Comparative Effectiveness Review
Number 215

Adverse Effects of Pharmacologic Treatments of Major Depression in Older Adults

Evidence Summary

Background

Depression is a common psychiatric disease in older adults. Prevalence of depression in adults 65 years of age and older is estimated to be 15–20 percent in the United States.[1] Multiple systematic reviews have shown that antidepressant medications are better than placebo for treating depression in older patients, but with modest efficacy.[2] In addition, clinicians must consider the balance of the risks and benefits of antidepressant medications, especially in comparison to other treatment options.

The American Geriatrics Society (AGS) regularly compiles the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.[3] This source identifies potentially inappropriate medications that are best avoided for most adults with specific conditions, or used with caution, at lower doses, or with careful monitoring. In 2015, this list recommended that clinicians avoid prescribing selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) in older adults with a history of falls or fractures.[3] They noted that there may be situations when use of these medications may be appropriate and clinicians and patients must carefully weigh both benefits and potential harms.[4] Suggested alternatives to TCAs and SSRIs

Purpose of Review

To assess adverse events of antidepressants in the treatment of major depressive disorder in adults 65 years of age or older.

Key Messages

In people 65 years of age or older:

- Serotonin norepinephrine reuptake inhibitors (SNRIs) (duloxetine and venlafaxine) cause adverse events more often than placebo and most likely lead to discontinuation of therapy during treatment of up to 12 weeks.
- Selective serotonin reuptake inhibitors (SSRIs) (escitalopram and fluoxetine) most likely cause adverse events at a similar frequency to placebo therapy but still may lead to discontinuation of therapy during treatment of up to 12 weeks.
- Duloxetine most likely increases the risk of falls over longer treatment (<24 weeks)
- Adverse events contributing to discontinuation of therapy were rarely reported in a way that allowed clear characterization of what adverse events to expect.
- Few studies compared other antidepressants to placebo or to each other, or reported other outcomes. Trial data were sparse, and trials were short in duration, underpowered, and studied low doses of antidepressants. Observational studies had limitations related to their design. Long-term, rigorous comparative studies are needed.

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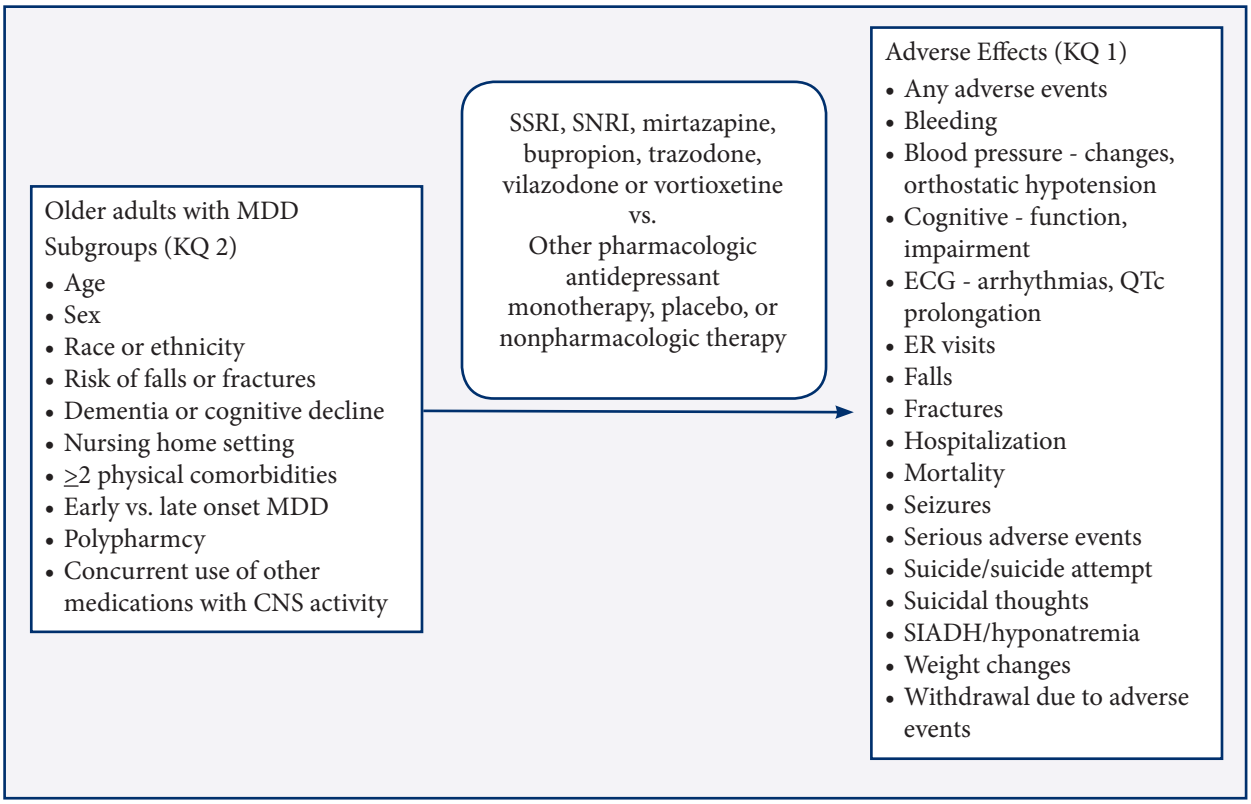
include serotonin-norepinephrine reuptake inhibitors (SNRIs) and bupropion.[5] However, the AGS also recommended using SSRIs and SNRIs with caution due to the potential to exacerbate or cause hyponatremia as a result of the syndrome of inappropriate antidiuretic hormone (SIADH).[3]

Given these concerns of potential adverse events in the older population with drugs commonly recommended to treat major depressive disorder (MDD), clinicians may be left selecting therapy based on comparative adverse effects. The objective of this review is to assess comparative adverse effects of pharmacologic antidepressants for treatment of MDD in adults 65 years of age or older (Figure A).

This review focuses on patients and drugs as classified in Table A and Figure A. The drugs selected for inclusion were therapies that were considered most likely to be used in this population, according to the expert opinion of the partner, key informants, technical expert panel and public comments received at the protocol development stage.

Figure A. Analytic framework



Abbreviations: CNS=central nervous system; ECG=electrocardiogram; ER=emergency room; KQ=Key Question; MDD= major depressive disorder; SIADH=syndrome of inappropriate antidiuretic hormone; SNRI=selective serotonin norepinephrine inhibitor; SSRI=selective serotonin reuptake inhibitor

Table A. Included pharmacologic treatments for major depressive disorder in older adults

Class	Drugs
SSRI	Paroxetine, sertraline, citalopram, escitalopram, fluoxetine, fluvoxamine
SNRI	Venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran
Other	Bupropion, mirtazapine, trazodone, vilazodone, vortioxetine

Abbreviations: SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

Data Sources

Data sources were MEDLINE®, Embase®, Cochrane Central, and PsychINFO bibliographic databases from earliest date through May 15, 2018; hand searches of references of relevant studies; www.clinicaltrials.gov and the International Controlled Trials Registry Platform. The systematic review protocol is available in the full report.

Methods

The protocol was registered in PROSPERO (CRD42018088648) and posted on the Agency for Healthcare Research and Quality website.[6] The draft report was posted for public and peer review and we revised the report based on these comments. We considered a variety of potential outcomes on which to focus, and after Technical Expert Panel input, we decided to grade strength of evidence (SOE) for the following outcomes: any adverse event, withdrawal due to adverse events, mortality, hospitalization, serious adverse events, arrhythmias, QTc prolongation, falls, fractures, cognitive impairment and SIADH. SOE was graded for the calculated effect estimates with interpretation based on statistical significance. SOE could have four grades (high (+++), moderate (++), low (+), or insufficient). We calculated number needed to treat (NNT) or harm (NNH) for graded outcomes with statistically significant findings. Outcomes that were not graded are reported in the full report.

Results

Twenty-one studies[7-27] (19 randomized controlled trials [RCTs], 2 observational studies) are included in this review (Table B). RCTs enrolled patients 65 years of age and older and mostly studied moderate severity MDD and treatment of the acute phase of MDD (<12 weeks). RCTs consistently required patients to be free from uncontrolled medical comorbidities or other neuropsychological conditions and relied on spontaneous reporting of adverse events. Doses of antidepressants were low relative to suggested usual doses in older adults.[28,29] Risk of bias of individual studies varied (13 studies, low; 7 studies, high; 1 study, unclear). High risk of bias was attributed to high overall or differential attrition, open-label periods in which patients were withdrawn due to adverse events prior to randomization, or exclusion of patients from continuation or maintenance phases due to adverse events during acute treatment. Evidence was overall scarce and conclusions for a given comparison and outcome are often based on a single study. None of the RCTs were powered or designed to capture adverse events and SOE was most frequently downgraded due to imprecision and suspected selective outcome reporting.

Table B. Distribution of included trials by intervention, comparator, and reported outcomes

Intervention/ Comparator	Number of Studies	Outcomes Reported
SSRI vs. placebo/no antidepressant	7 RCTs[8,10-15] 1 OBS[26]	Any AE, bleed-UGI, blood pressure, cognitive function, falls, fracture, mortality, seizures, serious AEs, hyponatremia, suicide/ attempt, weight, withdrawal due to AE
SSRI vs. TCA	3 RCTs[16-18]	Any AE, cognitive impairment, hospitalization, mortality, serious AE, withdrawal due to AE
SSRI vs. SSRI	4 RCTs[7-9,21] 1 OBS[27]	Any AE, blood pressure, cognitive function, hospitalization, mortality, serious AE, suicide/attempt, withdrawal due to AE
SNRI vs. placebo/no antidepressant	4 RCTs[10,19,24,25] 1 OBS[26]	Any AE, bleed-UGI, blood pressure, cognitive function, ECG- arrhythmia, ECG-QTc, falls, fractures, mortality, serious ADEAE, seizures, sodium/hyponatremia, suicidal thoughts, suicide/ attempt, weight, withdrawal due to AE
SNRI vs. SSRI	2 RCTs[10,20]	Any AE, blood pressure, falls, fractures, mortality, serious AE, weight, withdrawal due to AE
Bupropion vs. placebo	1 RCT[23]	Any AE, blood pressure, ECG-arrhythmia, mortality, seizures, serious AE, suicidal thoughts, withdrawal due to AE
Mirtazapine vs. no antidepressant	1 OBS[26]	Any AE, bleed-UGI, falls, fractures, mortality, seizures, hyponatremia, suicide attempt
Mirtazapine vs. SSRI	1 RCT[22]	Any AE, blood pressure, hospitalization, serious AE, weight, withdrawal due to AE
Trazodone vs. no antidepressant	1 OBS[26]	Any AE, bleed-UGI, falls, fractures, mortality, seizures, hyponatremia, suicide attempt
Vortioxetine vs. placebo	1 RCT[25]	Any AE, blood pressure, cognitive function, ECG-QTc, fractures, serious AE, sodium, suicidal thoughts, suicide/attempt, weight, withdrawal due to AE
Vortioxetine vs. SNRI	1 RCT[25]	Any AE, blood pressure, cognitive function, ECG-QTc, fractures, serious AE, sodium, suicidal thoughts, suicide/attempt, weight, withdrawal due to AE

Abbreviations: AE=adverse event; ECG=electrocardiogram; OBS=observational; RCT=randomized controlled trial; SNRI=selective norepinephrine reuptake inhibitor; SSRI= selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; UGI=upper gastrointestinal

Key Question (KQ) 1 aimed to evaluate the adverse events and comparative adverse events of antidepressants. Results for KQ 1 are presented in Tables C and D. Although we aimed to evaluate SSRIs and SNRIs on a class basis, data for few individual drugs within the classes were identified. Thus, within Tables C and D, the representative drugs that contributed to the listed result are identified. Only outcomes with a graded SOE appear in this summary and the remaining findings are presented in the full report. Blank cells in either table indicate that we found no evidence. SOE grading is noted with the following symbols: (+)=low SOE; (++)=moderate SOE; (+++)=high SOE. Outcomes graded with insufficient evidence are listed as such.

Adverse Effects of Antidepressants

Table C. Adverse events of antidepressants versus placebo or no therapy: summary statements based on findings and statistical significance[a]

Comparison/ Study design	Acute Phase (< 12 weeks) (SOE)	Continuation Phase (12 weeks to 48 weeks) (SOE)	Maintenance Phase (>48 weeks) (SOE)
SSRI vs. placebo (RCT)	**Adverse events** Similar with escitalopram, fluoxetine (++)[8,10] **Withdrawals due to adverse events** More with citalopram, escitalopram, fluoxetine (+), NNH 11 (8 to 20)[8,10,14] Insufficient evidence: mortality	**Adverse events** Fewer with escitalopram (+), NNT 5 (3 to 19)[12] Insufficient: withdrawals due to adverse events	Insufficient evidence: mortality, serious adverse events, withdrawals due to adverse events
SSRI vs. no anti-depressant use (OBS)	No data	No data	**Adverse events** Increased with SSRIs (+)[b,26] **Falls** Increased with SSRIs (+)[b,26] **Fractures** Increased with SSRIs (+)[b,26] **Mortality** Increased with SSRIs (+)[b,26]

Table C. Adverse events of antidepressants versus placebo or no therapy: summary statements based on findings and statistical significance[a] (continued)

Comparison/ Study design	Acute Phase (< 12 weeks) (SOE)	Continuation Phase (12 weeks to 48 weeks) (SOE)	Maintenance Phase (>48 weeks) (SOE)
SNRI vs. placebo (RCT)	**Adverse events** More with duloxetine and venlafaxine (+++), NNH 10 (7 to 34)[10,19,25] **Falls** Similar with duloxetine (+)[19,24] **QTc interval** Similar with duloxetine (++)[19] **Serious adverse events** Fewer with duloxetine (+), NNT 50 (25 to 1000)[19,25] **Withdrawals due to adverse events** More with duloxetine and venlafaxine (++), NNH 17 (-7 to 33)[10,19,25] Insufficient evidence : fractures, mortality	**Falls** More with duloxetine (++), NNH 10 (6 to 114)[c,24] **QTc interval** Similar with duloxetine (+++)[c,24] **Serious adverse events** Similar with duloxetine (++)[c,24] **Withdrawals due to adverse events** More with duloxetine (++), NNH 12 (7 to 33)[c,24] Insufficient evidence: arrhythmias, fractures, mortality	No data
SNRI vs. no anti-depressant use (OBS)	No data	No data	**Adverse events** Similar with venlafaxine (+)[b,26] **Falls** Increased with venlafaxine (+)[b,26] **Fractures** Increased with venlafaxine (+)[b,26] **Mortality** Increased with venlafaxine (+)[b,26]
Bupropion XR vs. placebo (RCT)	**Adverse events** Similar with bupropion XR (++)[23] **Serious adverse events** Similar with bupropion XR (+)[23] **Withdrawals due to adverse events** Similar with bupropion XR (+)[23] Insufficient evidence: arrhythmias, mortality	No data	No data

Table C. Adverse events of antidepressants versus placebo or no therapy: summary statements based on findings and statistical significance[a] (continued)

Comparison/ Study design	Acute Phase (< 12 weeks) (SOE)	Continuation Phase (12 weeks to 48 weeks) (SOE)	Maintenance Phase (>48 weeks) (SOE)
Mirtazapine vs. no anti-depressant (OBS)	No data	No data	**Adverse events** Similar with mirtazapine (+)[b,26] **Falls** Increased with mirtazapine (+)[b,26] **Fractures** Increased with mirtazapine (+)[b,26] **Mortality** Increased with mirtazapine (+)[b,26]
Trazadone vs. no anti-depressant (OBS)	No data	No data	**Adverse events** Similar with trazodone (+)[b,26] **Falls** Increased with trazodone (+)[b,26] **Fractures** Similar with trazodone (+)[b,26] **Mortality** Increased with trazodone (+)[b,26]
Vortioxetine vs. placebo (RCT)	**Adverse events** Similar with vortioxetine (+++)[25] **Serious adverse events** Similar with vortioxetine (++)[25] **Withdrawal due to adverse events** Similar with vortioxetine (+)[25] Insufficient: fractures	No data	No data

Abbreviations: NNH=number needed to harm; NNT=number needed to treat; OBS=observational; RCT=randomized controlled trial; SOE=strength of evidence; SNRI=serotonin norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitor; vs=versus; XR=extended release

[a] Conclusions based on statistical significance may miss small differences from insufficient studies

[b] 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

[c] Results reflect 24 weeks (12 acute plus 12 continuation weeks)

Comparative Adverse Effects of Antidepressants

Table D. Comparative adverse events of antidepressants versus each other: summary statements based on findings and statistical significance[a]

Comparison/ Study design	Acute Phase (< 12 weeks) (SOE)	Continuation Phase (12 weeks to 48 weeks) (SOE)	Maintenance Phase (>48 weeks) (SOE)
SSRI vs. SSRI (RCT)	**Adverse events** Similar with sertraline or escitalopram vs. fluoxetine (++)[8,16] **Withdrawal due to adverse events** Similar with paroxetine, sertraline or escitalopram vs. fluoxetine (+)[7,8,16] Insufficient evidence: mortality	No data	**Adverse events** Similar with paroxetine vs. fluoxetine (++)[9] **Serious adverse events** Similar with paroxetine vs. fluoxetine (++)9 Insufficient evidence: mortality
SSRI vs. SSRI (OBS)	No data	**Hospitalization** Similar with escitalopram vs. other SSRI or SNRI (+)[27]	No data
SNRI vs. SSRI (RCT)	**Adverse events** Similar with venlafaxine vs. fluoxetine (++)10 **Withdrawals due to adverse events** Similar with venlafaxine vs. fluoxetine (+)[10]	**Adverse events** Similar with venlafaxine vs. citalopram (++)[20] **Serious adverse events** Similar with venlafaxine vs. citalopram (++)[20] **Withdrawals due to adverse events** Similar with venlafaxine vs. citalopram (++)[20] Inconclusive: falls, fractures, mortality	No data
SSRI vs. TCA (RCT)	**Adverse events** Fewer with paroxetine and citalopram vs. amitriptyline (+), NNT 6 (4 to 11)[17,18] **Withdrawals due to adverse effects** Fewer with paroxetine, citalopram, and sertraline vs. amitriptyline and nortriptyline (+), NNT 13 (7 to 100)1[6-18] Inconclusive: cognitive impairment, hospitalization, mortality, serious adverse events	No data	No data

Table D. Comparative adverse events of antidepressants versus each other: summary statements based on findings and statistical significance[a] (continued)

Comparison/ Study design	Acute Phase (< 12 weeks) (SOE)	Continuation Phase (12 weeks to 48 weeks) (SOE)	Maintenance Phase (>48 weeks) (SOE)
Mirtazapine vs. paroxetine (RCT)	**Adverse events** Similar with mirtazapine (++)[22] **Serious adverse events** Similar with mirtazapine (+)[22] **Withdrawals due to adverse events** Fewer with mirtazapine (+), NNT 9 (5 to 72)[22] Inconclusive: hospitalization	Adverse events Similar with mirtazapine (+)[22]	No data
Vortioxetine vs. duloxetine (RCT)	**Adverse events** Fewer with vortioxetine (+++), NNT 6 (4 to 17)[25] **Serious adverse events** Similar with vortioxetine (++)[25] **Withdrawals due to adverse events** Similar with vortioxetine (++)[25] Inconclusive: fractures	No data	No data

Abbreviations: NNH=number needed to harm; NNT=number needed to treat; OBS=observational; RCT=randomized controlled trial; SOE=strength of evidence; SNRI=serotonin norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitor; vs=versus; XR=extended release

[a] Conclusions based on statistical significance may miss small differences from insufficient studies

Subgroups of Interest

KQ 2 aimed to address subgroups of interest (Figure A) and their impact on adverse events and comparative adverse events of antidepressants.

- Increasing age (≥75 years) was not associated with increased risk of withdrawals due to adverse events with escitalopram or duloxetine (low SOE) but was associated with greater incidence of serious adverse events (as defined by the study) with escitalopram (low SOE).[19,30]
- According to a single post-hoc analysis on a RCT, risk of falls on duloxetine may be associated with the presence of any cardiovascular or pulmonary disorder (low SOE).[31]

Discussion

Applicability of results. This review exclusively included studies that required an age of 65 years or older. The studies were consistent in excluding patients with uncontrolled/unstable comorbidities or other psychological conditions,

particularly patients with high suicide risk. None of the studies were specific to nursing facility residents. Unfortunately this limits applicability of results given that older adults commonly have multiple comorbidities and are subject to taking multiple medications. Major depression was mostly diagnosed using DSM criteria. Based on scores from the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Asberg Depression Scale (MADRS) for study eligibility, the population represents those with moderate severity depression. The doses of antidepressants studied were rarely reflective of the full range cited in guideless as the usual dose range for older adults, and were more often reflective of the lower half of that range. The data in this report does not reflect higher usual antidepressant doses.

The majority of trials evaluated treatment of the acute phase of MDD which is up to 12 weeks. Although we aimed to evaluate some therapies on a class basis (SSRI and SNRI), we did not find evidence for multiple drugs within any class, limiting the ability to extrapolate results to the entire class. Concurrent pharmacologic therapies allowed, when described, were usually as-needed therapies for sleep. Importantly, consistent with inclusion criteria, studies focused on the outpatient setting and did not include hospitalized inpatient or urgent care scenarios.

Limitations of the evidence base. Several limitations pertain to the literature base of this review. Interpretations of findings were made based on statistical significance, which may miss small differences due to inadequate power. Readers should not assume a failure to find a difference means that the given interventions are similar in adverse event profiles, particularly when SOE ratings are low or for outcomes that do not have a SOE grade. None of the trials were powered to evaluate harms as they were all designed to assess efficacy. Many adverse events were not observed or reported rarely, such that there were only one or two events in the intervention arm and zero in the comparator arm. For several other adverse events, data were not reported in the peer reviewed literature at all. The issue of sparse data throughout the evidence base was further complicated by the treatment phases that studies used, as most were specific to treating the acute phase of MDD (<12 weeks), but others evaluated only the continuation (12 weeks up to 48 weeks) or maintenance (beyond 48 weeks) phases of treatment. Data beyond the acute treatment phase were very limited. Furthermore, when studies did evaluate continuation or maintenance, they were considered to have higher risk of bias because open-label acute treatment periods were used and subjects experiencing adverse events were withdrawn prior to randomization into the longer treatment period. Thus, events were less likely to occur during the randomized period.

We found no evidence for several of the specific medications and neither did evidence exist for some of the adverse events we aimed to analyze. Most data were available in comparison with placebo and little direct comparative data were found to inform comparative harms of antidepressants. Even when studies were eligible for this review, the small number of trials and smaller samples sizes posed limitations.

Most RCTs relied on spontaneous reporting of adverse events rather than active surveillance. Determining if adverse outcomes were defined or pre-specified was difficult. Commonly we suspected selective outcome reporting because studies stated that certain measurements were part of the routine clinical monitoring protocol (e.g. vitals, electrocardiogram were to be measured) although were not subsequently reported in the results. We attempted to contact authors for this information but the yield was small. Lastly, few data exist regarding subgroups that are of interest in this field and although we sought to collect and analyze such data when possible, we found only data regarding the impact of age and comorbidities.

Evidence gaps and future research needs. Important research gaps must be addressed to understand more fully the harms associated with antidepressant therapy in elderly patients with MDD. We found no evidence to assess harms for several therapies of interest including fluvoxamine,

desvenlafaxine, milnacipran, levomilnacipran or vilazodone. Even within the classes of SSRIs and SNRIs, evidence for an outcome was often specific to one or two drugs within the class because others have not been studied in this age group. There were important outcomes (e.g. emergency room visits, hospitalizations) and subgroups (e.g. comorbidities, polypharmacy) that were not reported in the eligible studies despite their being important to clinicians and decision makers as identified by the key informants, technical expert panelists and partners on this project. Future studies should include these outcomes and subgroups as well as other specific populations such as nursing facility residents. Overall, additional research is needed to characterize important harms associated with therapies used to treat MDD in older patients, particularly well controlled studies powered to assess adverse events.

Conclusions

In patients 65 years of age or older with MDD, treatment of the acute phase of MDD with SNRIs (duloxetine and venlafaxine) led to a greater number of adverse events compared with placebo while adverse events were statistically similar to placebo with SSRIs (escitalopram, fluoxetine). SSRIs (citalopram, escitalopram and fluoxetine) and SNRIs (duloxetine and venlafaxine) led to a greater number of study withdrawals due to adverse events compared with placebo, and duloxetine increased the risk of falls. Further characterization of the comparative safety of antidepressants is difficult because few studies were identified, comparisons were based on statistical significance, trials were not powered to identify small difference in adverse events and observational studies may be confounded. Comparative, long-term, well-designed studies that report specific adverse events are needed to better inform decision making in this population.

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Full Report

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