Nonpharmacological Versus Pharmacological Treatment for Patients With Major Depressive Disorder: Current State of the Evidence

Focus of This Summary

This is a summary of a systematic review evaluating the evidence regarding the comparative benefits and adverse effects of second-generation antidepressants (SGAs) and of psychological, complementary and alternative medicine (CAM), and exercise treatment options as first-step interventions for adult outpatients with acute-phase major depressive disorder (MDD) and as second-step interventions for patients with MDD who did not achieve remission after a first treatment attempt with SGAs. The systematic review included 44 trials published between January 1, 1990, and January 13, 2015. Patients in the included studies had mild to severe MDD. The full report, listing all studies, is available at *www.effectivehealthcare.ahrq.gov/major-depressive-disorder*. This summary is provided to assist in informed clinical decisionmaking. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

MDD is the most prevalent and disabling form of depression and affects 16 percent of U.S. adults over their lifetime. In any given year, 7 percent of the U.S. adult population (approximately 17.5 million people in 2014) experiences an episode of MDD warranting treatment.

MDD can be characterized as mild, moderate, or severe. Characterization of MDD is based on symptom severity, functional impairment, and level of patient distress. Nearly one-third of patients with MDD are severely depressed.

Many patients with MDD are treated in primary care settings, where SGAs are the most prescribed treatment. Other treatment options that may be considered include psychological interventions, CAM approaches, and exercise. Psychological interventions may include cognitive behavioral therapy (CBT), interpersonal therapy, and psychodynamic therapies. Commonly used CAM therapies include acupuncture, meditation, omega-3 fatty acids, s-adenosyl-L-methionine (SAMe), St. John's wort (*Hypericum perforatum*), and yoga. Exercise options may involve short- or long-duration programs.

Approximately 40 percent of patients treated with SGAs do not respond to first-step treatment and approximately 70 percent do not achieve remission, indicating the need for a different treatment strategy.

Conclusions

First-Step Interventions for Managing MDD

- CBT appears to be as effective as SGAs in relieving symptoms as first-step treatments for adult outpatients with mild to severe MDD (*see Table 1*).
- Low-level evidence suggests that there is a trend toward a higher rate of treatment discontinuation due to adverse events with SGAs when compared with CBT. However, the difference is not statistically different (*see Table 2*).
- The evidence is too limited to permit firm conclusions regarding the benefits and adverse effects of other interventions (including other psychological therapies, CAM, and exercise) when compared with SGAs.
- The evidence is also insufficient to permit conclusions about differences in serious adverse events, such as suicidal ideas and behavior, between SGAs and other therapies.

Second-Step Interventions for Managing MDD

For patients who do not achieve remission after first-step therapy with an SGA, second-step treatment options include switching to a different SGA or to CBT or adding a second SGA or CBT to the initial SGA (i.e., augmentation).

- Switching to another SGA as second-step therapy improves response and remission rates regardless of the SGA chosen (*see Table 3*).
- Limited evidence suggests that switching to another SGA, versus switching to CBT, has similar beneficial effects on response and remission rates (*see Table 3*).
- Response and remission rates may be improved by augmentation with a second SGA or with CBT, although evidence for this finding is low level (*see Table 3*).
- Low-level evidence suggests that the risk of adverse events and the rates of discontinuation due to adverse events may be similar for second-step therapies for MDD.

Given the comparable levels of effectiveness of SGAs and CBT, clinicians and patients might consider the benefits and harms of treatment and other factors (e.g., severity of depression, costs, adherence) when selecting treatment options.

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Overview of Clinical Research Evidence

Table 1: Summary of the Strength of Evidence for the Benefits of SGAs Versus CBT as First-Step Interventions for Managing Major Depressive Disorder

Intervention	Response Rate			Remission Rate		
	Effect	RR (95% CI)	SOE	Effect	RR (95% CI)	SOE
SGAs versus CBT	⬌	0.91 (0.77 to 1.07)	●●○	⬌	0.98 (0.73 to 1.32)	●○○
SGAs versus SGAs + CBT	⬌	1.03 (0.85 to 1.26)	●○○	⬌	1.06 (0.82 to 1.38)	●○○

Please see below Table 3 for the abbreviation key.

Table 2: Summary of the Strength of Evidence for the Adverse Outcomes of SGAs Versus CBT as First-Step Interventions for Managing Major Depressive Disorder

Intervention	Overall Discontinuation of Treatment			Discontinuation Due to Adverse Effects		
	Effect	RR (95% CI)	SOE	Effect	RR (95% CI)	SOE
SGAs versus CBT	⬌	1.00 (0.59 to 1.69)	●●○	⬌	2.54 (0.39 to 16.47)	●○○
SGAs versus SGAs + CBT	⬌	0.77 (0.37 to 1.60)	●○○	⬌	2.93 (0.72 to 11.91)	●○○

Please see below Table 3 for the abbreviation key.

Table 3: Summary of Key Outcomes and Strength of Evidence for the Benefits of Second-Step Interventions* for Managing Major Depressive Disorder

Intervention	Response Rate		Remission Rate	
	Effect	SOE	Effect	SOE
Switching to another SGA as second-step therapy because of lack of benefit	⬌ (among various SGAs)	●●○	⬌ (among various SGAs)	●●○
Switching to another SGA versus switching to CBT because of lack of benefit†	⬌	●○○	⬌	●○○
Augmentation with a different pharmacotherapy (an SGA or a non-SGA) as a second-step therapy	⬌ (among various SGAs)	●○○	⬌ (among various SGAs)	●○○
Augmentation with an SGA or with CBT††	⬌	●●○	⬌	●○○

⬌ = no statistically significant difference; CBT = cognitive behavioral therapy; CI = confidence interval; RR = relative risk; SGA = second-generation antidepressant; SOE = strength of evidence

* For patients who do not achieve remission after first-step therapy, treatment options include switching or augmentation. With switching, patients can receive a different SGA or psychotherapy. With augmentation, a second SGA or psychotherapy can be added to the initial SGA.

† Response rates in patients who were switched to a different SGA or to CBT ranged from 22 to 27 percent, while remission rates ranged from 25 to 28 percent.

†† Response rates in patients for whom a second SGA or CBT was added to the initial SGA ranged from 28 to 35 percent, while remission rates ranged from 23 to 33 percent.

Strength of Evidence Scale**

- High: ●●● High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: ●●○ Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: ●○○ Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient: ○○○ Evidence either is unavailable or does not permit a conclusion.

** The overall evidence grade was assessed based on the ratings for the following domains: study limitations, directness, consistency, precision, and reporting bias. Other domains that were considered, as appropriate, included dose-response association, plausible confounding, and strength of association (i.e., magnitude of effect). For additional details on the methodology used to assess strength of evidence, please refer to: Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.

Overview of Clinical Research Evidence *(Continued)*

Table 4: Common Adverse Effects Reported in Studies of Interventions Used To Treat MDD

Intervention	Common Adverse Effects Reported
SGAs	■ Nausea/vomiting ■ Headache ■ Diarrhea ■ Insomnia ■ Sleepiness/fatigue ■ Weight gain
Psychotherapies	■ Dissatisfaction with treatment

MDD = major depressive disorder
SGA = second-generation antidepressant

Table 5: FDA Black Box Warnings for Drugs Used To Treat MDD

Drug(s)	FDA Black Box Warning
All SGAs	■ Increased risks of suicidal thinking and behavior in children, adolescents, and young adults (ages 18 to 24 years) have been observed during initial treatment. ■ Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidal thinking and behavior, or unusual changes in behavior.

FDA = U.S. Food and Drug Administration
MDD = major depressive disorder
SGA = second-generation antidepressant

Other Findings of the Review

- Only a few studies evaluated other MDD interventions. The evidence was limited regarding the benefits and adverse effects of various other MDD interventions—alone or in combination with SGAs—when compared with SGAs alone. These interventions included:
  - Interpersonal psychotherapy
  - Psychodynamic therapy
  - Acupuncture
  - Omega-3 fatty acids
  - s-adenosyl-L-methionine
  - St. John's wort
  - Exercise therapy
- Low-level evidence suggested that these interventions (with the exception of omega-3 fatty acids) may be similar to SGAs in effectiveness; however, the evidence was too limited to permit firm conclusions.
- Limited evidence suggested that the risk of adverse events and rates of discontinuation due to adverse events were similar (1) when patients were switched to a different SGA or to CBT as second-step therapy or (2) when an SGA or CBT was added on as second-step therapy.

Gaps in Knowledge and Limitations of the Evidence Base

Interventions

- No eligible studies were found comparing SGAs to a range of other therapeutic modalities, including humanistic therapy, yoga, and mindfulness interventions.
- No data exist comparing SGAs with CAM or exercise treatments as second-step therapy.

Study design and applicability

- Evidence was too limited to permit conclusions about the efficacy of treatments for patient subgroups (i.e., those characterized by age, sex, race, ethnicity, medical comorbidities, or coexisting psychiatric conditions).
- Very few studies evaluated the effectiveness and adverse effects of MDD interventions in the long term.
- The applicability of the findings of this review may be limited by the availability and experience of the psychotherapists who provide CBT.

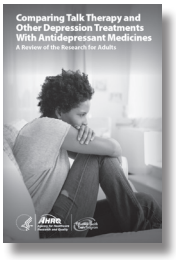
Outcomes

- Evidence-based information about the comparative risk of adverse effects and patient-centered outcomes related to a range of issues, including functional capacity and quality of life, is generally lacking.

What To Discuss With Your Patients and Their Caregivers

- That effective nonpharmacological and pharmacological treatment options are available for MDD
- The risks associated with not treating or ineffectively treating MDD, such as worsening or persisting depression and suicide
- That treatment decisions may take the following factors into account:
  - Patient factors (e.g., history of trauma or abuse)
  - Severity of the patient's depression
  - Potential adverse effects
  - Likely adherence to the intervention
  - Patient preferences
  - Availability of the intervention
  - Availability of psychotherapists who can offer CBT
  - Costs associated with the intervention
- That it is important for patients to comply with the treatment that has been recommended to them
- The potential adverse effects associated with MDD treatments, including the potential serious adverse effects associated with SGAs
- That it is important for patients and caregivers to discuss with their health care professional any adverse effects they observe after treatment begins
- What treatment options are available if first-step therapy for MDD does not work or if first-step therapy causes adverse effects

Companion Resource for Patients



Comparing Talk Therapy and Other Depression Treatments With Antidepressant Medicines: A Review of the Research for Adults is a free companion to this clinician research summary. It can help patients and their caregivers talk with their health care professionals about the various treatment options that are available to treat depression.

Ordering Information

For electronic copies of this clinician research summary, the companion patient resource, and the full systematic review, visit *www.effectivehealthcare.ahrq.gov/major-depressive-disorder.* To order free print copies of the patient resource, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

The information in this summary is based on *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 for the Agency for Healthcare Research and Quality, December 2015. Available at *www.effectivehealthcare.ahrq.gov/major-depressive-disorder.* This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

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