16 per 100	16 per 100 (9 to 27)	RR, 1.00 (0.59 to 1.69)	611 (4 trials[1,2,4,5])[m]	Moderate[b]	Second-generation antidepressants are limited to fluoxetine, fluvoxamine, and paroxetine.
Overall discontinuation Followup: mean 24 weeks	40 per 100	65 per 100 (51 to 81)	RR, 1.61 (1.28 to 2.02)	301 (1 RCT{Segal, 2006 #1719})	Low[n]	Second-generations used to treat patients could have included sertraline, paroxetine, or venlafaxine.

Table E1. Benefits and risks of second-generation antidepressants compared with cognitive behavioral therapy monotherapy (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with CBT monotherapy*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Discontinuation because of adverse events Followup: range 8 to 14 weeks	3 per 100	7 per 100 (1 to 45)	RR, 2.54 (0.39 to 16.47)	441 (3 trials[2,4,5])[o]	Low[i,k]	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: few events.

[c] Downgraded for inconsistency: inconsistent direction of point estimates.

[d] Downgraded for imprecision: sample size that does not fulfill optimal information size (OIS).

[e] Downgraded for risk of bias: outcomes reporting bias; most trials did not report on functional capacity.

[f] Includes high risk of bias evidence because number of studies with lower risk of bias insufficient to allow meta-analysis of findings.

[g] Downgraded 2 steps for serious imprecision: very few events.

[h] Downgraded for risk of bias: one of 3 studies had a high risk of bias due to high overall and differential attrition rates, and available data based on completers analysis only.

[i] Not upgraded for large effect because of extreme imprecision.

[j] Downgraded for risk of bias: one study's data for subset of patients with MDD not based on ITT analysis.

[k] Downgraded 2 steps for serious imprecision: very few events; 95% confidence intervals wide.

[l] Downgraded for risk of bias: adverse events reported only for study completers.

[m] Does not include data from 3 high risk of bias studies because sensitivity analysis including those studies did not change meta-analysis findings.

[n] Downgraded 2steps for serious risk of bias: method of randomization unclear, and error in how N's randomized and attrition reported raise doubt about whether attrition rates in SGA and CBT groups were accidentally transposed.

[o] Does not include data from one high risk of bias study because sensitivity analysis including that study did not change meta-analysis findings.

CBT = cognitive behavioral therapy; CI = confidence interval; CT = cognitive therapy; HAM-D = Hamilton Depression Rating Scale; ITT = intent-to-treat; MDD = major depressive disorder; NA = not applicable; PST = problem solving therapy; REBT = rational emotive behavior therapy; RR = risk ratio; SGA = second-generation antidepressant

Table E2. Benefits and risks of second-generation antidepressants compared with combinations of second-generation antidepressants and cognitive behavioral therapy

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with combination of SGA and CBT*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response Assessed with: MADRS or HAM-D Followup: mean 12 weeks	68 per 100	70 per 100 (58 to 85)	RR, 1.03 (0.85 to 1.26)	174 (2 trials[4,10])	Low[b,c]	Comparison limited to escitalopram, fluvoxamine, or paroxetine and problem solving therapy or telephone CBT.
Remission Assessed with: MADRS or HAM-D Followup: mean 12 weeks	55 per 100	58 per 100 (45 to 76)	RR, 1.06 (0.82 to 1.38)	174 (2 trials[4,10])	Low[b,c]	Comparison limited to escitalopram, fluvoxamine, or paroxetine and problem solving therapy or telephone CBT.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity Assessed with: Multiple scales Followup: mean 12 weeks	Patients receiving the combination reported greater improvement on 3 of 5 work functioning measures compared with patients on SGA alone	Patients receiving the combination reported greater improvement on 3 of 5 work functioning measures compared with patients on SGA alone	Not estimable	170 (2 trials[4,10])	Low[b,c]	Comparison limited to escitalopram, fluvoxamine, or paroxetine and problem solving therapy or telephone CBT.
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Followup: mean 16 weeks	16 per 100	12 per 100 (6 to 26)	RR, 0.77 (0.37 to 1.6)	176 (2 trials[4,10])	Low[e]	Comparison limited to escitalopram with escitalopram combined with telephone CBT

Table E2. Benefits and risks of second-generation antidepressants compared with combinations of second-generation antidepressants and cognitive behavioral therapy (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with combination of SGA and CBT*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Discontinuation because of adverse events Followup: mean 12 weeks	2 per 100	7 per 100 (2 to 27)	RR, 2.93[f] (0.72 to 11.91)	176 (2 trials[4,10])	Low[d,e]	Comparison limited to escitalopram with escitalopram combined with telephone CBT

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for inconsistency: inconsistent direction of point estimates.

[c] Downgraded for imprecision: sample size that does not fulfill optimal information size (OIS).

[d] Downgraded 2 steps for imprecision: very few events; very wide 95% confidence interval across both thresholds of appreciable differences.

[e] RR corrected for zero cell case.

CBT = cognitive behavioral therapy; CT = cognitive therapy; MADRS = Montgomery-Åsberg Depression Rating Scale; NA = not applicable; RR = risk ratio; SGA = second-generation antidepressant

Table E3. Benefits and risks of second-generation antidepressants compared with integrative therapies (interpersonal psychotherapy) monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with integrative therapies*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Followup: mean 6 weeks	61 per 100	62 per 100 (53 to 75)	RR, 1.02 (0.86 to 1.22)	318 (1 trial[11])	Low[b,c]	Comparison limited to escitalopram and IPT.
Remission Assessed with: HAM-D Followup: range 8 to 12 weeks	50 per 100	46 per 100 (39 to 54)	RR, 0.92 (0.78 to 1.08)	605 (2 trials[11,12])	Low[d,e]	Comparison limited to citalopram, escitalopram, or sertraline and IPT. A third study (rated high risk of bias)[12] reported no significant difference in effect but did not present rates of remission.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors Followup: mean 12 weeks	16 per 100	6 per 100 (3 to 13)	RR, 0.39 (0.19 to 0.82)	291 (2 trials[12-14])	Insufficient[f,g]	Comparison is limited to escitalopram vs. IPT
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Followup: mean 13 weeks	11 per 100	16 per 100 (9 to 26)	RR, 1.38 (0.83 to 2.3)	384 (2 trials[11,15])	Insufficient[h, i]	Comparison limited to citalopram, nefazodone, and sertraline vs. interpersonal therapy

Table E3. Benefits and risks of second-generation antidepressants compared with integrative therapies (interpersonal psychotherapy) monotherapy (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with integrative therapies*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Discontinuation because of adverse events Followup: mean 13 weeks	NR	NR	RR, 0.33[j] (0.01 to 8.06)	287 (1 trial[11])	Insufficient[I,k]	Comparison limited to citalopram and sertraline versus interpersonal therapy

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: sample size that does not fulfill optimal information size (OIS).

[c] Downgraded for risk of bias: high risk of bias due to insufficient reporting of methods and baseline differences between groups in duration of illness.

[d] Downgraded for inconsistency: inconsistent direction of point estimates.

[e] Downgraded for risk of bias: one of the trials was rated high risk of bias due to insufficient reporting of methods and baseline differences between groups in duration of illness.

[f] Downgraded 2 steps for imprecision: very few events in both studies, and in one study, 95% confidence interval crosses both thresholds of appreciable differences.

[g] Downgraded for risk of bias: high attrition rate; unclear whether outcome assessors were masked; in one study, no indication that incidence data for suicidal ideas or behaviors adjusted for baseline presence of suicidal ideas or behaviors or that ITT analysis applied to these data.

[h] Downgraded for risk of bias: one of two available studies did not report discontinuations taking place between randomization and onset of treatment; impossible to determine how unreported discontinuations would have affected our findings.

[i] Downgraded 2 steps for serious imprecision: very few events.

[j] RR corrected for zero cell case.

[k] Downgraded for risk of bias: outcomes reporting bias; most studies did not report on discontinuation because of adverse events.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; IPT = Interpersonal Psychotherapy; ITT = intent-to-treat; NA = not applicable; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table E4. Benefits and risks of second-generation antidepressants compared with combinations of second-generation antidepressants and integrative therapies (interpersonal psychotherapy)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with combination of SGA and interpersonal therapy*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission Assessed with: HAM-D Followup: range 8 to 12 weeks	NR	NR	OR, 3.22 (1.02 to 10.12)	97 (1 trial[15])	Low[b]	Comparison limited to nefazodone and combination of nefazodone and IPT.
Remission in patients with comorbid anxiety disorder Assessed with: HAM-D Followup: mean 8 weeks	64 per 100	70 per 100 (49 to 100)	RR, 1.09 (0.76 to 1.58)	55 (1 trial[11])	Insufficient [c,d]	Comparisons limited to sertraline or citalopram and IPT.
Remission in patients without comorbid anxiety disorder Assessed with: HAM-D Followup: mean 8 weeks	67 per 100	46 per 100 (36 to 59)	RR, 0.69 (0.54 to 0.89)	209 (1 trial[11])	Insufficient [c,d]	Comparisons limited to sertraline or citalopram and IPT.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events Followup: mean 12 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Followup: mean 16 weeks	24 per 100	24 per 100 (16 to 47)	RR, 1.11 (0.64 to 1.93)	96 (1 trial[15])	Low[e]	Comparison limited to one trial of nefazodone with a combination of nefazodone and IPT

Table E4. Benefits and risks of second-generation antidepressants compared with combinations of second-generation antidepressants and integrative therapies (interpersonal psychotherapy) (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with combination of SGA and interpersonal therapy*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded 2 steps for imprecision: very few events.

[c] Downgraded 2 steps for serious imprecision: single study, small sample size, unable to estimate an effect.

[d] Downgraded for risk of bias: secondary subgroup analyses not prespecified.

[e] Downgraded 2 steps for imprecision: very few events; very wide 95% confidence interval across both thresholds of appreciable differences.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; IPT = interpersonal psychotherapy; NA = not applicable; NR = not reported; RR = risk ratio; SGA = second-generation antidepressant

Table E5. Benefits and risks of second-generation antidepressants compared with psychodynamic therapies monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit and risk of psychodynamic therapies*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission assessed with: HAM-D followup: mean 16 weeks	46 per 100	48 per 100 (27 to 86)	RR, 1.04 (0.58 to 1.86)	51 (1 trial[16])	Low[b,c]	Comparison limited to fluoxetine. Intervention was short-term psycho-dynamic therapy.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity Followup: mean 16 weeks (one trial followed to 24 months)	Few statistically significant differences in various scales. In one study, the proportion of patients on sick leave was higher in the SGA group than the PSYD group (12% vs. 4%, not significant),	Few statistically significant differences in various scales. In one study, the proportion of patients on sick leave was higher in the SGA group than the PSYD group (12% vs. 4%,not significant)	Not estimable	221 (2 trials[16,17])	Low[b,d]	Comparison limited to fluoxetine. One trial's intervention was short-term PSYD; the other's was long-term.
Suicidal ideas or behaviors Followup: mean 8 weeks	16 per 100	16 per 100 (7 to 34)	RR, 1.01 (0.47 to 2.09)	141 (1 trial[18])	Insufficient[e,f]	Comparison limited to one trial of venlafaxine with short-term psychodynamic therapy
Suicidal ideas or behaviors Followup: mean 96 weeks	3 per 100	4 per 100 (1 to 19)	RR, 1.32 (0.3 to 5.73)	181 (1 trial[17])	Low[e]	Comparison limited to one trial of fluoxetine with long-term psychodynamic therapy
Serious adverse	NA	NA	NA	0 (0 trials)	Insufficient	None

Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

Table E5. Benefits and risks of second-generation antidepressants compared with psychodynamic therapies monotherapy (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk of psychodynamic therapies*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Overall discontinuation Followup: mean 8 to 16 weeks	24 per 100	24 per 100 (16 to 36)	RR, 1.01 (0.68 to 1.52)	298 (3 trials[16,18,19])	Low[e]	Comparisons are limited to fluoxetine and venlafaxine with short-term psychodynamic therapy
Overall discontinuation Followup: mean 48 weeks	19 per 100	24 per 100 (9 to 69)	RR, 1.25 (0.44 to 3.57)	51 (1 trial[16])	Low[e]	Comparison limited to one trial of fluoxetine with short-term psychodynamic therapy
Overall discontinuation Followup: mean 96 weeks	19 per 100	15 per 100 (8 to 29)	RR, 0.81 (0.43 to 1.55)	181 (1 trial[17])	Low[e]	Comparison limited to one trial of fluoxetine with long-term psychodynamic therapy
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: few events; sample size that does not fulfill optimal information size (OIS).

[c] Downgraded for risk of bias: outcomes reporting bias; most trials did not report on remission.

[d] Downgraded for inconsistency: inconsistent direction of point estimates.

[e] Downgraded 2 steps for imprecision: very few events; 95% confidence interval crosses both thresholds of appreciable differences.

[f] Downgraded for risk of bias: high overall attrition and unclear how that attrition affected incidence rates of suicidal ideas or behaviors, despite use of modified ITT analysis.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; ITT = intent-to-treat; NA = not applicable; NR = not reported; PSYD = psychodynamic therapy; RR = Risk ratio; SGA = second-generation antidepressant

Table E6. Benefits and risks of second-generation antidepressants compared with combinations of second-generation antidepressants and psychodynamic therapies

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with combination of SGA and psychodynamic therapies*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission	NA	NA	NA	0 (0 trials)	Insufficient	None
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	Effects on WAIS-III measures were similar for SGA and the combination of SGA and PSYD.	Effects on WAIS-III measures were similar for SGA and the combination of SGA and PSYD.	Not estimable	181 (1 trial[17])	Low[b]	Comparison limited to fluoxetine with long-term PSYD.
Suicidal ideas or behaviors Followup: mean 96 weeks	1 per 100	4 per 100 (1 to 39)	RR, 4.00 (0.46 to 35.1)	182 (1 trial[17])	Low[c]	Comparison limited to fluoxetine with long-term psychodynamic therapy
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Followup: mean 96 weeks	32 per 100	15 per 100 (9 to 27)	RR, 0.48 (0.27 to 0.85)	182 (1 trial[17])	Low[c]	Comparison limited to fluoxetine with a combination of fluoxetine and long-term psychodynamic therapy
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded 2 steps for serious imprecision: sample size that does not fulfill optimal information size (OIS).

[c] Downgraded 2 steps for serious imprecision: very few events; 95% confidence interval crosses both thresholds of appreciable differences.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NR: not reported; RR = risk ratio; PSYD = psychodynamic therapy; SGA = second-generation antidepressant

Table E7. Benefits and risks of second-generation antidepressants compared with third-wave cognitive behavioral therapy monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with third wave CBT*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Followup: range 13 to 16 weeks	71 per 100	55 per 100 (45 to 67)	RR, 0.77 (0.64 to 0.94)	243 (2 trials[5,20])	Insufficient[b,c]	Comparison limited to sertraline and paroxetine.
Remission Assessed with: HAM-D Followup: range 13 to 16 weeks	67 per 100	38 per 100 (29 to 49)	RR, 0.57 (0.44 to 0.74)	243 (2 trials[5,20])	Insufficient[b,c]	Comparison limited to sertraline and paroxetine.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events Followup: mean 13 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Followup: mean 13 to 16 weeks	10 per 100	27 per 100 (14 to 52)	RR, 2.76 (1.4 to 5.41)	243 (2 trials[5,20])	Low[d,e,f]	Comparisons limited to paroxetine or sertraline with third-wave CBT
Discontinuation because of adverse events Followup: mean 13 to 16 weeks	3 per 100	17 per 100 (5 to 54)	RR, 5.17 (1.6 to 16.64)	243 (2 trials[5,20])	Low[d,e,f]	Comparisons limited to paroxetine or sertraline with third-wave CBT

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded 2 steps for serious risk of bias: dosage for one study capped below the upper limit of typically prescribed range; :suspected bias from one study's extremely high reported rates of response.

[c] Downgraded for imprecision: sample size does not fulfill optimal information size (OIS).

[d] Not upgraded for large effect because of imprecision.

[e] Downgraded for imprecision: few events; 95% confidence interval wide.

[f] Downgraded for risk of bias: in one of 2 available studies, high differential attrition rate between SGA and third-wave CBT groups may have affected the findings, although use of ITT analysis may partially offset the potentially increased bias.

CBT = cognitive behavioral therapy; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; ITT = intent-to-treat; NA = not applicable; RR: Risk ratio; SGA = second-generation antidepressant

Table E8. Benefits and risks of second-generation antidepressants compared with any psychological therapy monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with any psychological therapy*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission	NA	NA	NA	0 (0 trials)	Insufficient	None
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors Followup: range 8 to 16 weeks	7 per 100	10 per 100 (6 to 16)	RR, 1.36 (0.87 to 2.14)	796 (4 trials[2,5,9,11,18])[b]	Low[c,d]	Interventions limited to: 1) fluoxetine, paroxetine, citalopram, sertraline, escitalopram, sertraline, and 2) CBT, short-term psychodynamic therapy, interpersonal therapy, integrative therapy, and third-wave CBT
Serious adverse events Followup: mean 8 weeks	NA	NA	RR, 4.54[e] (0.25 to 82.92)	180 (1 trial[2,9])	Insufficient[f, g]	Interventions limited to paroxetine and CBT
Overall risk for adverse events: Followup: mean 14 weeks	1 per 100	16 per 100 (2 to 100)	RR, 17.84 (2.32 to 137.4)	170 (1 trial[1])	Insufficient[g,h]	Interventions limited to fluoxetine and CBT
Overall discontinuation Followup: range 8 to 16 weeks	13 per 100	19 per 100 (12 to 30)	RR, 1.47 (0.94 to 2.30)	1092 (7 trials[1,2,4,5,9,11,16,20])	Moderate[c]	Interventions are limited to: 1) fluoxetine, fluvoxamine, paroxetine, sertraline, and 2) behavioral activation, cognitive therapy, problem solving therapy, rational emotive behavior therapy, short-term psychodynamic supportive psychotherapy

Table E8. Benefits and risks of second-generation antidepressants compared with any psychological therapy monotherapy (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with any psychological therapy*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Discontinuation because of adverse events Followup: range 8 to 16 weeks	2 per 100	6 per 100 (2 to 18)	RR, 2.73 (0.89 to 8.38)	871 (5 trials [2,4,5,9,11,20])	Moderate[c]	Interventions are limited to: 1) fluoxetine, fluvoxamine, paroxetine, sertraline, and 2) behavioral activation, cognitive therapy, problem solving therapy, rational emotive therapy

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Includes data from three high risk of bias studies because sensitivity analysis including those studies led to findings with different directionality than primary analysis.

[c] Downgraded for imprecision: few events.

[d] Downgraded for risk of bias: very high attrition in two studies, and use of completers analysis only for suicidality data in a third study.

[e] RR corrected for zero cell cases.

[f] Downgraded 2 steps for serious imprecision: very few events, 95% confidence interval extremely wide and crosses both thresholds of appreciable differences.

[g] Downgraded for risk of bias: serious adverse events data that was received from authors reported only for study completers.

[h] Downgraded for risk of bias: overall risk of adverse events reported only for study completers.

CBT = cognitive behavioral therapy; CI = confidence interval; CT = cognitive therapy; NA = not applicable; RR = risk ratio; SGA = second-generation antidepressant

Table E9. Benefits and risks of second-generation antidepressants compared with combinations of any second-generation antidepressants and psychological therapy

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with combination of SGA and any psychological therapy*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGAs*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission	NA	NA	NA	0 (0 trials)	Insufficient	None
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	1 per 100	4 per 100 (1 to 39)	RR, 3.96 (0.45 to 34.71)	181 (1 trial[17])	Low[b]	Comparison limited to fluoxetine vs. long-term psychodynamic therapy
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall risk for adverse events:	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Followup: mean 12 weeks	22 per 100	21 per 100 (13 to 32)	RR, 0.93 (0.59 to 1.47)	272 (3 trials[4,10,15])	Low[b]	Comparisons limited to escitalopram, fluvoxamine, or paroxetine vs. escitalopram, fluvoxamine, or paroxetine + CBT, or nefazodone vs. nefazodone + integrative therapy.
Overall discontinuation Followup: mean 96 weeks	32 per 100	15 per 100 (9 to 27)	RR, 0.48 (0.27 to 0.85)	182 (1 trial[17])	Low[b]	Comparison limited to fluoxetine vs. long-term psychodynamic therapy
Discontinuation because of adverse events	2 per 100	8 per 100 (2 to 37)	RR, 3.42 (0.73 to 16.01)	176 (2 trials[4,10])	Low[b]	Comparisons limited to escitalopram, fluvoxamine, or paroxetine vs. CBT.

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded 2 steps for serious imprecision: very few events; 95% confidence interval extremely wide and crosses both thresholds of appreciable differences.

CBT = cognitive behavioral therapy; CI = confidence interval; NA = not applicable; RR = risk ratio; SGA = second-generation antidepressant

Table E10. Benefits and risks of second-generation antidepressants compared with acupuncture monotherapy

Outcomes	Anticipated Absolute Effects[a]: *Benefit and risk with Acupuncture*	Anticipated Absolute Effects[a] (95% CI): *Benefit and risk with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D followup: mean 6 weeks	55 per 100	63 per 100 (49 to 81)	RR, 1.15 (0.89 to 1.47)	173 (2 trials[21,22])	Low[b,c]	Direct evidence limited to comparisons of fluoxetine vs acupuncture. Results consistent with NWMA comparisons to SGA medications (RR, 0.75, 95% CI, 0.43-1.30).
Remission Assessed with: HAM-D followup: mean 6 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall risk for adverse events: direct evidence Followup: mean 6 weeks	6 per 100	4 per 100 (1 to 24)	RR, 0.69 (0.12 to 3.98)	98 (1 trial[21])	Insufficient[d,e]	None
Overall risk for adverse events: indirect evidence Followup: mean 8 weeks	10 per 100	40 per 100 (35 to 47)	RR, 3.96 (3.4 to 4.62)	3128 (21 trials as reported in Zhang et. al.,[23])	Moderate[f]	A systematic review which did not meet our eligibility criteria because it also included other depressive disorders than MDD provides the most comprehensive assessment of the comparative risk of harms between SGAs and acupuncture.
Overall discontinuation Followup: mean 6 weeks	56 per 100	2 per 100 (0 to 31)	RR, 0.03 (0 to 0.56)	50 (1 trial[22])	Insufficient[e,g,h]	None

Table E10. Benefits and risks of second-generation antidepressants compared with acupuncture monotherapy (continued)

Outcomes	Anticipated Absolute Effects[a]: *Benefit and risk with Acupuncture*	Anticipated Absolute Effects[a] (95% CI): *Benefit and risk with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for risk of bias: high dropout; uncertainty about randomization and allocation concealment; no masking of outcome assessors.

[c] Downgraded for imprecision: few events not meeting optimal information size (OIS).

[d] Downgraded for risk of bias: validity of data in question due to lack of reporting about key components of study design, including randomization, allocation concealment, between-group similarity of baseline characteristics, and use of blinded outcome assessment.

[e] Downgraded 2 steps for serious imprecision: very few events; 95% confidence interval crosses both thresholds of appreciable differences.

[f] Downgraded for indirectness: numbers are based on a systematic review that included all depressive disorders and some first generation antidepressants.

[g] Downgraded for risk of bias: outcome reporting bias in that only 1 of 3 available trials comparing SGAs with acupuncture reported overall risks of adverse events.

[h] Not upgraded for large effect because of extreme imprecision.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; ITT = intent-to-treat; NA = not applicable; NWMA = network meta-analysis; RR: Risk ratio; SGA = second-generation antidepressant

Table E11. Benefits and risks of second-generation antidepressants compared with combination of SGA and acupuncture

Outcomes	Anticipated Absolute Effects[a]: *Benefit and risk with Combination of SGA and Acupuncture*	Anticipated Absolute Effects[a] (95% CI): *Benefit and risk with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D followup: mean 6 weeks	71 per 100	58 per 100 (47 to71)	RR, 0. 82 (0.66 to 1.00)	288 (2 trials[24-26])	Low[b,c]	Direct evidence limited to two studies comparing either fluoxetine or paroxetine with acupuncture plus SGA.
Remission Assessed with: HAM-D followup: mean 6 weeks	25 per 100	23 per 100 (13 to 42)	RR, 0.92 (0.50 to 1.69)	160 (1 trial[25,26])	Low[d]	Direct evidence limited to a single trial of paroxetine with combined acupuncture plus paroxetine.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors Followup: mean 8 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall risk for adverse events Followup: mean 8 weeks	4 per 100	9 per 100 (2 to 40)	RR, 2.0 (0.43 to 9.4)	105 (1 trial[26])	Low[d]	None
Overall discontinuation Followup: mean 6 weeks	9 per 100	10 per 100 (5 to 23)	RR, 1.11 (0.50 to 2.46)	240 (2 trials[24-26])	Low[d]	None
Discontinuation because of adverse events Followup: mean 6 weeks	2 per 100	1 per 100 (0 to 10)	RR, 0.74 (0.11 to 4.9)	240 (2 trials[24,25])	Low[d]	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: few events.

[c] Downgraded for inconsistency: large effect size differences between studies.

[d] Downgraded two steps for imprecision: very few events; 95% confidence interval crosses both thresholds of appreciable differences.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NA = not applicable; OIS = optimal information size; RR: Risk ratio; SGA = second-generation antidepressant

Table E12. Benefits and risks of second-generation antidepressants compared with omega-3 fatty acids monotherapy

Outcomes	Anticipated Absolute Effects[a]: *Benefit and risk with Omega-3 Fatty Acids*	Anticipated Absolute Effects[a] (95% CI): *Benefit and risk with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Followup: mean 8 weeks	45 per 100	40 per 100 (19 to 82)	RR, 1.96 (1.26 to 3.05)	NA, Network meta-analysis	Low[b,c]	Direct evidence is limited to a comparison of fluoxetine with Omega-3 fatty acids. Results from network meta-analyses conflict with findings of the RCT and indicate greater efficacy of SGAs (RR, 1.96; 95% CI, 1.26 to 3.05) compared with Omega-3 fatty acids
Remission Assessed with: HAM-D Followup: mean 8 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors Followup: mean 8 weeks	5 per 100	2 per 100 (0 to 39)	RR, 0.33 (0.01 to 7.72)	40 (1 trial[27])	Insufficient[d,e]	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall risk for adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Followup: mean 4 weeks	15 per 100	15 per 100 (3 to 66)	RR, 1.0 (0.23 to 4.37)	40 (1 trial[27])	Low[d]	None
Discontinuation because of adverse events Followup: mean 8 weeks	5 per 100	5 per 100 (0 to 75)	RR, 1.0 (0.07 to 14.9)	40 (1 trial[27])	Insufficient[d,e]	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for indirectness: results are based on network meta-analyses.

[c] Downgraded for risk of bias: suspected outcomes reporting bias; only one of two studies reported response rates.

[d] Downgraded 2 steps for serious imprecision: very few events; 95% confidence intervals crosses both thresholds of appreciable differences.

[e] Downgraded for risk of bias: high dropout rates, no intention-to-treat analyses available.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NA = not applicable; RR: Risk ratio; SGA = second-generation antidepressant

Table E13. Benefits and risks of second-generation antidepressants compared with combination of SGA and omega-3 fatty acids

Outcomes	Anticipated Absolute Effects[a]: *Benefit and risk with combination of SGA and Omega-3 Fatty Acids*	Anticipated Absolute Effects[a] (95% CI): *Benefit and risk with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Followup mean 8 weeks	47 per 100	29 per 100 (16 to 54)	RR, 0.62 (0.33 to 1.14)	74[b] (2 trials[27,28])	Insufficient[c,d]	Direct evidence is limited to a comparison of fluoxetine with omega-3 fatty acids.
Remission Assessed with: HAM-D Followup mean 8 weeks	44 per 100	18 per 100 (7 to 51)	RR, 0.41 (0.15 to 1.14)	42 (1 trial[28])	Insufficient[c,d]	Direct evidence is limited to a comparison of fluoxetine with omega-3 fatty acids.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall risk for adverse events Followup: mean 12 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Followup: mean 4 weeks	10 per 100	24 per 100 (8 to 70)	RR, 2.38 (0.81 to 6.98)	82 (2 trials[27,28])	Low[e]	Overall discontinuation rates were also similar between fluoxetine and a combination of fluoxetine and omega-3 fatty acids
Discontinuation because of adverse events Followup: mean 8 weeks	10 per 100	5 per 100 (1 to 51)	RR, 0.5 (0.05 to 5.08)	40 (1 trial[27])	Insufficient[e,f]	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Includes two post randomization exclusions from Gertsik, 2012[28] and counted as treatment failures.

[c] Downgraded 2 steps for serious risk of bias: high attrition and lack of ITT analysis.

[d] Downgraded for imprecision: few events and confidence interval crosses threshold of appreciable difference.

[e] Downgraded 2 steps for serious imprecision: very few events; 95% confidence interval crosses both thresholds of appreciable differences.

[f] Downgraded for risk of bias: outcome reporting bias.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NA = not applicable; RR: Risk ratio; SGA = second-generation antidepressant

Table E14. Benefits and risks of second-generation antidepressants compared with S-Adenosyl methionine monotherapy

Outcomes	Anticipated Absolute Effects[a]: *Benefit and risk with combination of SGA and Integrative Therapy*	Anticipated Absolute Effects[a] (95% CI): *Benefit and risk with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Followup mean 12 weeks	36 per 100	34 per 100 (21 to 54)	RR, 1.22 (0.66 to 2.26)	NA; results based on network meta-analyses	Low[b,c]	Direct evidence is limited to a single comparison of escitalopram with SAMe. Network meta-analyses found no statistically significant differences in response rates between SGA estimate: 1.22 (0.66, 2.26) compared with SAMe.
Remission Assessed with: HAM-D Followup mean 12 weeks	28 per 100	28 per 100 (16 to 48)	RR, 0.98 (0.57 to 1.71)	129 (1 trial[29])	Insufficient[d,e]	Direct evidence is limited to a single comparison of escitalopram with SAMe.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors Followup: mean 8 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall risk for adverse events	NA	NA	NA	0 (0 trials)	Insufficient	No information on overall risk of adverse events. One study provided data about selected adverse events only.
Overall discontinuation Followup: mean 12 weeks	44 per 100	52 per 100 (34 to 79)	RR, 1.19 (0.78 to 1.8)	129 (1 trial[29])	Low[d]	None

Table E14. Benefits and risks of second-generation antidepressants compared with S-Adenosyl methionine monotherapy (continued)

Outcomes	Anticipated Absolute Effects[a]: *Benefit and risk with combination of SGA and Integrative Therapy*	Anticipated Absolute Effects[a] (95% CI): *Benefit and risk with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Discontinuation because of adverse events Followup: mean 12 weeks	5 per 100	12 per 100 (3 to 44)	RR, 2.63 (0.73 to 9.46)	129 (1 trial[29])	Insufficent [d,e]	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for imprecision: small study size.

[c] Downgraded for indirectness: results are based on network meta-analyses.

[d] Downgraded 2 steps for serious imprecision: few events; 95% confidence interval nearly crosses both thresholds of appreciable differences.

[e] Downgraded for risk of bias: very high overall drop out rate.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NA = not applicable; NR: not reported; RR: Risk ratio; SAMe = S-Adenosylmethionine; SGA = second-generation antidepressant

Table E15. Benefits and risks of second-generation antidepressants compared with St. John's wort monotherapy

Outcomes	Anticipated Absolute Effects[a]: *Benefit and risk with St. John's Wort*	Anticipated Absolute Effects[a] (95% CI): *Benefit and risk with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D Followup: range 4-12 weeks	54 per 100	52 per 100 (45 to 60)	RR, 0.96 (0.83 to 1.10)	1517 (9 trials[30-39])	Low[b,c]	Evidence is based on the comparison of SSRIs with SJW.
Response in subgroup of older adults Assessed with: HAM-D Followup: mean 6 weeks	64 per 100	55 per 100 (43 to 71)	RR, 0.83 (0.67 to 1.11)	161 (1 trial[36])	Low[e]	Comparison limited to fluoxetine and SJW in older adults (60 to 80 years)
Remission Assessed with: HAM-D followup: mean 13 weeks	36 per 100	30 per 100 (24 to 36)	RR, 0.82 (0.67 to 1.00)	768 (5 trials[31,33,37,39-41])	Low[c,d]	Evidence is based on the comparison of SSRIs with SJW.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	1 per 100	1 per 100 (0 to 6)	RR, 1.03 (0.11 to 9.81)	331 (2 trials[34,42])	Insufficient[e,g]	None
Serious adverse events	2 per 100	1 per 100 (0 to 5)	RR, 0.79 (0.23 to 2.72)	840 (4 trials[34,35,39,42])	Low[e]	None
Overall risk for adverse events	39 per 100	47 per 100 (41 to 53)	RR, 1.19 (1.05 to 1.34)	1427 (8 trials[30,31,34-36,38,39,42])	Moderate[d]	None
Overall risk for adverse events in subgroup based on older age	16 per 100	20 per 100 (10 to 40)	RR, 1.30 (0.66 to 2.54)	131 (1 trial[36])	Low[e]	Comparison limited to fluoxetine and SJW in older adults (60 to 80 years)
Overall discontinuation	15 per 100	19 per 100 15 to 24)	RR, 1.28 (1.01 to 1.62)	1651 (9 trials[30,31,33-36,38,39,42])	Moderate[c]	None
Discontinuation because of adverse events	4 per 100	7 per 100 (5 to 11)	RR, 1.7 (1.12 to 2.6)	1651 (9 trials[30,31,33-36,38,39,42])	Moderate[c]	None

Table E15. Benefits and risks of second-generation antidepressants compared with St. John's wort monotherapy (continued)

Outcomes	Anticipated Absolute Effects[a]: *Benefit and risk with St. John's Wort*	Anticipated Absolute Effects[a] (95% CI): *Benefit and risk with SGA*	Relative Effect (95% CI)	Number of Participants (Trials)	Strength of Evidence	Comments
Discontinuation because of adverse events in subgroup based on older age	65 per 100	79 per 100 (29 to 218)	RR, 1.22 (0.44 to 3.36)	161 (1 trial[29])	Low[e]	Comparison limited to fluoxetine and SJW in older adults (60 to 80 years)

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for inconsistency: moderate heterogeneity (I^2=47%).

[c] Downgraded for indirectness: most studies compared to low or moderate dose SGA.

[d] Downgraded for imprecision: few events.

[e] Downgraded 2 steps for serious imprecision: few events overall and confidence interval crosses threshold of appreciable difference.

[f] Downgraded for risk of bias: Conflicting definitions of suicidal ideas or behaviors and suspected outcomes reporting bias.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; N = number of participants; NWMA = network meta-analyses; OIS = optimal information size; RR: Risk ratio; SGA = second-generation antidepressant; SJW = St. John's wort; SSRI = selective serotonin reuptake inhibitor

Table E16. Benefits and risks of second-generation antidepressants compared with exercise monotherapy

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with exercise*	Anticipated absolute effects[a] (95% CI) : *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response Assessed with: HAM-D17 Followup: mean 16 weeks	82 per 100	94 per 100 (41 to 217)	RR, 1.86 (0.81 to 4.27)[b]	NA; results based on network meta-analyses	Low[c,d]	Estimates based on network meta-analyses.
Remission Assessed with: HAM-D17 <8, no longer meeting criteria for MDD Followup: mean 16 weeks	50 per 100	55 per 100 (44 to 70)	RR, 1.1 (0.87 to 1.39)[d]	254 (2 trials[43,44])	Moderate[c]	Comparison is limited to sertraline versus exercise.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Followup: mean 16 weeks	2 per 100	1 per 100 (1 to 3)	RR, 0.87 (0.48 to 1.59)	254 (2 trials[43,45])	Low[e]	None
Discontinuation because of adverse events Followup: mean 16 weeks	NA	NA	RR, 20.96 (1.19 to 367.97)	254 (2 trials[43,45])	Low[e,f]	Comparison limited to sertraline vs. exercise. Patients treated with a combination of sertraline and exercise had similar discontinuation rates because of adverse events as patients on sertraline monotherapy (9% vs. 10%).

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Crude RR.

[c] Downgraded for imprecision: few events, confidence intervals cross threshold of appreciable difference.

[d] Downgraded for indirectness: estimates are based on network meta-analyses.

[e] Downgraded 2 steps for imprecision: very few events; 95% confidence interval crosses both thresholds of appreciable difference.

[f] Not upgraded for large effect size because of extreme imprecision.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; NA = not applicable; RR = risk ratio; SGA = second-generation antidepressant

Table E17. Benefits and risks of second-generation antidepressants compared with combination of second-generation antidepressants and exercise

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with combination of SGA and exercise*	Anticipated absolute effects[a] (95% CI) : *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of Evidence	Comments
Response	NA	NA	NA	0 (0 trial)	Insufficient	None
Remission Assessed with: HAM-D17 and no longer meeting criteria for MDD Followup: mean 16 weeks	66 per 100	69 per 100 (52 to 90)	RR, 1.05 (0.8 to 1.03)[b]	103 (1 trial;[45,46])	Low[c]	Comparison is limited to sertraline versus sertraline plus exercise.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events Followup: mean 12 weeks	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation Followup: mean 16 weeks	20 per 100	15 per 100 (6 to 35)	RR, 0.73 (0.31 to 1.73)	103 (1 trial[45])	Low[c]	None
Discontinuation because of adverse events Followup: mean 16 weeks	9 per 100	10 per 100 (3 to 34)	RR, 1.15 (0.35 to 3.72)	103 (1 trial[45])	Low[c]	Comparison limited to sertraline vs. sertraline and exercise

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Crude RR.

[c] Downgraded 2 steps for imprecision: very few events, confidence intervals cross threshold of appreciable difference.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; NA = not applicable; RR: Risk ratio; SGA = second-generation antidepressant

Table E18. Benefits and risks of second-generation antidepressants compared with cognitive behavioral therapy as a function of severity

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with CBT monotherapy*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response to treatment for high severity patients Assessed with: HAM-D Followup: mean 16 weeks	56 per 100	40 per 100 (25 to 64)	RR, 0.72 (0.45 to 1.15)	82 (1 trial[5])	Insufficient [b,c]	Comparisons limited to paroxetine and CT.
Response to treatment for low severity patients Assessed with: HAM-D Followup: mean 16 weeks	60 per 100	47 per 100 (29 to 75)	RR, 0.78 (0.48 to 1.25)	63 (1 trial[5])	Insufficient [b,c]	Comparisons limited to paroxetine and CT.
Remission in high severity patients Assessed with: HAM-D Followup: mean 16 weeks	36 per 100	23 per 100 (11 to 46)	RR, 0.63 (0.31 to 1.29)	82 (1 trial[5])	Insufficient [b,c]	Comparisons limited to paroxetine and CT.
Remission in low severity patients Assessed with: HAM-D Followup: mean 16 weeks	50 per 100	33 per 100 (18 to 60)	RR, 0.65 (0.35 to 1.2)	63 (1 trial[5])	Insufficient [b,c]	Comparisons limited to paroxetine and CT.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation	NA	NA	NA	0 (0 trials)	Insufficient	None
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval).

[b] Downgraded for imprecision: single study, small sample size, does not meet optimal information size (OIS).

[c] Downgraded 2 steps for serious risk of bias: high attrition and small sample size.

CI = confidence interval; CT, cognitive therapy; HAM-D = Hamilton Depression Rating Scale; NA = not applicable; RR = risk ratio; SGA = second-generation antidepressant

Table E19. Benefits and risks of second-generation antidepressants compared with integrative therapies as a function of severity

Outcomes	Anticipated absolute effects[a] (95% CI): *Benefit and risk with integrative therapies monotherapy*	Anticipated absolute effects[*] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response to treatment for high severity patients	NA	NA	NA	0 (0 trials)	Insufficient	None
Response to treatment for low severity patients	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission in high severity patients Assessed with: HAM-D Followup: mean 8 weeks	45 per 100	40 per 100 (26 to 62)	RR, 0.89 (0.58 to 1.37)	111 (1 trial[11])	Insufficient[b,c]	Comparisons limited to sertraline or citalopram and IPT.
Remission in low severity patients Assessed with: HAM-D Followup: mean 8 weeks	75 per 100	56 per 100 (43 to 71)	RR, 0.75 (0.58 to 0.96)	153 (1 trial[11])	Insufficient[b,c]	Comparisons limited to sertraline or citalopram and IPT.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation	NA	NA	NA	0 (0 trials)	Insufficient	None
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval).

[b] Downgraded 2 steps for serious imprecision: single study, small sample size, does not meet optimal information size (OIS).

[c] Downgraded for risk of bias: secondary subgroup analyses not prespecified.CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; IPT = interpersonal therapy; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table E20. Benefits and risks of second-generation antidepressants compared with third-wave cognitive behavioral therapy monotherapy as a function of severity

Outcomes	Anticipated absolute effects[a] (95% CI): *Benefit and risk with third wave cognitive behavioral therapy monotherapy*	Anticipated absolute effects[*] (95% CI): *Benefit and risk with SGA*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response to treatment for high severity patients Assessed with: HAM-D Followup: mean 16 weeks	60 per 100	40 per 100 (26 to 63)	RR, 0.67 (0.43 to 1.05)	82 (1 trial[5])	Insufficient[b,c]	Comparison limited to paroxetine and BA.
Response to treatment for low severity patients Assessed with: HAM-D Followup: mean 16 weeks	39 per 100	47 per 100 (24 to 90)	RR, 1.5 (0.62 to 2.32)	61 (1 trial[5])	Insufficient[b,c]	Comparison limited to paroxetine and BA.
Remission in high severity patients Assessed with: HAM-D Followup: mean 16 weeks	36 per 100	17 per 100 (9 to 31)	RR, 0.47 (0.26 to 0.87)	82 (1 trial[5])	Insufficient[b,c]	Comparison limited to paroxetine and BA.
Remission in low severity patients Assessed with: HAM-D Followup: mean 16 weeks	44 per 100	37 per 100 (18 to 76)	RR, 0.84 (0.41 to 1.72)	61 (1 trial[5])	Insufficient[b,c]	Comparison limited to paroxetine and BA.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	NR
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	NR
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation	NA	NA	NA	0 (0 trials)	Insufficient	None
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval).

[b] Downgraded 2 steps for serious imprecision; single study, small sample size does not meet optimal information size (OIS).

[c] Downgraded for risk of bias: high attrition.

CI = confidence interval; BA = behavioral activation therapy; HAM-D = Hamilton Depression Rating Scale; NR: not reported; RR = risk ratio; SGA = second-generation antidepressant

Table E21. Benefits and risks of second-generation antidepressants compared with SAMe as a function of baseline depressive severity

Outcomes	Anticipated Absolute Effects[a]): *Benefit and risk with SAMe*	Anticipated Absolute Effects[a] (95% CI): *Benefit and risk with SGA*	Impact of severity as an effect modifier	Number of Participants (Trials)	Strength of Evidence	Comments
Response – change in HAM-D score Assessed with: HAM-D Followup mean 12 weeks	The mean change in HAM-D score in the control group was 6.19	The mean change in HAM-D score in the intervention group was 6.31 Absolute mean difference was 0.21 higher.	No statistically significant interaction between baseline HAM-D score and treatment groups for reduction in HAM-D scores over time (p=0.87).	129 (1 trial[29])	Insufficient[b,c]	Direct evidence is limited to a single study of SAMe versus escitalopram.
Remission	NA	NA	NA	(0 trials)	Insufficient	None
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation	NA	NA	NA	0 (0 trials)	Insufficient	None
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Downgraded for high risk of bias: high dropout.

[c] Downgraded 2 steps for serious imprecision: few events, single study, does not meet optimal information size (OIS).

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; NR: not reported; RR: Risk ratio; SAMe = S-Adenosyl methionine; SGA = second-generation antidepressant

Table E22. Benefits and risks of SGA switches compared with other SGA switches for MDD in adults not responding to an initial adequate SGA treatment attempt

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with other SGA switches*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA switches*	Relative effect (95% CI)	Number of partici-pants (Trials)	Strength of evidence	Comments
Response Assessed with HAM-D-17 Followup: 12 to 14 weeks	NA	NA	RR, 0.96 (0.71 to 1.30)[b, c]	727 (1 trial[47])	Moderate[d]	Comparisons limited to switch strategies to bupropion vs. sertraline.
	NA	NA	RR, 0.91 (0.68 to 1.22)[b, c]	727 (1 trial[47])	Moderate[d]	Comparisons limited to switch strategies to bupropion vs. venlafaxine.
	NA	NA	RR, 0.95 (0.71 to 1.26)[b, c]	727 (1 trial[47])	Moderate[d]	Comparisons limited to switch strategies: sertraline vs. venlafaxine.
Remission Assessed with HAM-D-17 Followup: 14 weeks	NR	NR	RR, 1.21 (0.84 to 1.75)[b, c]	727 (1 trial[47])	Low[e,f]	Comparisons limited to bupropion vs. sertraline. No statistically significant differences between any of the individual switch strategies regardless of the measure used.
	NR	NR	RR, 0.86 (0.62 to 1.19)[b, c]	727 (1 trial[47])	Low[e,f]	Comparisons limited to bupropion vs. venlafaxine switch strategies. No statistically significant differences between any of the individual switch strategies regardless of the measure used.
	NR	NR	RR, 0.71 (0.50 to 1.01)[b, c]	727 (1 trial[47])	Low[e,f]	Comparisons limited to sertraline vs. venlafaxine switch strategies. No statistically significant differences between any of the individual switch strategies regardless of the measure used.
Mean change in HAM-D score from baseline Followup: 14 weeks	63 per 100	57 per 100 (49 to 68)	RR, 0.91 (0.78 to 1.07)[f]	406 (1 trial[48])	Low[e,f]	Comparison limited to venlafaxine vs. citalopram switch strategies
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional	NA	NA	NA	0 (0 trials)	Insufficient	None

E-35

Table E22. Benefits and risks of SGA switches compared with other SGA switches for MDD in adults not responding to an initial adequate SGA treatment attempt (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with other SGA switches*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA switches*	Relative effect (95% CI)	Number of partici-pants (Trials)	Strength of evidence	Comments
Suicidal ideas or behaviors	1 per 100	0 per 100 (0 to 3)	RR, 0.2 (0.01 to 4.13)	477 (1 trial[47])	Low[g]	Comparison limited to citalopram switch to bupropion vs. citalopram switch to sertraline
	1 per 100	0 per 100 (0 to 3)	RR, 0.21 (0.01 to 4.33)	489 (1 trial[47])	Low[g]	Comparison limited to citalopram switch to bupropion vs. citalopram switch to venlafaxine
	1 per 100	1 per 100 (0 to 6)	RR, 1.05 (0.15 to 7.4)	488 (1 trial[47])	Low[g]	Comparison limited to citalopram switch to sertraline vs. citalopram switch to venlafaxine
Serious adverse events	4 per 100	2 per 100 (1 to 6)	RR, 0.5 (0.17 to 1.43)	477 (1 trial[47])	Low[g]	Comparison limited to citalopram switch to bupropion vs. citalopram switch to sertraline
	2 per 100	2 per 100 (1 to 7)	RR, 0.5 (0.17 to 1.43)	488 (1 trial[47])	Low[g]	Comparison limited to citalopram switch to bupropion vs. citalopram switch to venlafaxine
	2 per 100	4 per 100 (2 to 11)	RR, 1.75 (0.65 to 4.74)	488 (1 trial[47])	Low[g]	Comparison limited to citalopram switch to sertraline vs. citalopram switch to venlafaxine
Risk for overall adverse events Followup: mean 12 weeks	63 per 100	57 per 100 (49 to 68)	RR, 0.91 (0.78 to 1.07)	406 (1 trial[48])	Low[f,h]	Comparison limited to switch to venlafaxine vs. switch to citalopram
Overall discontinuation Followup: mean 12 weeks	21 per 100	24 per 100 (17 to 35)	RR, 1.17 (0.82 to 1.68)	406 (1 trial[48])	Low[f,h]	Comparison limited to switch to venlafaxine vs. switch to citalopram

Table E22. Benefits and risks of SGA switches compared with other SGA switches for MDD in adults not responding to an initial adequate SGA treatment attempt (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with other SGA switches*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA switches*	Relative effect (95% CI)	Number of partici-pants (Trials)	Strength of evidence	Comments
Discontinuation because of adverse events Followup: 14 weeks	21 per 100	27 per 100 (20 to 38)	RR, 1.29 (0.94 to 1.79)	477 (1 trial[47])	Moderate[f]	Comparison limited to citalopram switch to bupropion vs. citalopram switch to sertraline
	21 per 100	27 per 100 (20 to 37)	RR, 1.28 (0.93 to 1.76)	489 (1 trial[47])	Moderate[f]	Comparison limited to citalopram switch to bupropion vs. citalopram switch to venlafaxine
	21 per 100	21 per 100 (15 to 30)	RR, 0.99 (0.7 to 1.4)	488 (1 trial[47])	Moderate[f]	Comparison limited to citalopram switch to sertraline vs. citalopram switch to venlafaxine

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Relative Risk as reported in the article.

[c] Crude RR.

[d] Downgraded for risk of bias: less than 80% of sample provided outcomes at study completion; medication options not all maximized.

[e] Downgraded for risk of bias: less than 80% of sample provided outcomes at study completion (~50% did); medication options not all maximized.

[f] Downgraded for imprecision: few events.

[g] Downgraded 2 steps for serious imprecision: very few events.

[h] Downgraded for risk of bias: potential confounding from prior treatment attempts with psychotherapy, which was not accounted for at baseline.

CGI-S = Clinical Global Impressions Scale - Severity; CI = confidence interval; CT = cognitive therapy; HAM-D-17 = Hamilton Depression Scale – 17; NA = not applicable; OIS = optimal information size; NR = not reported; QIDS-SR = Quick Inventory of Depressive Symptoms – Self Report-16; RR = risk ratio; SGA = second-generation antidepressant

Table E23. Benefits and risks of SGA switches compared with nonpharmacologic switches for MDD in adults not responding to an initial adequate SGA treatment attempt

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with nonpharmacologic switches*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA switches*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response Assessed with QIDS-SR-16 Followup: 12 to 14 weeks	22 per 100	27 to 100 (13 to 54)	RR, 1.2 (0.6 to 2.43)[b]	122 (1 trial[49])[c]	Low[d,e]	Comparison limited to SGA (sertraline, bupropion, or venlafaxine) vs. CT switch strategies.
Remission Assessed with HAM-D-17 or QIDS-SR-16 Followup: 14 weeks	25 per 100	28 to 100 (15 to 54)	RR, 1.12 (0.58 to 2.16)[c,b]	122 (1 trial[49])[c]	Low[d,e]	Comparison limited to SGA (sertraline, bupropion, or venlafaxine) vs. CT switch strategies.
Mean change in HAM-D score from baseline Followup:14 weeks	NA	NA	Not estimable	122 (1 trial[49])[c]	Low[d,e]	Comparison limited to SGA (sertraline, bupropion, or venlafaxine) vs. CT switch strategies.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation	NA	NA	NA	0 (0 trials)	Insufficient	None

Table E23. Benefits and risks of SGA switches compared with nonpharmacologic switches for MDD in adults not responding to an initial adequate SGA treatment attempt (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with nonpharmacologic switches*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA switches*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Discontinuation because of adverse events Followup: 14 weeks	17 per 100	27 per 100 (12 to 60)	RR, 1.6 (0.71 to 3.61)	122 (1 trial[49])	Low[f]	Comparison limited to citalopram switch to sertraline, bupropion, or venlafaxine vs. citalopram switch to CT

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Crude RR.

[c] QIDS-SR-16 remission rates led to similar conclusions as those measured by HAM-D-17: RR (95% CI) = 0.88 (0.48 to 1.60).

[d] Downgraded for risk of bias: less than 80% of sample provided outcomes at study completion (~50% did); medication options not all maximized.

[e] Downgraded for imprecision: single study, few events.

.

CI = confidence interval; CT = cognitive therapy; HAM-D-17 = Hamilton Depression Scale – 17; NA = not applicable; QIDS-SR = Quick Inventory of Depressive Symptoms – Self Report-16; RR = risk ratio; SGA = second-generation antidepressant; vs. = versus

Table E24. Benefits and risks of SGA augmentation compared with SGA augmentation for MDD in adults not responding to an initial adequate SGA treatment attempt

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with SGA augmentation*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA augmentation*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response Assessed with QIDS-SR-16 Followup:14 weeks	27 per 100	32 to 100 (25 to 41)	RR, 1.18 (0.92 to 1.53)[b]	565 (1 trial[50])	Low[c,d]	Comparison limited to bupropion vs. buspirone augmentation of citalopram treatment.
Remission Assessed with HAM-D-17 or QIDS-SR-16 Followup:14 weeks	30 per 100	30 to 100 (23 to 38)	RR, 0.99 (0.77 to 1.27)[e,b]	565 (1 trial[50])	Low[c,d]	Comparison limited to bupropion vs. buspirone augmentation of citalopram treatment
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	1 per 100	0 per 100 (0 to 3)	RR, 0.26 (0.03 to 2.28)	565 (1 trial[50])	Low[f]	Comparison limited to citalopram augmentation with bupropion vs. citalopram augmentation with buspirone.
Serious adverse events Followup: 14 weeks	4 per 100	4 per 100 (2 to 8)	RR, 0.85 (0.38 to 1.95)	565 (1 trial[50])	Low[e]	Comparison limited to citalopram augmentation with bupropion vs. citalopram augmentation with buspirone.
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation	NA	NA	NA	0 (0 trials)	Insufficient	None

Table E24. Benefits and risks of SGA augmentation compared with SGA augmentation for MDD in adults not responding to an initial adequate SGA treatment attempt

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with SGA aumentation*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA augmentation*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Discontinuation because of adverse events Followup: 14 weeks	21 per 100	13 per 100 (8 to 18)	RR, 0.61 (0.41 to 0.89)	565 (1 trial[50])	Moderate[d]	Comparison limited to citalopram augmentation with bupropion vs. citalopram augmentation with buspirone.

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Crude RR.

[c] Downgraded for risk of bias: less than 80% of sample provided outcomes at study completion (~50% did); medication options not all maximized.

[d] Downgraded for imprecision: few events.

Downgraded 2 steps for serious imprecision: very small number of events; 95% confidence interval crosses both thresholds of appreciable differences.

CI = confidence interval; HAM-D-17 = Hamilton Depression Scale – 17; NA = not applicable; QIDS-SR = Quick Inventory of Depressive Symptoms – Self Report-16; RR = risk ratio; SGA = second-generation antidepressant

Table E25. Benefits and risks of SGA augmentation compared with nonpharmacologic augmentation for MDD in adults not responding to an initial adequate SGA treatment attempt

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with nonpharma-cologic augmentation*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA augmentation*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response Assessed with QIDS-SR-16 Followup: 14 weeks	35 per 100	28 to 100 (18 to 43)	RR, 0.8 (0.51 to 1.23)[b]	182 (1 trial[49])	Low[c,d]	Comparison limited to SGA (bupropion or buspirone) vs. CT augmentation of citalopram treatment.
Remission Assessed with HAM-D-17 or QIDS-SR-16 Followup: 14 weeks	23 per 100	33 to 100 (20 to 56)	RR, 1.44 (0.87 to 2.41)[e,b]	182 (1 trial[49])	Low[c,d]	Comparison limited to SGA (bupropion or buspirone) vs. CT augmentation of citalopram treatment.
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events Followup: 14 weeks	6 per 100	3 per 100 (1 to 13)	RR, 0.56 (0.14 to 2.15)	182 (1 trial[49])	Low[e]	Comparison limited to citalopram augmentation with bupropion or buspirone vs. citalopram augmentation with CT.
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation	NA	NA	NA	0 (0 trials)	Insufficient	None

Table E25. Benefits and risks of SGA augmentation compared with nonpharmacologic augmentation for MDD in adults not responding to an initial adequate SGA treatment attempt (continued)

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with nonpharma-cologic augmentation*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with SGA augmentation*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Discontinuation because of adverse events Followup: 14 weeks	9 per 100	20 per 100 (8 to 46)	RR, 2.13 (0.91 to 4.96)	182 (1 trial[49])	Low[e]	Comparison limited to citalopram augmentation with bupropion or buspirone vs. citalopram augmentation with CT.

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Crude RR.

[c] Downgraded for risk of bias: less than 80% of sample provided outcomes at study completion (~50% did); medication options not all maximized.

[d] Downgraded for imprecision: few events.

[e] Downgraded 2 steps for serious imprecision: very small number of events; 95% confidence interval crosses both thresholds of appreciable differences.

CI = confidence interval; CT = cognitive therapy; HAM-D-17 = Hamilton Depression Scale – 17; NA = not applicable; QIDS-SR = Quick Inventory of Depressive Symptoms – Self Report-16; RR = risk ratio; SGA = second-generation antidepressant

Table E26. Benefits and risks of SGA switches for MDD in adults not responding to an initial adequate SGA treatment attempt as a function of baseline severity

Outcomes	Anticipated absolute effects[a]: *Benefit and risk with higher severity*	Anticipated absolute effects[a] (95% CI): *Benefit and risk with lower severity*	Relative effect (95% CI)	Number of participants (Trials)	Strength of evidence	Comments
Response	NA	NA	NA	0 (0 trials)	Insufficient	None
Remission Assessed with HAM-D-17 Followup: 12 to 14 weeks	NA	NA	Not estimable	1,123 (2 trials[47,48,51])[b]	Insufficient [c,d]	Comparisons limited to venlafaxine vs. citalopram switch strategies or to bupropion vs. sertraline vs. venlafaxine switch strategies. Conflicting results from 2 studies (data not reported).
Quality of life	NA	NA	NA	0 (0 trials)	Insufficient	None
Functional capacity	NA	NA	NA	0 (0 trials)	Insufficient	None
Suicidal ideas or behaviors	NA	NA	NA	0 (0 trials)	Insufficient	None
Serious adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Risk for overall adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None
Overall discontinuation	NA	NA	NA	0 (0 trials)	Insufficient	None
Discontinuation because of adverse events	NA	NA	NA	0 (0 trials)	Insufficient	None

[a] The benefit or risk in the intervention group (and its 95% confidence interval) is based on the assumed benefit or risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] Two secondary analyses of two different RCTs.

[c] Downgraded two steps for risk of bias: less than 80% of sample provided outcomes at study completion (~50% did), medication options not all maximized.

[d] Downgraded for inconsistency: two studies reported contrasting results.

CI = confidence interval; CT = cognitive therapy; HAM-D-17 = Hamilton Depression Scale – 17; NA = not applicable; OIS = optimal information size; QIDS-SR-16 = = Quick Inventory of Depressive Symptoms – Self Report-16; RR = risk ratio; SGA = second-generation antidepressant

References for Appendix E

1.   David D, Szentagotai A, Lupu V, et al. Rational emotive behavior therapy, cognitive therapy, and medication in the treatment of major depressive disorder: a randomized clinical trial, posttreatment outcomes, and six-month follow-up. J Clin Psychol. 2008 Jun;64(6):728-46. Epub: 2008/05/14. PMID: 18473339.

2.   DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch Gen Psychiatry. 2005 Apr;62(4):409-16. Epub: 2005/04/06. PMID: 15809408.

3.   Hegerl U, Hautzinger M, Mergl R, et al. Effects of pharmacotherapy and psychotherapy in depressed primary-care patients: a randomized, controlled trial including a patients' choice arm. Int J Neuropsychopharmacol. 2010;13(1):31-44. PMID: 19341510.

4.   Mynors-Wallis LM, Gath DH, Day A, et al. Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. BMJ. 2000 Jan 1;320(7226):26-30. Epub: 2000/01/05. PMID: 10617523.

5.   Dimidjian S, Hollon SD, Dobson KS, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol. 2006 Aug;74(4):658-70. Epub: 2006/08/03. PMID: 16881773.

6.   McGrath CL, Kelley ME, Holtzheimer PE, et al. Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatry. 2013 Aug;70(8):821-9. Epub: 2013/06/14. PMID: 23760393.

7.   Kennedy SH, Konarski JZ, Segal ZV, et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry. 2007 May;164(5):778-88. Epub: 2007/05/04. PMID: 17475737.

8.   Segal ZV, Kennedy S, Gemar M, et al. Cognitive reactivity to sad mood provocation and the prediction of depressive relapse. Arch Gen Psychiatry. 2006 Jul;63(7):749-55. Epub: 2006/07/05. PMID: 16818864.

9.   Landenberger NAD. Self-concept and attributional style in the treatment of depression: ProQuest Information & Learning; 2002.

10.   Lam RW, Parikh SV, Ramasubbu R, et al. Effects of combined pharmacotherapy and psychotherapy for improving work functioning in major depressive disorder. Br J Psychiatry. 2013 Nov;203(5):358-65. PMID: 24029535.

11.   Menchetti M, Rucci P, Bortolotti B, et al. Moderators of remission with interpersonal counselling or drug treatment in primary care patients with depression: randomised controlled trial. Br J Psychiatry. 2014 Feb;204(2):144-50. PMID: 24311553.

12.   Frank E, Cassano GB, Rucci P, et al. Predictors and moderators of time to remission of major depression with interpersonal psychotherapy and SSRI pharmacotherapy. Psychol Med. 2011 Jan;41(1):151-62. Epub: 2010/04/13. PMID: 20380782.

13.   Raue PJ, Schulberg HC, Heo M, et al. Patients' depression treatment preferences and initiation, adherence, and outcome: a randomized primary care study. Psychiatr Serv. 2009 Mar;60(3):337-43. Epub: 2009/03/03. PMID: 19252046.

14.   Rucci P, Frank E, Scocco P, et al. Treatment-emergent suicidal ideation during 4 months of acute management of unipolar major depression with SSRI pharmacotherapy or interpersonal psychotherapy in a randomized clinical trial. Depress Anxiety. 2011 Apr;28(4):303-9. Epub: 2011/02/11. PMID: 21308882.

15.   Blom MB, Jonker K, Dusseldorp E, et al. Combination treatment for acute depression is superior only when psychotherapy is added to medication. Psychother Psychosom. 2007;76(5):289-97. Epub: 2007/08/19. PMID: 17700049.

16.   Salminen JK, Karlsson H, Hietala J, et al. Short-term psychodynamic psychotherapy and fluoxetine in major depressive disorder: a randomized comparative study. Psychother Psychosom. 2008;77(6):351-7. Epub: 2008/08/15. PMID: 18701831.

17.   Bastos AG, Guimaraes LS, Trentini CM. Neurocognitive changes in depressed patients in psychodynamic psychotherapy, therapy with fluoxetine and combination therapy. J Affect Disord. 2013 Dec;151(3):1066-75. PMID: 24103853.

18. Dekker JJ, Koelen JA, Van HL, et al. Speed of action: the relative efficacy of short psychodynamic supportive psychotherapy and pharmacotherapy in the first 8 weeks of a treatment algorithm for depression. J Affect Disord. 2008 Jul;109(1-2):183-8. Epub: 2007/12/07. PMID: 18061276.

19. Barber JP, Barrett MS, Gallop R, et al. Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial. J Clin Psychiatry. 2012 Jan;73(1):66-73. Epub: 2011/12/14. PMID: 22152401.

20. Moradveisi L, Huibers MJ, Renner F, et al. Behavioural activation v. antidepressant medication for treating depression in Iran: randomised trial. Br J Psychiatry. 2013 Mar;202(3):204-11. Epub: 2013/02/09. PMID: 23391727.

21. Huang Y, Htut W, Li D, et al. Studies on the clinical observation and cerebral glucose metabolism in depression treated by electro-scalp acupuncture compared to fluoxetine. Int J Clin Acupunct. 2005;14(1):7-26. PMID: 0077160.

22. Sun H, Zhao H, Ma C, et al. Effects of electroacupuncture on depression and the production of glial cell line-derived neurotrophic factor compared with fluoxetine: a randomized controlled pilot study. J Altern Complement Med. 2013 Sep;19(9):733-9. PMID: 23647408.

23. Zhang ZJ, Chen HY, Yip KC, et al. The effectiveness and safety of acupuncture therapy in depressive disorders: systematic review and meta-analysis. J Affect Disord. 2010 Jul;124(1-2):9-21. Epub: 2009/07/28. PMID: 19632725.

24. Zhang WJ, Yang XB, Zhong BL. Combination of acupuncture and fluoxetine for depression: a randomized, double-blind, sham-controlled trial. J Altern Complement Med. 2009 Aug;15(8):837-44. Epub: 2009/08/15. PMID: 19678773.

25. Qu SS, Huang Y, Zhang ZJ, et al. A 6-week randomized controlled trial with 4-week follow-up of acupuncture combined with paroxetine in patients with major depressive disorder. J Psychiatr Res. 2013 Jun;47(6):726-32. Epub: 2013/03/19. PMID: 23498306.

26. Chen JQ, Lin WR, Wang SX, et al. Acupuncture/electroacupuncture enhances antidepressant effect of seroxat: the symptom checklist-90 scores. Neural Regen Res. 2014;9(2):213-22.

27. Jazayeri S, Tehrani-Doost M, Keshavarz SA, et al. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. Aust N Z J Psychiatry. 2008 Mar;42(3):192-8. Epub: 2008/02/06. PMID: 18247193.

28. Gertsik L, Poland RE, Bresee C, et al. Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. J Clin Psychopharmacol. 2012 Feb;32(1):61-4. Epub: 2011/12/27. PMID: 22198441.

29. Mischoulon D, Price LH, Carpenter LL, et al. A double-blind, randomized, placebo-controlled clinical trial of S-adenosyl-L-methionine (SAMe) versus escitalopram in major depressive disorder. J Clin Psychiatry. 2014 Dec 24. Epub: 2014/02/07. PMID: 24500245.

30. Behnke K, Jensen GS, Graubaum HJ, et al. Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression. Adv Ther. 2002 Jan-Feb;19(1):43-52. Epub: 2002/05/15. PMID: 12008860.

31. Bjerkenstedt L, Edman GV, Alken RG, et al. Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. Eur Arch Psychiatry Clin Neurosci. 2005 Feb;255(1):40-7. Epub: 2004/11/13. PMID: 15538592.

32. Brenner R, Azbel V, Madhusoodanan S, et al. Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. Clin Ther. 2000 Apr;22(4):411-9. PMID: 10823363.

33. Davidson JRT, Gadde KM, Fairbank JA, et al. Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: a randomized controlled trial. J Am Med Assoc. 2002;287(14):1807-14.

34. Gastpar M, Singer A, Zeller K. Efficacy and tolerability of hypericum extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. Pharmacopsychiatry. 2005 Mar;38(2):78-86. PMID: 15744631.

35. Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study. Pharmacopsychiatry. 2006 Mar;39(2):66-75. Epub: 2006/03/24. PMID: 16555167.

36.   Harrer G, Schmidt U, Kuhn U, et al. Comparison of equivalence between the St. John's wort extract LoHyp-57 and fluoxetine. Arzneimittelforschung. 1999 Apr;49(4):289-96. Epub: 1999/05/25. PMID: 10337446.

37.   Moreno RA, Teng CT, Almeida KM, et al. *Hypericum perforatum* versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample. Rev Bras Psiquiatr. 2006 Mar;28(1):29-32. PMID: 16612487.

38.   Schrader E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. Int Clin Psychopharmacol. 2000 Mar;15(2):61-8. PMID: 10759336.

39.   Szegedi A, Kohnen R, Dienel A, et al. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. BMJ. 2005 Mar 5;330(7490):503. Epub: 2005/02/15. PMID: 15708844.

40.   Fava M, Alpert J, Nierenberg AA, et al. A double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. J Clin Psychopharmacol. 2005 Oct;25(5):441-7. Epub: 2005/09/15. PMID: 16160619.

41.   Papakostas GI, Crawford CM, Scalia MJ, et al. Timing of clinical improvement and symptom resolution in the treatment of major depressive disorder. A replication of findings with the use of a double-blind, placebo-controlled trial of Hypericum perforatum versus fluoxetine. Neuropsychobiology. 2007;56(2-3):132-7. Epub: 2008/02/09. PMID: 18259086.

42.   van Gurp G, Meterissian GB, Haiek LN, et al. St John's wort or sertraline? Randomized controlled trial in primary care. Can Fam Physician. 2002 May;48:905-12. Epub: 2002/06/11. PMID: 12053635.

43.   Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom Med. 2007 Sep-Oct;69(7):587-96. Epub: 2007/09/12. PMID: 17846259.

44.   Hoffman BM, Blumenthal JA, Babyak MA, et al. Exercise fails to improve neurocognition in depressed middle-aged and older adults. Med Sci Sports Exerc. 2008 Jul;40(7):1344-52. Epub: 2008/06/27. PMID: 18580416.

45.   Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older patients with major depression. Arch Intern Med. 1999 Oct 25;159(19):2349-56. Epub: 1999/11/05. PMID: 10547175.

46.   Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom Med. 2000 Sep-Oct;62(5):633-8. Epub: 2000/10/06. PMID: 11020092.

47.   Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med. 2006 Mar 23;354(12):1231-42. Epub: 2006/03/24. PMID: 16554525.

48.   Lenox-Smith AJ, Jiang Q. Venlafaxine extended release versus citalopram in patients with depression unresponsive to a selective serotonin reuptake inhibitor. Int Clin Psychopharmacol. 2008 May;23(3):113-9. Epub: 2008/04/15. PMID: 18408525.

49.   Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. Am J Psychiatry. 2007 May;164(5):739-52. Epub: 2007/05/04. PMID: 17475733.

50.   Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med. 2006 Mar 23;354(12):1243-52. Epub: 2006/03/24. PMID: 16554526.

51.   Rush AJ, Wisniewski SR, Warden D, et al. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. Arch Gen Psychiatry. 2008 Aug;65(8):870-80. Epub: 2008/08/06. PMID: 18678792.

Appendix F. Studies Included in Network Meta-Analyses

1. Allen JJ, Schnyer RN, Chambers AS, et al. Acupuncture for depression: a randomized controlled trial. J Clin Psychiatry. 2006 Nov;67(11):1665-73. Epub: 2007/01/02. PMID: 17196044.

2. Allen JJB, Schnyer RN, Hitt SK. The efficacy of acupuncture in the treatment of major depression in women. Psychol Sci. 1998;9(5):397-401. PMID: 1998-11225-010. First Author & Affiliation: Allen, John J. B.

3. Alvarez E, Perez V, Dragheim M, et al. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. Int J Neuropsychopharmacol. 2012 Jun;15(5):589-600. Epub: 2011/07/20. PMID: 21767441.

4. Alves C, Cachola I, Brandao J. Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. Primary Care Psychiatry. 1999;5(2):57-63.

5. Bakish D, Bose A, Gommoll C, et al. Levomilnacipran ER 40 mg and 80 mg in patients with major depressive disorder: a phase III, randomized, double-blind, fixed-dose, placebo-controlled study. J Psychiatry Neurosci. 2014 Jan;39(1):40-9. Epub: 2013/10/23. PMID: 24144196.

6. Barber JP, Barrett MS, Gallop R, et al. Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial. J Clin Psychiatry. 2012 Jan;73(1):66-73. Epub: 2011/12/14. PMID: 22152401.

7. Beasley CM, Dornseif BE, Pultz JA, et al. Fluoxetine versus trazodone: efficacy and activating-sedating effects. J Clin Psychiatry. 1991;52(7):294-9. PMID: CN-00076754.

8. Behnke K, Jensen GS, Graubaum HJ, et al. Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression. Adv Ther. 2002 Jan-Feb;19(1):43-52. Epub: 2002/05/15. PMID: 12008860.

9. Benkert O, Szegedi A, Kohnen R. Mirtazapine compared with paroxetine in major depression. J Clin Psychiatry. 2000 Sep;61(9):656-63. Epub: 2000/10/13. PMID: 11030486.

10. Bielski RJ, Ventura D, Chang CC. A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. J Clin Psychiatry. 2004 Sep;65(9):1190-6. Epub: 2004/09/16. PMID: 15367045.

11. Bjerkenstedt L, Edman GV, Alken RG, et al. Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. Eur Arch Psychiatry Clin Neurosci. 2005 Feb;255(1):40-7. Epub: 2004/11/13. PMID: 15538592.

12. Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom Med. 2007 Sep-Oct;69(7):587-96. Epub: 2007/09/12. PMID: 17846259.

13. Boyer P, Montgomery S, Lepola U, et al. Efficacy, safety, and tolerability of fixed-dose desvenlafaxine 50 and 100 mg/day for major depressive disorder in a placebo-controlled trial. Int Clin Psychopharmacol. 2008 Sep;23(5):243-53. Epub: 2008/08/16. PMID: 18703933.

14. Brannan SK, Mallinckrodt CH, Brown EB, et al. Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. J Psychiatr Res. 2005 Jan;39(1):43-53. Epub: 2004/10/27. PMID: 15504423.

15. Brenner R, Azbel V, Madhusoodanan S, et al. Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. Clin Ther. 2000 Apr;22(4):411-9. PMID: 10823363.

16. Claghorn JL. The safety and efficacy of paroxetine compared with placebo in a double-blind trial of depressed outpatients. J Clin Psychiatry. 1992 Feb;53 Suppl:33-5. Epub: 1992/02/01. PMID: 1531821.

17. Clayton AH, Tourian KA, Focht K, et al. Desvenlafaxine 50 and 100 mg/d versus placebo for the treatment of major depressive disorder: a phase 4, randomized controlled trial. J Clin Psychiatry. 2014 Oct 28Epub: 2014/11/07. PMID: 25375652.

18. Cohn CK, Robinson DS, Roberts DL, et al. Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. J Clin Psychiatry. 1996;57 Suppl 2:15-8. Epub: 1996/01/01. PMID: 8626358.

19. Coleman CC, Cunningham LA, Foster VJ, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. Ann Clin Psychiatry. 1999 Dec;11(4):205-15. Epub: 1999/12/22. PMID: 10596735.

20. Coleman CC, King BR, Bolden-Watson C, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin Ther. 2001 Jul;23(7):1040-58. Epub: 2001/08/25. PMID: 11519769.

21. Company ELa. Duloxetine versus placebo in the treatment of major depression: study F1J-MC-HMAQ, study group B; clinical study summary #3327 2006. p. In: ClinicalStudyResults.

22. Company ELa. Duloxetine versus placebo and paroxetine in the acute treatment of major depression: study F1J-MC-HMAT, study group A; clinical study summary #4091. 2006. p. In: ClinicalStudyResults.

23. Corrigan MH, Denahan AQ, Wright CE, et al. Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress Anxiety. 2000;11(2):58-65. Epub: 2000/05/17. PMID: 10812530.

24. Croft H, Settle E, Jr., Houser T, et al. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clin Ther. 1999 Apr;21(4):643-58. Epub: 1999/06/11. PMID: 10363731.

25. De Nayer A, Geerts S, Ruelens L, et al. Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety. Int J Neuropsychopharmacol. 2002;5(2):115-20. PMID: 2002-06574-003. PMID: 12135535. First Author & Affiliation: De Nayer, Andre.

26. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry. 2002 Apr;63(4):308-15. Epub: 2002/05/10. PMID: 12000204.

27. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res. 2002 Nov-Dec;36(6):383-90. Epub: 2002/10/24. PMID: 12393307.

28. Detke MJ, Wiltse CG, Mallinckrodt CH, et al. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Neuropsychopharmacol. 2004 Dec;14(6):457-70. Epub: 2004/12/14. PMID: 15589385.

29. Dierick M, Ravizza L, Realini R, et al. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. Prog Neuropsychopharmacol Biol Psychiatry. 1996 Jan;20(1):57-71. Epub: 1996/01/01. PMID: 8861177.

30. Dunlop BW, Reddy S, Yang L, et al. Symptomatic and functional improvement in employed depressed patients: a double-blind clinical trial of desvenlafaxine versus placebo. J Clin Psychopharmacol. 2011 Oct;31(5):569-76. Epub: 2011/08/27. PMID: 21869698.

31. Dunn AL, Trivedi MH, Kampert JB, et al. Exercise treatment for depression: efficacy and dose response. Am J Prev Med. 2005 Jan;28(1):1-8. Epub: 2005/01/01. PMID: 15626549.

32. Fabre L, Birkhimer LJ, Zaborny BA, et al. Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. Int Clin Psychopharmacol. 1996 Jun;11(2):119-27. Epub: 1996/06/01. PMID: 8803649.

33. Fava M, Amsterdam JD, Deltito JA, et al. A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression. Ann Clin Psychiatry. 1998 Dec;10(4):145-50. Epub: 1999/02/13. PMID: 9988054.

34. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry. 1996;57 Suppl 2:53-62. Epub: 1996/01/01. PMID: 8626364.

35. Feiger AD, Tourian KA, Rosas GR, et al. A placebo-controlled study evaluating the efficacy and safety of flexible-dose desvenlafaxine treatment in outpatients with major depressive disorder. CNS Spectr. 2009 Jan;14(1):41-50. Epub: 2009/01/27. PMID: 19169187.

36.   Feighner JP, Boyer WF. Paroxetine in the treatment of depression: a comparison with imipramine and placebo. J Clin Psychiatry. 1992 Feb;53 Suppl:44-7. Epub: 1992/02/01. PMID: 1531824.

37.   Feighner JP, Gardner EA, Johnston JA, et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. J Clin Psychiatry. 1991 Aug;52(8):329-35. Epub: 1991/08/01. PMID: 1907963.

38.   Fontaine R, Ontiveros A, Elie R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry. 1994;55(6):234-41. PMID: 1995-02824-001. PMID: 8071277. Partial author list. First Author & Affiliation: Fontaine, R.

39.   Frank E, Cassano GB, Rucci P, et al. Predictors and moderators of time to remission of major depression with interpersonal psychotherapy and SSRI pharmacotherapy. Psychol Med. 2011 Jan;41(1):151-62. Epub: 2010/04/13. PMID: 20380782.

40.   Gastpar M, Singer A, Zeller K. Efficacy and tolerability of hypericum extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. Pharmacopsychiatry. 2005 Mar;38(2):78-86. PMID: 15744631.

41.   Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study. Pharmacopsychiatry. 2006 Mar;39(2):66-75. Epub: 2006/03/24. PMID: 16555167.

42.   GmbH WP. A double-blind, placebo-controlled, comparative efficacy study of venlafaxine and sertraline in producing remission in outpatients with major depressive disorder: study 0600C1-402-US-CA-CSR-48579

43.   GmbH WP. A double-blind, placebo-controlled, comparative study of extended release formulation of venlafaxine and imipramine on the time of onset of antidepressant response in patients with severe major depression: study 0600B1-384-US-EU-CA-CSR-41642.

44.   GmbH WP. Randomized, double-blind comparison of venlafaxine (WY-45, 030), imipramine, and placebo capsules in outpatients with major depression: study 600A-303-US-303-EXT-GMR-20448.

45.   GmbH WP. Randomized, double-blind comparison of venlafaxine (WY-45, 030), imipramine, and placebo capsules in outpatients with major depression: study 600A-303-US-303-EXT-GMR-20448.

46.   GmbH WP. A randomized double-blind comparision of venlafaxine XR and paroxetine in outpatients with moderate to severe major depression: study 0600-428-IT-SDC-3993.

47.   Golden RN, Nemeroff CB, McSorley P, et al. Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. J Clin Psychiatry. 2002 Jul;63(7):577-84. Epub: 2002/07/30. PMID: 12143913.

48.   Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. J Clin Psychopharmacol. 2004 Aug;24(4):389-99. Epub: 2004/07/03. PMID: 15232330.

49.   Goldstein DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. J Clin Psychiatry. 2002 Mar;63(3):225-31. Epub: 2002/04/03. PMID: 11926722.

50.   Hansgen KD, Vesper J, Ploch M. Multicenter double-blind study examining the antidepressant effectiveness of the hypericum extract LI 160. J Geriatr Psychiatry Neurol. 1994 Oct;7 Suppl 1:S15-8. Epub: 1994/10/01. PMID: 7857501.

51.   Hegerl U, Hautzinger M, Mergl R, et al. Effects of pharmacotherapy and psychotherapy in depressed primary-care patients: a randomized, controlled trial including a patients' choice arm. Int J Neuropsychopharmacol. 2010;13(1):31-44. PMID: 19341510.

52.   Henigsberg N, Mahableshwarkar AR, Jacobsen P, et al. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. J Clin Psychiatry. 2012 Jul;73(7):953-9. Epub: 2012/08/21. PMID: 22901346.

53.   Hicks JA, Argyropulous S, Rich AS, et al. Randomised controlled study of sleep after nefazodone or paroxetine treatment in out-patients with depression. Br J Psychiatry. 2002;180(6):528-35. PMID: 2002-13724-013. First Author & Affiliation: Hicks, Jane A.

54.   Higuchi T, Hong JP, Jung HY, et al. Paroxetine controlled-release formulation in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled study in Japan and Korea. Psychiatry Clin Neurosci. 2011 Dec;65(7):655-63. Epub: 2011/09/08. PMID: 21895859.

55.   Hong CJ, Hu WH, Chen CC, et al. A double-blind, randomized, group-comparative study of the tolerability and efficacy of 6 weeks' treatment with mirtazapine or fluoxetine in depressed Chinese patients. J Clin Psychiatry. 2003;64(8):921-6.

56.   Huang Y, Htut W, Li D, et al. Studies on the clinical observation and cerebral glucose metabolism in depression treated by electro-scalp acupuncture compared to fluoxetine. Int J Clin Acupunct. 2005;14(1):7-26. PMID: 0077160.

57.   Institute for Quality and Efficiency in Health Care (IQWiG). Selektive Serotonin und Noradrenalin Wiederaufnahmehemmer (SNRI) bie Patienten mit Depressionen, A05-20A, Version 1.0. Institute for Quality and Efficiency in Health Care (IQWiG) (c) IQWiG (Institute for Quality and Efficiency in Health Care). Cologne, Germany: 2009.

58.   Iwata N, Tourian KA, Hwang E, et al. Efficacy and safety of desvenlafaxine 25 and 5050% shaded blockmg/day in a randomized, placebo-controlled study of depressed outpatients. J Psychiatr Pract. 2013 Jan;19(1):5-14. Epub: 2013/01/22. PMID: 23334675.

59.   Jazayeri S, Tehrani-Doost M, Keshavarz SA, et al. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. Aust N Z J Psychiatry. 2008 Mar;42(3):192-8. Epub: 2008/02/06. PMID: 18247193.

60.   Kalb R, Trautmann-Sponsel RD, Kieser M. Efficacy and tolerability of hypericum extract WS 5572 versus placebo in mildly to moderately depressed patients. A randomized double-blind multicenter clinical trial. Pharmacopsychiatry. 2001;34(3):96-103. PMID: CN-00354554.

61.   Kasper S, Olivieri L, Di Loreto G, et al. A comparative, randomised, double-blind study of trazodone prolonged-release and paroxetine in the treatment of patients with major depressive disorder. Curr Med Res Opin. 2005 Aug;21(8):1139-46. Epub: 2005/08/09. PMID: 16083521.

62.   Kennedy SH, Konarski JZ, Segal ZV, et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry. 2007 May;164(5):778-88. Epub: 2007/05/04. PMID: 17475737.

63.   Khan A, Bose A, Alexopoulos GS, et al. Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. Clin Drug Investig. 2007;27(7):481-92. Epub: 2007/06/15. PMID: 17563128.

64.   Laakmann G, Schule C, Baghai T, et al. St. John's wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. Pharmacopsychiatry. 1998 Jun;31 Suppl 1:54-9. Epub: 1998/07/31. PMID: 9684948.

65.   Lee P, Shu L, Xu X, et al. Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil. Psychiatry Clin Neurosci. 2007 Jun;61(3):295-307. Epub: 2007/05/03. PMID: 17472599.

66.   Liebowitz MR, Tourian KA, Hwang E, et al. A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/day in adult outpatients with major depressive disorder. BMC Psychiatry. 2013;13:94. Epub: 2013/03/23. PMID: 23517291.

67.   Liebowitz MR, Yeung PP, Entsuah R. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. J Clin Psychiatry. 2007 Nov;68(11):1663-72. Epub: 2007/12/07. PMID: 18052559.

68.   Lydiard RB, Stahl SM, Hertzman M, et al. A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. J Clin Psychiatry. 1997 Nov;58(11):484-91. Epub: 1997/12/31. PMID: 9413414.

69.   Mehtonen OP, Sogaard J, Roponen P, et al. Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. Venlafaxine 631 Study Group. J Clin Psychiatry. 2000 Feb;61(2):95-100. Epub: 2000/03/25. PMID: 10732656.

70.   Mischoulon D, Nierenberg AA, Schettler PJ, et al. A double-blind, randomized controlled clinical trial comparing eicosapentaenoic acid versus docosahexaenoic acid for depression. J Clin Psychiatry. 2014 Sep 16Epub: 2014/10/02. PMID: 25272149.

71.   Mischoulon D, Price LH, Carpenter LL, et al. A double-blind, randomized, placebo-controlled clinical trial of S-adenosyl-L-methionine (SAMe) versus escitalopram in major depressive disorder. J Clin Psychiatry. 2014 Dec 24. Epub: 2014/02/07. PMID: 24500245.

72.   Montgomery SA, Mansuy L, Ruth A, et al. Efficacy and safety of levomilnacipran sustained release in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled, proof-of-concept study. J Clin Psychiatry. 2013 Apr;74(4):363-9. Epub: 2013/05/10. PMID: 23656841.

73.   Munizza C, Olivieri L, Di Loreto G, et al. A comparative, randomized, double-blind study of trazodone prolonged-release and sertraline in the treatment of major depressive disorder. Curr Med Res Opin. 2006 Sep;22(9):1703-13. Epub: 2006/09/14. PMID: 16968574.

74.   Nemeroff CB, Thase ME. A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. J Psychiatr Res. 2007;41(3-4):351-9. PMID: 2006-22968-021. PMID: 16165158. First Author & Affiliation: Nemeroff, Charles B.

75.   Nierenberg AA, Greist JH, Mallinckrodt CH, et al. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. Curr Med Res Opin. 2007 Feb;23(2):401-16. Epub: 2007/02/10. PMID: 17288694.

76.   Oakes TM, Myers AL, Marangell LB, et al. Assessment of depressive symptoms and functional outcomes in patients with major depressive disorder treated with duloxetine versus placebo: primary outcomes from two trials conducted under the same protocol. Hum Psychopharmacol. 2012 Jan;27(1):47-56. Epub: 2012/01/14. PMID: 22241678.

77.   Olie JP, Gunn KP, Katz E. A double-blind placebo-controlled multicentre study of sertraline in the acute and continuation treatment of major depression. Eur Psychiatry. 1997;12(1):34-41. PMID: CN-00189012.

78.   Perahia DG, Wang F, Mallinckrodt CH, et al. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Psychiatry. 2006 Sep;21(6):367-78. Epub: 2006/05/16. PMID: 16697153.

79.   Philipp M, Kohnen R, Hiller KO. Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. BMJ. 1999 Dec 11;319(7224):1534-8. Epub: 1999/12/11. PMID: 10591711.

80.   Qu SS, Huang Y, Zhang ZJ, et al. A 6-week randomized controlled trial with 4-week follow-up of acupuncture combined with paroxetine in patients with major depressive disorder. J Psychiatr Res. 2013 Jun;47(6):726-32. Epub: 2013/03/19. PMID: 23498306.

81.   Quah-Smith I, Smith C, Crawford JD, et al. Laser acupuncture for depression: a randomised double blind controlled trial using low intensity laser intervention. J Affect Disord. 2013 Jun;148(2-3):179-87. Epub: 2013/01/23. PMID: 23337655.

82.   Reimherr FW, Chouinard G, Cohn CK, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. J Clin Psychiatry. 1990 Dec;51 Suppl B:18-27. Epub: 1990/12/01. PMID: 2258378.

83.   Rickels K, Amsterdam J, Clary C, et al. The efficacy and safety of paroxetine compared with placebo in outpatients with major depression. J Clin Psychiatry. 1992 Feb;53 Suppl:30-2. Epub: 1992/02/01. PMID: 1531820.

84.   Rickels K, Schweizer E, Clary C, et al. Nefazodone and imipramine in major depression: a placebo-controlled trial. Br J Psychiatry. 1994 Jun;164(6):802-5. Epub: 1994/06/01. PMID: 7952987.

85.   Rudolph RL, Fabre LF, Feighner JP, et al. A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. J Clin Psychiatry. 1998 Mar;59(3):116-22. Epub: 1998/04/16. PMID: 9541154.

86.   Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J Affect Disord. 1999 Dec;56(2-3):171-81. Epub: 2000/03/04. PMID: 10701474.

87.   Rush AJ, Trivedi MH, Carmody TJ, et al. Response in relation to baseline anxiety levels in major depressive disorder treated with bupropion sustained release or sertraline. Neuropsychopharmacology. 2001 Jul;25(1):131-8. Epub: 2001/05/30. PMID: 11377926.

88.   Schrader E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. Int Clin Psychopharmacol. 2000 Mar;15(2):61-8. PMID: 10759336.

89.   Septien-Velez L, Pitrosky B, Padmanabhan SK, et al. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. Int Clin Psychopharmacol. 2007 Nov;22(6):338-47. Epub: 2007/10/06. PMID: 17917552.

90.   Shahidi M, Mojtahed A, Modabbernia A, et al. Laughter Yoga versus group exercise program in elderly depressed women: A randomized controlled trial. Int J Geriatr Psychiatry. 2011;26(3):322-7. PMID: 2011-05494-014. PMID: 20848578. First Author & Affiliation: Shahidi, Mahvash.

91.   Sheehan DV, Croft HA, Gossen ER, et al. Extended-release Trazodone in Major Depressive Disorder: A Randomized, Double-blind, Placebo-controlled Study. Psychiatry (Edgmont). 2009 May;6(5):20-33. Epub: 2009/09/03. PMID: 19724732.

92.   Shelton RC, Haman KL, Rapaport MH, et al. A randomized, double-blind, active-control study of sertraline versus venlafaxine XR in major depressive disorder. J Clin Psychiatry. 2006 Nov;67(11):1674-81. Epub: 2007/01/02. PMID: 17196045.

93.   Silverstone PH, Ravindran A. Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group. J Clin Psychiatry. 1999 Jan;60(1):22-8. Epub: 1999/03/13. PMID: 10074873.

94.   Sir A, D'Souza RF, Uguz S, et al. Randomized trial of sertraline versus venlafaxine XR in major depression: efficacy and discontinuation symptoms. J Clin Psychiatry. 2005 Oct;66(10):1312-20. Epub: 2005/11/02. PMID: 16259546.

95.   Smith WT, Glaudin V. A placebo-controlled trial of paroxetine in the treatment of major depression. J Clin Psychiatry. 1992 Feb;53 Suppl:36-9. Epub: 1992/02/01. PMID: 1531822.

96.   Smith WT, Glaudin V, Panagides J, et al. Mirtazapine vs. amitriptyline vs. placebo in the treatment of major depressive disorder. Psychopharmacol Bull. 1990;26(2):191-6. Epub: 1990/01/01. PMID: 2236455.

97.   Soares CN, Thase ME, Clayton A, et al. Desvenlafaxine and escitalopram for the treatment of postmenopausal women with major depressive disorder. Menopause. 2010 Jul;17(4):700-11. Epub: 2010/06/12. PMID: 20539246.

98.   Stevinson C. Negative result for St John's wort in major depression. Focus on Alternative and Complementary Therapies. 2001 Sep;6(3):196-7. PMID: 0029317.

99.   Sun H, Zhao H, Ma C, et al. Effects of electroacupuncture on depression and the production of glial cell line-derived neurotrophic factor compared with fluoxetine: a randomized controlled pilot study. J Altern Complement Med. 2013 Sep;19(9):733-9. PMID: 23647408.

100.   Szegedi A, Kohnen R, Dienel A, et al. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. BMJ. 2005 Mar 5;330(7490):503. Epub: 2005/02/15. PMID: 15708844.

101.   Thase ME. Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. The Venlafaxine XR 209 Study Group. J Clin Psychiatry. 1997 Sep;58(9):393-8. Epub: 1997/10/29. PMID: 9378690.

102.   Tourian KA, Padmanabhan SK, Groark J, et al. Desvenlafaxine 50 and 100 mg/d in the treatment of major depressive disorder: an 8-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial and a post hoc pooled analysis of three studies. Clin Ther. 2009 Jun;31 Pt 1:1405-23. Epub: 2009/08/25. PMID: 19698901.

103.   Uebelhack R, Gruenwald J, Graubaum HJ, et al. Efficacy and tolerability of Hypericum extract STW 3-VI in patients with moderate depression: a double-blind, randomized, placebo-controlled clinical trial. Adv Ther. 2004 Jul-Aug;21(4):265-75. Epub: 2004/12/21. PMID: 15605620.

104.   van Moffaert M, de Wilde J, Vereecken A, et al. Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression. Int Clin Psychopharmacol. 1995 Mar;10(1):3-9. Epub: 1995/03/01. PMID: 7622801.

105.   Ventura D, Armstrong EP, Skrepnek GH, et al. Escitalopram versus sertraline in the treatment of major depressive disorder: a randomized clinical trial. Curr Med Res Opin. 2007 Feb;23(2):245-50. Epub: 2007/02/10. PMID: 17288677.

106.   Wade A, Crawford GM, Angus M, et al. A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. Int Clin Psychopharmacol. 2003 May;18(3):133-41. Epub: 2003/04/19. PMID: 12702891.

107.   Wade A, Gembert K, Florea I. A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. Curr Med Res Opin. 2007 Jul;23(7):1605-14. Epub: 2007/06/15. PMID: 17559755.

Appendix G. Data From Network Meta-Analyses

Table G1. Results from network meta-analyses of antidepressants as a class versus low and medium risk of bias trials

Comparator	Intervention	Relative Risk (95% CI)	p-value
Antidepressant medications	Acupuncture	0.75 (0.43, 1.30)	0.298
Antidepressant medications	SAMe	1.22 (0.66, 2.26)	0.530
Antidepressant medications	Omega-3 fatty acids	1.96 (1.26, 3.05)	0.003
Antidepressant medications	St. John's wort	0.79 (0.67, 0.94)	0.008
Antidepressant medications	Exercise	1.86 (0.81, 4.27)	0.143
Antidepressant medications	IPT	1.01 (0.63, 1.60)	0.982