Implementing AHRQ Effective Health Care Reviews

Helping Clinicians Make Better Treatment Choices

Adverse Events of Pharmacologic Treatments of Major Depression in Older Adults

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Key Clinical Issue

What are the adverse events of antidepressants prescribed to treat major depressive disorder in adults 65 years and older?

Evidence-Based Answer

Selective serotonin reuptake inhibitors (SSRIs) cause adverse events at a similar frequency to placebo and have lower discontinuation rates than tricyclic antidepressants during up to 12 weeks of treatment. (Strength of Recommendation [SOR]: B, based on inconsistent or limited-quality patient-oriented evidence.) Serotonin-norepinephrine reuptake inhibitors (SNRIs) cause more adverse events and greater discontinuation of therapy during up to 12 weeks of treatment compared with placebo. (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) Duloxetine increases the risk of falls over 12 to 24 weeks of treatment compared with placebo.[1] (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Approximately 15% to 20% of adults 65 years and older have depression.[2] The American Psychiatric Association recommends antidepressants as an initial treatment option. SSRIs, SNRIs, mirtazapine, and bupropion are suggested as first-line agents for the general adult population and for older adults.[3] Meta-analyses of randomized controlled trials (RCTs) have shown that among adults 60 years and older, antidepressants are more effective than placebo for treating depression, although effect size is modest.[4] However, the 2019 Beers Criteria for Potentially Inappropriate Medication Use in Older Adults recommend that SSRIs, SNRIs, and tricyclic antidepressants be avoided in older adults with a history of falls or fractures.[5] The Agency for Healthcare Research and Quality (AHRQ) review aims to synthesize research on adverse event profiles of antidepressants in older adults.

This AHRQ review includes 19 RCTs and two observational studies. The RCTs include only patients 65 years and older, mostly with moderate severity major depressive disorder. Trials studied the acute phase of major depressive disorder (less than 12 weeks), the continuation phase (12 to 48 weeks), or the maintenance phase (more than 48 weeks). Although the authors attempted to evaluate SSRIs and SNRIs by drug class, most studies included only a few individual drugs.

In trials comparing SSRIs (paroxetine, citalopram, or sertraline) head-to-head with tricyclic antidepressants (amitriptyline or nortriptyline) during the acute phase of treatment, patients taking SSRIs were less likely to withdraw from trials because of adverse events. One large cohort study of people 65 years and older who had depression found that SSRIs were associated with an increased risk of falls, fractures, and all-cause mortality compared

Additional table at https://www.aafp.org/afp/2020/0201/p179.html.

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to produce evidence to improve health care and to make sure the evidence is understood and used. A key clinical question based on the AHRQ Effective Health Care Program systematic review of the literature is presented, followed by an evidence-based answer based on the review. AHRQ's summary is accompanied by an interpretation by an *AFP* author that will help guide clinicians in making treatment decisions. For the full review and consumer summary, go to https://effectivehealthcare.ahrq.gov/products/depression-harms/research.

This series is coordinated by Kenny Lin, MD, MPH, deputy editor.

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

CME **This clinical content** conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 141.

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Comparative Adverse Events of Antidepressants vs. Each Other: Summary Statements Based on Findings and Statistical Significance*

Comparison (study design)	Acute phase (< 12 weeks)	Continuation phase (12 to 48 weeks)	Maintenance phase (> 48 weeks)
SSRI vs. SSRI (RCT)	Adverse events similar with sertraline or escitalopram vs. fluoxetine ●●○ Withdrawal due to adverse events similar with paroxetine, sertraline, or escitalopram vs. fluoxetine ●○○ Insufficient evidence: mortality	No data	Adverse events similar with paroxetine vs. fluoxetine ●●○ Serious adverse events similar with paroxetine vs. fluoxetine ●●○ Insufficient evidence: mortality
SSRI vs. SSRI (observational)	No data	Hospitalization similar with escitalopram vs. other SSRI or SNRI ●○○	No data
SNRI vs. SSRI (RCT)	Adverse events similar with venlafaxine vs. fluoxetine ●●○ Withdrawals due to adverse events similar with venlafaxine vs. fluoxetine ●○○	Adverse events similar with venlafaxine vs. citalopram ●●○ Serious adverse events similar with venlafaxine vs. citalopram ●●○ Withdrawals due to adverse events similar with venlafaxine vs. citalopram ●●○ Inconclusive: falls, fractures, mortality	No data
SSRI vs. tricyclic antidepressant (RCT)	Adverse events fewer with paroxetine and citalopram vs. amitriptyline ●○○, NNT = 6 (95% CI, 4 to 11) Withdrawals due to adverse events fewer with paroxetine, citalopram, and sertraline vs. amitriptyline and nortriptyline ●○○, NNT = 13 (95% CI, 7 to 100) Inconclusive: cognitive impairment, hospitalization, mortality, and serious adverse events	No data	No data

continues

Strength of evidence scale

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

NNT = number needed to treat; RCT = randomized controlled trial; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

*—Conclusions based on statistical significance may miss small differences from insufficient studies.

with no antidepressant use over a longer treatment period (median of 364 days).[6]

One RCT of the SNRI duloxetine reported an increased risk of treatment withdrawal due to adverse events and increased risk of falls compared with placebo over 12 to 24 weeks. Venlafaxine was associated with an increased risk of falls, fractures, and mortality compared with no antidepressant use in a large cohort study with a median treatment period of 364 days.[7]

Mirtazapine had a decreased risk of treatment withdrawal due to adverse events during the acute phase of major depressive disorder compared with paroxetine.[8] One RCT found no increased risk of any adverse event or treatment withdrawal due to adverse events for bupropion compared with placebo.[9]

Comparative Adverse Events of Antidepressants vs. Each Other: Summary Statements Based on Findings and Statistical Significance*

Comparison (study design)	Acute phase (< 12 weeks)	Continuation phase (12 to 48 weeks)	Maintenance phase (> 48 weeks)
Mirtazapine vs. paroxetine (RCT)	Adverse events similar with mirtazapine ●●○ Serious adverse events similar with mirtazapine ●○○ Withdrawals due to adverse events fewer with mirtazapine ●○○, NNT = 9 (95% CI, 5 to 72) Inconclusive: hospitalization	Adverse events similar with mirtazapine ●○○	No data
Vortioxetine vs. duloxetine (RCT)	Adverse events fewer with vortioxetine ●●●, NNT = 6 (95% CI, 4 to 17) Serious adverse events similar with vortioxetine ●●○ Withdrawals due to adverse events similar with vortioxetine ●●○ Inconclusive: fractures	No data	No data

NNT = number needed to treat; RCT = randomized controlled trial; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

*—Conclusions based on statistical significance may miss small differences from insufficient studies.

Adapted from Sobieraj DM, Baker WL, Martinez BK, et al. Adverse effects of pharmacologic treatments of major depression in older adults. Comparative Effectiveness Review No. 215. (Prepared by the University of Connecticut Evidence-based Practice Center under Contract No. 290-2015-00012- I.) AHRQ Publication No. 19-EHC011-EF. Rockville, Md.: Agency for Healthcare Research and Quality; March 2019. Accessed May 15, 2019. https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-215-depression-older-adults-executive-summary.pdf

There were limitations to this analysis, including significant risk of bias in seven out of 19 studies, lower than usual medication dosages in many studies, and inadequate power to detect differences in adverse events in individual RCTs.

For patients 65 years and older with major depressive disorder, first-line antidepressants are SSRIs, SNRIs, mirtazapine, and bupropion. Available evidence suggests that SNRIs have higher rates of adverse events and treatment withdrawal due to adverse events compared with placebo, and that duloxetine is associated with an increased risk of falls. Long-term comparative studies that are specifically designed to assess adverse events among adults 65 and older are needed to better inform decision-making for this population.

Editor's Note: *American Family Physician* SOR ratings are different from the AHRQ Strength of Evidence ratings. Dr. Salisbury-Afshar is an *AFP* contributing editor.

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eTABLE A

Adverse Events of Antidepressants vs. Placebo or No Therapy: Summary Statements Based on Findings and Statistical Significance*

Comparison (study design)	Acute phase (< 12 weeks)	Continuation phase (12 to 48 weeks)	Maintenance phase (> 48 weeks)
SSRI vs. placebo (RCT)	Adverse events similar with escitalopram and fluoxetine ●●○ Withdrawals due to adverse events more with citalopram, escitalopram, and fluoxetine ●○○, NNH = 11 (95% CI, 8 to 20) Insufficient evidence: mortality	Adverse events fewer with escitalopram ●○○, NNT = 5 (95% CI, 3 to 19) Insufficient: withdrawals due to adverse events	Insufficient evidence: mortality, serious adverse events, withdrawals due to adverse events
SSRI vs. no antidepressant use (observational)	No data	No data	Adverse events increased with SSRIs ●○○† Falls increased with SSRIs ●○○† Fractures increased with SSRIs ●○○† Mortality increased with SSRIs ●○○†
SNRI vs. placebo (RCT)	Adverse events more with duloxetine and venlafaxine ●●●, NNH = 10 (95% CI, 7 to 34) Falls similar with duloxetine ●○○ QTc interval similar with duloxetine ●●○ Serious adverse events fewer with duloxetine ●○○, NNT = 50 (95% CI, 25 to 1,000) Withdrawals due to adverse events more with duloxetine and venlafaxine ●●○, NNH = 17 (95% CI, −7 to 33) Insufficient evidence: fractures, mortality	Falls more with duloxetine ●●○, NNH = 10 (95% CI, 6 to 114)‡ QTc interval similar with duloxetine ●●●‡ Serious adverse events similar with duloxetine ●●○‡ Withdrawals due to adverse events more with duloxetine ●●○, NNH = 12 (95% CI, 7 to 33)‡ Insufficient evidence: arrhythmias, fractures, and mortality	No data
SNRI vs. no antidepressant use (observational)	No data	No data	Adverse events similar with venlafaxine ●○○† Falls increased with venlafaxine ●○○† Fractures increased with venlafaxine ●○○† Mortality increased with venlafaxine ●○○†

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Strength of evidence scale

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

NNH = number needed to harm; NNT = number needed to treat; RCT = randomized controlled trial; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

*—Conclusions based on statistical significance may miss small differences from insufficient studies.
†—This cohort study had a median of 364 days on treatment, although whether patients were treated for an acute, continuation, or maintenance period was not specified.
‡—Results reflect 24 weeks (12 acute plus 12 continuation weeks).

eTABLE A *(continued)*

Adverse Events of Antidepressants vs. Placebo or No Therapy: Summary Statements Based on Findings and Statistical Significance*

Comparison (study design)	Acute phase (< 12 weeks)	Continuation phase (12 to 48 weeks)	Maintenance phase (> 48 weeks)
Bupropion extended release vs. placebo (RCT)	Adverse events similar with bupropion extended release ●●○ Serious adverse events similar with bupropion extended release ●○○ Withdrawals due to adverse events similar with bupropion extended release ●○○ Insufficient evidence: arrhythmias and mortality	No data	No data
Mirtazapine vs. no antidepressant use (observational)	No data	No data	Adverse events similar with mirtazapine ●○○† Falls increased with mirtazapine ●○○† Fractures increased with mirtazapine ●○○† Mortality increased with mirtazapine ●○○†
Trazadone vs. no antidepressant use (observational)	No data	No data	Adverse events similar with trazodone ●○○† Falls increased with trazodone ●○○† Fractures similar with trazodone ●○○† Mortality increased with trazodone ●○○†
Vortioxetine vs. placebo (RCT)	Adverse events similar with vortioxetine ●●● Serious adverse events similar with vortioxetine ●●○ Withdrawal due to adverse events similar with vortioxetine ●○○ Insufficient: fractures	No data	No data

NNH = number needed to harm; NNT = number needed to treat; RCT = randomized controlled trial; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

*—Conclusions based on statistical significance may miss small differences from insufficient studies.
†—This cohort study had a median of 364 days on treatment, although whether patients were treated for an acute, continuation, or maintenance period was not specified.
‡—Results reflect 24 weeks (12 acute plus 12 continuation weeks).

Adapted from Sobieraj DM, Baker WL, Martinez BK, et al. Adverse effects of pharmacologic treatments of major depression in older adults. Comparative Effectiveness Review No. 215. (Prepared by the University of Connecticut Evidence-based Practice Center under Contract No. 290-2015-00012- I.) AHRQ Publication No. 19-EHC011-EF. Rockville, Md.: Agency for Healthcare Research and Quality; March 2019. Accessed May 15, 2019. https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-215-depression-older-adults-executive-summary.pdf