Annals of Internal Medicine REVIEW

Comparative Benefits and Harms of Antidepressant, Psychological, Complementary, and Exercise Treatments for Major Depression: An Evidence Report for a Clinical Practice Guideline From the American College of Physicians

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Background: Primary care patients and clinicians may prefer options other than second-generation antidepressants for the treatment of major depressive disorder (MDD). The comparative benefits and harms of antidepressants and alternative treatments are unclear.

Purpose: To compare the benefits and harms of second-generation antidepressants and psychological, complementary and alternative medicine (CAM), and exercise treatments as first- and second-step interventions for adults with acute MDD.

Data Sources: English-, German-, and Italian-language studies from multiple electronic databases (January 1990 to September 2015); trial registries and gray-literature databases were used to identify unpublished research.

Study Selection: Two investigators independently selected comparative randomized trials of at least 6 weeks' duration on health outcomes of adult outpatients; nonrandomized studies were eligible for harms.

Data Extraction: Reviewers abstracted data on study design, participants, interventions, and outcomes; rated the risk of bias; and graded the strength of evidence. A senior reviewer confirmed data and ratings.

Data Synthesis: 45 trials met inclusion criteria. On the basis of moderate-strength evidence, cognitive behavioral therapy (CBT) and antidepressants led to similar response rates (relative risk [RR], 0.90 [95% CI, 0.76 to 1.07]) and remission rates (RR, 0.98 [CI, 0.73 to 1.32]). In trials, antidepressants had higher risks for adverse events than most other treatment options; no information from nonrandomized studies was available. The evidence was too limited to make firm conclusions about differences in the benefits and harms of antidepressants compared with other treatment options as first-step therapies for acute MDD. For second-step therapies, different switching and augmentation strategies provided similar symptom relief.

Limitation: High dropout rates, dosing inequalities, small sample sizes, and poor assessment of adverse events limit confidence in the evidence.

Conclusion: Given their similar efficacy, CBT and antidepressants are both viable choices for initial treatment of MDD.

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For author affiliations, see end of text.
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Major depressive disorder (MDD) (1) is the most prevalent and disabling form of depression, affecting more than 16% of U.S. adults during their lifetime (2). Most patients receiving care for depression obtain treatment in primary care settings (3) where second-generation antidepressants are the most commonly prescribed agents (4). These drugs include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and other drugs with related mechanisms of action that selectively target neurotransmitters.

Despite the dominance of second-generation antidepressants, primary care patients and clinicians may want to consider other options for treating MDD. These include psychological interventions, complementary and alternative medicine (CAM) options, exercise, or a combination of these treatments. Several systematic reviews indicate that such treatments are efficacious for MDD compared with placebo or other inactive interventions (5–10).

Psychological interventions include acceptance and commitment therapy, cognitive and behavioral approaches, interpersonal therapy, and psychodynamic and attachment-based approaches. Commonly used CAM interventions are acupuncture, meditation, ω-3 fatty acids, *S*-adenosyl-L-methionine, St. John's wort, and yoga. Exercise covers a range of activities that can be done over varying durations.

Regardless of the intervention used, a substantial proportion of patients does not adequately respond or achieve remission after initial treatment. For example, about 40% of patients treated with second-generation antidepressants do not respond, and approximately 70% do not achieve remission (11). Accordingly, various other interventions–such as medication combina-

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tions, psychotherapy, or CAM treatments—are important options for patients and clinicians as second-step interventions.

We summarize a systematic review funded by the Agency for Healthcare Research and Quality (AHRQ) (12) that focused on 2 key issues. First, how effective are second-generation antidepressants compared with alternative pharmacologic and nonpharmacologic interventions as an initial treatment choice? Second, for patients who do not achieve remission with a second-generation antidepressant, what is the comparative effectiveness of augmentation of the original drug or switching to another treatment?

METHODS

The methods for this comparative effectiveness review follow the guidance provided in the AHRQ publication "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (www.effectivehealthcare.ahrq.gov/methodsguide.cfm). We developed key questions by using an open process involving the public, the AHRQ Effective Health Care program's Topic Triage group, and various stakeholder groups. The protocol of the review was posted on AHRQ's Web site for public comment (www.effectivehealthcare.ahrq.gov) from 3 February 2014 through 24 February 2014, and was subsequently revised as needed. A panel of experts representing various stakeholder groups (consumers, professional organizations, researchers, and payers) provided feedback during all critical stages of the review.

Data Sources and Searches

We searched MEDLINE (via PubMed), EMBASE, the Cochrane Library, the Allied and Complementary Medicine Database, PsycINFO, and CINAHL from January 1990 to 23 September 2015. We used a combination of Medical Subject Heading terms and keywords, focusing on terms to describe the relevant population and interventions of interest. We limited electronic searches to "adult 19+ years"; "human"; and "English, German, and Italian languages." Table 1 of the Supplement (available at www.annals.org) shows the electronic search strategy. To detect unpublished studies, we searched 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, the Conference Proceedings Citation Index, and reference lists of pertinent reviews and included trials.

The AHRQ Scientific Resource Center requested scientific information packets from relevant manufacturing companies, asking for any unpublished studies or relevant data. We received information packets from Eli Lilly and Company (Indianapolis, Indiana) and Merck & Co. (Kenilworth, New Jersey).

Study Selection

Two trained team members independently reviewed all abstracts and full-text articles by using predefined inclusion and exclusion criteria. Our population of interest was adult outpatients of all races and ethnicities with MDD during 1) an initial treatment attempt or 2) a second treatment attempt in patients who did not achieve remission after treatment with a second-generation antidepressant. For patients with an initial treatment attempt, we were interested in the benefits and harms of second-generation antidepressants compared with common depression-focused psychological interventions, CAM interventions, and exercise as 1) monotherapies, 2) in combination with one another, or 3) in combination with a second-generation antidepressant. For patients who did not achieve remission after an adequate trial with a second-generation antidepressant, we were interested in second-step therapies that could involve a switch to a new treatment or an augmentation of an existing treatment with a pharmacologic or nonpharmacologic option. The Table shows the interventions that we reviewed.

To assess the comparative benefits, we limited studies to randomized, controlled trials (RCTs) of at least 6 weeks' duration that compared 2 interventions of interest. In general, we included only double-blinded RCTs. For interventions for which double-blinding was not possible (such as psychological interventions or yoga), we required that outcomes assessors be blinded. For harms (evidence pertaining to safety, tolerability, and adverse events), we intended to examine data from both randomized and nonrandomized studies (minimum sample size of 500), but found no eligible nonrandomized studies.

We excluded studies that both reviewers agreed did not meet eligibility criteria. Investigators resolved disagreements about inclusion or exclusion by consensus or by involving a third reviewer. Detailed inclusion and exclusion criteria are presented in the AHRQ report (12).

Data Extraction and Quality Assessment

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 evaluated the completeness and accuracy of the data abstraction.

We classified patients' severity of depression by using the categorization systems of the University of Pittsburgh Epidemiology Data Center (13) and Zimmerman and colleagues (14).

To assess the risk of bias of studies, we used definitions based on AHRQ guidance (15). 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 RCTs (16). Two independent reviewers assigned risk-of-bias ratings. They resolved any disagreements by discussion and consensus or by consultation with a third reviewer.

Data Synthesis and Analysis

To determine whether meta-analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies under consideration by

Table. Eligible First- or Second-Step Treatments for Major Depressive Disorder in Adults

Second-Generation Antidepressants	Common Depression-Focused Psychotherapies	Complementary and Alternative Medicines	Exercise	Other Pharmacotherapies for Combination or Augmentation as Second-Step Treatments
Bupropion Citalopram Desvenlafaxine Duloxetine Fluoxetine Escitalopram Fluvoxamine Levomilnacipran Mirtazapine Nefazodone Paroxetine Sertraline Trazodone Venlafaxine Vilazodone Vortioxetine	Acceptance and commitment therapy* Cognitive and behavioral approaches† Interpersonal therapy‡ Psychodynamic and attachment-based approaches§	Acupuncture Meditation (e.g., mindfulness-based stress reduction) ω-3 fatty acids *S*-adenosyl-L-methionine St. John's wort (*Hypericum*) 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, methylphenidate, modafinil) Buspirone Levothyroxine Lithium Pindolol Triiodothyronine

* A third-generation behavioral therapy that incorporates acceptance and mindfulness-based intervention to help people obtain a more fulfilling life by overcoming negative thoughts and feelings. Acceptance and commitment therapy accomplishes this by teaching people how to act effectively in the presence of difficult psychological events.
† These therapies are based on the idea that faulty thinking patterns generate maladaptive behaviors and negative emotions. Cognitive and behavioral interventions focus on changing an individual's thoughts (cognitive patterns) in order to change behavior and emotional states.
‡ Focuses on an individual's relationships with peers and family members and the way in which they see themselves. The goal of interpersonal therapy is to help people to identify and modify interpersonal problems and to understand and to manage relationship problems.
§ These therapies focus on helping people understand the historical roots of their problems or symptoms. The goals of psychodynamic and attachment-based therapies are a client's self-awareness and understanding of the influence of the past on present behavior.

following established guidance (17). We combined studies that were similar in populations and interventions, and assessed outcomes at similar follow-up times (most commonly 8 to 16 weeks). For all analyses, we used random- and fixed-effects models to estimate comparative effects. We used restricted maximum likelihood models for random-effects analyses. For efficacy, we conducted meta-analyses on the relative risk for achieving response (as defined by the study authors, most commonly as a ≥50% improvement from baseline) on the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery–Åsberg Depression Rating Scale at study end point, and the relative risk for achieving remission (as defined by the study authors, most commonly as a HAM-D score <7) at study end point. For harms, we conducted meta-analyses on the relative risk for experiencing an adverse event, discontinuing treatment, and discontinuing treatment because of harms.

For each meta-analysis, we tested for heterogeneity by using the Cochran Q test and estimated the extent of heterogeneity with the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity). If heterogeneity was high (>60%), we explored differences in clinical and methodological characteristics among studies considered for meta-analyses.

Previous investigations have demonstrated that no substantial differences in benefits and harms exist among second-generation antidepressants (11); therefore, in all meta-analyses, we compared second-generation antidepressants as a class with other interventions of interest. We categorize types of psychological interventions according to the Cochrane Depression, Anxiety and Neurosis Review Group classification system (18).

For all meta-analyses, we conducted sensitivity analyses with and without high risk-of-bias studies.

We assessed publication bias by using funnel plots and Kendall τ rank correlation. However, given the small number of component studies in our meta-analyses, these tests have low sensitivity to detect publication bias. We conducted meta-analyses by using OpenMetaAnalyst.

Grading the Strength of Evidence

Two reviewers independently graded the strength of evidence on the basis of the guidance established for the Evidence-based Practice Center Programs (19). They resolved disagreements by discussion and consensus or by consultation with a third reviewer. Grades reflect the confidence that the estimate of an outcome of interest is close to the true effect.

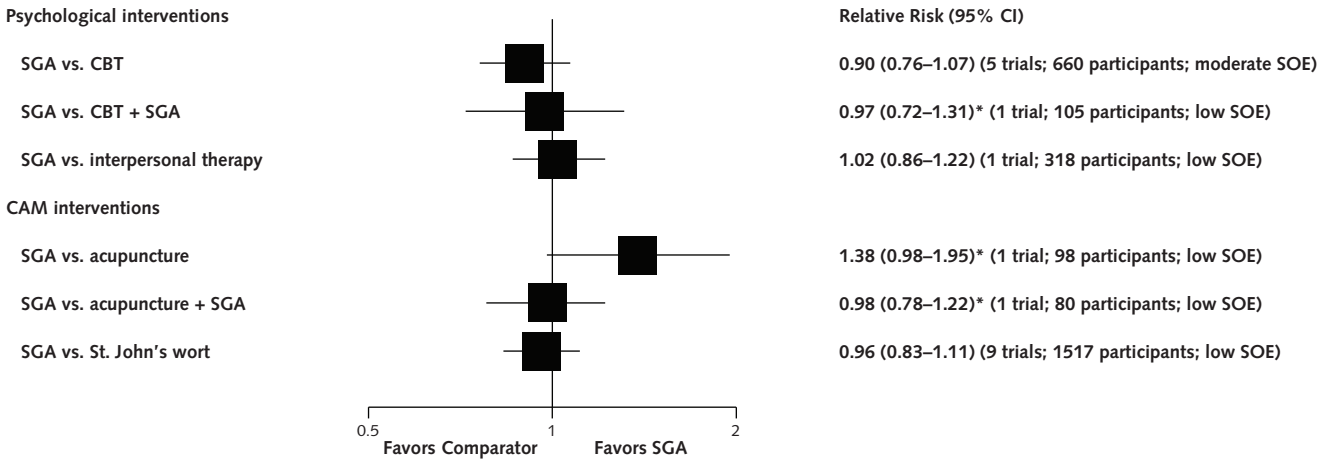
Role of the Funding Source

Staff at AHRQ participated in formulating key questions and in reviewing planned methods and data analyses and the interim and final evidence reports. These AHRQ staff had no role in study selection, risk-of-bias ratings, strength of evidence grading, or interpretation of the evidence.

RESULTS

Our searches identified 8316 citations (**Appendix Figure**, available at www.annals.org). Of the 45 included head-to-head trials (56 publications) (**Tables 2** through **9** of the **Supplement**), 42% were financially supported by governmental agencies or independent funds and 22% by pharmaceutical companies; 22% had mixed funding, and 13% had undetermined sources.

Figure 1. Comparison of response rates of SGAs with other eligible interventions.



CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; SGA = second-generation antidepressant; SOE = strength of evidence.
* Estimate is based on trial with lowest risk of bias.

To obtain unreported data from published trials, we contacted authors. Additional outcomes data were obtained for 10 trials.

Comparative Benefits and Harms of First-Step Treatments

Forty-three head-to-head trials compared the benefits and harms of second-generation antidepressants with other options as first-step treatments for acute-phase MDD. Most patients in these studies had moderate to severe MDD. Many of the available trials, however, had serious methodological limitations, such as lack of blinding of outcomes assessors or high loss to follow-up; we rated 16 trials (37%) as high risk of bias for outcomes related to benefits (20–35).

Overall, we found no statistically significant differences in efficacy between second-generation antidepressants and most other treatments for adult outpatients with mild to severe MDD. The risks for adverse events and discontinuation of treatment because of adverse events were generally higher in patients treated with second-generation antidepressants. The strength of evidence for those findings, however, was generally low, with the exception of the comparison of second-generation antidepressants with cognitive behavioral therapy (CBT), which was rated moderate. In particular, the assessment of adverse events was inadequate in many trials. Even common adverse events associated with antidepressants, such as diarrhea, nausea, or sexual dysfunction, were rarely assessed or reported. Similarly, few trials addressed adverse events that are commonly associated with psychological interventions, such as worsening of symptoms or onset of new depression-associated symptoms.

Figures 1 through 3 provide graphical overviews of response, remission, and discontinuation rates because of adverse events for comparisons that had at least low strength of evidence.

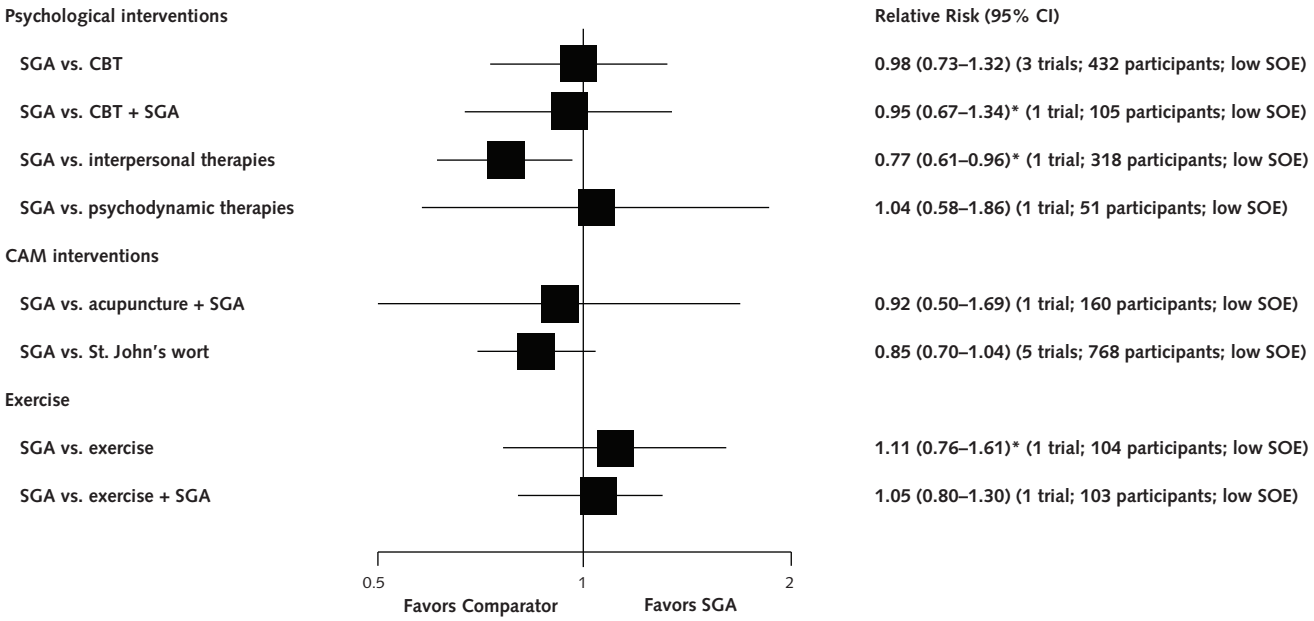
Second-Generation Antidepressants Compared With Psychological Interventions

We identified 20 RCTs in 22 publications (Table 2 of the Supplement) with data on 3000 patients comparing second-generation antidepressants with psychological interventions, either alone or in combination (22, 24, 26, 27, 29, 31–33, 36–49). Table 10 of the Supplement summarizes the results and strength of evidence of findings.

Five trials (31, 39, 44–46) were conducted in primary care settings; the remainder took place in mental health care locations. Most trials excluded patients with medical comorbidities or suicidal ideation and behaviors. Few studies included elderly patients; the mean age of patients in most studies was between 35 and 45 years. Most patients in all trials were female. In the few trials that reported race or ethnicity, 3 (31, 36, 39) included more than 33% nonwhite patients.

Of the 20 included trials on psychological interventions, 11 assessed various CBTs (24, 26, 27, 32, 33, 37, 39, 40, 43, 44, 47, 50). Meta-analysis of 5 trials with low or medium risk of bias (24, 37, 40, 41, 44, 47) (660 patients with moderate to severe MDD) indicated similar response rates after 8 to 16 weeks for patients receiving CBT or second-generation antidepressants (44% vs. 46%; relative risk [RR], 0.90 [95% CI, 0.76 to 1.07]). Likewise, remission rates were similar between treatment groups (41% vs. 48%; RR, 0.98 [CI, 0.73 to 1.32]) in a meta-analysis of 3 trials (432 patients) after 12 to 16 weeks of follow-up (40, 41, 44, 47). In both treatment groups, 16% of patients discontinued treatments (RR, 1.00 [CI, 0.55 to 1.81]), on the basis of a meta-analysis of 4 trials (611 patients) (37, 40, 44, 47).

Figure 2. Comparison of remission rates of SGAs with other eligible interventions.

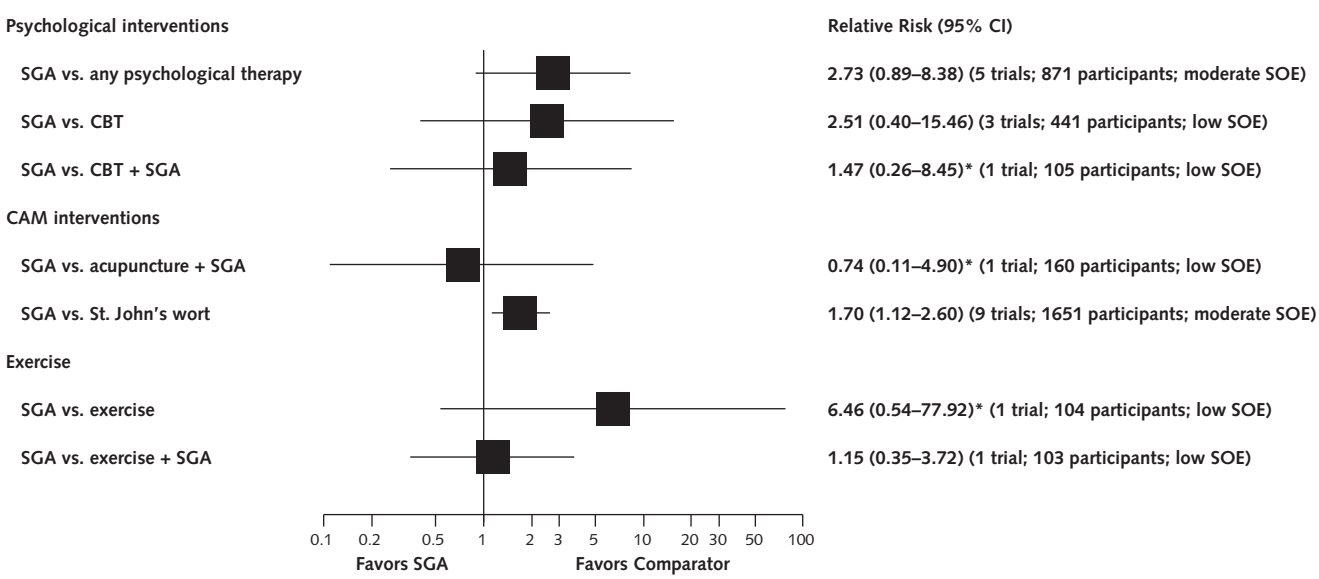


CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; SGA = second-generation antidepressant; SOE = strength of evidence.
* Estimate is based on trial with lowest risk of bias.

In a meta-analysis of 3 trials (441 patients) (37, 40, 44), treatment discontinuations because of adverse events were numerically higher for patients on second-generation antidepressants but did not reach statistical significance (8% vs. 3%; RR, 2.51 [CI, 0.40 to 15.46]). Sensitivity analyses including 3 high risk-of-bias trials (26, 27, 32) yielded similar, nonsignificant differences for the above-mentioned outcomes.

Two trials with medium risk of bias reported lower relapse rates for patients treated with CBT (range, 2% to 39%) than for those on second-generation antidepressants (range, 11% to 59%) (39, 47).

Figure 3. Comparison of discontinuation rates because of adverse events of SGAs with other eligible interventions.



CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; SGA = second-generation antidepressant; SOE = strength of evidence.
* Estimate is based on trial with lowest risk of bias.

Adding CBT to an antidepressant did not lead to statistically significant different rates of response (ranges, 61% to 78% vs. 63% to 74%) or remission (ranges, 53% to 67% vs. 56% to 66%) compared with antidepressant monotherapies after 12 to 52 weeks of treatment (33, 43, 44).

Studies comparing second-generation antidepressants with other forms of psychological interventions, such as third-wave behavioral therapy (29, 40), interpersonal therapies (22, 31, 46, 49, 51), or psychodynamic therapies (36, 42, 45, 48, 52), often provided mixed or indeterminate results on differences in efficacy. Only the combination of an antidepressant and interpersonal psychotherapy had statistically significantly higher remission rates than nefazodone monotherapy (odds ratio, 3.22 [CI, 1.02 to 10.12]) on the basis of a single trial (49). Our confidence in these findings, however, is limited (Table 10 of the Supplement) because of small sample sizes of single studies or methodological limitations, such as high loss to follow-up and unclear blinding of outcomes assessors.

Most studies on psychological interventions reported higher risks for discontinuation because of adverse events among patients treated with antidepressants (Figure 3). The evidence was insufficient to draw any conclusions about the comparative risk for serious adverse events, such as suicidal thoughts or behaviors, between second-generation antidepressants and any psychological therapies.

Second-Generation Antidepressants Compared With CAM Therapies

We identified 20 RCTs including 2600 patients comparing second-generation antidepressants with 1 of 4 CAM therapies (Tables 3 through 6 of the Supplement) (20, 21, 23, 25, 28, 30, 34, 35, 53–66). We did not find any eligible evidence on meditation and yoga. Table 11 of the Supplement summarizes results and strength of evidence of findings.

Eight trials were conducted in mental health care facilities, and the remainder in various primary care settings. Most participants in CAM trials were female and between 30 and 50 years of age. Five trials included exclusively Chinese patients.

Twelve trials (1806 participants) compared second-generation antidepressants with St. John's wort (20, 21, 30, 57–62, 64–66), using a variety of commercially available standardized extracts (most often standardized to 0.12% to 0.28% hypericin); dosages ranged from 300 mg/d to 1800 mg/d. The majority of trials took place in outpatient primary care clinics and enrolled more women than men.

Meta-analyses of 9 trials (1513 participants, predominantly with severe depression) (20, 57–61, 64–66) indicated similar response rates for patients treated with second-generation antidepressants or St. John's wort (52% vs. 54%; RR, 0.96 [CI, 0.83 to 1.11) after 6 to 12 weeks of treatment. Meta-analysis of 5 trials (768 participants) (21, 58, 59, 65, 66) demonstrated no statistically significant difference in remission rates (30% vs. 36%; RR, 0.85 [CI, 0.70 to 1.04]) between treatment groups. Of note, all trials compared St. John's wort with moderate- or low-dose second-generation antidepressant regimens (Table 3 of the Supplement) but did not fully using the approved range of antidepressant doses.

Despite the low dosing, patients treated with antidepressants had a significantly higher risk for treatment discontinuation (16% vs. 12%; RR, 1.28 [CI, 1.01 to 1.62]) and discontinuation because of adverse events (7% vs. 4%; RR, 1.70 [CI, 1.12 to 2.60]) than those on St. John's wort, on the basis of a meta-analysis of 9 trials (1651 patients) (20, 56–60, 63–65). We found no trials comparing a combination of St. John's wort plus an antidepressant with antidepressant monotherapy.

Five trials in 6 publications (503 participants) (34, 35, 53–56) evaluated acupuncture, reporting mostly inconclusive results (Table 4 of the Supplement). Two trials did not find statistically significant differences in response rates between patients receiving antidepressants (range, 60% to 65%) or acupuncture (range, 56% to 75%) after 6 weeks of treatment (35, 54). The CIs for these results, however, were wide and encompassed clinically significant differences for both treatment options. Two trials reported mixed results on an incremental benefit of adding acupuncture to antidepressants (55, 56). All trials had been conducted in China, where publication bias for trials of acupuncture continues to be problematic (67, 68).

The evidence was insufficient to draw conclusions about the benefits and harms of second-generation antidepressants compared with Ω-3 fatty acids or *S*-adenosyl-L-methionine. The available studies were compromised by unclear randomization methods, high loss to follow-up, small sample sizes, and lack of intention-to-treat analyses (23, 25, 28) (Table 5 of the Supplement).

Second-Generation Antidepressants Compared With Exercise

Two trials in 4 publications (Table 7 of the Supplement) indicated no significant difference in remission after 16 weeks for patients treated with sertraline (range, 47% to 69%) and those assigned to aerobic exercise (range, 40% to 47%) (69–72). Two trials that assessed the combination of an antidepressant regimen and exercise yielded mixed results (71, 73). One study reported similar remission rates (69% vs. 66%) between treatment groups (71); the other found statistically significantly lower remission rates in elderly patients (aged ≥65 years) receiving sertraline monotherapy than those assigned to a combination of sertraline and aerobic exercise (45% vs. 81%) (73). Table 11 of the Supplement summarizes results and strength of evidence of findings.

Severity as a Moderator of Comparative Treatment Effectiveness

Five trials yielded insufficient evidence to determine whether the comparative efficacy of second-generation antidepressants versus psychological or

CAM treatments changes as a function of MDD severity (Table 8 of the Supplement) (28, 29, 36, 40, 46).

Comparative Benefits and Harms of Second-Step Treatments

Only 2 trials addressed the comparative benefits and harms of second-step treatment strategies for adult patients with acute-phase MDD who did not recover after initial treatment with a second-generation antidepressant (Table 9 of the Supplement) (74, 75). One trial compared switching to different second-generation antidepressants (74). The other trial, the STAR*D study, provided data for multiple comparisons: switching to another antidepressant (75), switching to CBT versus switching to an antidepressant (76), augmenting with a second medication versus augmenting with an antidepressant (76), and augmenting with one non–antidepressant medication versus augmenting with an antidepressant (77). None of these second-step treatment strategies, however, had greater efficacy or a greater risk of harms than another. Table 12 of the Supplement (available at www.annals.org) summarizes results and strength of evidence of findings.

We found no eligible switch or augmentation trials directly comparing second-generation antidepressants with either CAM or exercise. Moreover, we found no direct comparison of switching strategies versus augmentation strategies.

DISCUSSION

In our systematic review, we found that second-generation antidepressants and most other interventions of interest do not differ significantly in benefit as first-step treatments for adult outpatients with mild to severe MDD. In addition, patients treated with second-generation antidepressants in general had higher risks for adverse events or treatment discontinuation because of adverse events than patients receiving psychological, CAM, or exercise interventions.

Our confidence in these findings is mixed. The strongest body of evidence was available for the comparison of second-generation antidepressants with CBT. For all of the other comparisons, the evidence for at least some of the outcomes rated as critical or important for decision making by our technical expert panel had substantial weaknesses, such as methodological limitations, small study sizes, or dosing inequalities. In addition, for many comparisons that are limited to single trials, determining whether similar treatment effects between second-generation antidepressants and other interventions were based on similar efficacy or high placebo response rates is impossible.

The limited amount of data offers no conclusions on how selection of treatment strategies might differ on the basis of a patient's severity of depression. A recent meta-analysis using individual patient data found that baseline severity did not moderate the comparative efficacy of antidepressants and CBT in patients with MDD and dysthymia (78).

Likewise, beyond the 2 studies comparing switch and augmentation strategies, 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) (79, 80) was also striking.

Our findings are consistent with those of several prior systematic reviews and meta-analyses that compared second-generation antidepressants with alternative interventions (9, 81–84). Most of these reviews, however, included populations that were ineligible for our review, such as patients with minor depression, bipolar disorder, or dysthymia. Findings of our review do not support recommendations that combining pharmacotherapy and psychotherapy may be necessary in cases of moderate to severe depression (85, 86).

Our review and the underlying evidence base have several limitations. First, no reliable evidence was available assessing the comparative effectiveness or risk for harms of several of our eligible interventions.

Second, many trials had methodological shortcomings that reduced our confidence in the results. Of the 45 trials meeting our eligibility criteria, we rated 16 as high risk of bias and only 5 as low risk of bias. In addition, some comparisons were based on single, small trials, which led to indeterminate results with wide CIs that encompassed appreciable benefits for both comparators. In addition, for most trials of St. John's wort, we had concerns about adequate dosing of second-generation antidepressants.

Third, trials often did not assess harms adequately (or at all). Of the 45 included trials, only 1 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. Authors rarely reported whether adverse events were prespecified or defined. Short trial durations and small sample sizes also limited the validity of adverse event assessment in many trials. Consequently, assessing the balance between benefits and harms was often not possible.

Fourth, of the limited body of evidence, most trials were explanatory rather than pragmatic: That is, they were designed to test whether a treatment worked under ideal circumstances rather than in everyday practice. Moreover, most trials provided information for only 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.

Fifth, 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 (59). In this 3-group study comparing sertraline, St. John's wort, and placebo, they concluded that participants' beliefs about treatment assignment were more strongly associated with clinical outcomes than the actual treatment received (87), a finding echoed in other studies of MDD (88, 89). 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.

Sixth, how the diagnosis of MDD was ascertained in individual studies was not always clear. Some studies used structured interviews based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, but others did not report the method of ascertainment.

Finally, publication bias and selective outcome reporting are potential limitations. Although we searched for gray and unpublished literature, the extent and impact of publication and reporting biases in this body of evidence are impossible to determine.

What are the implications of our findings for practicing clinicians? Given comparable efficacy, CBT and antidepressants are both viable choices for initial MDD treatment. Treatment should be chosen after discussion with patients about the advantages and disadvantages of each option, including risks for particular adverse effects, potential drug interactions, and patient preferences (for example, regarding costs, patient beliefs, availability of treatment). The available evidence does not provide definitive answers about the comparative benefits and harms of other treatment options and antidepressants as first-step treatments. In general, we would like to emphasize that the absence of a statistically significant difference cannot be equated with equivalence of 2 treatment options.

For second-step therapies, the evidence supports switching to another antidepressant, switching to cognitive therapy, or augmenting with a particular medication or cognitive therapy as reasonable options. However, compared with the actual treatment choice, the more important decision appears to be simply to try a different evidence-based approach.

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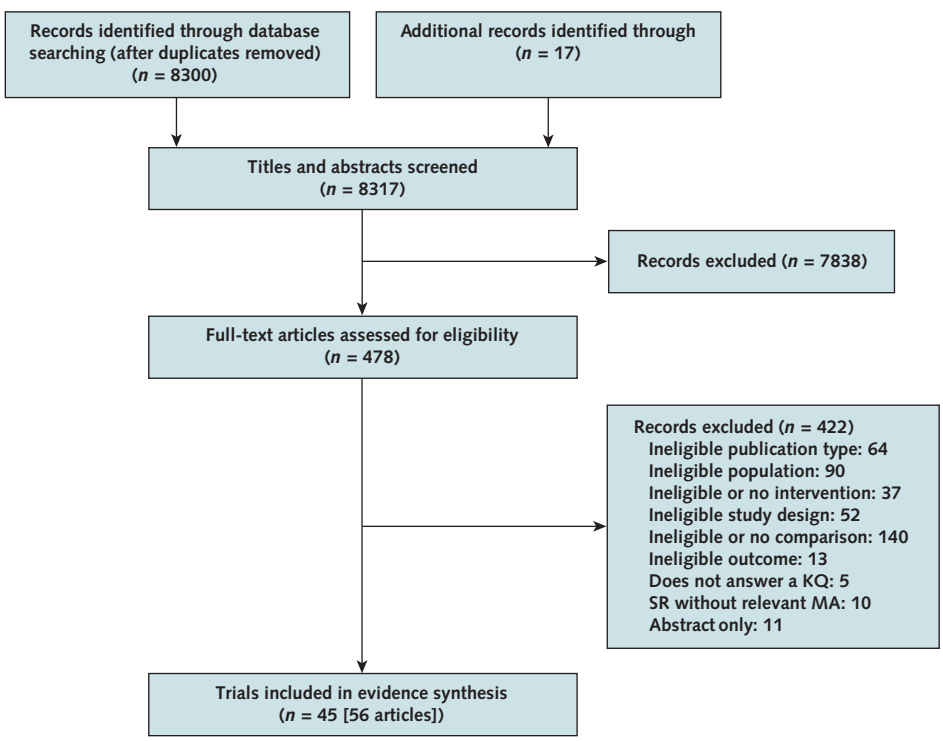
Appendix Figure. Summary of evidence search and selection.



KQ = key question; MA = meta-analysis; SR = systematic review.