CLINICAL GUIDELINE

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With Major Depressive Disorder: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Michael J. Barry, MD; and Devan Kansagara, MD, MCR, for the Clinical Guidelines Committee of the American College of Physicians

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the comparative effectiveness of treatment with second-generation antidepressants versus nonpharmacologic treatments for major depressive disorder in adults.

Methods: This guideline is based on a systematic review of published, English-language, randomized, controlled trials from 1990 through September 2015 identified using several databases and through hand searches of references of relevant studies. Interventions evaluated include psychotherapies, complementary and alternative medicines (including acupuncture, ω-3 fatty acids, *S*-adenosyl-L-methionine, St. John's wort [*Hypericum perforatum*]), exercise, and second-generation antidepressants. Evaluated outcomes included response, remission, functional capacity, quality of life, reduction of suicidality or hospitalizations, and harms. The target audience for this guideline includes all clinicians, and the target patient population includes adults with major depressive disorder. This guideline grades the evidence and recommendations using ACP's clinical practice guidelines grading system.

Recommendation: *ACP recommends that clinicians select between either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient (Grade: strong recommendation, moderate-quality evidence).*

Ann Intern Med. doi:10.7326/M15-2570 **www.annals.org**
For author affiliations, see end of text.
This article was published at www.annals.org on 9 February 2016.

Depressive disorders are a major health care issue and one of the foremost causes of disability in adults around the world, resulting in significant costs to society and health care systems (1). The estimated economic burden associated with depression was $83.1 billion in 2000 and is probably higher today (2). Depressive disorders include major depressive disorder (MDD); dysthymia; and subsyndromal depression, including minor depression. Major depressive disorder is the most prevalent depressive disorder, with an estimated lifetime prevalence of 16% in the United States (3). An average of 8 million ambulatory care visits per year result in a primary diagnosis of MDD (4). The American Psychiatric Association (5) defines MDD as depressed mood or loss of pleasure or interest along with other symptoms, including significant change in weight or appetite, insomnia or hypersomnia, psychomotor agitation or retardation nearly every day, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, indecisiveness or decreased ability to concentrate, and recurrent thoughts of death or suicide, that last for at least 2 weeks and affect normal functioning. Dysthymia is less severe, but symptoms last for 2 or more years. In contrast, subsyndromal depression is associated with less severe symptoms of depression that do not qualify for MDD or dysthymia diagnoses.

See also:

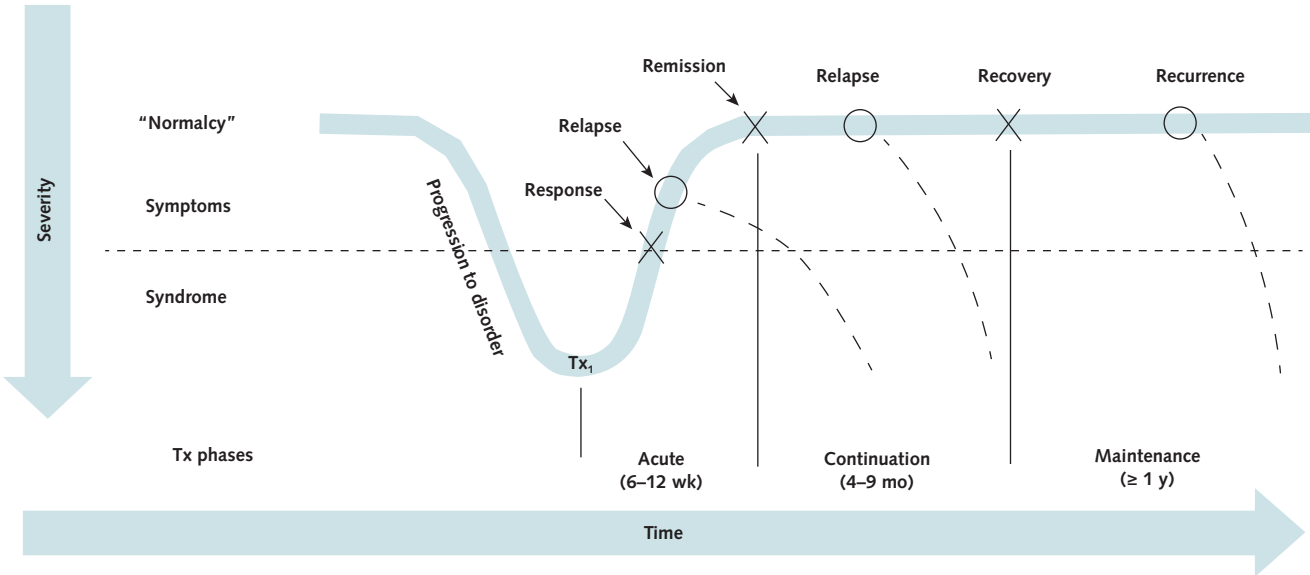
Related article 331
Editorial comment 372
Summary for Patients 3

The treatment of depression can be characterized by 3 phases (Figure 1): acute (6 to 12 weeks), continuation (4 to 9 months), and maintenance (≥1 year) (7). Relapse is defined as the return of depressive symptoms during the acute or continuation phases and is therefore considered part of the same depressive episode, whereas recurrence is defined as the return of depressive symptoms during the maintenance phase and is considered a new, distinct episode. Response to treatment (typically defined as ≥50% reduction in measured severity) can be quantified using various tools, such as the Patient Health Questionnaire-9 (PHQ-9) (7) or the Hamilton Depression Rating Scale (HAM-D) (8).

Various treatment approaches can be used to manage MDD, such as psychotherapy, complementary and alternative medicine (CAM), exercise, and pharmaco-

* This paper, written by Amir Qaseem, MD, PhD, MHA; Michael J. Barry, MD; and Devan Kansagara, MD, MCR, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were Mary Ann Forciea†, MD (*Chair*); Thomas D. Denberg‡, MD, PhD (*Immediate Past Chair*); Michael J. Barry‡, MD; Cynthia Boyd‡, MD, MPH; R. Dobbin Chow‡, MD, MBA; Nick Fitterman‡, MD; Russell P. Harris‡, MD, MPH; Linda L. Humphrey‡, MD, MPH; Devan Kansagara‡, MD, MCR; Scott Manaker†, MD, PhD; Robert McLean‡, MD; Sandeep Vijan†, MD, MS; and Timothy Wilt‡, MD, MPH. Approved by the ACP Board of Regents on 7 November 2015.
† Nonauthor contributor (participated in discussion but excluded from voting).
‡ Author (participated in discussion and voting).

Figure 1. Phases of treatment of major depression.



Adapted from reference 6. T_X = treatment.

therapy. The psychological interventions used to treat depression include acceptance and commitment therapy, cognitive therapy, cognitive behavioral therapy (CBT), interpersonal therapy, and psychodynamic therapies (Table 1). The CAM treatments include acupuncture, meditation, ω-3 fatty acids, *S*-adenosyl-L-methionine (SAMe), St. John's wort, and yoga. Exercise includes a broad range of activities that can be done for varying durations, in classes, individually, or in informal groups. For pharmacologic therapy, the scope of this guideline is limited to second-generation antidepressants (SGAs) (selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and selective serotonin norepinephrine reuptake inhibitors). First-generation antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors) are very rarely used because SGAs have lower toxicity in overdose than first-generation antidepressants and similar efficacy.

Guideline Focus and Target Population

The purpose of this guideline from the American College of Physicians (ACP) is to summarize and grade the evidence on the comparative effectiveness and safety of nonpharmacologic treatments and SGAs (including serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, bupropion, mirtazapine, nefazodone, and trazodone), alone or in combination, for MDD. The target audience for this guideline includes all clinicians, and the target patient population includes all adults with MDD. These recommendations are based on a background evidence article (9) and a systematic evidence review sponsored by the Agency for Healthcare Research and Quality (AHRQ) (6).

Methods

Systematic Review of the Evidence

The systematic evidence review was conducted by the AHRQ's RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center (6). Additional methodological details can be found in the Appendix (available at www.annals.org), accompanying background evidence article (9), and full report (6). Reviewers searched several databases for studies published in English, German, or Italian from 1 January 1990 through September 2015. Studies on efficacy were limited to randomized, controlled trials and systematic reviews and meta-analyses, although evidence on harms included observational studies. Reviewers combined data when possible using meta-analysis and assessed the risk of bias and quality of studies according to established methods. The study population included adult outpatients (aged ≥18 years) with MDD

Table 1. Common Psychological Interventions to Treat Depression

Intervention	Description
Acceptance and commitment therapy	Uses mindfulness techniques to overcome negative thoughts and accept difficulties
Cognitive therapy	Helps patients correct false self-beliefs and negative thoughts
Cognitive behavioral therapy	Includes a behavioral component in cognitive therapy, such as activity scheduling and homework
Interpersonal therapy	Focuses on relationships and how to address issues related to them
Psychodynamic therapy	Focuses on conscious and unconscious feelings and past experiences
Third-wave cognitive behavioral therapy	Targets thought processes to help persons with awareness and acceptance

during either an initial or a second treatment attempt who did not remit after an initial adequate trial with an SGA.

The review evaluated the following classes of interventions: depression-focused psychotherapy, CAM, exercise, and SGAs. Outcomes assessed included benefits in response (often defined as ≥50% improvement in HAM-D scores), remission (often defined as a HAM-D score ≤7), speed of response, speed of remission, relapse, quality of life, functional capacity (as assessed by various scales), reduction of suicidality, or reduction of hospitalization. Harms assessed included overall adverse events, withdrawals because of adverse events, serious adverse events, and specific adverse events. Quality of life, functional status, suicidality, and hospitalizations were rarely reported.

Grading the Evidence and Developing Recommendations

This guideline was developed by the ACP Clinical Guidelines Committee according to the ACP guideline development process, which has been described (10). The Clinical Guidelines Committee used the evidence tables in the accompanying systematic review and full report (9) when reporting the evidence and graded the recommendations using ACP's guideline grading system (Table 2).

Peer Review

The AHRQ evidence review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments. The guideline was peer-reviewed through the journal and was posted online for comments from ACP Governors and Regents.

Table 2. The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

COMPARATIVE BENEFITS OF PHARMACOLOGIC VERSUS NONPHARMACOLOGIC TREATMENT OPTIONS FOR INITIAL MANAGEMENT

Refer to Appendix Table 1 (available at www.annals.org) and the accompanying systematic review (9) for additional details of the evidence.

SGA Versus Psychological Interventions

SGA Versus CBT

Monotherapy. Moderate-quality evidence from 5 trials (11–15) showed no difference in response when comparing SGAs (fluoxetine, fluvoxamine, paroxetine, or sertraline) with CBT in patients with MDD after 8 to 52 weeks of treatment. Low-quality evidence from 3 trials (11, 14, 15) showed no difference between remission rates (fluoxetine, fluvoxamine, and paroxetine) and functional capacity (14) (fluvoxamine and paroxetine) for SGAs compared with CBT.

Combination Therapy. Low-quality evidence from 2 trials (14, 16) showed no difference in response or remission when comparing monotherapy using SGAs (escitalopram, fluvoxamine, or paroxetine) with combination therapy using SGAs plus CBT (problem-solving therapy or telephone-based CBT) in patients with MDD after 12 to 52 weeks of treatment. Low-quality evidence from 2 trials (14, 16) assessed function, and 1 trial showed that patients who received the combination therapy reported more improvement on 3 of 5 work-functioning measures than those who received SGA monotherapy, although clinically important differences on these measures are uncertain.

SGA Versus Interpersonal Therapy

Monotherapy. Low-quality evidence showed no difference in response (1 trial; escitalopram) (17) or remission (2 trials; citalopram, escitalopram, or sertraline) (17, 18) for SGAs compared with interpersonal therapy for patients with MDD after 12 weeks of treatment.

Combination Therapy. Low-quality evidence from 1 trial (19) showed increased remission for SGA monotherapy compared with SGA combined with interpersonal therapy (with nefazodone) in patients with MDD after 12 weeks of treatment.

SGA Versus Psychodynamic Therapies

Monotherapy. Low-quality evidence from 1 trial (20) showed no difference in remission for fluoxetine compared with psychodynamic monotherapy in patients with MDD after 16 weeks of treatment. Low-quality evidence from 2 trials (20, 21) showed few differences in functional capacity between the treatments.

Combination Therapy. Low-quality evidence from 1 trial (21) showed no difference in functional capacity for SGA monotherapy compared with SGA plus psychodynamic combination therapy.

SGA Versus CAM Interventions

SGA Versus Acupuncture

Monotherapy. Low-quality evidence from 2 trials (22, 23) showed no difference in treatment response when comparing fluoxetine with acupuncture monotherapy for patients with MDD after 6 weeks of treatment.

Combination Therapy. Low-quality evidence from 2 trials (24, 25) showed that combination therapy of SGAs with acupuncture improved treatment response compared with monotherapy with SGAs (fluoxetine or paroxetine) in patients with MDD after 6 weeks of treatment. However, low-quality evidence from 1 trial (24) showed no difference in remission when comparing paroxetine monotherapy with paroxetine plus acupuncture combination therapy.

SGA Versus ω-3 Fatty Acids

Monotherapy. Low-quality evidence from network meta-analysis showed that SGAs (fluoxetine) were associated with a greater response than ω-3 fatty acids in patients with MDD.

SGA Versus SAMe

Monotherapy. Low-quality evidence from network meta-analysis showed no difference in response between treatment with escitalopram and SAMe in patients with MDD after 12 weeks of treatment.

SGA Versus St. John's Wort

Monotherapy. Low-quality evidence from 9 trials (26–34) showed no difference in response or remission (26, 27, 33–35) when comparing treatment using SGAs with St. John's wort in patients with MDD after 4 to 12 weeks of treatment. Levels of SGAs used in the comparative effectiveness studies with St. John's wort were capped at levels lower than usual dosing ranges in comparative studies. Thus, this evidence is rated as low quality.

SGA Versus Yoga

The evidence is insufficient to compare SGAs with meditation or yoga because there were no eligible trials.

SGA Versus Exercise

Monotherapy. Low-quality evidence from network meta-analysis showed no difference in response for SGAs versus exercise. Moderate-quality evidence from 2 trials (36, 37) showed no difference in remission for sertraline compared with exercise in patients with MDD after 16 weeks of treatment.

Combination Therapy. Low-quality evidence from 1 trial (38, 39) showed no difference in remission for treatment with sertraline compared with combination therapy of sertraline and exercise in patients with MDD after 16 weeks of treatment.

Comparative Effectiveness of Switching or Augmenting Strategies Involving SGAs

Refer to Appendix Table 2 (available at www.annals.org) and the accompanying systematic review (9) for additional details of the evidence.

Switching to Other SGAs

Moderate-quality evidence from 1 trial (40) showed no difference in response when switching from 1 SGA to another (bupropion vs. sertraline or venlafaxine and sertraline vs. venlafaxine). Low-quality evidence from 1 trial (40) showed no difference in remission (bupropion vs. sertraline or venlafaxine and sertraline vs. venlafaxine) or depression severity (venlafaxine vs. citalopram) when switching from 1 SGA to another.

Low-quality evidence showed no difference in risk for overall adverse events, discontinuation due to serious adverse events, overall discontinuation rates, or suicidal thoughts associated with switching to venlafaxine versus switching to citalopram (40, 41).

Switching From an SGA to a Different SGA Versus Switching to Cognitive Therapy

Low-quality evidence from 1 trial (42) showed no difference in response or remission when switching from 1 SGA to another (sertraline, bupropion, or venlafaxine) compared with switching to cognitive therapy.

Low-quality evidence also showed no difference in discontinuation due to adverse events when switching from 1 SGA (citalopram) to another (sertraline, bupropion, or venlafaxine) compared with switching to cognitive therapy (42).

Augmenting With Another SGA

Low-quality evidence from 1 trial (43) showed no difference in response or remission for augmentation of citalopram treatment with bupropion compared with augmentation with buspirone. However, augmenting with bupropion decreases depression severity more than augmentation with buspirone (43).

Low-quality evidence showed no difference in suicidal ideas and behavior or serious adverse events, and moderate-quality evidence showed that discontinuation due to adverse events was lower with bupropion than with buspirone (43).

Augmenting With Another SGA Versus Augmenting With Cognitive Therapy

Low-quality evidence from 1 trial (43) showed no difference in response, remission, or depression severity for augmentation of citalopram treatment with another SGA (bupropion or buspirone) versus augmentation with cognitive therapy.

Low-quality evidence showed no difference between augmenting with bupropion or buspirone for serious adverse events or discontinuation due to adverse events (43).

Comparative Harms of Pharmacologic Versus Nonpharmacologic Treatment Options for Initial Treatment Management

SGA Versus Psychological Interventions

SGA Versus CBT

Monotherapy. Moderate-quality evidence from 4 trials (12, 14, 15, 26) showed no difference in overall discontinuation rates between SGAs (fluoxetine, fluvoxamine, or paroxetine) and CBT at 8 to 14 weeks of follow-up. Low-quality evidence from 1 trial (44) showed increased discontinuation of treatment (sertraline, paroxetine, or venlafaxine) at 24-week follow-up compared with CBT. Low-quality evidence from 3 trials (12, 14, 15) showed a non–statistically significant increase in discontinuation due to adverse events with SGAs compared with CBT at 8 to 14 weeks of follow-up.

Combination Therapy. Low-quality evidence from 2 trials (14, 16) showed no difference in overall discontinuation rates for treatment with escitalopram versus a combination of escitalopram and telephone-based

CBT. Low-quality evidence showed a non–statistically significant increase in discontinuation due to adverse events with SGAs compared with CBT (14, 16).

SGA Versus Interpersonal Therapy

Monotherapy. The evidence is insufficient to determine the comparative risk of treatment with SGAs versus interpersonal therapy.

Combination Therapy. Low-quality evidence from 1 trial (19) showed no difference in overall discontinuation rates for treatment with nefazodone versus a combination of nefazodone and interpersonal therapy.

SGA Versus Third-Wave CBT

Low-quality evidence from 2 trials (15, 45) showed that overall discontinuation rates and discontinuation due to adverse events were higher in patients treated with SGAs than with third-wave CBT.

SGA Versus Psychodynamic Therapies

Monotherapy. Low-quality evidence from 1 trial showed no difference between SGAs and psychodynamic therapy for suicidality at 96 weeks of follow-up (21) or overall discontinuation rates at 8 to 16 weeks (20, 46, 47), 48 weeks (20), or 96 weeks (21) of follow-up.

Combination Therapy. Low-quality evidence from 1 trial (21) showed that overall discontinuation rates were lower for patients treated with fluoxetine than for those treated with fluoxetine combined with psychodynamic therapy. Low-quality evidence from 1 trial (21) showed a non–statistically significant increase in suicidality when comparing SGAs with a combination of SGAs and psychodynamic therapy after 96 weeks of follow-up.

SGA Versus CAM Interventions

SGA Versus Acupuncture

Monotherapy. Moderate-quality evidence from a systematic review of 21 trials (48) showed that the overall risk for adverse events is higher with SGAs than with acupuncture.

Combination Therapy. Low-quality evidence from 1 trial showed no difference in risk for overall adverse events (49), and low-quality evidence from 2 trials showed no difference in overall discontinuation rates (24, 25) or discontinuation due to adverse events (24, 49) for SGA monotherapy versus a combination of SGA plus acupuncture.

SGA Versus ω-3 Fatty Acids

Monotherapy. Low-quality evidence from 1 trial (50) showed no difference in overall discontinuation rates of treatment using SGAs compared with ω-3 fatty acids.

Combination Therapy. Low-quality evidence from 2 trials (51, 52) showed no difference in overall discontinuation rates for SGA monotherapy compared with combination therapy of SGAs plus ω-3 fatty acids.

SGA Versus SAMe

Monotherapy. Low-quality evidence from 1 trial (52) showed no difference in overall discontinuation rates between treatment with SGAs or SAMe.

SGA Versus St. John's Wort

Monotherapy. Moderate-quality evidence from 9 trials (25–29, 31–33, 53) showed increased risks for discontinuation and discontinuation due to adverse events with SGAs compared with St. John's wort. Moderate-quality evidence from 8 trials (27, 29–34, 54) also showed a non–statistically significant increase in the risk for overall adverse events with SGAs compared with St. John's wort. Low-quality evidence from 4 trials (27, 30, 31, 34) showed no difference in serious adverse events with SGAs compared with St. John's wort.

SGA Versus Yoga

The evidence is insufficient to compare SGAs with meditation or yoga because there were no eligible trials.

SGA Versus Exercise

Monotherapy. Low-quality evidence from 2 trials (36, 38) showed that sertraline was associated with an increased risk for discontinuation due to adverse effects compared with exercise, although both had similar overall discontinuation rates.

Combination Therapy. Low-quality evidence from 1 trial (38) showed no difference in overall discontinuation rates or discontinuation due to adverse events for sertraline monotherapy compared with combination therapy of sertraline plus exercise.

VARIATION IN RISKS FOR BENEFITS AND HARMS BY SEVERITY OF MDD

The evidence is inconclusive about whether MDD severity is a predictor of the risk for harms, serious adverse events, or discontinuation of treatment.

COMPARATIVE BENEFITS AND RISKS FOR HARMS FOR SELECTED SUBGROUPS

For demographic characteristics, no trials assessed the difference in benefits or harms between sexes or by race/ethnicity. For accompanying psychiatric symptoms, no trials assessed coexisting anxiety, insomnia, low energy, or somatization.

Low-quality evidence from 1 trial (54) showed no difference in response rates, overall adverse events, or discontinuation due to adverse effects when comparing treatment using SGAs with St. John's wort in older adults (aged 60 to 80 years).

SUMMARY

For most comparisons studied, low-quality evidence showed no difference in effectiveness or adverse effects between first-line intervention using pharmacologic (SGAs) or nonpharmacologic (CAM or

Table 3. Durations and Dosages of SGAs Used in the Trials Reviewing the Comparative Efficacy and Effectiveness of MDD*

Drug	Duration, *wk*	Dosage, *mg/d*	Comparative or Drug-Specific Adverse Effects (58, 60)
Bupropion	12–14	200–450	Lower rate of sexual adverse events than escitalopram, fluoxetine, paroxetine, and sertraline
Bupropion SR	14	150–400	Lower rate of sexual adverse events than escitalopram, fluoxetine, paroxetine, and sertraline
Citalopram	6–8	20–40	Possible increased risk for QT interval prolongation and torsade de pointes (dosages >40 mg/d)
Escitalopram	12–24	10–20	NA
Fluoxetine	4–96	10–80	Lowest rates of discontinuation syndrome compared with other SSRIs
Fluvoxamine	52	40–120	NA
Nefazodone	12	200–600	NA
Paroxetine	4–52	20–60	Highest rates of sexual dysfunction among SSRIs; higher rates of weight gain; highest rates of discontinuation syndrome
Sertraline	8–49	50–200	Higher incidence of diarrhea
Venlafaxine	8–16	75–375	Higher rates of nausea and vomiting; higher rates of discontinuations due to adverse events than SSRIs as a class; highest rates of discontinuation syndrome
Venlafaxine XR	14	75–225	Higher rates of nausea and vomiting; higher rates of discontinuations due to adverse events than SSRIs as a class; highest rates of discontinuation syndrome

MDD = major depressive disorder; NA = not available; SGA = second-generation antidepressant; SR = sustained release; SSRI = selective serotonin reuptake inhibitor; XR = extended release.
* Common adverse effects associated with SGAs include constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence.

exercise monotherapies or combination therapies) treatments in patients with MDD. Moderate-quality evidence showed no difference in response or discontinuation of treatment when comparing SGAs with CBT.

Patients are often treated for depression by primary care physicians who frequently prescribe SGAs (55, 56). A previous systematic review and the 2008 ACP guideline (57, 58) have shown similar safety and efficacy among the different SGAs. Most patients do not achieve remission after initial treatment with SGAs (59), in which case switching therapies or augmenting with additional interventions may be warranted. Table 3 summarizes the typical duration, dosages, and comparative adverse effects associated with SGAs (60).

Adverse effects commonly associated with SGAs include constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence (58). Adverse effects associated with St. John's wort include gastrointestinal symptoms, dizziness or confusion, and fatigue or sedation.

For second-line treatment after unsuccessful treatment with SGAs, low-quality evidence showed that strategies to switch to or augment with another drug or nonpharmacologic therapy are similarly effective. Most evidence came from the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study (40, 42, 43).

Data on population subgroups were limited; however, in older persons, St. John's wort was equally effective and had similar rates of adverse events compared with SGAs (low-quality evidence). Evidence was insufficient to determine whether depression severity was a modulator of treatment efficacy or harms.

St. John's Wort

Low-quality evidence showed that St. John's wort may be as effective as SGAs for treating MDD, and moderate-quality evidence showed that St. John's wort was better tolerated than SGAs. However, St. John's wort is not currently regulated by the U.S. Food and Drug Administration, and there is no current standard in place about the contents and potency of the medication. Therefore, patients in the United States may not be able to get a quality-controlled medication or reliably obtain preparations with similar effectiveness as those used in the included studies. Adverse effects associated with St. John's wort may include mild gastrointestinal symptoms, skin reactions, fatigue, sedation, restlessness, dizziness, headache, and dry mouth (61, 62). St. John's wort is associated with important drug–drug interactions and is known to induce cytochrome P450 isoenzyme 3A4 (63). It may reduce the bioavailability or efficacy of some drugs, such as oral contraceptives and immunosuppressants, and is contraindicated in patients receiving monoamine oxidase or serotonin reuptake inhibitors (64–66).

Recommendation

Recommendation: ACP recommends that clinicians select between either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient. (Grade: strong recommendation, moderate-quality evidence)

Moderate-quality evidence shows that CBT and SGAs are similarly effective treatments for MDD. Moderate-quality evidence suggests that discontinuation rates are similar for CBT and SGAs, although discontinuation due to adverse events is non–statistically significantly increased with SGAs. However, harms associated with SGAs are probably underrepresented in the included trials. Thus, we conclude that CBT has no more—and probably fewer—adverse effects than SGAs. In addition, lower relapse rates have been reported with CBT than SGAs (11, 15). Although SGAs are often initially prescribed for patients with depression, CBT is a reasonable approach for initial treatment and should be strongly considered as an alternative treatment to

Figure 2. Summary of the American College of Physicians guideline on nonpharmacologic versus pharmacologic treatment with second-generation antidepressants for adult patients with major depressive disorder.

Summary of the American College of Physicians Guideline on Nonpharmacologic Versus Pharmacologic Treatment With Second-Generation Antidepressants for Adult Patients With Major Depressive Disorder

Disease/Condition	Major depressive disorder
Target Audience	Internists, family physicians, and other clinicians
Target Patient Population	Adults with major depressive disorder
Interventions Evaluated	Second generation antidepressants; psychotherapies for treating depression; and complementary and alternative medicines, including acupuncture, ω-3 fatty acids, S-adenosyl-L-methionine, St. John's wort (*Hypercium perforatum*), and exercise
Outcomes Evaluated	Response, remission, functional capacity, quality of life, reduction of suicidality or hospitalizations, and harms
Benefits	Response and remission from depression and increased functional capacity Rates were similar when comparing different treatment methods to SGAs with the exception of the following: increased functional capacity for SGA + CBT combination therapy vs. SGA monotherapy; increased remission for SGA + IT combination therapy vs. SGA monotherapy; increased response for SGA + acupuncture combination therapy vs. SGA monotherapy; and increased response for SGA vs. ω-3 fatty acids monotherapy.
Harms	SGAs: constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence Psychotherapies: sparsely reported St. John's wort: gastrointestinal symptoms, dizziness or confusion, and tiredness or sedation Exercise: none reported Similar rates of adverse events and discontinuation of treatment were noted when comparing different treatment methods with the exception of the following: increased overall discontinuation of treatment with SGA compared to CBT monotherapy; increased overall discontinuation of treatment with SGA + PSYD combination therapy vs. SGA monotherapy; increased overall discontinuation of treatment and discontinuation due to adverse events with SGA vs. third-wave CBT monotherapy; increased overall risk of adverse events with SGA vs. acupuncture; increased discontinuation of treatment, and discontinuation of treatment due to adverse events with SGA vs. St. John's wort; and increased discontinuation of treatment due to adverse events with SGA vs. exercise.
Recommendations	***Recommendation: ACP recommends that clinicians select between either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient. (Grade: strong recommendation, moderate-quality evidence)***
Clinical Considerations	Preparations of St. John's wort differ widely, and there are currently no standards for purity or potency in the United States. The evidence on efficacy is limited to preparations used in the included studies. St. John's wort is associated with drug–drug interactions and is known to induce CYP 3A4.

CBT = cognitive behavioral therapy; CYP 3A4 = cytochrome P450 isoenzyme 3A4; IT = interpersonal therapy; PSYD = psychodynamic therapy; SGA = second-generation antidepressant.

SGAs where available. Further, there are reported differences among SGAs in mild (constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence) to major (sexual dysfunction and suicidality) adverse effects. Bupropion is associated with a lower rate of sexual adverse events than fluoxetine and sertraline, whereas paroxetine has higher rates of sexual dysfunction than fluoxetine, fluvoxamine, nefazodone, and sertraline (57). Physicians and patients should discuss adverse event profiles before selecting a medication.

Figure 2 summarizes the recommendations and clinical considerations.

Inconclusive Areas of Evidence

Evidence was insufficient to determine the comparative effectiveness of SGAs to third-wave CBT. Further, there was insufficient evidence to determine the comparative harms of SGAs versus monotherapy using interpersonal therapy or combination therapy with SGAs. For second-line therapy of switching or augmentation strategies, no studies directly compared SGAs with CAM or exercise. No studies directly compared switching versus augmentation strategies. Evidence was insufficient to determine whether the comparative effectiveness of SGAs to other treatments is a function of disease severity, and there were limited data on assessing the efficacy of treatments for MDD based on the subgroups of populations. In addition, there is insufficient evidence about the applicability of studies of St. John's wort to patients in the United States, especially about the purity and potency of St. John's wort preparations available in this country.

From American College of Physicians, Philadelphia, Pennsylvania; Massachusetts General Hospital, Boston, Massachusetts; and Portland Veterans Affairs Medical Center, Portland, Oregon.

Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

Disclaimer: The authors of this article are responsible for its contents, including any clinical or treatment recommendations.

Financial Support: Financial support for the development of this guideline comes exclusively from the ACP operating budget.

Disclosures: All financial and intellectual disclosures of interest were declared and potential conflicts were discussed and managed. Dr. Forciea was recused from voting on this guideline and from chairing during the discussion of the guideline for an active indirect financial conflict. Dr. Manaker was recused from voting on the guideline for an active indirect financial conflict. Dr. Vijan was recused from voting on the guideline for an active direct intellectual conflict. Authors not named here have disclosed no conflicts of interest. Authors followed the policy regarding conflicts of interest described at www.annals.org/article.aspx?articleid=745942. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-2570. A record of disclosures of interest and management of conflicts of is kept for each Clinical Guidelines Committee meeting and conference call and can be viewed at www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm.

Requests for Single Reprints: Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106; e-mail, aqaseem@acponline.org.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al.** Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163-96. [PMID: 23245607] doi:10.1016/S0140-6736(12)61729-2

2. **Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, et al.** The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry. 2003;64:1465-75. [PMID: 14728109]

3. **Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al; National Comorbidity Survey Replication.** The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289:3095-105. [PMID: 12813115]

4. **Centers for Disease Control and Prevention.** FastStats: depression. Atlanta, GA: Centers for Disease Control and Prevention; 2015. Accessed at www.cdc.gov/nchs/fastats/depression.htm on 6 January 2016.

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

6. **Gartlehner G, Gaynes BN, Amick HR, Asher G, Morgan LC, Coker-Schwimmer M, et al.** 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; 2015. Accessed at www.effectivehealthcare.ahrq.gov/ehc/products/568/2155/major-depressive-disorder-report-151202.pdf on 6 January 2016.

7. **Kroenke K, Spitzer RL, Williams JB.** The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606-13. [PMID: 11556941]

8. **Hamilton M.** A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62. [PMID: 14399272]

9. **Gartlehner G, Gaynes BN, Amick HR, Asher GN, Morgan LC, Coker-Schwimmer E, et al.** 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. Ann Intern Med. 2016. [Epub ahead of print] doi:10.7326/M15-1813

10. **Qaseem A, Snow V, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians.** The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. Ann Intern Med. 2010;153:194-9. [PMID: 20679562] doi:10.7326/0003-4819-153-3-201008030-00010

11. **David D, Szentagotai A, Lupu V, Cosman D.** 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;64:728-46. [PMID: 18473339] doi:10.1002/jclp.20487

12. **DeRubeis RJ, Hollon SD, Amsterdam JD, Shelton RC, Young PR, Salomon RM, et al.** Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch Gen Psychiatry. 2005;62:409-16. [PMID: 15809408]

13. **Hegerl U, Hautzinger M, Mergl R, Kohnen R, Schütze M, Scheunemann W, 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;13:31-44. [PMID: 19341510] doi:10.1017/S1461145709000224

14. **Mynors-Wallis LM, Gath DH, Day A, Baker F.** Randomised controlled trial of problem solving treatment, antidepressant medica-

tion, and combined treatment for major depression in primary care. BMJ. 2000;320:26-30. [PMID: 10617523]
15. **Dimidjian S, Hollon SD, Dobson KS, Schmaling KB, Kohlenberg RJ, Addis ME, 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;74:658-70. [PMID: 16881773]
16. **Lam RW, Parikh SV, Ramasubbu R, Michalak EE, Tam EM, Axler A, et al.** Effects of combined pharmacotherapy and psychotherapy for improving work functioning in major depressive disorder. Br J Psychiatry. 2013;203:358-65. [PMID: 24029535] doi:10.1192/bjp.bp.112.125237
17. **Menchetti M, Rucci P, Bortolotti B, Bombi A, Scocco P, Kraemer HC, et al; DEPICS group.** Moderators of remission with interpersonal counselling or drug treatment in primary care patients with depression: randomised controlled trial. Br J Psychiatry. 2014;204:144-50. [PMID: 24311553] doi:10.1192/bjp.bp.112.122663
18. **Frank E, Cassano GB, Rucci P, Thompson WK, Kraemer HC, Fagiolini A, et al.** Predictors and moderators of time to remission of major depression with interpersonal psychotherapy and SSRI pharmacotherapy. Psychol Med. 2011;41:151-62. [PMID: 20380782] doi:10.1017/S0033291710000553
19. **Blom MB, Jonker K, Dusseldorp E, Spinhoven P, Hoencamp E, Haffmans J, et al.** Combination treatment for acute depression is superior only when psychotherapy is added to medication. Psychother Psychosom. 2007;76:289-97. [PMID: 17700049]
20. **Salminen JK, Karlsson H, Hietala J, Kajander J, Aalto S, Markkula J, et al.** Short-term psychodynamic psychotherapy and fluoxetine in major depressive disorder: a randomized comparative study. Psychother Psychosom. 2008;77:351-7. [PMID: 18701831] doi:10.1159/000151388
21. **Bastos AG, Guimarães LS, Trentini CM.** Neurocognitive changes in depressed patients in psychodynamic psychotherapy, therapy with fluoxetine and combination therapy. J Affect Disord. 2013;151:1066-75. [PMID: 24103853] doi:10.1016/j.jad.2013.08.036
22. **Sun H, Zhao H, Ma C, Bao F, Zhang J, Wang DH, 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;19:733-9. [PMID: 23647408] doi:10.1089/acm.2011.0637
23. **Huang Y, Htut WM, Li D, Tang A, Li Q, Shi N, et al.** Studies on the clinical observation and cerebral glucose metabolism in depression treated by electro-scalp acupuncture compared to fluoxetine. International Journal of Clinical Acupuncture. 2005;14:7-26.
24. **Qu SS, Huang Y, Zhang ZJ, Chen JQ, Lin RY, Wang CQ, 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;47:726-32. [PMID: 23498306] doi:10.1016/j.jpsychires.2013.02.004
25. **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;15:837-44. [PMID: 19678773] doi:10.1089/acm.2008.0607
26. **Hypericum Depression Trial Study Group.** Effect of *Hypericum perforatum* (St. John's wort) in major depressive disorder: a randomized controlled trial. JAMA. 2002;287:1807-14. [PMID: 11939866]
27. **Szegedi A, Kohnen R, Dienel A, Kieser M.** 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;330:503. [PMID: 15708844]
28. **Brenner R, Azbel V, Madhusoodanan S, Pawlowska M.** Comparison of an extract of *hypericum* (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. Clin Ther. 2000;22:411-9. [PMID: 10823363]
29. **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;15:61-8. [PMID: 10759336]
30. **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;39:66-75. [PMID: 16555167]
31. **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;38:78-86. [PMID: 15744631]
32. **Behnke K, Jensen GS, Graubaum HJ, Gruenwald J.** *Hypericum perforatum* versus fluoxetine in the treatment of mild to moderate depression. Adv Ther. 2002;19:43-52. [PMID: 12008860]
33. **Bjerkenstedt L, Edman GV, Alken RG, Mannel M.** *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;255:40-7. [PMID: 15538592]
34. **van Gurp G, Meterissian GB, Haiek LN, McCusker J, Bellavance F.** St. John's wort or sertraline? Randomized controlled trial in primary care. Can Fam Physician. 2002;48:905-12. [PMID: 12053635]
35. **Fava M, Alpert J, Nierenberg AA, Mischoulon D, Otto MW, Zajecka J, et al.** A double-blind, randomized trial of St. John's wort, fluoxetine, and placebo in major depressive disorder. J Clin Psychopharmacol. 2005;25:441-7. [PMID: 16160619]
36. **Blumenthal JA, Babyak MA, Doraiswamy PM, Watkins L, Hoffman BM, Barbour KA, et al.** Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom Med. 2007;69:587-96. [PMID: 17846259]
37. **Hoffman BM, Blumenthal JA, Babyak MA, Smith PJ, Rogers SD, Doraiswamy PM, et al.** Exercise fails to improve neurocognition in depressed middle-aged and older adults. Med Sci Sports Exerc. 2008;40:1344-52. [PMID: 18580416] doi:10.1249/MSS.0b013e31816b877c
38. **Blumenthal JA, Babyak MA, Moore KA, Craighead WE, Herman S, Khatri P, et al.** Effects of exercise training on older patients with major depression. Arch Intern Med. 1999;159:2349-56. [PMID: 10547175]
39. **Babyak M, Blumenthal JA, Herman S, Khatri P, Doraiswamy M, Moore K, et al.** Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom Med. 2000;62:633-8. [PMID: 11020092]
40. **Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, et al; STAR*D Study Team.** Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med. 2006;354:1231-42. [PMID: 16554525]
41. **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;23:113-9. [PMID: 18408525] doi:10.1097/YIC.0b013e3282f424c2
42. **Thase ME, Friedman ES, Biggs MM, Wisniewski SR, Trivedi MH, Luther JF, et al.** Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. Am J Psychiatry. 2007;164:739-52. [PMID: 17475733]
43. **Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, et al; STAR*D Study Team.** Medication augmentation after the failure of SSRIs for depression. N Engl J Med. 2006;354:1243-52. [PMID: 16554526]
44. **Segal ZV, Kennedy S, Gemar M, Hood K, Pedersen R, Buis T.** Cognitive reactivity to sad mood provocation and the prediction of depressive relapse. Arch Gen Psychiatry. 2006;63:749-55. [PMID: 16818864]
45. **Moradveisi L, Huibers MJ, Renner F, Arasteh M, Arntz A.** Behavioural activation v. antidepressant medication for treating depression in Iran: randomised trial. Br J Psychiatry. 2013;202:204-11. [PMID: 23391727] doi:10.1192/bjp.bp.112.113696
46. **Dekker JJ, Koelen JA, Van HL, Schoevers RA, Peen J, Hendriksen M, 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;109:183-8. [PMID: 18061276]
47. **Barber JP, Barrett MS, Gallop R, Rynn MA, Rickels K.** Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial. J Clin Psychiatry. 2012;73:66-73. [PMID: 22152401] doi:10.4088/JCP.11m06831

48. **Zhang ZJ, Chen HY, Yip KC, Ng R, Wong VT.** The effectiveness and safety of acupuncture therapy in depressive disorders: systematic review and meta-analysis. J Affect Disord. 2010;124:9-21. [PMID: 19632725] doi:10.1016/j.jad.2009.07.005
49. **Chen J, Lin W, Wang S, Wang C, Li G, Qu S, et al.** Acupuncture/electroacupuncture enhances anti-depressant effect of Seroxat: the Symptom Checklist-90 scores. Neural Regen Res. 2014;9:213-22. [PMID: 25206803] doi:10.4103/1673-5374.125353
50. **Jazayeri S, Tehrani-Doost M, Keshavarz SA, Hosseini M, Djazayery A, Amini H, 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;42:192-8. [PMID: 18247193] doi:10.1080/00048670701827275
51. **Gertsik L, Poland RE, Bresee C, Rapaport MH.** Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. J Clin Psychopharmacol. 2012;32:61-4. [PMID: 22198441] doi:10.1097/JCP.0b013e31823f3b5f
52. **Mischoulon D, Price LH, Carpenter LL, Tyrka AR, Papakostas GI, Baer L, 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;75:370-6. [PMID: 24500245] doi:10.4088/JCP.13m08591
53. **Papakostas GI, Crawford CM, Scalia MJ, Fava M.** 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;56:132-7. [PMID: 18259086] doi:10.1159/000115779
54. **Harrer G, Schmidt U, Kuhn U, Biller A.** Comparison of equivalence between the St. John's wort extract LoHyp-57 and fluoxetine. Arzneimittelforschung. 1999;49:289-96. [PMID: 10337446]
55. **Institute of Medicine Committee on Quality of Health Care in America.** Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academies Pr; 2001. Accessed at www.nap.edu/read/10027/chapter/1 on 6 January 2016.
56. **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;69:1064-74. [PMID: 18399725]
57. **Gartlehner G, Gaynes BN, Hansen RA, Thieda P, DeVeaugh-Geiss A, Krebs EE, et al.** Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. Ann Intern Med. 2008;149:734-50. [PMID: 19017592]
58. **Qaseem A, Snow V, Denberg TD, Forciea MA, Owens DK; Clinical Efficacy Assessment Subcommittee of American College of Physicians.** Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008;149:725-33. [PMID: 19017591]
59. **Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux L, Van Noord M, et al.** Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med. 2011;155:772-85. [PMID: 22147715] doi:10.7326/0003-4819-155-11-201112060-00009
60. **Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux LJ, Van Noord M, et al.** Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review. Comparative effective review no. 46. (Prepared by the RTI-UNC 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; 2011. Accessed at www.effectivehealthcare.ahrq.gov/ehc/products/210/863/CER46_Antidepressants-update_20111206.pdf on 6 January 2016.
61. **Hammerness P, Basch E, Ulbricht C, Barrette EP, Foppa I, Basch S, et al; Natural Standard Research Collaboration.** St. John's wort: a systematic review of adverse effects and drug interactions for the consultation psychiatrist. Psychosomatics. 2003;44:271-82. [PMID: 12832592]
62. **Knüppel L, Linde K.** Adverse effects of St. John's Wort: a systematic review. J Clin Psychiatry. 2004;65:1470-9. [PMID: 15554758]
63. **Mueller SC, Majcher-Peszynska J, Uehleke B, Klammt S, Mundkowski RG, Miekisch W, 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;62:29-36. [PMID: 16341856]
64. **Markowitz JS, Donovan JL, DeVane CL, Taylor RM, Ruan Y, Wang JS, et al.** Effect of St. John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. JAMA. 2003;290:1500-4. [PMID: 13129991]
65. **Mills E, Montori VM, Wu P, Gallicano K, Clarke M, Guyatt G.** Interaction of St. John's wort with conventional drugs: systematic review of clinical trials. BMJ. 2004;329:27-30. [PMID: 15231618]
66. **Miller LG.** Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. Arch Intern Med. 1998;158:2200-11. [PMID: 9818800]

Current Author Addresses: Dr. Qaseem: American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106.
Dr. Kansagara: Portland Veterans Affairs Medical Center, Mailcode RD71, 3710 SW U.S. Veterans Hospital Road, Portland, OR 97239.
Dr. Barry: Massachusetts General Hospital, 50 Staniford Street, Boston, MA 02114.

Author Contributions: Conception and design: M.J. Barry, R.P. Harris, A. Qaseem.
Analysis and interpretation of the data: C. Boyd, N. Fitterman, R.P. Harris, L.L. Humphrey, D. Kansagara, A. Qaseem.
Drafting of the article: T.D. Denberg, D. Kansagara, A. Qaseem.
Critical revision of the article for important intellectual content: M.J. Barry, C. Boyd, T.D. Denberg, R.P. Harris, L.L. Humphrey, D. Kansagara, A. Qaseem.
Final approval of the article: M.J. Barry, C. Boyd, D. Chow, T.D. Denberg, N. Fitterman, R.P. Harris, L.L. Humphrey, D. Kansagara, R. McLean, A. Qaseem, T.J. Wilt.
Provision of study materials or patients:
Statistical expertise: A. Qaseem.
Obtaining of funding:
Administrative, technical, or logistic support: A. Qaseem.
Collection and assembly of data: A. Qaseem

Appendix: Detailed Methods

The evidence review was conducted by the AHRQ's RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center. Details of the ACP guideline development process can be found in ACP's methods paper (10).

Key Questions Addressed

Key Question 1a: In adult patients with MDD who are attempting initial treatment, what is the effectiveness of SGA monotherapy compared with either nonpharmacologic monotherapy or combination therapy (involving nonpharmacologic treatments alone or in combination with an SGA)?

Key Question 1b: Does comparative treatment effectiveness vary by MDD severity?

Key Question 2a: In adult patients with MDD who did not achieve remission after an initial adequate trial with 1 SGA, what is the comparative effectiveness of second-line therapies?

Key Question 2b: Does comparative treatment effectiveness vary by MDD severity?

Key Question 3a: In adult patients with MDD, what are the comparative risks for harms of these treatment options for those attempting initial treatment or those who did not achieve remission after an initial adequate trial with an SGA?

Key Question 3b: Do the comparative risks for treatment harms vary by MDD severity?

Key Question 4: Do the benefits and risks for 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)?

The Clinical Guidelines Committee was particularly interested in comparative effectiveness of treatment according to MDD severity (key questions 1b, 2b, and 3b) because depression screening is becoming more widespread, which will tend to increase the proportion of patients being diagnosed with milder MDD.

Search Strategy

Reviewers searched MEDLINE (via PubMed), EMBASE, the Cochrane Library, AMED, PsycINFO, and CINAHL from 1 January 1990 through September 2015 for studies in English, German, or Italian. Studies on efficacy were limited to randomized, controlled trials and systematic reviews and meta-analyses, although evidence on harms included observational studies. For additional information, including inclusion and exclusion criteria, refer to the accompanying systematic review (9) and the full evidence report sponsored by AHRQ (6). Further, there were no limitations on study duration or length of follow-up.

Meta-analysis and Network Meta-analysis

Direct comparisons were made using meta-analytic techniques. Network meta-analysis was used when there was a lack of studies on direct comparisons. The reviewers used a hierarchical frequentist approach and random-effects models, including placebo- and active-controlled randomized, controlled trials that were homogenous in study populations and outcome assessments and were part of a connected network (67, 68).

Quality Assessment

The quality of studies was assessed using the AHRQ handbook (69). The risk of bias for studies was assessed using AHRQ guidance (70) and the Cochrane Risk of Bias tool (71). Tests for publication bias had low sensitivity because of the small number of studies. This guideline rates the evidence and recommendations using ACP's guideline grading system (Table 1).

Population

The population included adult outpatients (aged ≥18 years) with MDD during either an initial or a second treatment attempt who did not remit after an initial adequate trial with an SGA.

Interventions Evaluated

The interventions evaluated are as follows: depression-focused psychotherapy; CAM, including acupuncture, meditation (for example, mindfulness-based stress reduction), ω-3 fatty acids, SAMe, St. John's wort (*Hypericum perforatum*), and yoga; exercise; and SGAs, including bupropion, citalopram, desvenlafaxine, duloxetine, fluoxetine, escitalopram, fluvoxamine, levomilnacipran, mirtazapine, nefazodone,

paroxetine, sertraline, trazodone, venlafaxine, vilazodone, and vortioxetine. Drugs evaluated for combination or augmentation therapies included atypical antipsychotics (aripiprazole, asenapine maleate, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone), psychostimulants (amphetamine–dextroamphetamine, armodafinil, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, and modafinil), buspirone, L-thyroxine (T_4), lithium, and pindolol triiodothyronine (T_3).

Comparators

The SGAs were compared with monotherapy that involved nonpharmacologic interventions or combination therapies of SGAs and nonpharmacologic interventions. To assess second-line treatment, modifications of initial treatment with SGAs were compared with nonpharmacologic interventions; other pharmacologic interventions, including CAM; or combinations of nonpharmacologic and pharmacologic strategies as either switches to new treatment or augmentation of existing therapy.

Outcomes

Benefits assessed included response (often defined as ≥50% improvement in HAM-D scores), remission (often defined as a HAM-D score ≤7), speed of response, speed of remission, relapse, quality of life, functional capacity (as assessed by various scales), reduction of suicidality, or reduction of hospitalization. Quality of life, functional status, suicidality, and hospitalizations were rarely reported.

Harms assessed included overall adverse events, withdrawals because of adverse events, serious adverse events, specific adverse events (including hyponatremia, seizures, suicidality, hepatotoxicity, weight gain, gastrointestinal symptoms, and sexual adverse events), withdrawals because of specific adverse events, or drug interactions.

Target Audience

The target audience for this guideline includes all clinicians, patients, health system leaders, and policymakers.

Target Patient Population

The target patient population includes all adults with MDD.

Peer Review

The AHRQ evidence review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments. The guideline underwent a peer-review process through the journal and was posted online for comments from ACP Governors and Regents.

Web-Only References

67. **Hong H, Carlin BP, Shamliyan TA, Wyman JF, Ramakrishnan R, Sainfort F, et al.** Comparing Bayesian and frequentist approaches for multiple outcome mixed treatment comparisons. Med Decis Making. 2013;33:702-14. [PMID: 23549384] doi:10.1177/0272989X13481110

68. **Jones B, Roger J, Lane PW, Lawton A, Fletcher C, Cappelleri JC, et al; PSI Health Technology Special Interest Group, Evidence Synthesis sub-team.** Statistical approaches for conducting network meta-analysis in drug development. Pharm Stat. 2011;10:523-31. [PMID: 22213533] doi:10.1002/pst.533

69. **Berkman ND, Lohr KN, Ansari M, McDonagh M, Balk E, Whitlock E, 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. AHRQ publication no. 13(14)-EHC130-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2013. Accessed at www.effectivehealthcare.ahrq.gov/ehc/products/457/1752/methods-guidance-grading-evidence-131118.pdf on 6 January 2016.

70. **Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, et al.** Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. AHRQ publication no. 12-EHC047-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Accessed at www.effectivehealthcare.ahrq.gov/ehc/products/322/998/MethodsGuideforCERs_Viswanathan_IndividualStudies.pdf on 6 January 2016.

71. **Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al; Cochrane Bias Methods Group.** The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. [PMID: 22008217] doi:10.1136/bmj.d5928

Appendix Table 1. First-Line Treatment for MDD: SGAs Versus Nonpharmacologic Therapies*

Interventions	Finding	Quality of Evidence	Data
SGA vs. CBT monotherapy			
Response (8-16 wk follow-up)	No difference	Moderate 5 studies (11–15)	HAM-D RR, 0.91 (95% CI, 0.77 to 1.07) (fluoxetine, fluvoxamine, paroxetine, or sertraline vs. CBT, CT, PST, or REBT)
Remission (12-16 wk follow-up)	No difference	Low 3 studies (11, 14, 15)	HAM-D RR, 0.98 (95% CI, 0.73 to 1.32) (fluoxetine, fluvoxamine, or paroxetine vs. CBT, CT, PST, or REBT)
Functional capacity (mean 12 wk follow-up)	No difference	Low 1 study (14)	Social Adjustment Scale No substantial differences (fluvoxamine or paroxetine vs. PST)
Overall discontinuation of treatment (8-14 wk follow-up)	No difference	Moderate 4 studies (12, 14, 15, 26)	RR, 1.00 (95% CI, 0.59 to 1.69) (fluoxetine, fluvoxamine, and paroxetine)
Overall discontinuation of treatment (mean 24 wk follow-up)	Increased with SGA	Low 1 study (44)	RR, 1.61 (95% CI, 1.28 to 2.02) (sertraline, paroxetine, or venlafaxine)
Discontinuation of treatment due to adverse events (8-14 wk follow-up)	Non-statistically significant increase with SGA	Low 3 studies (12, 14, 15)	RR, 2.54 (95% CI, 0.39 to 16.47)
SGA vs. SGA + CBT combination therapy			
Response (mean 12 wk follow-up)	No difference	Low 2 studies (14, 16)	MADRS or HAM-D RR, 1.03 (95% CI, 0.85 to 1.26) (escitalopram, fluvoxamine, or paroxetine vs. PST or telephone CBT)
Remission (mean 12 wk follow-up)	No difference	Low 2 studies (14, 16)	MADRS or HAM-D RR, 1.06 (95% CI, 0.82 to 1.38) (escitalopram, fluvoxamine, or paroxetine vs. PST or telephone CBT)
Functional capacity (mean 12 wk follow-up)	Increased with CBT + SGA	Low 2 studies (14, 16)	Multiple Scales Patients receiving the combination of escitalopram plus telephone CBT reported greater improvement on 3 of 5 work functioning measures compared with patients on SGA alone
Overall discontinuation of treatment (mean 16 wk follow-up)	No difference	Low 2 studies (14, 16)	RR, 0.77 (95% CI, 0.37 to 1.6) (escitalopram vs. escitalopram + telephone CBT)
Discontinuation of treatment due to adverse events (mean 12 wk follow-up)	Non-statistically significant increase with SGA	Low 2 studies (14, 16)	RR, 2.93 (95% CI, 0.72 to 11.91) (escitalopram vs. escitalopram + telephone CBT)
SGA vs. IT monotherapy			
Response (mean 6 wk follow-up)	No difference	Low 1 study (17)	HAM-D RR, 1.02 (95% CI, 0.86 to 1.22) (escitalopram vs. IT)
Remission (8-12 wk follow-up)	No difference	Low 2 studies (17, 18)	HAM-D RR, 0.92 (95% CI, 0.78 to 1.08) (escitalopram, citalopram, or sertraline vs. IT)
SGA vs. SGA + IT combination therapy			
Remission (8-12 wk follow-up)	Increased with SGA + IT	Low 1 study (19)	HAM-D OR, 3.22 (95% CI, 1.02 to 10.12) (nefazodone vs. nefazodone + IT)
Overall discontinuation (mean 16 wk follow-up)	No difference	Low 1 study (19)	RR, 1.11 (95% CI, 0.64 to 1.93) (nefazodone vs. nefazodone + IT)
SGA vs. PSYD monotherapy			
Remission (mean 16 wk follow-up)	No difference	Low 1 study (20)	HAM-D RR, 1.04 (95% CI, 0.58 to 1.86) (fluoxetine vs. short-term PSYD)
Functional capacity (mean 16 wk follow-up, 1 trial followed to 24 months)	Few statistically significant differences	Low 2 studies (20, 21)	Few statistically significant differences (fluoxetine) 1 study showed non-statistically significant increase in sick leave with SGAs compared to PSYD (12% vs. 4%)
Suicidal ideas or behaviors (mean 96 wk follow-up)	No difference	Low 1 study (21)	RR, 1.32 (95% CI, 0.3 to 5.73) (fluoxetine vs. long-term PSYD)

Continued on following page

Appendix Table 1–Continued

Interventions	Finding	Quality of Evidence	Data
Overall discontinuation of treatment	No difference	Low 3 studies 16 wk (20, 46, 47) 1 study 48 wk (20) 1 study 96 wk (21)	RR, 1.01 (95% CI, 0.68 to 1.52) 16 wk of follow-up (fluoxetine and venlafaxine vs. short-term PSYD) RR, 1.25 (95% CI, 0.44 to 3.57) 48 wk of follow-up (fluoxetine vs. short-term PSYD) RR, 0.81 (95% CI, 0.43 to 1.55) 96 wk of follow-up (fluoxetine vs. long-term PSYD)
SGA vs. SGA + PSYD combination therapy			
Functional capacity	No difference	Low 1 study (21)	Similar effects on WAIS-III measures (fluoxetine vs. long-term PSYD)
Suicidal ideas or behaviors (mean 96 wk follow-up)	Non-statistically significant increase with SGA	Low 1 study (21)	RR, 4.00 (95% CI, 0.46 to 35.1) (fluoxetine vs. long-term PSYD)
Overall discontinuation of treatment (mean 96 wk follow-up)	Increased with SGA + PSYD	Low 1 study (21)	RR, 0.48 (95% CI, 0.27 to 0.85) (fluoxetine vs. fluoxetine + long-term PSYD)
SGA vs. third-wave CBT monotherapy			
Overall discontinuation of treatment (mean 13 to 16 wk follow-up)	Increased with SGA	Low 2 studies (15, 45)	RR, 2.76 (95% CI, 1.4 to 5.41) (paroxetine or sertraline)
Discontinuation due to adverse events (mean 13 wk follow-up)	Increased with SGA	Low 2 studies (15, 45)	RR, 5.17 (95% CI, 1.6 to 16.64) (paroxetine or sertraline)
SGA vs. acupuncture monotherapy			
Response (mean 6 wk follow-up)	No difference	Low 2 studies, network meta-analysis (22, 23)	HAM-D RR, 1.15 (95% CI, 0.89 to 1.47) (fluoxetine) Results consistent with network meta-analysis
Overall risk of adverse events (mean 8 wk follow-up) (indirect evidence)	Increased with SGA	Moderate Systematic review of 21 trials* not included in AHRQ report (6) due to inclusion of other depressive disorders (48)	RR, 3.96 (95% CI, 3.4 to 4.62)
SGA vs. SGA + acupuncture combination therapy			
Response (mean 6 wk follow-up)	Increased with SGA + acupuncture	Low 2 studies (24, 25)	HAM-D RR, 0.82 (95% CI, 0.66 to 1.00) (fluoxetine or paroxetine)
Remission (mean 6 wk follow-up)	No difference	Low 1 study (25)	HAM-D RR, 0.92 (95% CI, 0.50 to 1.69) (paroxetine)
Overall risk of adverse events (mean 8 wk follow-up)	No difference	Low 1 study (49)	RR, 2.0 (95% CI, 0.43 to 9.4)
Overall discontinuation of treatment (mean 6 wk follow-up)	No difference	Low 3 studies (24, 25, 49)	RR, 1.11 (95% CI, 0.50 to 2.46)
Discontinuation of treatment due to adverse events (mean 6 wk follow-up)	No difference	Low 2 studies (24, 25)	RR, 0.74 (95% CI, 0.11 to 4.9)
SGA vs. ω-3 fatty acids monotherapy			
Response (mean 8 wk follow-up)	Increased with SGA	Low Network meta-analysis	HAM-D RR, 1.96 (95% CI, 1.26 to 3.05) (fluoxetine)
Overall discontinuation of treatment (mean 4 wk follow-up)	No difference	Low 1 study (50)	RR, 1.0 (95% CI, 0.23 to 4.37)
SGA vs. SGA + ω-3 fatty acids combination therapy			
Overall discontinuation of treatment (mean 4 wk follow-up)	No difference	Low 2 studies (50, 51)	RR, 2.38 (95% CI, 0.81 to 6.98) (fluoxetine)
SGA vs. SAMe monotherapy			
Response (mean 12 wk follow-up)	No difference	Low Network meta-analysis	HAM-D RR, 1.22 (95% CI, 0.66 to 2.26) (escitalopram)
Overall discontinuation of treatment (mean 12 wk follow-up)	No difference	Low 1 study (52)	RR, 1.19 (95% CI, 0.78 to 1.8)

Continued on following page

Appendix Table 1–Continued

Interventions	Finding	Quality of Evidence	Data
SGA vs. St. John's wort monotherapy			
Response (4-12 wk follow-up)	No difference	Low 9 studies (25–29, 31–33, 53) Older adults: Low, 1 study (54)	HAM-D RR, 0.96 (95% CI, 0.83 to 1.10) (SSRIs) Older adults: RR, 0.83 (95% CI, 0.67 to 1.11) at mean 6 wk follow-up (fluoxetine)
Remission (mean 13 wk follow-up)	No difference	Low 5 studies (27, 30, 36, 37, 55)	HAM-D RR, 0.82 (95% CI, 0.67 to 1.00) (SSRIs)
Serious adverse events	No difference	Low 4 studies (27, 30, 31, 34)	RR, 0.79 (95% CI, 0.23 to 2.72)
Overall risk of adverse events	Non-statistically significant increase with SGA	Moderate 8 studies (27, 29–34, 54) Older adults: Low, 1 study (54)	RR, 1.19 (1.05 to 1.34) Older adults: RR, 1.30 (95% CI, 0.66 to 2.54) (fluoxetine)
Overall discontinuation of treatment	Increased with SGA	Moderate 9 studies (26, 27, 29–34, 54)	RR, 1.28 (95% CI, 1.01 to 1.62)
Discontinuation of treatment due to adverse events	Increased with SGA	Moderate 9 studies (26, 27, 29–34, 54) Older adults: Low, 1 study (54)	RR, 1.70 (1.12 to 2.6) Older adults: RR, 1.22 (95% CI, 0.44 to 3.36) (fluoxetine)
SGA vs. exercise monotherapy			
Response (mean 16 wk follow-up)	No difference	Low Network meta-analysis	HAM-D-17 RR, 1.86 (95% CI, 0.81 to 4.27)
Remission (mean 16 wk follow-up)	No difference	Moderate 2 studies (36, 37)	HAM-D-17 RR, 1.1 (95% CI, 0.87 to 1.39) (sertraline)
Overall discontinuation of treatment (mean 16 wk follow-up)	No difference	Low 2 studies (36, 38)	RR, 0.87 (95% CI, 0.48 to 1.59)
Discontinuation of treatment due to adverse events (mean 16 wk follow-up)	Increased with SGA	Low 2 studies (36, 38)	RR, 20.96 (95% CI, 1.19 to 367.97) (sertraline)
SGA vs. SGA + exercise combination therapy			
Remission (mean 16 wk follow-up)	No difference	Low 1 study (38, 39)	HAM-D-17 RR, 1.05 (95% CI, 0.8 to 1.03) (sertraline)
Overall discontinuation of treatment (mean 16 wk follow-up)	No difference	Low 1 study (38)	RR, 0.73 (95% CI, 0.31 to 1.73)
Discontinuation of treatment due to adverse events (mean 16 wk follow-up)	No difference	Low 1 study (38)	RR, 1.15 (95% CI, 0.35 to 3.72) (sertraline)

CBT = cognitive behavioral therapy; CT = cognitive therapy; HAM-D = Hamilton Depression Rating Scale; IT = interpersonal therapy; MADRS = Montgomery–Asberg Depression Rating Scale; MDD = major depressive disorder; OR = odds ratio; PST = problem-solving therapy; PSYD = psychodynamic therapy; REBT = rational emotive behavior therapy; RR = risk ratio; SAMe = *S*-adenosyl-L-methionine; SGA = second-generation antidepressant; SSRI = selective serotonin reuptake inhibitor; WAIS-III = Wechsler Adult Intelligence Scale–Third Edition.
* Adapted from reference 6. Values reported in the background evidence paper (9) were based only on the highest-quality trials, whereas the values reported in this table are based on all included studies from the Agency for Healthcare Research and Quality report (6).

Appendix Table 2. Second-Line Treatment in Patients With MDD Who Failed Initial Treatment With SGAs: Switching or Augmenting Strategies*

Interventions	Finding	Quality of Evidence	Data
Switching strategies: pharmacologic (SGA switch vs. SGA switch)			
Response (12-14 wk follow-up)	No difference	Moderate 1 study (40)	HAM-D-17 RR, 0.96 (95% CI, 0.71 to 1.30) (bupropion vs. sertraline) RR, 0.91 (95% CI, 0.68 to 1.22) (bupropion vs. venlafaxine) RR, 0.95 (95% CI, 0.71 to 1.26) (sertraline vs. venlafaxine)
Remission (14 wk follow-up)	No difference	Low 1 study (40)	HAM-D-17 RR, 1.21 (95% CI, 0.84 to 1.75) (bupropion vs. sertraline) RR, 0.86 (95% CI, 0.62 to 1.19) (bupropion vs. venlafaxine) RR, 0.71 (95% CI, 0.50 to 1.01) (sertraline vs. venlafaxine)
Severity	No difference	Low (45)	Mean change in HAM-D score from baseline RR, 0.91 (95% CI, 0.78 to 1.07)
Suicidal ideas or behavior	No difference	Low 1 study (40)	RR, 0.2 (95% CI, 0.01 to 4.13) (citalopram switch to bupropion vs. sertraline) RR, 0.21 (95% CI, 0.01 to 4.33) (citalopram switch to bupropion vs. venlafaxine) RR, 1.05 (95% CI, 0.15 to 7.4) (citalopram switch to sertraline vs. venlafaxine)
Serious adverse events	No difference	Low 1 study (40)	RR, 0.5 (95% CI, 0.17 to 1.43) (citalopram switch to bupropion vs. sertraline) RR, 0.87 (95% CI, 0.27 to 2.82) (citalopram switch to bupropion vs. venlafaxine) RR, 1.75 (95% CI, 0.65 to 4.74) (citalopram switch to sertraline vs. venlafaxine)
Risk for overall adverse events (mean 12 wk follow-up)	No difference	Low 1 study (41)	RR, 0.91 (95% CI, 0.78 to 1.07) (venlafaxine vs. citalopram)
Overall discontinuation (mean 12 wk follow-up)	No difference	Low 1 study (41)	RR, 1.17 (95% CI, 0.82 to 1.68) (venlafaxine vs. citalopram)
Discontinuation due to adverse events (14 wk follow-up)	No difference	Moderate 1 study (40)	RR, 1.29 (95% CI, 0.94 to 1.79) (citalopram switch to bupropion vs. sertraline) RR, 1.28 (95% CI, 0.93 to 1.76) (citalopram switch to bupropion vs. venlafaxine RR, 0.99 (95% CI, 0.7 to 1.4) (citalopram switch to sertraline vs. venlafaxine)
Switching strategies: nonpharmacologic (SGA switch vs. CT switch)			
Response (12-14 wk follow-up)	No difference	Low 1 study (42)	QIDS-SR-16 RR, 1.2 (95% CI, 0.6 to 2.43) (sertraline, bupropion or venlafaxine vs. CT switch)
Remission (14 wk follow-up)	No difference	Low 1 study (42)	HAM-D-17 or QIDS-SR-16 RR, 1.12 (95% CI, 0.58 to 2.16) (sertraline, bupropion or venlafaxine vs. CT switch)
Discontinuation due to adverse events (14 wk follow-up)	No difference	Low 1 study (42)	RR, 1.6 (95% CI, 0.71 to 3.61) (citalopram switch to sertraline, bupropion or venlafaxine vs. CT switch)
Augmenting strategies: pharmacologic (SGA augment vs. SGA augment)			
Response (14 wk follow-up)	No difference	Low 1 study (43)	QIDS-SR-16 RR, 1.18 (95% CI, 0.92 to 1.53) (citalopram augmented with bupropion vs. buspirone)
Remission (14 wk follow-up)	No difference	Low 1 study (43)	QIDS-SR-16 RR, 0.99 (95% CI, 0.77 to 1.27) (citalopram augmented with bupropion vs. buspirone)
Suicidal ideas and behavior	No difference	Low 1 study (43)	RR, 0.26 (95% CI, 0.03 to 2.28) (citalopram augmented with bupropion vs. buspirone)
Serious adverse events (14 wk follow-up)	No difference	Low 1 study (43)	RR, 0.85 (95% CI, 0.38 to 1.95) (citalopram augmented with bupropion vs. buspirone)
Discontinuation due to adverse events (14 wk follow-up)	Lower with bupropion than buspirone	Moderate 1 study (43)	RR, 0.61 (95% CI, 0.41 to 0.89) (citalopram augmented with bupropion vs. buspirone)

Continued on following page

Appendix Table 2–Continued

Interventions	Finding	Quality of Evidence	Data
Augmenting strategies: nonpharmacologic (SGA augment vs. CBT augment)			
Response (14 wk follow-up)	No difference	Low 1 study (42)	QIDS-SR-16 RR, 0.8 (95% CI, 0.51 to 1.23) (citalopram augmented with bupropion or buspirone vs CT)
Remission (14 wk follow-up)	No difference	Low 1 study (42)	HAM-D-17 or QIDS-SR-16 RR, 1.44 (95% CI, 0.87 to 2.41) (citalopram augmented with bupropion or buspirone vs CT)
Severity	No difference	Low 1 study (42)	QIDS-SR revealed no difference between the percentage decrease in depressive severity (39.6% vs. 40.5%, $P = 0.83$)
Serious adverse events (14 wk follow-up)	No difference	Low 1 study (42)	RR, 0.56 (95% CI, 0.14 to 2.15) (citalopram augmented with bupropion or buspirone vs. CT)
Discontinuation due to adverse events (14 wk follow-up)	No difference	Low 1 study (42)	RR, 2.13 (95% CI, 0.91 to 4.96) (citalopram augmented with bupropion or buspirone vs. CT)

CBT = cognitive behavioral therapy; CT = cognitive therapy; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report; RR = risk ratio; SGA = second-generation antidepressant.
* Adapted from reference 6. Values reported in the background evidence paper (9) were based only on the highest-quality trials, whereas the values reported in this table are based on all included studies from the AHRQ report (6).