

Second-Generation Antidepressants for Treating Adult Depression: An Update

Focus of Research for Clinicians

As an update to a 2007 report, a systematic review of 248 clinical studies published between January 1980 and January 2011 examined the comparative effectiveness, benefits, and adverse effects of second-generation antidepressants for adults with depression. This review did not cover nonpharmaceutical treatments for depression, the comparative effectiveness of first-generation antidepressants, or the use of second-generation antidepressants in treating other axis 1 disorders including substance use disorders, bipolar disorder, bulimia nervosa, or schizophrenia. The full report is available at www.effectivehealthcare.ahrq.gov/secondgenantidep.cfm. This summary is provided to inform discussions of options with patients and to assist in decisionmaking along with consideration of a patient's values and preferences. Reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

Depressive disorders, including major depressive disorder (MDD), dysthymia, and subsyndromal depression, affect approximately one in five people in the United States. Pharmacotherapy dominates the medical management of depressive disorders. Most first- and second-generation antidepressants both have about a 60-percent response rate when used to treat adults with MDD. However, first-generation antidepressants often have intolerable side effects and a high risk for harm when taken in excess or in combination with certain medications. Second-generation antidepressants have a more favorable side-effect profile and thus play a prominent role in managing patients with MDD.

The 2007 comparative effectiveness review on second-generation antidepressants summarized the available evidence on 12 medications (see Table 1) and their comparative efficacy, effectiveness, and adverse effects for treating adults with depression, maintaining remission, and treating accompanying symptoms such as anxiety, insomnia, and chronic pain. This updated review includes additional comparative data, one new medication, and additional studies on formulas of included medications.

Conclusion

New evidence included in the current review continues to support the original conclusions from the 2007 review, namely that second-generation antidepressants used to treat MDD in adults have similar effectiveness, efficacy, and effects on quality of life. Some clinically significant differences among individual drugs do exist with respect to onset of action and adverse effects, which may affect treatment choices. For example, mirtazapine has a faster onset of action but is associated with greater weight gain. Also, bupropion has fewer sexual side effects than many comparators. More research is needed to evaluate whether the benefits or adverse effects of second-generation antidepressants differ in subgroups or in populations with accompanying symptoms such as anxiety, insomnia, or chronic pain.

Clinical Bottom Line

Major Depressive Disorder

Overall, second-generation antidepressants have similar efficacy, effectiveness, and effects on quality of life. ●●○

Elderly patients (≥60 years) with MDD had similar efficacy with second-generation antidepressants ●●○ but may experience differences in adverse effects ●○○.

Mirtazapine has a faster onset of action (1–2 weeks) than do citalopram, fluoxetine, paroxetine, and sertraline; however, response rates were similar for these drugs after 4 weeks of treatment. ●●○

Fluoxetine daily and fluoxetine weekly have similar response and remission rates. ●●○

Paroxetine IR (immediate release) and paroxetine CR (controlled release) have similar response rates. ●●○

One trial reported higher response rates for venlafaxine XR (extended release) than venlafaxine IR. ●○○

Adults With Dysthymia or Subsyndromal Depression

For adults with subsyndromal depression, limited evidence supports no difference in comparative efficacy between citalopram and sertraline. ●○○

Evidence is unavailable or inconclusive regarding all other outcomes for treatment of dysthymia or subsyndromal depression with second-generation antidepressants. ○○○

Maintaining Remission

Most second-generation antidepressants effectively maintain remission (prevent relapse and recurrence) with similar efficacy. ●●○

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Strength of Evidence Scale

- High: ●●● There is 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 estimation of an effect.



Clinical Bottom Line *(Continued from front)*

Resistant or Refractory Depression

Venlafaxine may be modestly superior to other selective serotonin reuptake inhibitors (SSRIs); however, results on comparative effectiveness are mixed. ●○○

Treatment for Symptoms That May Accompany Depression

Anxiety

Second-generation antidepressants have similar efficacy for treating depression in patients who also have anxiety. ●●○
Improvements in anxiety scores were similar among second-generation antidepressants in adults with depression. ●●○

Pain

Paroxetine and duloxetine showed similar improvements in pain scores for patients with depression. ●●○

Insomnia

Several second-generation antidepressants are equally effective at treating insomnia symptoms in patients with depression. ●○○

Adherence and Persistence

Adherence rates were similar for the following comparisons (●●○):

- Citalopram versus sertraline
- Bupropion versus trazodone
- Bupropion SR versus fluoxetine, paroxetine, or sertraline
- Paroxetine IR versus paroxetine CR

Adherence rates in patients with MDD were higher for fluoxetine weekly versus fluoxetine daily. ●○○

Patients with MDD refilled prescriptions for bupropion XL more frequently than for bupropion SR. ●○○

Comparative Adverse Effects

Overall rates of adverse effects were similar among second-generation antidepressants, though incidence of specific adverse events differed across antidepressants. ●●●

Overall differences in formulations

No differences in harms were found between fluoxetine daily and fluoxetine weekly or between venlafaxine IR and venlafaxine XR. ●●○

Nausea and vomiting

Venlafaxine has a 52-percent higher incidence than SSRIs as a class. ●●●
Paroxetine IR may lead to higher rates of nausea than paroxetine CR. ●○○

Weight gain

Mirtazapine is associated with more weight gain than are citalopram, fluoxetine, paroxetine, and sertraline (0.8–3.0 kg after 6–8 weeks). ●●●

Diarrhea

Sertraline was associated with an 8-percent higher incidence of diarrhea than were bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine. ●●○

Somnolence

Trazodone was associated with a 16-percent higher incidence of somnolence than were bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine. ●●○

Discontinuation rates

Higher discontinuation rates due to adverse effects were seen with duloxetine (67% higher risk) and venlafaxine (40% higher risk) when compared with most SSRIs. ●●●

Venlafaxine had lower discontinuation rates due to lack of efficacy (35% lower risk). ●●●

Withdrawal symptoms

The highest rates of withdrawal symptoms (headache, dizziness, light-headedness, nausea, and anxiety) were reported after discontinuing paroxetine or venlafaxine. ●●○

Fluoxetine had the lowest rate of withdrawal symptoms. ●●○

Sexual dysfunction

Bupropion had fewer sexual side effects than escitalopram, fluoxetine, paroxetine, and sertraline. ●●●
Paroxetine had the highest rate of sexual side effects when compared with SSRIs as a class (16% vs. 6%). ●●○
Sexual side effects may occur at different rates between men and women. ●○○

Suicidality

Evidence is insufficient to evaluate the comparative risk of suicidal thoughts and behavior. ○○○

Severe adverse effects

Evidence is insufficient to evaluate the comparative risk for rare but severe events such as seizures, cardiovascular events, hyponatremia, hepatotoxicity, and serotonin syndrome. ○○○

Noncomparative Evidence for Diabetes, Fractures, and Bleeding

Unrated evidence on second-generation antidepressants shows:

- An increased risk for diabetes in patients on recent long-term use (>24 months) of moderate to high doses of fluvoxamine, paroxetine, or venlafaxine.
- An increased risk for fractures (hip and other fractures, except fractures of forearm or spine) for patients on high-dose citalopram, fluoxetine, paroxetine, and sertraline.
- An increased risk for upper gastrointestinal tract bleeding during SSRI treatment.

Table 1. List of Second-Generation Antidepressants Included in the 2011 Updated Review

Generic Name	U.S. Trade Name ^a	Labeled Uses ^b	Therapeutic Classification
Bupropion ^c	Wellbutrin [®] ; Wellbutrin SR [®] ; Wellbutrin XL [®]	MDD; seasonal affective disorder	Other
Citalopram ^c	Celexa [®]	MDD	SSRI
Desvenlafaxine ^d	Pristiq [®]	MDD	SNRI
Duloxetine	Cymbalta [®]	MDD; GAD; neuropathic pain; fibromyalgia	SSNRI
Escitalopram	Lexapro [®]	MDD; GAD	SSRI
Fluoxetine ^c	Prozac [®] ; Prozac Weekly [®]	MDD; OCD; PMDD; panic disorder; bulimia nervosa	SSRI
Fluvoxamine ^c	Luvox [®]	OCD	SSRI
Mirtazapine ^c	Remeron [®] ; Remeron SolTab [®]	MDD	Other
Nefazodone ^c	Serzone ^{®e}	MDD	Other
Paroxetine ^c	Paxil [®] ; Paxil CR ^{®f}	MDD; OCD; panic disorder; social anxiety disorder; GAD; PTSD; PMDD ^f	SSRI
Sertraline ^c	Zoloft [®]	MDD; OCD; panic disorder; PTSD; PMDD; social anxiety disorder	SSRI
Trazodone ^c	Desyrel [®]	MDD	Other
Venlafaxine ^c	Effexor [®] ; Effexor XR [®]	MDD; GAD; ^g panic disorder; social anxiety disorder ^g	SNRI

^a CR = controlled release; SR = sustained release; XL or XR = extended release

^b GAD = generalized anxiety disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = post-traumatic stress disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSNRI = selective serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

^c A generic is available for some dosage forms.

^d Desvenlafaxine was not included in the 2007 report but is included in the 2011 updated review.

^e Only generic nefazodone is available in the United States.

^f Only Paxil CR (not Paxil) is approved for treating PMDD.

^g Only Effexor XR (not Effexor) is approved for treating GAD and social anxiety disorder.

Gaps in Knowledge

- The general efficacy of second-generation antidepressants for treating dysthymia and subsyndromal depression.
- Differences in benefits and harms in subgroups such as the very elderly or patients with common comorbidities.
- The most appropriate duration of antidepressant treatment for maintaining remission.
- The effect of drug dosage on the risk of relapse or recurrence.
- The effect of switching to a new drug after successful completion of acute- or continuation-phase treatment.
- The most effective second-generation antidepressant in patients who either did not respond to or could not tolerate a first-line treatment.
- How combinations of antidepressants compare with monotherapy in treatment-resistant depression.
- How outcomes of second-generation antidepressants differ in populations with accompanying symptoms such as anxiety, insomnia, pain, or fatigue.
- The comparative risks of second-generation antidepressants with respect to rare but serious adverse effects such as suicidality, hyponatremia, hepatotoxicity, seizures, cardiovascular adverse events, and serotonin syndrome.

What To Discuss With Your Patients (About Second-Generation Antidepressants)

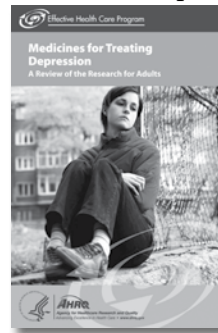
- The benefits of the different second-generation antidepressants for treating their specific symptoms.
- How they will know if their medication is working.
- How to identify the potential adverse effects of the medications and how to handle them.
- How long they may need to take their current antidepressant.
- The importance of adhering to their treatment regimens and what to expect if they stop taking their medicines, including the risk of withdrawal or discontinuation syndrome.
- To always consult their health care provider before discontinuing any medication.
- How their medications will affect the symptoms that may be accompanying their depression such as anxiety, insomnia, or chronic pain.
- Their comorbidities and other medications they may be taking and how these may influence their depression-related outcomes.

Source

The information in this summary is based on *Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review*, Comparative Effectiveness Review No. 46, prepared by the RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-2007-10056-I for the Agency for Healthcare Research and Quality, December 2011. Available at www.effectivehealthcare.ahrq.gov/secondgenantidep.cfm. This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

Resource for Patients

Medicines for Treating Depression, A Review of the Research for Adults is a free companion to this clinician research summary that is written specifically for patients. It can help patients talk with their health care professionals about treatments for depression and related symptoms. It provides information about:



- Antidepressants available for treating adults with depression
- Side effects related to medications used to treat depression
- Questions for patients to ask their health care providers

Ordering Information

For electronic copies of *Medicines for Treating Depression, A Review of the Research for Adults*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/secondgenantidep.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

