Implementing AHRQ Effective Health Care Reviews

Helping Clinicians Make Better Treatment Choices

Second-Generation Antidepressants for Depression in Adults

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The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. A key clinical question based on the AHRQ Effective Health Care Program review is presented, followed by an evidence-based answer and an interpretation that will help guide clinicians in making treatment decisions. For the full review, clinician summary, consumer summary, and CME activity, go to http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=862.

A collection of Implementing AHRQ Effective Health Care Reviews published in *AFP* is available at http://www.aafp.org/afp/ahrq.

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 643.

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Key Clinical Issue

What are the comparative effectiveness and adverse effects of second-generation antidepressants for treating depression in adults?

Evidence-Based Answer

Second-generation antidepressants (antidepressants other than tricyclics and monoamine oxidase inhibitors) used to treat major depressive disorder in adults have similar effectiveness. However, some clinically significant differences among individual drugs 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 adverse 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. (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

All second-generation antidepressants, have similar effectiveness for treatment of major depressive disorder, with a 60% overall response rate.[1] Therefore, it is reasonable to make the initial choice of a second-generation antidepressant for depression based on known adverse effect profiles, as recommended in current guidelines from the American Psychiatric Association[2] and the American College of Physicians.[3] For example, paroxetine (Paxil) is associated with more sexual adverse effects, and mirtazapine (Remeron) with more weight gain. Trazodone causes increased somnolence, and may be a good choice in patients with difficulty sleeping. Formulation (e.g., daily vs. weekly dosing, immediate vs. controlled release) does not impact clinical effectiveness.[1]

For patients with resistant depression, a large randomized trial showed no difference in response rates among sustained-release bupropion (Wellbutrin SR), sertraline (Zoloft), and extended-release venlafaxine (Effexor XR).[4] Some lower-quality studies suggest venlafaxine may be slightly superior to fluoxetine (Prozac), mirtazapine, paroxetine, sertraline, and citalopram (Celexa).[5] No studies have compared second-generation antidepressants for relapsed depression.

Evidence from 31 studies in the AHRQ review suggests that most second-generation antidepressants are effective for preventing relapse. No particular second-generation antidepressant is superior at maintaining remission based on existing head-to-head studies.[1] No evidence currently exists to help guide patients in switching from one second-generation antidepressant to another.

Evidence from seven fair-quality head-to-head trials in the AHRQ review suggests that antidepressants do not differ substantially in effectiveness for patients with major depressive disorder and comorbid anxiety symptoms. Five trials included in the AHRQ review showed no substantial differences in effectiveness among second-generation antidepressants for treatment of major depressive disorder with accompanying insomnia.[1]

Clinical Bottom Line: Second-Generation Antidepressants for Depression in Adults

Comparative benefits

Major depressive disorder

- Overall, second-generation antidepressants have similar efficacy, effectiveness, and effects on quality of life. ●●○
- Mirtazapine has a faster onset of action (one to two weeks) than citalopram, fluoxetine, paroxetine, and sertraline. ●●○
- Response rates after four weeks of treatment were similar among mirtazapine, citalopram, fluoxetine, paroxetine, and sertraline. ●●○
- Most second-generation antidepressants maintain remission (prevent relapse and recurrence) with similar efficacy. ●●○
- Efficacy of second-generation antidepressants does not differ in treatment of older adults (at least 60 years of age). ●●○
- Adherence and persistence
  - Adherence rates were similar in the following comparisons (●●○): Bupropion vs. trazodone; bupropion SR (sustained release) vs. fluoxetine, paroxetine, or sertraline; citalopram vs. sertraline.
- Comparing effects of different formulations
  - Fluoxetine daily and fluoxetine weekly have similar response and remission rates. ●●○
  - Paroxetine IR (immediate release) and paroxetine CR (controlled release) have similar response rates. Adherence and persistence rates are also similar. ●●○

Dysthymia or subsyndromal depression

- For adults with subsyndromal depression, limited evidence supports no difference in efficacy between citalopram and sertraline. ●○○
- Evidence is either unavailable or inconclusive regarding all other outcomes for treatment of dysthymia or subsyndromal depression with second-generation antidepressants. ○○○

Depression with accompanying symptoms

- Anxiety: Second-generation antidepressants have similar efficacy for treating anxiety and depression in patients who have both major depressive disorder and anxiety symptoms. ●●○
- Pain: Paroxetine and duloxetine showed similar improvements in pain scores for patients with depression. ●●○
- Insomnia: Fluoxetine, paroxetine, and sertraline are similarly effective for treating insomnia and depression in patients who have both major depressive disorder and insomnia. ●○○

Comparative adverse effects

The spectrum of adverse effects is similar across the second-generation antidepressants, but the specific incidence of adverse effects differs among the drugs. ●●●

Persons older than 60 years may experience different adverse effects. ●○○

Nausea and vomiting: Venlafaxine has a 52% higher incidence than SSRIs as a class. ●●●

Weight gain: Mirtazapine is associated with more weight gain (1.8 to 6.6 lb [0.8 to 3.0 kg] after six to eight weeks) than are citalopram, fluoxetine, paroxetine, and sertraline. ●●●

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

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

Discontinuation rates: Higher discontinuation rates because of adverse effects were seen with duloxetine (67% higher risk) and venlafaxine (40% higher risk) compared with most SSRIs. ●●●

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 rates of withdrawal symptoms. ●●○

Sexual dysfunction:

- Bupropion had fewer sexual adverse effects than escitalopram, fluoxetine, paroxetine, and sertraline. ●●●
- Paroxetine had the highest rate of sexual adverse effects compared with other SSRIs as a class (16% vs. 6%). ●●○
- Sexual adverse 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 of rare but severe events such as seizures, cardiovascular events, hyponatremia, hepatotoxicity, and serotonin syndrome. ○○○

Strength of evidence scale

High: ●●● There are consistent results from good-quality studies. Further research is very unlikely to change the conclusions.

Moderate: ●●○ Findings are supported, but further research could change the conclusions.

Low: ●○○ There are very few studies, or existing studies are flawed.

Insufficient: ○○○ Research is either unavailable or does not permit estimation of a treatment effect.

NOTE: *Second-generation antidepressants (therapeutic classification): bupropion (other); citalopram (SSRI); desvenlafaxine (SNRI); duloxetine (SSNRI); escitalopram (SSRI); fluoxetine (SSRI); fluvoxamine (SSRI); mirtazapine (other); nefazodone (other); paroxetine (SSRI); sertraline (SSRI); trazodone (other); venlafaxine (SNRI)*

SNRI = serotonin–norepinephrine reuptake inhibitor; SSNRI = selective serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Adapted from the Agency for Healthcare Research and Quality, Effective Health Care Program. Second-generation antidepressants for treating adult depression: An update. Clinician research summary. Rockville, Md.: Agency for Healthcare Research and Quality; July 2012. http://effectivehealthcare.ahrq.gov/ehc/products/210/1143/sec_gen_anti_dep_clin_fin_to_post.pdf. Accessed August 5, 2013.

Overall, second-generation antidepressants have similar adverse effects; these occur in 63% of patients and include constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual dysfunction, and somnolence. Nausea and vomiting are the most common reasons for discontinuation.[6] Venlafaxine has a higher incidence of nausea than the selective serotonin reuptake inhibitors.

A good systematic review indicates that paroxetine and venlafaxine have the highest rates of antidepressant discontinuation syndrome, whereas fluoxetine has the lowest.[7] More information on antidepressant discontinuation syndrome can be found at http://www.aafp.org/afp/2006/0801/p449.html. There is insufficient evidence on the comparative risks of second-generation antidepressants on the most serious adverse effects: suicidality, hyponatremia, cardiovascular events, seizures, hepatotoxicity, and serotonin syndrome.

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