Adverse Effects of Pharmacological Treatments of Major Depression in Older Adults
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Key Messages

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.
This report is based on research conducted by the University of Connecticut Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00012-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

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If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Adverse Effects of Pharmacologic Treatments of Major Depression in Older Adults

Structured Abstract

Objective. To assess selected adverse events of antidepressants in the treatment of major depressive disorder (MDD) in adults 65 years old or older. Antidepressants included in this review, as determined by expert opinion, are selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, trazodone, vilazodone, and vortioxetine.

Data sources. MEDLINE®, Embase®, Cochrane Central, and PsycINFO® 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.

Review methods. Two investigators screened abstracts and subsequently reviewed full-text files. We abstracted data, performed meta-analyses when appropriate, assessed the risk of bias of each individual study, and graded the strength of evidence (SOE) for each comparison and selected outcomes. Number needed to harm (NNH) is reported for graded outcomes with statistically significant findings.

Results. Nineteen randomized controlled trials (RCTs) and two observational studies reported in 41 articles were included. Studies mostly evaluated treatment of the acute phase (<12 weeks) of MDD that was of moderate severity in patients 65 years and older, required subjects to be free from uncontrolled medical comorbidities or psychological conditions, and relied on spontaneous reporting of adverse events. Evidence was scarce and conclusions (based on statistical significance) for a given comparison and outcome are based often on a single study, particularly for specific adverse events. None of the RCTs were powered or designed to capture adverse events and most RCTs studied low doses of antidepressants. Observational data were limited by residual confounding.

SSRIs (escitalopram and fluoxetine, moderate SOE), vortioxetine (high SOE), and bupropion extended release (moderate SOE) had a statistically similar frequency of adverse events compared with placebo, whereas SNRIs (duloxetine and venlafaxine) were found to cause a greater number of adverse events (high SOE, NNH 10) compared with placebo during treatment of the acute phase of MDD. Both SSRIs (citalopram, escitalopram, and fluoxetine) and SNRIs caused a greater number of withdrawals due to adverse events than placebo (SSRIs, low SOE, NNH 11; SNRIs, moderate SOE, NNH 17). Duloxetine led to a greater number of falls compared with placebo (moderate SOE, NNH 10) over 24 weeks of treatment. A single observational study provided evidence on long-term use of antidepressants (low SOE) and suggested increased risk of adverse events (SSRIs), falls (SSRIs, SNRI venlafaxine, mirtazapine, trazadone), fractures (SSRIs, SNRI venlafaxine, mirtazapine), and mortality (SSRIs, SNRI venlafaxine, mirtazapine, trazadone) compared to no antidepressant.
Evidence for the comparative harms of different antidepressants was limited to single RCTs, mostly studying treatment of the acute phase of MDD (≤12 weeks). Comparing SSRIs to each other or SSRIs to SNRIs showed statistically similar rates of adverse events (moderate SOE). SSRIs (paroxetine, citalopram, sertraline) had fewer withdrawals due to adverse events than tricyclic antidepressants (amitriptyline or nortriptyline) (low SOE, number needed to treat [NNT] 13), as did mirtazapine compared with paroxetine (low SOE, NNT 9). Vortioxetine had fewer adverse events than with duloxetine (high SOE, NNT 6).

Increasing age was associated with greater incidence of serious adverse events with escitalopram (low SOE). The increased risk of falls on duloxetine may be associated with the presence of cardiopulmonary conditions (low SOE).

**Conclusions.** In patients 65 years of age or older, 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), vortioxetine, and bupropion. SSRIs (citalopram, escitalopram, and fluoxetine) and SNRIs (duloxetine and venlafaxine) led to a greater number of study withdrawals due to adverse events than 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 differences 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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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 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).

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

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.

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>Paroxetine, sertraline, citalopram, escitalopram, fluoxetine, fluvoxamine</td>
</tr>
<tr>
<td>SNRI</td>
<td>Venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran</td>
</tr>
<tr>
<td>Other</td>
<td>Bupropion, mirtazapine, trazodone, vilazodone, vortioxetine</td>
</tr>
</tbody>
</table>

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. 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 (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. 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

<table>
<thead>
<tr>
<th>Intervention/Comparator</th>
<th>Number of Studies</th>
<th>Outcomes Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI vs. placebo/no antidepressant</td>
<td>7 RCTs^{8,10-15}</td>
<td>Any AE, bleed-UGI, blood pressure, cognitive function, falls, fracture, mortality, seizures, serious AEs, hyponatremia, suicide/attempt, weight, withdrawal due to AE</td>
</tr>
<tr>
<td></td>
<td>1 OBS^{26}</td>
<td></td>
</tr>
<tr>
<td>SSRI vs. TCA</td>
<td>3 RCTs^{16-18}</td>
<td>Any AE, cognitive impairment, hospitalization, mortality, serious AE, withdrawal due to AE</td>
</tr>
<tr>
<td>SSRI vs. SSRI</td>
<td>4 RCTs^{7,9,21}</td>
<td>Any AE, blood pressure, cognitive function, hospitalization, mortality, serious AE, suicide/attempt, withdrawal due to AE</td>
</tr>
<tr>
<td></td>
<td>1 OBS^{27}</td>
<td></td>
</tr>
<tr>
<td>SNRI vs. placebo/no antidepressant</td>
<td>4 RCTs^{10,19,24,25}</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>1 OBS^{26}</td>
<td></td>
</tr>
<tr>
<td>SNRI vs. SSRI</td>
<td>2 RCTs^{10,20}</td>
<td>Any AE, blood pressure, falls, fractures, mortality, serious AE, weight, withdrawal due to AE</td>
</tr>
<tr>
<td>Bupropion vs. placebo</td>
<td>1 RCT^{23}</td>
<td>Any AE, blood pressure, ECG-arrhythmia, mortality, seizures, serious AE, suicidal thoughts, withdrawal due to AE</td>
</tr>
<tr>
<td>Mirtazapine vs. no antidepressant</td>
<td>1 OBS^{26}</td>
<td>Any AE, bleed-UGI, falls, fractures, mortality, seizures, hyponatremia, suicide attempt</td>
</tr>
<tr>
<td>Mirtazapine vs. SSRI</td>
<td>1 RCT^{22}</td>
<td>Any AE, blood pressure, hospitalization, serious AE, weight, withdrawal due to AE</td>
</tr>
<tr>
<td>Trazodone vs. no antidepressant</td>
<td>1 OBS^{28}</td>
<td>Any AE, bleed-UGI, falls, fractures, mortality, seizures, hyponatremia, suicide attempt</td>
</tr>
<tr>
<td>Vortioxetine vs. placebo</td>
<td>1 RCT^{25}</td>
<td>Any AE, blood pressure, cognitive function, ECG-QTc, fractures, serious AE, sodium, suicidal thoughts, suicide/attempt, weight, withdrawal due to AE</td>
</tr>
<tr>
<td>Vortioxetine vs. SNRI</td>
<td>1 RCT^{25}</td>
<td>Any AE, blood pressure, cognitive function, ECG-QTc, fractures, serious AE, sodium, suicidal thoughts, suicide/attempt, weight, withdrawal due to AE</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Comparison/Study design</th>
<th>Acute Phase (&lt; 12 weeks) (SOE)</th>
<th>Continuation Phase (12 weeks to 48 weeks) (SOE)</th>
<th>Maintenance Phase (&gt;48 weeks) (SOE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI vs. placebo (RCT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>Similar with escitalopram, fluoxetine (+++), NNH 11 (8 to 20)\textsuperscript{8,10}</td>
<td>Fewer with escitalopram (+), NNT 5 (3 to 19)\textsuperscript{12}</td>
<td>Insufficient evidence: mortality, serious adverse events, withdrawals due to adverse events</td>
</tr>
<tr>
<td><strong>Withdrawals due to adverse events</strong></td>
<td>More with citalopram, escitalopram, fluoxetine (+), NNH 11 (8 to 20)\textsuperscript{8,10,14}</td>
<td>Insufficient: withdrawals due to adverse events</td>
<td></td>
</tr>
<tr>
<td><strong>Insufficient evidence:</strong> mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSRI vs. no anti-depressant use (OBS)</strong></td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>Increased with SSRIs (+), NNH 10 (7 to 34)\textsuperscript{16}</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Falls</strong></td>
<td>Increased with SSRIs (+), NNH 10 (6 to 114)\textsuperscript{c,24}</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fractures</strong></td>
<td>Increased with SSRIs (+), NNH 10 (6 to 114)\textsuperscript{c,24}</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Increased with SSRIs (+), NNH 10 (6 to 114)\textsuperscript{c,24}</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SNRI vs. placebo (RCT)</strong></td>
<td><strong>Adverse events</strong></td>
<td><strong>Falls</strong></td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td>More with duloxetine and venlafaxine (+++), NNH 10 (7 to 34)\textsuperscript{10,19,25}</td>
<td>Similar with duloxetine (+), NNH 10 (6 to 114)\textsuperscript{c,24}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Falls</strong></td>
<td>Similar with duloxetine (+), NNH 10 (6 to 114)\textsuperscript{c,24}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>QTc interval</strong></td>
<td>Similar with duloxetine (++)\textsuperscript{19}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Serious adverse events</strong></td>
<td>Fewer with duloxetine (+), NNT 50 (25 to 1000)\textsuperscript{19,25}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Withdrawals due to adverse events</strong></td>
<td>More with duloxetine and venlafaxine (++) , NNH 17 (-7 to 33)\textsuperscript{10,19,25}</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Insufficient evidence:</strong> fractures, mortality</td>
<td>Insufficient evidence: arrhythmias, fractures, mortality</td>
<td></td>
</tr>
<tr>
<td>Comparison/Study design</td>
<td>Acute Phase (&lt; 12 weeks) (SOE)</td>
<td>Continuation Phase (12 weeks to 48 weeks) (SOE)</td>
<td>Maintenance Phase (&gt;48 weeks) (SOE)</td>
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<tr>
<td>-------------------------</td>
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</tr>
<tr>
<td>SNRI vs. no anti-depressant use (OBS)</td>
<td>No data</td>
<td>No data</td>
<td>Adverse events Similar with venlafaxine (+)(b,26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Falls Increased with venlafaxine (+)(b,26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fractures Increased with venlafaxine (+)(b,26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mortality Increased with venlafaxine (+)(b,26)</td>
</tr>
<tr>
<td>Bupropion XR vs. placebo (RCT)</td>
<td><strong>Adverse events</strong> Similar with bupropion XR (++)(23)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td><strong>Serious adverse events</strong> Similar with bupropion XR (+)(23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Withdrawals due to adverse events</strong> Similar with bupropion XR (+)(23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insufficient evidence: arrhythmias, mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine vs. no anti-depressant (OBS)</td>
<td>No data</td>
<td>No data</td>
<td>Adverse events Similar with mirtazapine (+)(b,26)</td>
</tr>
<tr>
<td></td>
<td>Falls Increased with mirtazapine (+)(b,26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fractures Increased with mirtazapine (+)(b,26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortality Increased with mirtazapine (+)(b,26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazadone vs. no anti-depressant (OBS)</td>
<td>No data</td>
<td>No data</td>
<td>Adverse events Similar with trazodone (+)(b,26)</td>
</tr>
<tr>
<td></td>
<td>Falls Increased with trazodone (+)(b,26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fractures Similar with trazodone (+)(b,26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortality Increased with trazodone (+)(b,26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vortioxetine vs. placebo (RCT)</td>
<td><strong>Adverse events</strong> Similar with vortioxetine (+++)(25)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td><strong>Serious adverse events</strong> Similar with vortioxetine (++)(25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Withdrawal due to adverse events</strong> Similar with vortioxetine (+)(25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Insufficient:</strong> fractures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ES-5
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

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

a 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

b 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

<table>
<thead>
<tr>
<th>Comparison/Study design</th>
<th>Acute Phase (&lt; 12 weeks) (SOE)</th>
<th>Continuation Phase (12 weeks to 48 weeks) (SOE)</th>
<th>Maintenance Phase (&gt;48 weeks) (SOE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI vs. SSRI (RCT)</strong></td>
<td><strong>Adverse events</strong></td>
<td>Similar with sertraline or escitalopram vs. fluoxetine (++)&lt;sup&gt;8,16&lt;/sup&gt;</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td><strong>Withdrawal due to adverse events</strong></td>
<td>Similar with paroxetine, sertraline or escitalopram vs. fluoxetine (++)&lt;sup&gt;7,8,16&lt;/sup&gt;</td>
<td><strong>Serious adverse events</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insufficient evidence: mortality</td>
<td></td>
</tr>
<tr>
<td><strong>SSRI vs. SSRI (OBS)</strong></td>
<td>No data</td>
<td><strong>Hospitalization</strong></td>
<td>Similar with escitalopram vs. other SSRI or SNRI (++)&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>SNRI vs. SSRI (RCT)</strong></td>
<td><strong>Adverse events</strong></td>
<td>Similar with venlafaxine vs. fluoxetine (++)&lt;sup&gt;10&lt;/sup&gt;</td>
<td><strong>Serious adverse events</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Withdrawals due to adverse events</strong></td>
<td>Similar with venlafaxine vs. fluoxetine (++)&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inconclusive: falls, fractures, mortality</td>
<td></td>
</tr>
<tr>
<td><strong>SSRI vs. TCA (RCT)</strong></td>
<td><strong>Adverse events</strong></td>
<td>Fewer with paroxetine and citalopram vs. amitriptyline (+), NNT 6 (4 to 11)&lt;sup&gt;17,18&lt;/sup&gt;</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td><strong>Withdrawals due to adverse effects</strong></td>
<td>Fewer with paroxetine, citalopram, and sertraline vs. amitriptyline and nortriptyline (+), NNT 13 (7 to 100)&lt;sup&gt;16-18&lt;/sup&gt;</td>
<td>Inconclusive: cognitive impairment, hospitalization, mortality, serious adverse events</td>
</tr>
<tr>
<td>Comparison/Study design</td>
<td>Acute Phase (&lt; 12 weeks) (SOE)</td>
<td>Continuation Phase (12 weeks to 48 weeks) (SOE)</td>
<td>Maintenance Phase (&gt;48 weeks) (SOE)</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>-------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Mirtazapine vs. paroxetine (RCT)</td>
<td><strong>Adverse events</strong> Similar with mirtazapine (++)&lt;sup&gt;22&lt;/sup&gt;</td>
<td><strong>Adverse events</strong> Similar with mirtazapine (+)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td><strong>Serious adverse events</strong> Similar with mirtazapine (+)&lt;sup&gt;22&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Withdrawals due to adverse events</strong> Fewer with mirtazapine (+), NNT 9 (5 to 72)&lt;sup&gt;22&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inconclusive: hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vortioxetine vs. duloxetine (RCT)</td>
<td><strong>Adverse events</strong> Fewer with vortioxetine (+++), NNT 6 (4 to 17)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td><strong>Serious adverse events</strong> Similar with vortioxetine (++)&lt;sup&gt;25&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Withdrawals due to adverse events</strong> Similar with vortioxetine (++)&lt;sup&gt;25&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inconclusive: fractures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<sup>a</sup> 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).<sup>19,30</sup>
- 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).<sup>31</sup>

**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.

**References**


Introduction

Background

Depression is a common psychiatric disease in older adults. The prevalence of depression in adults 65 years of age and older is estimated to be 15–20 percent in the United States.1 The American Psychiatric Association (APA) published guidelines for major depressive disorder (MDD) in 20102 and the American College of Physicians (ACP) published their guidelines in 2016.3 Antidepressants are recommended as an initial treatment option. The guidelines cite similar efficacy within and between pharmacologic classes; thus the recommendation is to choose a medication based on adverse event profiles, patient preferences, dosing schedules, costs, and drug interactions. With all things considered, the guidelines suggest that selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), bupropion or mirtazapine are optimal initial treatment choices for the majority of patients.2 Although tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are recognized as pharmacologic classes that may be used to treat depression, these classes are not considered first-line due to safety concerns and drug properties (e.g., drug-drug interactions, complex dosing and dietary restrictions).

Specific to treating depression in older patients, the APA guidelines suggest treatment considerations follow those for younger patients,2 however they make several cautionary statements regarding side effect profiles for the primary pharmacologic treatments in older populations. Regimens should be adjusted for metabolic changes and potential drug interactions. SSRIs, SNRIs and other antidepressants are favored over TCAs and MAOIs due to orthostatic hypotension and cholinergic blockade. SSRIs are noted to increase the risk of syndrome of inappropriate antidiuretic hormone (SIADH) in older patients compared with other antidepressants.2

Effectiveness of Antidepressants

Initial treatment of MDD aims to acutely induce response and ultimately full symptomatic remission to baseline status. Acute treatment in the elderly is generally considered the first 12 weeks of treatment with antidepressants,4 with a modestly-sized body of evidence.5-13 When compared with placebo, commonly used antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine) improved response (≥50% improvement from baseline in Hamilton Depression Rating Scale (HAM-D) or Montgomery and Asberg Depression Rating Scale (MADRS)) and remission with a number needed to treat (NNT) of 13 for response and 20 for remission in a systematic review of 10 high quality RCTs (at least 60 years of age).11 The SSRIs as a class have been found to have significantly greater response rates than placebo with a NNT of 10, although in this analysis remission rates did not differ.7 Meta-regression analysis of SSRI trials (regardless of the comparator) in patients aged 60 and older showed that male sex, older age, and a longer mean duration of the MDD episode were predictive of lower response rates while Caucasian ethnicity, higher baseline severity, and being a first MDD episode were predictive of higher response rates.14 Evidence of antidepressant efficacy specifically in patients 65 years and older is more limited and suggests that SSRIs do not significantly impact MDD relapse or remission.12 Conversely, duloxetine,15,16 bupropion XR,16 and vortioxetine17 improved MDD response with duloxetine and vortioxetine also improving remission in this age group. This literature base is limited by low strength of evidence (SOE)
because of issues of imprecision, inconsistency and risk of bias; often high placebo response rates are observed.

Effectiveness of antidepressants in special populations is of particular interest in older adults. In a nursing facility population, two included trials showed no benefit of SSRIs versus placebo while another showed significant improvement in the Cornell Scale for Depression in Dementia favoring the SSRI sertraline over the SNRI venlafaxine. Benraad and colleagues examined how patient characteristics such as disability, medical comorbidities, frailty and cognitive function were addressed in 27 trials of antidepressants in older adults (defined as an age at least 60 years with a mean of at least 65 years). They found that, with the exception of cognitive function, all other geriatric characteristics were rarely, if at all, considered within the methods of drug treatment trials. A majority of the trials they identified excluded patients with baseline cognitive impairment, while three of the trials did not find a significant association between baseline cognitive function and depression outcomes.

**Comparative Effectiveness of Antidepressants**

Relatively few trials have directly compared the effectiveness of antidepressants in older adults with MDD. When compared with TCAs, the SSRIs paroxetine and citalopram have shown similar response and remission rates. A network meta-analysis suggests improved chances of partial response with duloxetine, but not venlafaxine, compared to the SSRIs citalopram and fluoxetine. While mirtazapine was found to have higher response and remission rates than the SSRI paroxetine, trials directly comparing various SSRIs to one another have been mixed. Taken together, the evidence (which often has a low rating due to inconsistency and risk of bias) suggests that SSRI effectiveness is likely a class effect and that some agents including duloxetine and mirtazapine potentially having superior effects in older adults.

Expert consensus suggests that in older patients who remit after a single lifetime episode of severe major depression, antidepressants should be continued for 1 year to prevent further relapse and recurrence. However, less evidence is available describing this period of continuation and maintenance treatment relative to the acute treatment phase. SSRIs reduce 12-month relapse and recurrence compared with placebo and are similarly efficacious as TCAs. While trials up to a year show efficacy of SSRIs versus placebo, benefits have not been sustained beyond 1 year. Similarly, continuing duloxetine for an additional 12-week continuation period did not impact relapse and recurrence rates versus placebo. Taken together, while some antidepressants maintain their efficacy after a 12 week acute period, these benefits are generally lost over time.

**Impetus for the Systematic Review**

The American Geriatric Society (AGS) regularly compiles the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. This source identifies potentially inappropriate medications that are best avoided by those with specific conditions, or used with caution, at lower doses, or with careful monitoring. In 2015, this list recommended that clinicians avoid prescribing SSRIs and TCAs in older adults with a history of falls or fractures. However 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. The AGS suggests that SNRIs and bupropion are alternatives to TCAs and SSRIs. However, the AGS also recommended using SSRIs and SNRIs with caution due to the potential to exacerbate or cause SIADH or hyponatremia.
Given these concerns of potential adverse events in the older population with drugs commonly recommended to treat MDD, clinicians may be left selecting therapy based on comparative adverse effects. This review sought to systematically review the comparative adverse effects of pharmacologic antidepressants for treatment in MDD older adults.

**Key Questions**

Key Question (KQ) 1. In older adults with major depressive disorder, what are the adverse effects and comparative adverse effects of pharmacologic treatments?

KQ 2. In subgroups of older adults (e.g., by age, sex, race, comorbidities) with major depressive disorder, what are the adverse effects and comparative adverse effects of pharmacologic treatments?

**Population, Intervention, Comparator, Outcomes, Timing, Setting**

For this systematic review, the following PICOTS criteria apply:

**Population(s):**

The population of interest is “older adults,” defined as 65 years of age and older, with MDD. This age is consistent with the cutpoint used by the AGS in the Beers Criteria, the qualifying age for Medicare benefits, and input of the Key Informant (KI) panel.

This review is focused on MDD. While identification of patients with MDD through Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or International Classification of Disease (ICD) codes would be most rigorous, we anticipated identification of “depression” in observational studies using a variety of validated tools and also patient self-report. Although these latter strategies are less rigorous, we considered them for inclusion and described these details in the evidence tables.

We excluded studies that focused enrollment solely on one of the given patient populations: 1) patients with MDD and comorbid seizures; 2) patients with MDD and comorbid psychiatric conditions with the exception of anxiety; 3) patients with a specific subtype of MDD (e.g., catatonic, melancholic, psychotic, or atypical features) rather than MDD generally; or 4) patients with bipolar depression.

The subgroups of interest were those that may inform further stratification of older adults’ risk for the adverse effects of interest. Subgroups included:

- Age group (65 to 74y, 75 to 84y, and ≥85y)
- Sex
- Race or ethnicity
- Risk of falls or history of fracture
• Dementia or cognitive impairment
• Nursing facility setting
• ≥2 physical (i.e. nonpsychiatric) comorbidities
• History of substance abuse
• Frailty
• Early versus late onset MDD
• Polypharmacy, defined as 5 or more concurrent prescription medications
• Concurrent use of one other medication with central nervous system activity, defined as antipsychotics, benzodiazepines, nonbenzodiazepine hypnotics, and opioids

Interventions:
We were interested in pharmacologic antidepressant treatments of MDD, as single interventions, categorized according to their mechanism of action. The drugs selected for inclusion are therapies that were considered most likely to be used in this population, according to the expert opinion of the partner, KIs, Technical Expert Panel and public comments received at the protocol development stage. Interventions listed as an SSRI or SNRI were evaluated on a class-basis. Interventions that are listed as “other” have a unique mechanism and were evaluated individually, not as a class.

Table 1. Included pharmacologic treatments for major depressive disorder in older adults

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>Paroxetine, sertraline, citalopram, escitalopram, fluoxetine, fluvoxamine</td>
</tr>
<tr>
<td>SNRI</td>
<td>Venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran</td>
</tr>
<tr>
<td>Other</td>
<td>Bupropion, mirtazapine, trazodone, vilazodone, vortioxetine</td>
</tr>
</tbody>
</table>

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

We excluded studies that evaluated nonpharmacologic interventions, complementary alternative medicines, pharmacologic therapies not listed in Table 1 or any combinations of therapies (pharmacologic or nonpharmacologic) for MDD treatment.

Comparators:
We were interested in direct comparisons of eligible interventions (Table 1) with a pharmacologic antidepressant for MDD (as listed in Table 1 or a TCA or MAOI) evaluated as a single intervention or in comparison with placebo or a nonpharmacologic therapy. Nonpharmacologic therapies of interest included psychotherapy-based interventions such as cognitive behavioral therapy, interpersonal psychotherapy, problem solving therapy, psychodynamic or supportive therapy, behavioral therapies, journaling as well as exercise. We included data for within class comparisons of SSRIs and SNRIs. We excluded complementary and alternative medicine or combination therapies.

Outcomes:
We were interested in the following adverse effects for KQ1 and KQ2:
• Any adverse event, as in the number of participants who experienced an adverse event during the study
• Bleeding (any reported bleeding or bruising)
• Blood pressure
  o Changes in blood pressure
  o Orthostatic blood pressure
• Cognitive measures
  o Cognitive function
  o Cognitive impairment
• Electrocardiogram related
  o Arrhythmias
  o QTc prolongation
• Emergency room visit
• Falls
• Fractures
• Hospitalizations
• Mortality
• Seizures
• Serious adverse events, as defined per the study
• Suicide/suicide attempt
• Suicidal thoughts
• SIADH or hyponatremia (as defined per study)
• Weight changes
• Withdrawal due to adverse events, as in the number of participants who were withdrawn from the study and withdrawal was attributed to an adverse event

**Timing:**
We had no limitations on study duration or length of follow-up. We considered study length for subgroup analysis if necessary.

**Settings:**
We were interested in non-acute care settings such as specialist or generalist outpatient setting, rehabilitation facility and nursing facilities. Inpatient or urgent care settings were excluded.
Methods

Initially a panel of Key Informants gave input on the Key Questions (KQs) to be examined; these KQs were posted on Agency for Healthcare Research and Quality’s Effective Health Care (EHC) website for public comment in September 2017 for 3 weeks. Members of the Beers Criteria Panel and the American Geriatrics Society membership were asked for input. We revised the KQs based on comments. We then drafted a protocol for the systematic review and recruited a panel of technical experts to provide high-level content and methodological expertise throughout the development of the review. The finalized protocol is posted on the EHC website at https://effectivehealthcare.ahrq.gov/topics/depression-harms/research-protocol. The PROSPERO registration is CRD42018088648.

We developed an a priori analytic framework to guide the systematic review process (Figure 1). The details of the analytic framework were determined in consultation with the partner, key informants, technical expert panelists and public comment. We identified relevant literature for KQ1 and KQ2 by searching Ovid MEDLINE, Ovid MEDLINE In-Process & Other Nonindexed Citations, EMBASE via Ovid, Cochrane Central Register of Controlled Trials and PsycINFO via OVID from earliest date through May 15, 2018 using subject headings and natural language terms reflecting major depression, older age and the interventions of interest (Appendix A). We supplemented the bibliographic database searches with backwards citation tracking of relevant publications. We searched the clinicaltrials.gov website and the World Health Organization International Controlled Trials Registry Platform (ICTRP) for ongoing studies and those completed with reported results.

Figure 1. 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

We managed citations using DistillerSR®. We screened titles and abstracts using two independent reviewers to determine if the citation met inclusion/exclusion criteria (Error! Reference source not found.). When both reviewers agreed that a citations met inclusion criteria, we reviewed the full text for inclusion into the review. A third reviewer resolved disagreements.
<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Older adults age ≥65(^a) years of all races and ethnicities with MDD. MDD will be determined as reported by the study, either with use of DSM, ICD codes, validated tools or patient self-report.</td>
<td>Patients &lt;65 years old; studies that focus enrollment on 1) patients with a subtype of MDD rather than general MDD; 2) bipolar disorder; 3) comorbid seizure disorder; 4) comorbid psychiatric conditions with exception of anxiety</td>
</tr>
<tr>
<td>Intervention</td>
<td>SSRI, SNRI, bupropion, mirtazapine, trazodone, vilazodone or vortioxetine (Error! Reference source not found.) as a single intervention</td>
<td>Other pharmacologic therapies, nonpharmacologic therapies, complementary alternative medicines, or combinations of therapies</td>
</tr>
<tr>
<td>Comparator</td>
<td>A pharmacologic antidepressant for MDD (Error! Reference source not found., or TCA or MAOI), as a single intervention, including within class comparisons of SSRIs and SNRIs; placebo; nonpharmacologic interventions as specified in PICOTS</td>
<td>Other pharmacologic therapies, invasive nonpharmacologic interventions, complementary alternative medicines, combinations of therapies</td>
</tr>
<tr>
<td>Outcomes</td>
<td>As defined in the PICOTS criteria</td>
<td>Studies without at least one outcome listed in the PICOTS</td>
</tr>
<tr>
<td>Timing</td>
<td>All study durations and follow-up lengths will be included</td>
<td>None</td>
</tr>
<tr>
<td>Setting</td>
<td>Non-acute care setting (i.e. specialist or generalist outpatient setting, rehabilitation or nursing facility)</td>
<td>Hospital or urgent care setting</td>
</tr>
<tr>
<td>Study Design</td>
<td>RCTs, nonrandomized controlled trials, prospective or retrospective controlled cohort studies, case-controlled studies</td>
<td>Case series, case reports, studies without an active comparator or non-active control group</td>
</tr>
<tr>
<td>Publication</td>
<td>No limits on publication date or language(^b)</td>
<td>Abstracts without published study manuscripts; non-English publications that do not have an English language abstract.</td>
</tr>
<tr>
<td>Language and Dates</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DSM=Diagnostic and Statistical Manual of Mental Disorders; ICD=International Classification of Diseases; MAOI=monoamine oxidase inhibitor; MDD=major depressive disorder; PICOTS=population, intervention, comparator, outcomes, timing, setting; RCT=randomized controlled trial; SNRI=selective norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

\(^a\)To be included, studies were required to use an inclusion criterion based on age, such that the enrolled patients were 65 years of age and older. A study that used an age threshold lower than 65 years would be excluded.

\(^b\)English language abstracts of non-English language articles will be reviewed at the abstract stage consistent with the process described by the Methods Guide.\(^32\)

We contacted corresponding authors when needed for clarification related to inclusion criteria and to solicit data for outcomes that were reported in the methods of the paper but not reported as a numerical result. All authors were given a minimum of 10 days to acknowledge queries. We matched results posted in clinical trial registries, abstracts and meeting presentations to their corresponding full text publication, which was always used as the primary data source, and reviewed for supplemental data. We considered post-hoc and subgroup analyses of included studies when they provide data on the outcomes of interest.

One investigator extracted data into standardized collection forms and evidence and outcomes tables and a second investigator verified the data. Two independent reviewers assessed risk of bias using the Cochrane Collaboration’s Risk of Bias Tool\(^33\) for randomized controlled trials (RCTs) and Newcastle Ottawa Scale\(^34\) for observational studies. We classified overall risk of bias for each study as low, moderate or high, according to the collective risk of bias per evaluated domain and the investigator’s confidence in the study results given the identified limitations.\(^32\) Risk of bias was considered unclear if the majority of domains evaluated were unclear.
We assessed clinical and methodologic heterogeneity to determine appropriateness of meta-analysis. We based data synthesis on pharmacologic class (e.g., selective-serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRI)) while drugs listed in the “other category” (Error! Reference source not found.) were each analyzed individually. We also considered the treatment phase (acute, continuation, maintenance) when synthesizing data. In older adults, the acute treatment phase is generally considered up to 12 weeks of therapy, followed by the continuation and maintenance treatment phases for which the durations were less clear in this population. Thus, studies that distinguished between continuation (>12 weeks up to 48 weeks) and maintenance phases (48 weeks or longer) were treated accordingly.

When there were two or more trials of similar pharmacologic comparisons and outcomes, we performed random effects meta-analysis utilizing inverse-variance weighting. Between-study variance was estimated using the Paule-Mandel estimator. Relative risks (RR) with corresponding 95 percent confidence intervals (CI) were estimated for binary outcomes and mean differences (MD) with corresponding 95 percent CI were estimated for continuous outcomes. Peto’s Odds ratio (OR) and 95 percent CI were estimated for binary outcomes with rare events (<5 percent) in place of a RR. For outcomes with zero events in one study arm continuity correction was used, except when a Peto’s OR was calculated which does not utilize continuity correction. For trials in which differences between groups were not reported for continuous outcomes, we calculated it from differences at baseline and at the end of follow-up using a correlation coefficient of 0.5. For single trials reporting binary outcomes, we calculated RR and 95 percent CI where applicable. If zero events occurred in an arm of a study, we calculated the risk difference (RD) and 95 percent confidence interval which avoids need for continuity correction. Statistical significance was set at a two sided alpha of 0.05. All analyses were performed using the ‘meta’ package (version 4.9-0) in R (version 3.4.3; the R Project for Statistical Computing).

When quantitative pooling of studies was possible, we assessed presence of statistical heterogeneity using the Cochrane p-value (p<0.10 significant) and the I² statistic which represents the percentage (0-100 percent) of variability in the treatment estimate that is attributable to heterogeneity. Tests for funnel plot asymmetry were planned when 10 or more studies reported a given outcome, although this never occurred.

We calculated number needed to treat (NNT) or number needed to harm (NNH) for outcomes that were graded for strength of evidence (SOE), had data reported in order to calculate absolute risk, and were found to have statistically significant difference.

Prior to analysis, we consulted our key informants, technical expert panelists and partner to determine subgroups of interest. This included age group, sex, race, ethnicity, risk of falls or history of fracture, dementia or cognitive impairment, nursing facility setting, ≥2 physical (i.e. nonpsychiatric) comorbidities, history of substance abuse, frailty, early versus late onset major depressive disorder (MDD), polypharmacy (defined as 5 or more concurrent prescription medications), concurrent use of one other medication with central nervous system activity, defined as antipsychotics, benzodiazepines, nonbenzodiazepine hypnotics, and opioids. We performed subgroup analysis when two or more trials per subgroup were available for a given outcome. Included studies that were not amenable to pooling were qualitatively summarized.

The decision of which outcomes to grade was aided by ranking of outcome importance by the Technical Expert Panel (TEP) followed by discussion of the ranking results between the TEP, partner and Evidence-based Practice Center (EPC). Two independent senior investigators graded the SOE for the effect estimates calculated for the following selected outcomes: any
adverse event, withdrawal due to adverse event, mortality, hospitalization, serious adverse events, arrhythmias, QTc prolongation, falls, fractures, cognitive impairment and syndrome of inappropriate antidiuretic hormone. The investigators discussed their assessments to arrive at a final SOE grade using established guidance. We evaluated SOE separately for RCT and observational studies. Five required domains included study risk of bias, consistency, directness, precision and publication bias. RCT data began with a grade of high and could be downgraded based on the assessment of the 5 domains. Observational data began with a grade of low and could be upgraded based on assessment of the 5 domains. We did not further contextualize the calculated effect estimates, rather interpretation was based on statistical significance. The SOE was assessed for the effect estimate generated for each comparison and outcome combination as of the following four grades:

- **High:** We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- **Moderate:** We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe the findings are likely to be stable, but some doubt remains.
- **Low:** We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- **Insufficient:** We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of the effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

We assessed applicability of studies using the population, intervention, comparator, outcomes, timing, setting (PICOTS) framework. Characteristics that may have influenced applicability included but are not limited to depression severity, age of onset, other inclusion/exclusion criteria, treatment period (acute vs. longer term), specific antidepressant, outcome definitions and surveillance techniques.

The contextual question (CQ) is not based on a systematic review as the aim of the CQ is to provide a qualitative overview of the state of the evidence without formal systematic review or analytic plans. The findings of the citations pertinent to the PICOTS are presented in the introduction.

Experts in geriatric medicine and psychiatry fields and individuals representing stakeholder and user communities were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a disposition of comments report that will be made available three months after the Agency posts the final systematic review on the EHC website.
Results

Organization of the Report

We begin by presenting the results of our literature search and citation screening. We then present the results for each Key Question (KQ), further organized by intervention/comparator combinations beginning with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and then drugs categorized as “other”. Although we attempted to make comparisons based on pharmacologic class, data for few drugs within a given class were identified in the literature. This led to reporting results for the classes of SSRI and SNRI using distinct drug names that are represented in the reported outcome. We present data versus placebo followed by data versus other active comparators. The same outcomes were sought from all studies and are reported when data were available. We first present outcomes for which strength of evidence (SOE) was graded (under heading “main outcomes”), followed by additional findings from outcomes that were not graded (under heading “additional findings”).

The first overview table at the start of each results section provides a list of analyzed outcomes for which we graded SOE. When two or more trials reported a given outcome, the result listed is based on meta-analysis. In cases when only 1 study was available for a given outcome, the result is reported for that single study. The SOE is graded for the calculated effect estimates and their 95% confidence intervals (e.g. relative risk, mean difference etc.) with interpretation based on statistical significance. Domains that contributed to downgrading the SOE for a given effect estimate are provided in parenthesis, when applicable. Number needed to treat (NNT) or harm (NNH) are presented when we were able to calculate absolute risk, for outcomes that were graded for SOE and statistically significant difference were found. The second overview table presents findings from outcomes that were not graded for SOE.

Supporting tables and figures relevant to the results appear in Appendixes C-F, including study and population characteristics, study level outcomes data, study risk of bias assessments and details regarding the strength of evidence grading of each outcome.

Search Results

Our search identified 4,361 nonduplicate records, of which 654 required full-text review after title and abstract screening, and 39 met eligibility criteria for inclusion in this review (Figure 2). These 39 citations\textsuperscript{15-17,24,25,42-75} reported results from 19 unique randomized controlled trials (RCTs) (reported in 37 citations) and 2 observational studies (reported in two citations). The distribution of studies by intervention and comparator combinations is presented in Table 3. Citations excluded at the full text review stage are presented in Appendix B. As a result of searching trial registries, we found data posted for three included studies\textsuperscript{76-78} to supplement publications. In addition, we received additional outcomes data from authors of three included studies.\textsuperscript{17,46,50}
Figure 2. Literature flow for Key Questions 1 and 2

Abbreviations: MDD=major depressive disorder; RCT=randomized controlled trial

Table 3. Distribution of included trials by intervention, comparator, and reported outcomes

<table>
<thead>
<tr>
<th>Intervention/Comparator</th>
<th>Number of Studies</th>
<th>Outcomes Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI vs. placebo/no antidepressant</td>
<td>7 RCTs, 1 OBS</td>
<td>Any AE, bleed-UGI, blood pressure, cognitive function, falls, fracture, mortality, seizures, serious AEs, hyponatremia, suicide/attempt, weight, withdrawal due to AE</td>
</tr>
<tr>
<td>SSRI vs. TCA</td>
<td>3 RCTs</td>
<td>Any AE, cognitive impairment, hospitalization, mortality, serious AE, withdrawal due to AE</td>
</tr>
<tr>
<td>SSRI vs. SSRI</td>
<td>4 RCTs, 1 OBS</td>
<td>Any AE, blood pressure, cognitive function, hospitalization, mortality, serious AE, suicide/attempt, withdrawal due to AE</td>
</tr>
<tr>
<td>SNRI vs. placebo/no antidepressant</td>
<td>4 RCTs, 1 OBS</td>
<td>Any AE, bleed-UGI, blood pressure, cognitive function, ECG-arrhythmia, ECG-QTc, falls, fractures, mortality, serious AE, seizures, sodium/hyponatremia, suicidal thoughts, suicide/attempt, weight, withdrawal due to AE</td>
</tr>
<tr>
<td>SNRI vs. SSRI</td>
<td>2 RCTs</td>
<td>Any AE, blood pressure, falls, fractures, mortality, serious AE, weight, withdrawal due to AE</td>
</tr>
<tr>
<td>Bupropion vs. placebo</td>
<td>1 RCT</td>
<td>Any AE, blood pressure, ECG-arrhythmia, mortality, seizures, serious AE, suicidal thoughts, withdrawal due to AE</td>
</tr>
<tr>
<td>Mirtazapine vs. no antidepressant</td>
<td>1 OBS</td>
<td>Any AE, bleed-UGI, falls, fractures, mortality, seizures, hyponatremia, suicide attempt</td>
</tr>
<tr>
<td>Mirtazapine vs. SSRI</td>
<td>1 RCT</td>
<td>Any AE, blood pressure, hospitalization, serious AE, weight, withdrawal due to AE</td>
</tr>
<tr>
<td>Trazodone vs. no antidepressant</td>
<td>1 OBS</td>
<td>Any AE, bleed-UGI, falls, fractures, mortality, seizures, hyponatremia, suicide attempt</td>
</tr>
<tr>
<td>Vortioxetine vs. placebo</td>
<td>1 RCT</td>
<td>Any AE, blood pressure, cognitive function, ECG-QTc, fractures, serious AE, sodium, suicidal thoughts, suicide/attempt, weight, withdrawal due to AE</td>
</tr>
<tr>
<td>Vortioxetine vs. SNRI</td>
<td>1 RCT</td>
<td>Any AE, blood pressure, cognitive function, ECG-QTc, fractures, serious AE, sodium, suicidal thoughts, suicide/attempt, weight, withdrawal due to AE</td>
</tr>
</tbody>
</table>
Key Question (KQ) 1. In older adults with major depressive disorder, what are the adverse effects and comparative adverse effects of pharmacologic treatments?

Selective Serotonin Reuptake Inhibitors

Key Points

- SSRIs are associated with more withdrawals from adverse events compared with placebo but fewer compared with tricyclic antidepressants (TCAs), during treatment of the acute phase of MDD and based on meta-analysis of RCTs.
  - More withdrawals with citalopram, escitalopram and fluoxetine compared with placebo, low SOE, NNH 11 (8 to 20)
  - Fewer withdrawals with paroxetine, citalopram, or sertraline compared with amitriptyline or nortriptyline, low SOE, NNT 13 (7 to 100)
- SSRIs vary in association with adverse events, based on the comparator and the treatment duration.
  - Statistically similar rates of adverse events with escitalopram and fluoxetine compared with placebo during treatment of the acute phase of MDD, moderate SOE
  - Fewer adverse events with paroxetine and citalopram compared with amitriptyline during treatment of the acute phase of MDD, low SOE, NNT 6 (4 to 11)
- SSRIs are associated with an increased risk of all-cause mortality (low SOE), falls (low SOE) and fractures (low SOE) compared with not using an antidepressant based on a large cohort study over a longer treatment period (median 364 days), low SOE.

SSRIs Versus Placebo or No Treatment

Study Characteristics

Seven trials \(^{43,45-50}\) (n=1403) and 1 observational study \(n=60,746\)^{56} compared SSRI versus placebo (Table 4-5). Fragus et. al.\(^{50}\) investigated exclusively patients with stable heart failure and MDD that occurred after cardiac symptoms thus was not pooled with other trials. Findings from Fragus et. al.\(^{50}\) can be found in Appendix C, Table C-3.

The mean age across the seven trials ranged from 71 to 79.8 years. Three trials studied citalopram \(10-40\text{mg/day}\),\(^{48-50}\) two trials\(^{43,45}\) studied fluoxetine \(20-60\text{mg/day}\), two trials\(^{43,47}\) studied escitalopram \(10-20\text{mg/day}\), and one trial\(^{46}\) studied paroxetine \(10-40\text{mg/day}\). One of these trials\(^{43}\) was a three-arm trial comparing either escitalopram or fluoxetine to placebo. When this trial was the only source of data for an outcome, the effect estimate for escitalopram vs. placebo and fluoxetine vs. placebo were reported separately and not pooled. Four trials\(^{45,47-49}\) studied the acute treatment phase for 8 weeks. One trial\(^{47}\) studied continuation treatment for 24 weeks after an open-label 12 week acute treatment phase. Two trials\(^{46,48}\) studied maintenance treatment for 48 weeks\(^{48}\) and 2 years,\(^{46}\) after open-label 8 week acute and 16 week continuation phases. Risk of bias was low in three trials\(^{43,45,49}\) and high in four trials.\(^{46-48,50}\) Four trials\(^{45,47-49}\) reported industry sponsorship. Risk of bias was low in the observational study.\(^{56}\)
## Results

### Main Outcomes

Table 4. Summary of findings and strength of evidence for adverse effects with SSRI versus placebo or no antidepressant

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Quantity and Type of Evidence (n)</th>
<th>Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)a</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>Acute</td>
<td>2 RCTs$^{43,45}$ (713)</td>
<td>RR 1.07 (0.98 to 1.16) No difference with escitalopram and fluoxetine</td>
<td>Moderate (suspected selective reporting)</td>
</tr>
<tr>
<td></td>
<td>Continuation (24 weeks)</td>
<td>1 RCT$^{17}$ (221)</td>
<td>RR 0.69 (0.53 to 0.90) NNT 5 (3 to 19) Lower risk with escitalopram</td>
<td>Low (high ROB, suspected selective reporting)</td>
</tr>
<tr>
<td></td>
<td>Unspecified</td>
<td>1 OBS$^{55,56}$ (60,746)</td>
<td>HR 1.20 (1.02 to 1.42) Increased risk with SSRI</td>
<td>Low</td>
</tr>
<tr>
<td>Falls</td>
<td>Unspecified</td>
<td>1 OBS$^{55,56}$ (60,746)</td>
<td>HR 1.66 (1.58 to 1.73) Increased risk with SSRI</td>
<td>Low</td>
</tr>
<tr>
<td>Fractures</td>
<td>Unspecified</td>
<td>1 OBS$^{55,56}$ (60,746)</td>
<td>HR 1.58 (1.48 to 1.68) Increased risk with SSRI</td>
<td>Low</td>
</tr>
<tr>
<td>Mortality</td>
<td>Acute</td>
<td>1 RCT$^{43}$ (517)</td>
<td>Escitalopram: RD 0.00 (-0.046 to 0.027) Fluoxetine: RD -0.01 (-0.05 to 0.02) Insufficient</td>
<td>Insufficient (imprecise, suspected selective reporting, 2 events occurred)</td>
</tr>
<tr>
<td></td>
<td>Maintenance (48 weeks)</td>
<td>1 RCT$^{46}$ (121)</td>
<td>RD 0.02 (-0.05 to 0.09) Insufficient with citalopram</td>
<td>Insufficient (high ROB, imprecise, suspected selective reporting)</td>
</tr>
<tr>
<td></td>
<td>Unspecified</td>
<td>1 OBS$^{55,56}$ (60,746)</td>
<td>HR 1.54 (1.48 to 1.59) Increased risk with SSRI</td>
<td>Low</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Maintenance (48 weeks)</td>
<td>1 RCT$^{46}$ (122)</td>
<td>RR 2.20 (0.81 to 5.96) Insufficient with citalopram</td>
<td>Insufficient (high ROB, imprecise, suspected selective reporting)</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>Acute</td>
<td>3 RCTs$^{43,45,48}$ (887)</td>
<td>RR 2.90 (1.16 to 5.06) NNT 11 (8 to 20) Increased risk with SSRIs citalopram, escitalopram, fluoxetine</td>
<td>Low (imprecise, suspected selective reporting)</td>
</tr>
<tr>
<td></td>
<td>Continuation (24 weeks)</td>
<td>1 RCT$^{47}$ (305)</td>
<td>RR 0.58 (0.17 to 1.92) Insufficient with escitalopram</td>
<td>Insufficient (high ROB, imprecise, suspected selective reporting)</td>
</tr>
<tr>
<td></td>
<td>Maintenance (48 weeks to 2 years)</td>
<td>2 RCTs$^{46,48}$ (174)</td>
<td>RR 0.81 (0.31 to 2.11) Insufficient with citalopram and paroxetine</td>
<td>Insufficient (high ROB, imprecise, suspected selective reporting)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; n=patient sample size; NNH=number needed to harm; NNT=number needed to treat; OBS=observational; RCT=randomized controlled trial; RD=risk difference; ROB=risk of bias; RR=risk ratio

a Interpretation of effect estimate based on statistical significance. May overestimate estimates of no difference due to inadequate sample size and type II error.

b This cohort study allowed the use of any SSRI to be included in analysis. Further details as to which SSRIs were represented were not reported.

During treatment of the acute phase of MDD data from three RCTs found SSRIs (citalopram, escitalopram, fluoxetine) to significantly increase the risk of withdrawal due to adverse events
compared with placebo [RR 2.90 (1.16 to 5.06)] (Figure 3). The single trial\textsuperscript{43} that elaborated on the type of adverse event that led to withdrawal cited nausea, abdominal pain and anxiety to be most common in SSRI (fluoxetine, escitalopram) treated patients. Data were insufficient to make a conclusion for mortality. In the single trial\textsuperscript{43} comparing escitalopram and fluoxetine to placebo, one death (a suicide) occurred in the placebo (0.6 percent) and one death in the escitalopram (0.6 percent) arms.

**Figure 3. Risk of (A) any adverse event and (B) withdrawal due to adverse events with SSRIs compared with placebo**

<table>
<thead>
<tr>
<th></th>
<th>Source</th>
<th>SSRI Events</th>
<th>Placebo Events</th>
<th>RR [95%-CI]</th>
<th>Favors SSRI</th>
<th>Favors Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Phase</strong></td>
<td>Kasper, 2005a (43)</td>
<td>88</td>
<td>173</td>
<td>0.95 [0.75; 1.22]</td>
<td>20.2%</td>
<td></td>
<td>80.8%</td>
</tr>
<tr>
<td></td>
<td>Kasper, 2005b (43)</td>
<td>93</td>
<td>164</td>
<td>1.06 [0.84; 1.34]</td>
<td>20.8%</td>
<td></td>
<td>80.8%</td>
</tr>
<tr>
<td></td>
<td>Schattberg, 2006 (45)</td>
<td>94</td>
<td>109</td>
<td>1.19 [0.91; 1.58]</td>
<td>41.0%</td>
<td></td>
<td>59.0%</td>
</tr>
<tr>
<td></td>
<td>Random effects model</td>
<td>276</td>
<td>437</td>
<td>1.97 [0.98; 1.96]</td>
<td>100.0%</td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

|                      |                      |             |                |                 |             |                |        |
| **Continuation Phase**| Gorwood, 2007 (47)   | 53          | 130            | 0.99 [0.80; 1.20] | 100.0%      |                | 100.0% |
|                      | Random effects model | 63          | 130            | 0.99 [0.83; 1.00] | 100.0%      |                | 100.0% |

<table>
<thead>
<tr>
<th></th>
<th>Source</th>
<th>SSRI Events</th>
<th>Placebo Events</th>
<th>RR [95%-CI]</th>
<th>Favors SSRI</th>
<th>Favors Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Phase</strong></td>
<td>Kasper, 2005a (43)</td>
<td>9</td>
<td>84</td>
<td>1.00 [0.86; 1.14]</td>
<td>14.0%</td>
<td></td>
<td>86.0%</td>
</tr>
<tr>
<td></td>
<td>Kasper, 2005b (43)</td>
<td>17</td>
<td>173</td>
<td>0.95 [0.80; 1.12]</td>
<td>24.3%</td>
<td></td>
<td>75.7%</td>
</tr>
<tr>
<td></td>
<td>Schattberg, 2006 (45)</td>
<td>20</td>
<td>164</td>
<td>0.97 [0.79; 1.2]</td>
<td>24.0%</td>
<td></td>
<td>76.0%</td>
</tr>
<tr>
<td></td>
<td>Schattberg, 2006 (45)</td>
<td>19</td>
<td>100</td>
<td>0.98 [0.80; 1.21]</td>
<td>37.1%</td>
<td></td>
<td>62.9%</td>
</tr>
<tr>
<td></td>
<td>Random effects model</td>
<td>65</td>
<td>521</td>
<td>2.90 [1.67; 5.06]</td>
<td>100.0%</td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

|                      |                      |             |                |                 |             |                |        |
| **Continuation Phase**| Gorwood, 2007 (47)   | 4           | 152            | 0.86 [0.67; 1.13] | 100.0%      |                | 100.0% |
|                      | Random effects model | 4           | 152            | 0.86 [0.67; 1.13] | 100.0%      |                | 100.0% |

<table>
<thead>
<tr>
<th></th>
<th>Source</th>
<th>SSRI Events</th>
<th>Placebo Events</th>
<th>RR [95%-CI]</th>
<th>Favors SSRI</th>
<th>Favors Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maintenance Phase</strong></td>
<td>Kryner, 2002 (46)</td>
<td>6</td>
<td>60</td>
<td>0.70 [0.28; 2.07]</td>
<td>81.4%</td>
<td></td>
<td>18.6%</td>
</tr>
<tr>
<td></td>
<td>Reynolds II, 2006 (46)</td>
<td>1</td>
<td>35</td>
<td>0.90 [0.67; 1.25]</td>
<td>10.0%</td>
<td></td>
<td>90.0%</td>
</tr>
<tr>
<td></td>
<td>Random effects model</td>
<td>7</td>
<td>95</td>
<td>0.81 [0.36; 2.01]</td>
<td>100.0%</td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; RR=relative risk; SSRI=selective serotonin reuptake inhibitor

In the single trial\textsuperscript{47} that studied continuation of escitalopram for 24 weeks after a 12 week open-label acute treatment phase, the risk of any adverse event was significantly lower with escitalopram versus placebo [RR 0.69 (0.53 to 0.90), low SOE]. Evidence was insufficient to conclude effects on the risk of withdrawal due to adverse events; notably 18 percent of subjects were withdrawn during the open-label period, of those the majority were due to adverse events (46 of 72 subjects, 64 percent), and did not continue to the continuation phase.

Two trials\textsuperscript{46,48} studied maintenance treatment with either citalopram or paroxetine after a total of 24 weeks of open-label treatment that constituted the acute and continuation phases. In both trials, patients experiencing adverse events during open-label periods were withdrawn from the study (ranging from 3.3 to 15% of subjects) and were not randomized into maintenance treatment arms. Data were insufficient to make a conclusion for mortality, serious adverse events
and withdrawal due to adverse events. In the single trial\textsuperscript{46} studying paroxetine and reporting suicide, no events occurred. In the single trial\textsuperscript{48} studying citalopram and reporting mortality, one death occurred in the control arm (1.6 percent). A large, \([n=60,746; 305,188 \text{ person-years of follow-up with a mean of 5.0 (3.3) years per patient}]\) retrospective population-based cohort study\textsuperscript{56} compared SSRIs as a class with not using an antidepressant. Taking an SSRI increased the adjusted hazard ratio (HR) for all-cause mortality [HR 1.54 (1.48 to 1.59)], falls [HR 1.66 (1.58 to 1.73)], and fractures [HR 1.58 (1.48 to 1.68)].

### Additional Findings

Table 5. Additional findings for adverse effects with SSRIs versus placebo or no antidepressant

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Quantity and Type of Evidence (n)</th>
<th>Findings- Effect Estimate (95 Percent CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleed- UGIB</td>
<td>Unspecified</td>
<td>1 OBS\textsuperscript{a,56} (60,746)</td>
<td>SSRIs: HR 1.22 (1.07 to 1.40)</td>
</tr>
<tr>
<td>Blood pressure-DBP, mmHg</td>
<td>Maintenance (48 weeks)</td>
<td>1 RCT\textsuperscript{48} (121)</td>
<td>Citalopram: MD -4.0 (-9.4 to 1.4)</td>
</tr>
<tr>
<td>Blood pressure-SBP, mmHg</td>
<td>Maintenance (48 weeks)</td>
<td>1 RCT\textsuperscript{48} (121)</td>
<td>Citalopram: MD -5.0 (-16.33 to 6.33)</td>
</tr>
<tr>
<td>Blood pressure-HTN</td>
<td>Acute</td>
<td>1 RCT\textsuperscript{43} (517)</td>
<td>Escitalopram: RR 0.38 (0.11 to 1.34)</td>
</tr>
<tr>
<td></td>
<td>Maintenance (48 weeks)</td>
<td>1 RCT\textsuperscript{48} (121)</td>
<td>Citalopram: RR 0.51 (0.05 to 5.46)</td>
</tr>
<tr>
<td>Blood pressure-BP increase\textsuperscript{b}</td>
<td>Acute</td>
<td>1 RCT\textsuperscript{45} (196)</td>
<td>Fluoxetine: RR 0.77 (0.21 to 2.78)</td>
</tr>
<tr>
<td>Blood pressure-Orthostatic hypotension</td>
<td>Acute</td>
<td>1 RCT\textsuperscript{43} (517)</td>
<td>Escitalopram: RR 2.08 (0.09 to 45.66)</td>
</tr>
<tr>
<td></td>
<td>Maintenance (2 years)</td>
<td>1 RCT\textsuperscript{46} (53)</td>
<td>Paroxetine: RR 1.49 (0.96 to 2.32)</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Acute</td>
<td>1 RCT\textsuperscript{49,66} (174)</td>
<td>Citalopram: MMSE MD -0.07 (-0.93 to 0.79)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Digital symbol MD -0.66 (-7.91 to 6.59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroop MD 0.00 (-0.26 to 0.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CRT MD 0.05 (-0.10 to 0.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>JoLO MD 1.32 (-1.19 to 3.83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Buschke SRT MD -2.62 (-7.15 to 1.91)</td>
</tr>
<tr>
<td>Seizure/ epilepsy</td>
<td>Unspecified</td>
<td>1 OBS\textsuperscript{a,56} (60,746)</td>
<td>SSRIs: HR 1.98 (1.62 to 2.43)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Unspecified</td>
<td>1 OBS\textsuperscript{a,56} (60,746)</td>
<td>SSRIs: HR 1.62 (1.42 to 1.86)</td>
</tr>
<tr>
<td>Suicide</td>
<td>Acute</td>
<td>1 RCT\textsuperscript{43} (517)</td>
<td>Escitalopram: RD 0.01 (-0.07 to 0.03)</td>
</tr>
<tr>
<td></td>
<td>Maintenance (2 years)</td>
<td>1 RCT\textsuperscript{46} (53)</td>
<td>Paroxetine: No events occurred</td>
</tr>
<tr>
<td>Suicide attempt/self-harm</td>
<td>Unspecified</td>
<td>1 OBS\textsuperscript{a,56} (60,746)</td>
<td>SSRIs: HR 2.16 (1.71 to 2.71)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>Maintenance (2 years)</td>
<td>1 RCT\textsuperscript{46} (52)</td>
<td>Paroxetine: MD 3.20 (-2.27 to 8.67)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Acute</td>
<td>1 RCT\textsuperscript{45} (196)</td>
<td>Fluoxetine: RD 0.06 (0.010 to 0.125)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; CRT=Cognitive Reflection Test; DBP=diastolic blood pressure; HTN=hypertension; JoLO=Benton Judgement of Line Orientation; MD=mean difference; MMSE=Mini Mental Status Exam; n=patient sample size; OBS=observational; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; SBP=systolic blood pressure; SSRI=selective serotonin reuptake inhibitor; UGIB=upper gastrointestinal bleed
Based on RCTs, SSRIs did not differ significantly from placebo in the remaining findings although the majority of these findings are based on data from single trials studying one SSRI (Table 5). Observational data suggests an association between SSRIs and upper gastrointestinal bleed (UGIB), epilepsy/seizure, and hyponatremia compared with not using antidepressants.

SSRIs Versus Tricyclic Antidepressants (TCAs)

Study Characteristics
Three trials\(^{51-53}\) (n=531) compared SSRIs versus TCAs, all during treatment of the acute phase of MDD (Table 6). The mean age across the trials ranged from 71.5 to 75 years. The drug comparisons included paroxetine 20mg daily versus amitriptyline 100mg daily,\(^{52}\) citalopram 20-40mg/day versus amitriptyline 50-100mg/day,\(^{52}\) and sertraline 50-150mg/day versus nortriptyline 25-100mg/day.\(^{51}\) Risk of bias was low in two trials,\(^{52,53}\) and high in one trial.\(^{51}\) Two trials\(^{51,53}\) reported industry sponsorship.

Table 6. Summary of findings and strength of evidence for adverse effects with SSRI versus TCA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Quantity and Type of Evidence (n)</th>
<th>Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)(^{a})</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>Acute</td>
<td>2 RCTs(^{52,53}) (455)</td>
<td>RR 0.71 (0.50 to 0.99) NNT 6 (4 to 11) Decreased risk with SSRIs paroxetine, citalopram vs. amitriptyline</td>
<td>Low (imprecise, suspected reporting bias)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Acute</td>
<td>1 RCT(^{51}) (75)</td>
<td>RR 0.39 (0.08 to 1.88) Insufficient with sertraline vs. nortriptyline</td>
<td>Insufficient (High ROB, imprecise, suspected reporting bias)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Acute</td>
<td>1 RCT(^{52}) (365)</td>
<td>RD -0.01 (-0.03 to 0.02) Insufficient with citalopram vs. amitriptyline</td>
<td>Insufficient (imprecise, 1 event occurred, suspected reporting bias)</td>
</tr>
<tr>
<td>Mortality</td>
<td>Acute</td>
<td>1 RCT(^{53}) (90)</td>
<td>RD -0.04 (-0.17 to 0.04) Insufficient with paroxetine vs. amitriptyline</td>
<td>Insufficient (imprecise, 1 event occurred, suspected reporting bias)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Acute</td>
<td>2 RCTs(^{51,52}) (441)</td>
<td>RR 0.54 (0.28 to 1.05) Insufficient with SSRIs (sertraline, citalopram) vs. amitriptyline</td>
<td>Insufficient (medium ROB, imprecise, suspected reporting bias)</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>Acute</td>
<td>3 RCTs(^{51-53}) (531)</td>
<td>RR 0.67 (0.48 to 0.94) NNT 13 (7 to 100) Decreased risk with SSRIs (citalopram, paroxetine, sertraline) vs. TCAs (amitriptyline, nortriptyline)</td>
<td>Low (imprecise, suspected reporting bias)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; n=patient sample size; NNT=number needed to treat; RCT=randomized controlled trial; RD=risk difference; ROB=risk of bias; RR=risk ratio
a Interpretation of effect estimate based on statistical significance. May overestimate estimates of no difference due to inadequate sample size and type II error.

During treatment of the acute phase of MDD, the risk of any adverse event [RR 0.71 (0.50 to 0.99)] and of withdrawal due to adverse events [RR 0.67 (0.48 to 0.94)] were reduced with SSRIs versus TCA (Table 6, Figure 4). Two studies52,53 further described the most common adverse events for SSRI (citalopram, paroxetine) treated patients as nausea, vomiting, dizziness, headache, fatigue, dry mouth, constipation and somnolence and for TCA (amitriptyline) treated patients as dry mouth, nausea, dizziness, somnolence, asthenia, headache, fatigue and constipation. The common adverse events that led to withdrawal were not described in these trials. Data were insufficient to make conclusions for cognitive impairment, hospitalization, mortality and serious adverse events. In the single trial52 reporting hospitalization, one occurred in the TCA (amitriptyline) arm (0.5 percent). One trial53 reported mortality and one death occurred in the TCA (amitriptyline) arm (3.1 percent). There were no additional findings for the comparison of SSRI vs. TCAs.

Figure 4. SSRI versus TCA and risk of any adverse event (A), withdrawal due to adverse event (B), and serious adverse event (C) during treatment of the acute phase of MDD

Abbreviations: CI=confidence interval; MDD=major depressive disorder; RR=relative risk; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

SSRIs Versus SSRIs

Study Characteristics

Four trials25,42-44 (n=760) compared one SSRI with another SSRI (Table 7-8). A single observational study57 compared escitalopram to other SSRIs or SNRIs collectively. The mean age across the trials ranged from 73.7 to 75.61 years. Three SSRIs (paroxetine 20-40mg/day, sertraline 50-100mg/day and escitalopram 10mg/day) were compared with fluoxetine 20-60mg/day in these trials. Three trials evaluated treatment of the acute phase of MDD25,42,43 and one evaluated maintenance therapy.44 Risk of bias was low in two trials,43,44 high in one trial25 and unclear in one trial.42 Two trials42,44 reported industry sponsorship.
## Results

### Main Outcomes

#### Table 7. Summary of findings and strength of evidence for adverse effects with SSRIs versus SSRIs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Quantity and Type of Evidence (n)</th>
<th>Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>Acute</td>
<td>2 RCTs&lt;sup&gt;25,43&lt;/sup&gt; (412)</td>
<td>Sertraline vs. Fluoxetine RR 0.99 (0.88 to 1.12) Escitalopram vs. Fluoxetine RR 0.90 (0.74 to 1.09) No difference</td>
<td>Moderate (suspected reporting bias)</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>1 RCT&lt;sup&gt;44&lt;/sup&gt; (242)</td>
<td>RR 0.84 (0.57 to 1.24) No difference with paroxetine vs. fluoxetine</td>
<td>Moderate (imprecise)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Unspecified</td>
<td>1 OBS&lt;sup&gt;57&lt;/sup&gt; (1976)</td>
<td>OR 0.87, p=0.293 No difference with escitalopram vs. other SSRI/SNRI</td>
<td>Low</td>
</tr>
<tr>
<td>Mortality</td>
<td>Acute</td>
<td>1 RCT&lt;sup&gt;43&lt;/sup&gt; (337)</td>
<td>RD 0.01 (-0.02 to 0.03) Insufficient with escitalopram vs. fluoxetine</td>
<td>Insufficient (1 event occurred, imprecise, suspected reporting bias)</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>1 RCT&lt;sup&gt;44&lt;/sup&gt; (242)</td>
<td>RR 0.97 (0.14 to 6.76) Insufficient with paroxetine vs. fluoxetine</td>
<td>Insufficient (2 events occurred, imprecise)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Maintenance</td>
<td>1 RCT&lt;sup&gt;44&lt;/sup&gt; (242)</td>
<td>RR 0.56 (0.23 to 1.38) No difference with paroxetine vs. fluoxetine</td>
<td>Moderate (imprecise)</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>Acute</td>
<td>3 RCTs&lt;sup&gt;25,42,43&lt;/sup&gt; (518)</td>
<td>Paroxetine [RR 0.83 (0.30 to 2.29)] or sertraline [RR 0.63 (0.28 to 1.41)] or escitalopram [RR 0.81 (0.44 to 1.48)] vs. fluoxetine No difference</td>
<td>Low (imprecise, suspected reporting bias)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; MD=mean difference; n=patient sample size; OBS=observational; OR=odds ratio; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

<sup>a</sup> Interpretation of effect estimate based on statistical significance. May overestimate estimates of no difference due to inadequate sample size and type II error.

During the acute and maintenance treatment phases, data did not suggest a difference between other SSRIs and fluoxetine, demonstrated by RCT findings that were not statistically significant across all reported adverse events (Table 7). Data were insufficient to make a conclusion for mortality. The single acute treatment trial<sup>43</sup> reported one death in the escitalopram arm (0.6 percent) which was a suicide (0.6 percent). The single maintenance treatment trial<sup>44</sup> reported two deaths in each paroxetine (1.6 percent) and fluoxetine (1.7 percent) arms; one death in the fluoxetine arm was a suicide (0.8 percent).

A single retrospective claims-based cohort study (n=1976)<sup>57</sup> compared escitalopram to other SSRIs or SNRIs. After adjustment for confounders, the odds of hospitalization at 6 months was not significantly different with escitalopram vs. other SSRI/SNRI [OR 0.87, p=0.293]. Escitalopram patients had 39 percent fewer hospital days [incident rate ratio 0.61, p=0.004].
Additional Findings

Data do not suggest statistically significant differences between other SSRIs and fluoxetine (Table 8).

Table 8. Additional findings for adverse effects with SSRIs versus SSRIs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Quantity and Type of Evidence (n)</th>
<th>Findings</th>
<th>Effect Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure-</td>
<td>Acute</td>
<td>1 RCT43 (337)</td>
<td>Escitalopram vs. fluoxetine</td>
<td>RR 0.95 (0.24 to 3.73)</td>
</tr>
<tr>
<td>HTN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure-</td>
<td>Acute</td>
<td>1 RCT43 (337)</td>
<td>Escitalopram vs. fluoxetine</td>
<td>RR 1.90 (0.17 to 20.71)</td>
</tr>
<tr>
<td>orthostatic Hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Acute</td>
<td>1 RCT25 (75)</td>
<td>Sertraline vs. fluoxetine</td>
<td>HamD Cognitive Factor MD 0.50 (-0.74 to 1.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DSST MD 0 (-8.26 to 8.26)</td>
</tr>
<tr>
<td>Suicide</td>
<td>Acute</td>
<td>1 RCT43 (337)</td>
<td>Escitalopram vs. fluoxetine</td>
<td>RD 0.01 (-0.02 to 0.03)</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>1 RCT44 (242)</td>
<td>Paroxetine vs. fluoxetine</td>
<td>RD -0.01 (-0.05 to 0.03)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; DSST=digital symbol substitution test; HTN=hypertension; MD=mean difference; n=patient sample size; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio.

Selective Norepinephrine Reuptake Inhibitors

Key Points
- SNRIs (duloxetine, venlafaxine) increased the risk of adverse events (high SOE, NNH 10 [7 to 34]) and withdrawal due to adverse events (moderate SOE, NNH 17 [-7 to 33]) compared with placebo during treatment of the acute phase of MDD, based on meta-analysis of RCTs.
- Duloxetine increased the risk of withdrawal due to adverse events (moderate SOE, NNH 12 [7 to 33]) and the risk of falls (moderate SOE, NNH 10 [6 to 114]) compared with placebo during 24 weeks of treatment in a single RCT.
- Venlafaxine is associated with increased risk of falls (low SOE), mortality (low SOE) and fractures (low SOE) based on a cohort study of a longer treatment period (median 364 days).

SNRIs vs. Placebo

Study Characteristics

Four trials15,17,45,54 (n=1177) compared an SNRI to placebo (Tables 9-10). Three trials15,17,54 studied the SNRI duloxetine (60-120mg/day), one trial45 studied the SNRI venlafaxine IR (37.5-112.5mg twice daily. The mean age across the four trials ranged from 70.3 to 73.3 years. All trials evaluated treatment of the acute phase of MDD. In addition, Robinson et al.15 randomized patients a second time after an initial 12 weeks of treatment for a 12 week continuation phase and reported outcomes for the acute phase and for the entire study period of 24 weeks (acute plus continuation phases). Patients with an adverse events during acute treatment did not continue further. Raskin et al.54 had a one week run-in period and patients who could not tolerate duloxetine were withdrawn from the study. Risk of bias was low for all trials except one trial54 considered to have high risk of bias. All trials reported industry sponsorship.
## Results

### Main Outcomes

Table 9. Summary of findings and strength of evidence for adverse effects with SNRIs versus placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Quantity and Type of Evidence (n)</th>
<th>Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>Acute</td>
<td>3 RCTs¹⁷,⁴⁵,⁵⁴ (805)</td>
<td>RR 1.14 (1.03 to 1.25) NeN 10 (7 to 34) Increased risk with duloxetine, venlafaxine</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Unspecified</td>
<td>1 OBS⁵⁶ (60,746)</td>
<td>HR 0.89 (0.55 to 1.46) No difference with venlafaxine</td>
<td>Low</td>
</tr>
<tr>
<td>ECG-Arrhythmia</td>
<td>Acute + Continuation</td>
<td>1 RCT¹⁵ (370)</td>
<td>RD 0.002 (-0.03 to 0.02) Insufficient with duloxetine</td>
<td>Insufficient (imprecise, 1 event occurred)</td>
</tr>
<tr>
<td>ECG-QTc, ms</td>
<td>Acute</td>
<td>1 RCT⁵⁴ (282)</td>
<td>Bazzett correction MD 0.59 (-3.87 to 5.05); Fridericia correction MD -1.05 (-5.53 to 3.43) No difference with duloxetine</td>
<td>Moderate (high ROB)</td>
</tr>
<tr>
<td></td>
<td>Acute + Continuation</td>
<td>1 RCT¹⁵ (262)</td>
<td>Bazzett correction MD 2.40 (-3.72 to 8.52); Fridericia correction MD 0.89 (-4.73 to 6.51) No difference with duloxetine</td>
<td>High</td>
</tr>
<tr>
<td>Falls</td>
<td>Acute</td>
<td>2 RCTs¹⁵,⁵⁴ (681)</td>
<td>RR 1.46 (0.84 to 2.55) No difference with duloxetine</td>
<td>Low (moderate ROB, imprecise)</td>
</tr>
<tr>
<td></td>
<td>Acute + Continuation</td>
<td>1 RCT¹⁵ (370)</td>
<td>RR 1.69 (1.03 to 2.76) NeN 10 (6 to 114) Increased risk with duloxetine</td>
<td>Moderate (imprecise)</td>
</tr>
<tr>
<td></td>
<td>Unspecified</td>
<td>1 OBS⁵⁶ (60,746)</td>
<td>HR 1.67 (1.48 to 1.88) Increased risk with venlafaxine</td>
<td>Low</td>
</tr>
<tr>
<td>Fractures</td>
<td>Acute</td>
<td>1 RCT¹⁷ (298)</td>
<td>RD -0.007 (-0.04 to 0.02) Insufficient with duloxetine</td>
<td>Insufficient (imprecise, 1 event occurred)</td>
</tr>
<tr>
<td></td>
<td>Acute + Continuation</td>
<td>1 RCT¹⁵ (370)</td>
<td>Ankle fractures RD 0.002 (-0.03 to 0.02); Hip fractures RD 0.002 (-0.03 to 0.02) Insufficient with duloxetine</td>
<td>Insufficient (imprecise, 1 event occurred)</td>
</tr>
<tr>
<td></td>
<td>Unspecified</td>
<td>1 OBS⁵⁶ (60,746)</td>
<td>HR 1.85 (1.58 to 2.18) Increased risk with venlafaxine</td>
<td>Low</td>
</tr>
<tr>
<td>Mortality</td>
<td>Acute</td>
<td>2 RCT¹⁷,⁵⁴ (681)</td>
<td>No events occurred Insufficient with duloxetine</td>
<td>Insufficient (moderate ROB, no events)</td>
</tr>
<tr>
<td></td>
<td>Acute + Continuation</td>
<td>1 RCT¹⁵ (370)</td>
<td>No events occurred Insufficient with duloxetine</td>
<td>Insufficient (no events)</td>
</tr>
<tr>
<td></td>
<td>Unspecified</td>
<td>1 OBS⁵⁶ (60,746)</td>
<td>HR 1.65 (1.50 to 1.82) Increased risk with venlafaxine</td>
<td>Low</td>
</tr>
<tr>
<td>Serious AE</td>
<td>Acute</td>
<td>2 RCTs¹⁷,⁴⁵,⁵⁴ (607)</td>
<td>RR 0.20 (0.04 to 0.97) NeN 50 (25 to 1000) Decreased risk with duloxetine</td>
<td>Low (moderate ROB, imprecise)</td>
</tr>
<tr>
<td></td>
<td>Acute + Continuation</td>
<td>1 RCT¹⁵ (370)</td>
<td>RR 1.58 (0.53 to 4.74) No difference with duloxetine</td>
<td>Moderate (imprecise)</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>Acute</td>
<td>3 RCTs¹⁷,⁴⁵,⁵⁴ (812)</td>
<td>RR 1.85 (1.05 to 3.27) NeN 17 (-7 to 33) Increased risk with duloxetine and venlafaxine</td>
<td>Moderate (imprecise)</td>
</tr>
<tr>
<td></td>
<td>Acute + Continuation</td>
<td>1 RCT¹⁵ (370)</td>
<td>RR 2.64 (1.21 to 5.73) NeN 12 (7 to 33) Increased risk with duloxetine</td>
<td>Moderate (imprecise)</td>
</tr>
</tbody>
</table>
The risk of any adverse event [RR 1.14 (1.03 to 1.25)] and withdrawal due to adverse events [RR 1.85 (1.05 to 3.27)] was increased with SNRIs (duloxetine and venlafaxine) versus placebo during treatment of the acute phase of MDD (Table 9, Figure 5). Of the trials\textsuperscript{45,54} reporting further details, the most common adverse events included nausea, headache, dry mouth, constipation, dizziness, diarrhea, fatigue and somnolence. Withdrawal due to adverse events was also increased with duloxetine vs. placebo during the acute plus continuation phases of a single trial [RR 2.64 (1.21 to 5.73)].\textsuperscript{15} Most common adverse events leading to withdrawal were not further specified. The risk of serious adverse events was lower with duloxetine vs. placebo during the acute period [two events versus seven events, RR 0.20 (0.04 to 0.97), low SOE] but the risk was not statistically significant (moderate SOE) in the acute plus continuation trial [13 events vs. four events, RR 1.58 (0.53 to 4.74)]. Contributing serious adverse events were not reported with exception of two cases in duloxetine treated subjects. One intentional overdose and one fracture after a fall occurred.

The risk of falls was not significantly different during the acute treatment phase but was significantly increased with duloxetine vs. placebo in the same\textsuperscript{15} during the 24 week trial period (acute plus continuation phases) [RR 1.69 (1.03 to 2.76), moderate SOE]. This 24 week trial\textsuperscript{15} employed active surveillance for falls and did not rely solely on patient reported falls as was done in the second trial\textsuperscript{54} reporting this outcome during the acute treatment period. A large \[n=60,746; 305,188 \text{ person-years of follow-up with a mean of 5.0 (3.3) years per patient}\] retrospective population-based cohort study\textsuperscript{56} compared venlafaxine with no use of an antidepressant. Venlafaxine was associated with an increased adjusted HR for all-cause mortality, falls and fracture, but not with the risk of any adverse event.

Data were insufficient to make conclusions for the following outcomes: arrhythmias [one event (0.5 percent) in the SNRI arm], fractures [one ankle (0.4 percent) and one hip (0.4 percent) fracture occurred in the SNRI arm] and mortality (no deaths occurred).
Figure 5. SNRI versus placebo on the risk of (A) any adverse event during treatment of the acute phase of MDD, (B) serious adverse events, (C) withdrawal due to adverse events

Abbreviations: CI=confidence interval; RR=relative risk; SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective-serotonin reuptake inhibitor

Additional Findings

Table 10. Additional findings for adverse effects with SNRIs versus placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Quantity and Type of Evidence (n)</th>
<th>Findings Effect Estimate (95 Percent CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleed-UGIB</td>
<td>Unspecified</td>
<td>1 OBS(^{56}) (60,746)</td>
<td>Venlafaxine: HR 1.70 (1.22 to 2.36)</td>
</tr>
<tr>
<td>Blood pressure- elevated supine DBP(^a)</td>
<td>Acute</td>
<td>1 RCT(^{54}) (303)</td>
<td>Duloxetine: RR 1.01 (0.31 to 3.29)</td>
</tr>
<tr>
<td></td>
<td>Acute + Continuation</td>
<td>1 RCT(^{15}) (308)</td>
<td>Duloxetine: RR 2.05 (0.80 to 5.26)</td>
</tr>
<tr>
<td>Blood pressure- elevated supine SBP(^b)</td>
<td>Acute</td>
<td>1 RCT(^{54}) (303)</td>
<td>Duloxetine: RR 2.29 (1.30 to 4.02)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Treatment Phase</td>
<td>Quantity and Type of Evidence (n)</td>
<td>Findings</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>---------------------</td>
<td>----------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Blood pressure- sustained elevated supine DBP</td>
<td>Acute + Continuation</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt; (177)</td>
<td>Duloxetine: RR 1.95 (0.91 to 4.20)</td>
</tr>
<tr>
<td>Blood pressure - sustained elevated supine SBP</td>
<td>Acute</td>
<td>1 RCT&lt;sup&gt;54&lt;/sup&gt; (303)</td>
<td>Duloxetine: RD -0.01 (-0.06 to 0.01)</td>
</tr>
<tr>
<td>Blood pressure- standing DBP, mmHg</td>
<td>Acute</td>
<td>2 RCTs&lt;sup&gt;17,54&lt;/sup&gt; (560)</td>
<td>Duloxetine: MD 0.17 (-1.37 to 1.71)</td>
</tr>
<tr>
<td>Blood pressure- standing SBP, mmHg</td>
<td>Acute</td>
<td>2 RCTs&lt;sup&gt;17,54&lt;/sup&gt; (560)</td>
<td>Duloxetine: MD -2.45 (-4.88 to -0.02)</td>
</tr>
<tr>
<td>Blood pressure- supine DBP, mmHg</td>
<td>Acute</td>
<td>3 RCTs&lt;sup&gt;15,17,54&lt;/sup&gt; (924)</td>
<td>Duloxetine: MD 1.65 (-0.14 to 3.44)</td>
</tr>
<tr>
<td>Blood pressure- supine SBP, mmHg</td>
<td>Acute</td>
<td>3 RCTs&lt;sup&gt;15,17,54&lt;/sup&gt; (924)</td>
<td>Duloxetine: MD 0.73 (-1.24 to 2.69)</td>
</tr>
<tr>
<td>Blood pressure- orthostatic hypotension</td>
<td>Acute</td>
<td>2 RCTs&lt;sup&gt;15,54&lt;/sup&gt; (667)</td>
<td>Duloxetine: RR 1.05 (0.79 to 1.38)</td>
</tr>
<tr>
<td>Blood pressure- orthostatic DBP, mmHg</td>
<td>Acute</td>
<td>2 RCTs&lt;sup&gt;15,54&lt;/sup&gt; (667)</td>
<td>Duloxetine: MD -1.71 (-4.71 to 1.30)</td>
</tr>
<tr>
<td>Blood pressure- orthostatic SBP, mmHg</td>
<td>Acute</td>
<td>2 RCTs&lt;sup&gt;15,54&lt;/sup&gt; (667)</td>
<td>Duloxetine: MD -2.58 (-4.30 to -0.86)</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Acute</td>
<td>3 RCTs&lt;sup&gt;15,17,54&lt;/sup&gt; (856)</td>
<td>Duloxetine: RAVLT-acquisition 1.41 (0.38 to 2.43) and RAVLT-longer delayed memory 0.64 (0.16 to 1.12)</td>
</tr>
<tr>
<td>ECG-treatment emergent abnormal ECG</td>
<td>Acute</td>
<td>1 RCT&lt;sup&gt;54&lt;/sup&gt; (282)</td>
<td>Duloxetine: RR 0.90 (0.65 to 1.24)</td>
</tr>
<tr>
<td>Seizures/epilepsy</td>
<td>Unspecified</td>
<td>1 OBS&lt;sup&gt;56&lt;/sup&gt; (60,746)</td>
<td>Venlafaxine: HR 2.94 (1.93 to 4.58)</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>Acute</td>
<td>2 RCTs&lt;sup&gt;17,54&lt;/sup&gt; (551)</td>
<td>Duloxetine: MD 0.51 (-1.00 to -0.03)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Unspecified</td>
<td>1 OBS&lt;sup&gt;56&lt;/sup&gt; (60,746)</td>
<td>Venlafaxine: HR 1.51 (1.07 to 2.13)</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>Acute</td>
<td>1 RCT&lt;sup&gt;17&lt;/sup&gt; (228)</td>
<td>Duloxetine: RR 0.73 (0.30 to 1.74)</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>Acute + Continuation</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt; (370)</td>
<td>Duloxetine: RD 0.006 (-0.03 to 0.03)</td>
</tr>
<tr>
<td>Suicide</td>
<td>Acute</td>
<td>1 RCT&lt;sup&gt;17&lt;/sup&gt; (228)</td>
<td>Duloxetine: RD 0.009 (-0.03 to 0.05)</td>
</tr>
<tr>
<td>Suicide attempt/self-harm</td>
<td>Unspecified</td>
<td>1 OBS&lt;sup&gt;56&lt;/sup&gt; (60,746)</td>
<td>Venlafaxine: HR 4.56 (3.02 to 6.79)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>Acute</td>
<td>3 RCTs&lt;sup&gt;15,17,54&lt;/sup&gt; (929)</td>
<td>Duloxetine: MD -0.70 (-0.98 to -0.42)</td>
</tr>
<tr>
<td>Weight gain ≥7 percent</td>
<td>Acute</td>
<td>1 RCT&lt;sup&gt;54&lt;/sup&gt; (311)</td>
<td>Duloxetine: RD 0.007 (-0.03 to 0.03)</td>
</tr>
<tr>
<td>Weight loss ≥7 percent</td>
<td>Acute + Continuation</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt; (369)</td>
<td>Duloxetine: RR 2.68 (0.60 to 11.92)</td>
</tr>
<tr>
<td>Weight gain ≥7 percent</td>
<td>Acute</td>
<td>2 RCTs&lt;sup&gt;45,54&lt;/sup&gt; (509)</td>
<td>Duloxetine and venlafaxine: RR 1.03 (0.22 to 4.85)</td>
</tr>
<tr>
<td>Weight loss ≥7 percent</td>
<td>Acute + Continuation</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt; (369)</td>
<td>Duloxetine: RR 1.22 (0.49 to 3.07)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; DBP=diastolic blood pressure; ECG=electrocardiogram; HR=hazard ratio; HTN=hypertension; kg=kilogram; MD=mean difference; mEq/L=miliequivalents per liter; ms=millisecond; n=patient sample
Outcomes of blood pressure were inconsistent when duloxetine was compared with placebo (Table 10). One trial\(^5\) found the risk of elevation in supine systolic blood pressure (SBP) to be increased with duloxetine [RR 2.29 (1.30 to 4.02)], but duloxetine decreased standing SBP compared with placebo [MD -2.45 mmHg (-4.88 to -0.02)] and decreased orthostatic SBP compared with placebo [MD -2.58 mmHg (-4.30 to -0.86)]. There was a significant difference in serum sodium and of body weight during treatment of the acute phase of MDD suggesting more of a reduction with duloxetine vs. placebo (Figure 6 and 7). Most other findings were not statistically significant with exception of some cognitive function tests (Table 10) suggesting improvement with duloxetine. Observational data suggest an association between the SNRI venlafaxine and upper gastrointestinal bleed (UGIB), seizure/epilepsy, hyponatremia, and suicide attempt/self-harm.

Figure 6. Change in serum sodium with SNRI (duloxetine) versus placebo during treatment of the acute phase of MDD

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor

Figure 7. Change in body weight with SNRI (duloxetine) versus placebo during treatment of the acute phase of MDD

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor
SNRIs Versus SSRIs

Study Characteristics
Two trials\textsuperscript{45,55} (n=352) compared SNRI with SSRI (Tables 11-12). The mean age across the trials ranged from 71 to 73.6 years. Both trials evaluated the SNRI venlafaxine (IR 37.5-115.5mg twice daily, ER 75-150mg/day) while one trial\textsuperscript{55} used citalopram 20-30mg/day and the other fluoxetine 20-60mg/day\textsuperscript{45} as the comparator SSRIs. One trial studied treatment of the acute phase of MDD (eight weeks) while the other trial was for a total of six months but reported some outcomes separately for the acute (eight weeks) and continuation (24 weeks) treatment phases. Risk of bias was low in both trials and one trial\textsuperscript{45} reported industry sponsorship.

Results

Main Outcomes

Table 11. Summary of findings and strength of evidence for adverse effects with SNRIs versus SSRIs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Quantity and Type of Evidence (n)</th>
<th>Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)\textsuperscript{a}</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>Acute</td>
<td>1 RCT\textsuperscript{45} (202)</td>
<td>RR 1.00 (0.93 to 1.07) No difference with venlafaxine vs. fluoxetine</td>
<td>Moderate (suspected reposting bias)</td>
</tr>
<tr>
<td></td>
<td>Continuation</td>
<td>1 RCT\textsuperscript{55} (148)</td>
<td>RR 0.81 (0.65 to 1.01) No difference with venlafaxine vs. citalopram</td>
<td>Moderate (imprecise)</td>
</tr>
<tr>
<td>Falls</td>
<td>Continuation</td>
<td>1 RCT\textsuperscript{55} (148)</td>
<td>RD -0.01 (-0.08 to 0.04) Insufficient with venlafaxine vs. citalopram</td>
<td>Insufficient (imprecise, 1 event occurred)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>Continuation</td>
<td>1 RCT\textsuperscript{55} (148)</td>
<td>RD 0.01 (-0.04 to 0.08) Insufficient with venlafaxine vs. citalopram</td>
<td>Insufficient (imprecise, 1 event occurred)</td>
</tr>
<tr>
<td>Mortality</td>
<td>Continuation</td>
<td>1 RCT\textsuperscript{55} (148)</td>
<td>RD -0.01 (-0.08 to 0.04) Insufficient with venlafaxine vs. citalopram</td>
<td>Insufficient (imprecise, 1 event occurred)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Continuation</td>
<td>1 RCT\textsuperscript{55} (148)</td>
<td>RR 1.28 (0.36 to 4.59) No difference with venlafaxine vs. citalopram</td>
<td>Moderate (imprecise)</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>Acute</td>
<td>1 RCT\textsuperscript{45} (204)</td>
<td>RR 1.37 (0.81 to 2.30) No difference with venlafaxine vs. fluoxetine</td>
<td>Low (imprecise, suspected reporting bias)</td>
</tr>
<tr>
<td></td>
<td>Continuation</td>
<td>1 RCT\textsuperscript{55} (148)</td>
<td>RR 1.54 (0.45 to 5.24) No difference with venlafaxine vs. citalopram</td>
<td>Moderate (imprecise)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; n=patient sample size; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio

\textsuperscript{a} Interpretation of effect estimate based on statistical significance. May overestimate estimates of no difference due to inadequate sample size and type II error.

There were no significant differences between venlafaxine and the SSRIs citalopram and fluoxetine, regardless of the duration of treatment (Table 11). Data were insufficient to make conclusions for falls, hip fractures and mortality. In a single trial,\textsuperscript{55} one fall (1.3 percent) and one
death (1.3 percent) occurred in the SSRI arm and one hip fracture (1.4 percent) occurred in the venlafaxine arm.

**Additional Findings**

**Table 12. Additional findings for adverse effects with SNRIs versus SSRIs**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Quantity and Type of Evidence (n)</th>
<th>Findings Effect Estimate (95 Percent CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure-increased supine DBP</td>
<td>Acute</td>
<td>1 RCT(^45) (202)</td>
<td>Venlafaxine vs. fluoxetine RR 1.23 (0.34 to 4.43)</td>
</tr>
<tr>
<td>Blood pressure-DBP, mmHg</td>
<td>Acute</td>
<td>1 RCT(^55) (148)</td>
<td>Venlafaxine vs. citalopram MD -1.46 (-4.4 to 1.48)</td>
</tr>
<tr>
<td></td>
<td>Continuation</td>
<td>1 RCT(^55) (148)</td>
<td>Venlafaxine vs. citalopram MD -0.41 (-3.08 to 2.26)</td>
</tr>
<tr>
<td>Blood pressure-SBP, mmHg</td>
<td>Acute</td>
<td>1 RCT(^55) (148)</td>
<td>Venlafaxine vs. citalopram MD -2.32 (-7.08 to 2.44)</td>
</tr>
<tr>
<td></td>
<td>Continuation</td>
<td>1 RCT(^57) (148)</td>
<td>Venlafaxine vs. citalopram MD -2.48 (-6.82 to 1.86)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Acute</td>
<td>1 RCT(^45) (202)</td>
<td>Venlafaxine vs. fluoxetine RR 0.16 (0.20 to 1.33)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>Acute</td>
<td>1 RCT(^55) (148)</td>
<td>Venlafaxine vs. citalopram MD -0.2 (-5.66 to 5.26)</td>
</tr>
<tr>
<td></td>
<td>Continuation</td>
<td>1 RCT(^55) (148)</td>
<td>Venlafaxine vs. citalopram MD 0.9 (-4.62 to 6.42)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; kg=kilogram; DBP=diastolic blood pressure; MD=mean difference; n=patient sample size; RCT=randomized controlled trial; RR=risk ratio; SBP=systolic blood pressure

There were no significant differences between venlafaxine and the SSRIs citalopram and fluoxetine, regardless of the duration of treatment (Table 12).

**Other Antidepressant Drugs**

**Key Points**

- Mirtazapine was associated with an increased risk of falls (low SOE), fractures (low SOE) and mortality (low SOE) compared with no antidepressant use based on an observational study over a longer treatment period (364 day median).
- Mirtazapine decreased the risk of withdrawal due to adverse events compared with paroxetine during treatment of the acute phase of MDD, based on a single RCT (low SOE, NNT 9 [5 to 72]).
- Vortioxetine decreased the risk of any adverse event (high SOE, NNT 6 [4 to 17]) but did not impact risk of withdrawal due to adverse events (moderate SOE) or serious adverse events (moderate SOE) compared with duloxetine during treatment of the acute phase of MDD, based on a single RCT.
- Trazodone was associated with an increased risk of falls (low SOE) and mortality (low SOE) compared with no antidepressant use based on an observational study over a longer treatment period (364 day median).
Bupropion Extended Release (XR) Versus Placebo

Study Characteristics

One trial\textsuperscript{16} (n=418) compared bupropion XR 150-300mg/day versus placebo for 10 weeks of treatment (Tables 13-14). The mean age of subjects ranged from 70.9 to 71.3 years. This study was rated with low risk of bias and reported industry sponsorship.

Results

Main Outcomes

Table 13. Summary of findings and strength of evidence for adverse effects with bupropion XR versus placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)\textsuperscript{a}</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>RR 0.97 (0.83 to 1.14) No difference</td>
<td>Moderate</td>
</tr>
<tr>
<td>ECG-supraventricular arrhythmia</td>
<td>RD -0.01 (-0.03 to 0.02) Insufficient</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Mortality</td>
<td>No events occurred</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>RR 0.28 (0.06 to 1.33) No difference</td>
<td>Low</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>RR 0.76 (0.41 to 1.39) No difference</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; n=patient sample size; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; XR=extended release

\textsuperscript{a} Interpretation of effect estimate based on statistical significance. May overestimate estimates of no difference due to inadequate sample size and type II error.

No statistically significant differences were found between bupropion XR and placebo for most outcomes. Since no deaths or seizures occurred during the randomized period data were Insufficient and we were unable to make a conclusion. After the randomized period and when patients had stopped taking therapy, two deaths were reported in patients who had been assigned placebo, two and six days after study drug was stopped. One subject has an arrhythmia in the placebo arm (0.5%).

Additional Findings

Table 14. Additional findings for adverse effects with bupropion XR versus placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Findings – Effect Estimate (95 Percent CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure-clinically significant increase in DBP\textsuperscript{a}</td>
<td>RR 1.24 (0.65 to 2.39)</td>
</tr>
<tr>
<td>Blood pressure-clinically significant increase in SBP\textsuperscript{a}</td>
<td>RR 0.64 (0.40 to 1.05)</td>
</tr>
<tr>
<td>Blood pressure-HTN DBP\textsuperscript{b}</td>
<td>RR 0.75 (0.37 to 1.51)</td>
</tr>
<tr>
<td>Blood pressure-HTN SBP\textsuperscript{b}</td>
<td>RR 1.31 (0.46 to 3.70)</td>
</tr>
<tr>
<td>Seizures</td>
<td>No events occurred</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>RD -0.01 (-0.03 to 0.02)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; DBP=diastolic blood pressure; HTN=hypertension; n=patient sample size; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; SBP=systolic blood pressure; XR=extended release
DBP increase of ≥15 mmHg; SBP increase of ≥ 20 mmHg
DBP increase ≥10 mmHg over 3 consecutive visits; SBP increase ≥15 mmHg over 3 consecutive visits

No differences in outcomes were detected between bupropion XR and placebo (Table 14). One subject was reported to have suicidal thoughts in the placebo arm (0.5 percent).

**Mirtazapine Versus No Antidepressant Use**

**Study Characteristics**
A large [n=60,746; 305,188 person-years of follow-up with a mean of 5.0 (3.3) years per patient] retrospective population-based cohort study\(^5\) compared mirtazapine with not using an antidepressant. This study had a low risk of bias.

**Results**

**Main Outcomes**
Mirtazapine was associated with an increased adjusted HR for all-cause mortality [HR 1.75 (1.61 to 1.91), low SOE], falls [HR 1.18 (1.04 to 1.36), low SOE], and fracture [HR 1.44 (1.23 to 1.73), low SOE] but not the risk of any adverse event [HR 1.02 (0.64 to 1.69), low SOE].

**Additional Findings**
The risk attempted suicide/self-harm was increased with mirtazapine compared with no antidepressant [HR 6.10 (4.16 to 8.81)] use although the risks of UGIB [HR 1.03 (0.70 to 1.56)], seizure/epilepsy [HR 1.55 (0.88 to 2.82)] and hyponatremia [HR 1.06 (0.72 to 1.62)] were no different.

**Mirtazapine Versus Paroxetine**

**Study Characteristics**
One trial\(^2\) (n=254) compared mirtazapine 30-45mg/day to paroxetine 20-40mg/day, first during the acute treatment phase for eight weeks followed by the continuation phase of an additional 16 weeks for responders according to Clinical Global Impression (CGI) and HAM-D scores (Table 15). The mean age of subjects ranged from 71.7 to 72.0 years. This study was rated with low risk of bias and reported industry sponsorship.

**Results**

**Main Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)(^a)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>Acute</td>
<td>RR 0.97 (0.86 to 1.09) No difference</td>
<td>Moderate (suspected selective reporting)</td>
</tr>
<tr>
<td></td>
<td>Continuation</td>
<td>RR 1.23 (0.91 to 1.72) No difference</td>
<td>Low (imprecise, suspected selective reporting)</td>
</tr>
</tbody>
</table>

Table 15. Summary of findings and strength of evidence for adverse effects with mirtazapine versus paroxetine
During treatment of the acute phase of MDD, the risk of withdrawal due to adverse events was significantly reduced with mirtazapine versus paroxetine [RR 0.57 (0.34 to 0.94)] (Table 15). The most common adverse events leading to withdrawal were reported to be somnolence, nausea, fatigue and dizziness in the mirtazapine arm and nausea, diarrhea, insomnia, dizziness and somnolence in the paroxetine arm. The risk of serious adverse effects was no different with mirtazapine vs. paroxetine. Data were insufficient to permit conclusion for hospitalizations; one hospitalization occurred in the paroxetine arm (0.8 percent).

### Additional Findings

The risk of patient reported weight gain was increased with mirtazapine versus paroxetine [RD 0.11 (0.05 to 0.18)]; 14 patients in the mirtazapine arm (10.9 percent) and no patients in the paroxetine arm reported weight gain. Although the risk of clinically significant weight gain, defined as a gain of 7 percent or more of baseline weight (kg), was not statistically different during either acute [RD 0.04 (-0.002 to 0.09)] or continuation periods [RR 3.93 (0.89 to 17.41)], more mirtazapine treated patients gained a clinically significant amount (7 percent or more) during both acute [3.9 percent vs. 0 percent, RD 0.04 (-0.002 to 0.09)] and continuation [14.3 percent vs. 3.6 percent, RR 3.93 (0.89 to 17.41)] periods. No hypotensive events occurred.

### Trazodone Versus No Antidepressant Use

#### Study Characteristics

A large [n=60,746; 305,188 person-years of follow-up with a mean of 5.0 (3.3) years per patient] retrospective population-based cohort study\(^5\) compared trazodone with not using an antidepressant. This study was rated with low risk of bias.

#### Results

### Main Outcomes

Trazodone was associated with an increased adjusted HR for all-cause mortality [HR 1.82 (1.60 to 2.08), low SOE] and falls [HR 1.54 (1.28 to 1.87), low SOE]. The risk of any adverse event [HR 1.06 (0.50 to 2.24), low SOE] or fractures [HR 0.95 (0.70 to 1.35), low SOE] was no different with trazodone vs. no antidepressant.
Additional Findings

Trazodone was associated with an increased adjusted HR for UGIB [HR 1.78 (1.11 to 2.92)], and attempted suicide/self-harm [HR 4.68 (2.54 to 8.45)]. The risk of seizures/epilepsy [HR 1.38 (0.60 to 3.53)] and hyponatremia [HR 1.48 (0.87 to 2.59)] was no different with trazodone vs. no antidepressant.

Vortioxetine Versus Placebo

Study Characteristics

One trial\(^1\) (n=452) compared vortioxetine 5mg/day (n=156) to placebo (n=145) and to duloxetine 60mg/day (n=151) during the treatment of the acute phase of MDD (eight weeks) (Table 16). The mean age of subjects ranged from 70.3 to 70.9 years. This study was rated with low risk of bias and reported industry sponsorship.

Results

Main Outcomes

Table 16. Summary of findings and strength of evidence for adverse effects with vortioxetine versus placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Findings – Effect Estimate (95 Percent CI)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>Acute</td>
<td>RR 1.01 (0.85 to 1.21) No difference</td>
<td>High</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>Acute</td>
<td>RD -0.01 (-0.04 to 0.02) Insufficient</td>
<td>Insufficient (imprecise, 1 event occurred)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Acute</td>
<td>RR 0.23 (0.03 to 2.05) No difference</td>
<td>Moderate (imprecise)</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>Acute</td>
<td>RR 2.09 (0.66 to 6.64) No difference</td>
<td>Low (very imprecise)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; n=patient sample size; RD=risk difference; RR=risk ratio

\(^a\) Interpretation of effect estimate based on statistical significance. May overestimate estimates of no difference due to inadequate sample size and type II error.

There was no significant impact of vortioxetine on any adverse events, serious adverse events or withdrawal due to adverse events. Data were insufficient to make a conclusion for hip fracture; one event occurred in the placebo arm (0.7 percent).

Additional Findings

Vortioxetine improved cognitive function according to two neuropsychological assessments used to measure this outcome. There was no significant impact of vortioxetine on the remaining outcomes compared with placebo (Table 17).

Table 17. Additional findings for adverse effects with vortioxetine versus placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Findings Effect Estimate (95 Percent CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure-standing DBP, mmHg</td>
<td>Acute</td>
<td>MD 1 (-1.17 to 3.17)</td>
</tr>
<tr>
<td>Blood pressure- standing SBP, mmHg</td>
<td>Acute</td>
<td>MD 2 (-1.27 to 5.27)</td>
</tr>
<tr>
<td>Blood pressure-supine DBP, mmHg</td>
<td>Acute</td>
<td>MD 0 (-2.05 to 2.05)</td>
</tr>
</tbody>
</table>
Vortioxetine Versus Duloxetine

Study Characteristics

One trial17 (n=452) compared vortioxetine 5mg/day (n=156) to placebo (n=145) and to duloxetine 60mg/day (n=151) during the treatment of the acute phase of MDD (eight weeks) (Table 18). The mean age of subjects ranged from 70.3 to 70.9 years. This study was rated with low risk of bias and reported industry sponsorship.

Results

Main Outcomes

Table 18. Summary of findings and strength of evidence for adverse effects with vortioxetine versus duloxetine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Findings – Effect Estimate (95 Percent CI)</th>
<th>Interpretation (Based on Statistical Significance)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure-supine SBP, mmHg</td>
<td>Acute</td>
<td>MD 3 (-0.02 to 6.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Acute</td>
<td>DSST MD 2.79 (0.28 to 5.30);</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RAVLT-acquisition MD 1.14 (0.12 to 2.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG- QTc, msec</td>
<td>Acute</td>
<td>MD 2 (-3.36 to 7.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>Acute</td>
<td>MD -0.24 (-0.87 to 0.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidal ideation or behavior</td>
<td>Acute</td>
<td>RR 1.20 (0.57 to 2.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>Acute</td>
<td>MD -0.2 (-0.68 to 0.28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; kg=kilogram; DBP=diastolic blood pressure; DSST=digital symbol substitution test; MD=mean difference; msec=millisecond; n=patient sample size; RAVLT=Rey Auditory Visual Learning Test; RCT=randomized controlled trial; RR=risk ratio; SBP=systolic blood pressure; SOE=strength of evidence

Vortioxetine decreased risk of any adverse event compared with duloxetine [RR 0.80 (0.69 to 0.92)]. The most common adverse events in this trial included nausea, dizziness, headache, fatigue, constipation, dry mouth, somnolence and hyperhidrosis. Data were insufficient to make a conclusion for hip fracture since no events occurred.

Additional Findings

The mean change in standing SBP was 0 mmHg in vortioxetine treated patients and -5 mmHg in duloxetine treated patients, resulting in a mean difference of 5 mmHg (1.61 to 8.39
mmHg), although there were no other statistically significant blood pressure outcomes (Table 19). There was no significant difference between vortioxetine and duloxetine for the majority of other outcomes: QTc interval, sodium, suicidal ideation or behavior, weight, withdrawal due to adverse events or cognitive function. One suicide occurred in the duloxetine arm (0.7 percent).

Table 19. Additional findings for adverse effects with vortioxetine versus duloxetine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Phase</th>
<th>Findings Effect Estimate (95 Percent CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure- standing DBP, mmHg</td>
<td>Acute</td>
<td>MD 1 (-1.07 to 3.07)</td>
</tr>
<tr>
<td>Blood pressure-stading SBP, mmHg</td>
<td>Acute</td>
<td>MD 5 (1.61 to 8.39)</td>
</tr>
<tr>
<td>Blood pressure-supine DBP, mmHg</td>
<td>Acute</td>
<td>MD -1 (-3.06 to 1.06)</td>
</tr>
<tr>
<td>Blood pressure-supine SBP, mmHg</td>
<td>Acute</td>
<td>MD 3 (-0.15 to 6.15)</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Acute</td>
<td>DSST MD 2.02 (-0.48 to 4.52); RAVLT-acquisition MD -0.27 (-1.28 to 0.75); RAVLT-longer delayed memory MD -0.17 (-0.64 to 0.31)</td>
</tr>
<tr>
<td>ECG- QTc, msec</td>
<td>Acute</td>
<td>MD 5 (-0.66 to 10.66)</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>Acute</td>
<td>MD 0.31 (-0.35 to 0.97)</td>
</tr>
<tr>
<td>Suicidal ideation or behavior</td>
<td>Acute</td>
<td>RR 1.65 (0.72 to 3.78)</td>
</tr>
<tr>
<td>Suicide</td>
<td>Acute</td>
<td>RD -0.009 (-0.05 to 0.03)</td>
</tr>
<tr>
<td>Weight</td>
<td>Acute</td>
<td>MD 0.4 (-0.12 to 0.92)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; DSST=digital symbol substitution test; kg=kilogram; DBP=diastolic blood pressure; MD=mean difference; msec=millisecond; n=patient sample size; NNT=number needed to treat; RAVLT=Rey Auditory Visual Learning Test; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; SBP=systolic blood pressure; SNRI=serotonin–norepinephrine reuptake inhibitor; SOE=strength of evidence

KQ 2. In subgroups of older adults (e.g., by age, sex, race, comorbidities) with major depressive disorder, what are the adverse effects and comparative adverse effects of pharmacologic treatments?

Key Points
- Increasing age (≥75 years) was not associated with greater withdrawals due to adverse events with escitalopram or duloxetine (low SOE); it was however associated with greater incidence of serious adverse events (as defined by the study) with escitalopram (low SOE).
- According to a single post-hoc analysis on a RCT, the risk of falls on duloxetine may be associated with the presence of any cardiopulmonary condition (low SOE).

Results

Age
A subgroup analysis of a trial by Gorwood et al. compared two age subgroups from the original cohort of patients 65 years and older; 65 to 74 years and ≥75 years. This trial began with a 12 week escitalopram open-label period followed by a 24 week continuation period where patients were randomized to escitalopram or placebo. During the open-label period, withdrawal due to adverse events occurred similarly in both age subgroups; 25 of the 39 (64.1 percent) withdrawals in the 65 to 74 years group versus 21 of the 33 (63.6 percent) withdrawals in the ≥75 years group (p=0.212). During the randomized continuation treatment period, withdrawal due to adverse events was similar in both age groups; 2.5 percent vs. 3.7 percent. In the overall study, any adverse event was reported similarly between age subgroups; 53.1 percent vs. 58.3 percent, respectively. The difference between age groups in withdrawal due to AE was numerically higher in the older subgroup, 14.2 percent vs. 18.5 percent, respectively, p=0.196.
The commonly reported adverse events that led to withdrawal in both groups included nausea, anxiety and depression. The older age group had a significantly greater number of serious adverse events than did patients 65 to 74 years old; 7.9 percent vs. 2.0 percent, \( p=0.008 \).

An included trial by Raskin et al.\(^5\) compared duloxetine to placebo for 8 weeks of treatment (acute MDD phase) and compared age subgroups of those 65 to 74 years to those \( \geq 75 \) years. Frequency of any adverse event was similar in both age groups and between duloxetine and placebo \(<75 \text{ years duloxetine (70.6 percent) vs. placebo (65.2 percent), } p=0.433; \geq 75 \text{ years duloxetine (68.8 percent) vs. placebo (62.9 percent), } p=0.656; \text{ p}=0.98 \text{ for therapy by subgroup interaction}. \)

Withdrawal due to adverse event rates in patients treated with duloxetine or with placebo were similar regardless of the age subgroup; \(<75 \text{ years duloxetine (7.7 percent) vs. placebo (7.2 percent), } p=1.00; \geq 75 \text{ years duloxetine (14.1 percent) vs. placebo (11.4 percent), } p=1.00. \text{ Comparisons of age subgroups were also made for standing systolic blood pressure which increased in duloxetine vs. placebo (0.12 vs. -0.63 mmHg, } p=0.717 \) patients in the subgroup \(<75 \text{ years of age but a mean decrease in duloxetine vs. placebo (-2.95 vs. 1.09 mmHg, } p=0.368 \) in patients \( \geq 75 \text{ years}. \)

Lastly, a post-hoc analysis\(^6\) of an included study by Robinson et al.\(^1\) evaluated the impact of age on falls. The original trial was conducted in two randomized phases- a 12 week acute phase treatment followed by a second randomization into 12 weeks of continuation treatment with either duloxetine or placebo. Occurrence of falls was actively solicited from each patient during this trial in addition to spontaneous adverse events reporting. The odds of falling on duloxetine were not significantly different in those ages \(<75 \text{ years (OR 1.7) vs. those ages } \geq 75 \text{ years (OR 1.6, } p=0.92. \)

**Risk Factors for Falling, Comorbidities, and Concurrent Medications**

The post hoc analysis\(^6\) of Robinson et. al.\(^1\) also evaluated whether the risk of falls in patients treated with duloxetine varied based on different patient characteristics. The odds of falls were greater in those with a cardiopulmonary condition than in those without such conditions (OR 3.7 vs. 1.2, \( p=0.06 \)). The remaining patient characteristics did not significantly influence odds of falls: orthostatic hypotension (OR 1.7 vs. 1.8, \( p=0.88 \)); neurologic conditions (OR 1.1 vs. 2.0, \( p=0.35 \)); gait conditions (OR 1.5 vs. 2.1, \( p=0.60 \)); alcohol use (OR 2.5 vs. 1.6, \( p=0.51 \)); benzodiazepine or nonbenzodiazepine sleep aid (OR 1.9 vs. 1.6, \( p=0.77 \)); or other sedating medications (OR 1.3 vs. 2.0, \( p=0.51 \)).
Discussion

Key Findings

Nineteen randomized controlled trials (RCTs) and two observational studies constituted the evidence base for this review. Six therapies were compared with placebo: selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, fluoxetine and sertraline), serotonin – norepinephrine reuptake inhibitors (SNRIs) (duloxetine and venlafaxine), bupropion extended release (XR), mirtazapine, trazodone and vortioxetine. Fewer direct comparisons of antidepressants exist: SSRI vs. tricyclic antidepressants (TCAs), within-class comparisons of the SSRIs, SNRI vs. SSRI, mirtazapine vs. paroxetine and vortioxetine vs. duloxetine. None of the RCTs were designed to evaluate adverse events and were not powered to do so, thus our confidence in the findings were attenuated in some circumstances, as reflected in the associated strength of evidence (SOE). Interpretation of these findings was based on statistical significance, thus potentially missing small differences in outcome. Suspected selective outcome reporting was an additional domain that was commonly downgraded, again contributing to lower SOE ratings.

SNRIs, but not SSRIs, were statistically significantly associated with adverse effects when used as treatment during the acute phase of major depressive disorder (MDD), although both classes led to more study withdrawals due to adverse events compared with placebo. SOE was relatively lower for SSRIs than for SNRIs because of imprecision and suspected selective outcome reporting. Unfortunately when studies reported the contributing adverse events they were mostly nonspecific and those most commonly expected according to prescribing information (e.g., nausea, dizziness). Observational data suggests increased adverse events with longer treatment durations for SSRIs and venlafaxine, although SOE was low given the observational design and residual confounding. Serious adverse events may be less frequent with duloxetine (low SOE) compared with placebo during treatment of the acute phase of MDD but not with longer treatment into the continuation phase (moderate SOE). SOE was low and moderate, respectively, owning to study risk of bias and imprecision. In addition, the details of the serious adverse events were not always provided.

Not surprising, we found SSRIs to have fewer adverse events or withdrawal due to adverse events compared with TCAs. Within the SSRI class comparisons, (paroxetine, escitalopram, and sertraline versus fluoxetine) data do not suggest a difference in evaluated harms although any given outcome was usually represented by a single trial with few events. Similarly, comparisons of SNRIs with SSRIs were usually based on a single trial; hence, outcomes did not differ significantly between these two classes. Compared with paroxetine, mirtazapine increased the risk of withdrawal due to adverse events. Vortioxetine was compared with duloxetine in a single trial and decreased the risk of any adverse events.

Clinically it is more informative to understand specific harms associated with antidepressants although we found specific harms to be less frequently reported than general outcomes (i.e. any adverse event or study withdrawals). In older adults, clinicians are often concerned with prescribing therapies that may increase the risk of falls or fractures, in part based on recommendations made in the Beers Criteria.28 Trial data supported an increased risk of falls with duloxetine and a cohort study suggested an association of venlafaxine with falls. The same cohort study found SSRIs as a class to be associated with falls although this outcome hasn’t been studied in RCTs to date; thus, confidence in the association of falls with SSRIs was lower than
with SNRIs. Data directly comparing SNRIs with SSRIs were insufficient regarding outcomes of falls or fractures.

An additional concern regarding prescribing of antidepressants in the elderly is the risk of syndrome of inappropriate antidiuretic hormone (SIADH).28 We found no evidence regarding SIADH for any of the included antidepressants.

Data regarding subgroups of interest (KQ 2) were scarce. Current data suggest that an age greater than 75 years is associated with a greater risk of serious adverse events and that the risk of falls with duloxetine is influenced by the presence of cardiopulmonary disease.

**Findings in Relationship to What Is Already Known**

Comparing our findings with those from prior systematic reviews is difficult for several reasons. First, many earlier reviews in MDD included populations ineligible in our review because their age thresholds were lower (less than 65), thus in this way our review is unique. In addition, earlier systematic reviews12,27 that included any assessment of harms tended to focus on general outcomes such as overall tolerability or discontinuation rates due to adverse events rather than any specific adverse events of more concern in the older population (i.e. falls, fractures, SIADH).

One prior systematic review and network meta-analysis9 in patients 60 years and older in age with MDD found falls to be rare. Three RCTs reported four falls, three in the SSRI arm and one in SNRI arm. Other systematic reviews on SSRIs in older adults allow inclusion of broad indications79,80 One review found SSRIs to be associated with fractures even when adjusted for presence of depression, based on observational studies.80 The second found no experimental study data regarding falls and SSRIs.79 Similarly, we did not find trial data for SSRIs and falls or fractures, although a single cohort study suggested an association with low SOE. This cohort study was not included in these prior reviews.

Recent systematic reviews in younger patients (<65y old) can inform how our findings compare to a younger population. Cipriani et al.81 evaluated safety as part of a large systematic review of 21 antidepressants, in patients 18y and older. Each of the 21 antidepressants were associated with increased drop outs due to adverse events versus placebo during treatment of the acute phase of MDD, including all of the therapies we reviewed in this report. Specific harms were not evaluated. A Cochrane review82 of antidepressants in primary care of patients under the age of 65 found the SSRIs citalopram and escitalopram were not associated with greater risk of adverse events versus placebo [RR 1.08 (0.96 to 1.22)] but did lead to more withdrawals due to harms [RR 2.05 (1.11 to 3.75). These findings were consistent with those in our review. Other than TCAs, additional antidepressants were not studied.

The Beers Criteria recommend that clinicians avoid prescribing SSRIs and TCAs in patients 65 years and older with a history of falls or fractures although note there may be situations where clinicians may decide use to be appropriate.28 The evidence base supporting this particular recommendation is not focused on prescribing SSRIs or TCAs for a specific disease state but rather the use of the class of drugs in the older population generally.83-86 Depression is a known risk factor for falls87 in older adults thus confounding by indication may influence results of analyses evaluating treatment of depression on the outcome of falls. Our review only included studies of patients diagnosed with MDD thus baseline risk of falls due to depression presence should be similar across compared treatment arms. Clinicians should balance risks identified on treatment with risks that may remain present, such as falls, with untreated depression.
Applicability

This review exclusively included studies that required an age of 65 years or older. The included studies were consistent in excluding patients with multiple 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 taking several therapies concurrently. Resulting drug-drug interactions and pharmacokinetic changes must be taken into consideration when prescribing antidepressants.

The doses of antidepressants studied in this evidence base were rarely reflective of the full range cited in guidelines or regulatory documents as the usual dose range in older adults and was most often reflective of the lower half of that range. For example, in 30 active antidepressant arms of the 19 included RCTs, only 6 arms allowed doses that reflect the guideline suggested usual range for older adults. The rest of the treatment arms either limited dose to the lower limit of this range or allowed dosing in the lower half of this dosage range. Therefore, the data in this report does not reflect higher usual antidepressant doses that may be clinically utilized for effective treatment of MDD in this population.

Studies diagnosed major depression mostly using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria and the severity of MDD in the population was moderate based on the mean Hamilton Depression Rating Scale (HAM-D) or Montgomery and Asberg Depression Rating Scale (MADRS) scores. The majority of trials evaluated the acute treatment period up to 12 weeks. Although we aimed to evaluate some therapies on a class basis (SSRI and SNRI), evidence for each drug within the class was not found thus results should not be extrapolated to the class. Concurrent treatments, when described, were usually as-needed therapies for sleep. It should be noted that the setting of focus was outpatient and did not include inpatient or urgent care scenarios.

Limitations

There are several limitations that pertain to the literature base of this review. No evidence was found for a number of the interventions of interest in this review, nor for many of the adverse events we aimed to analyze. Most of the available data featured comparison to placebo and few direct data were found to inform comparative harms of antidepressants. Even when studies were eligible for this review, the small number of trials and limited samples sizes posed an analytic challenge. As an example, the largest literature base was found for the comparison of SSRI to placebo (7 trials and 1 observational study) although for any given outcome, at most three trials were pooled.

None of the studies were powered to evaluate harms as they were all designed to assess efficacy. Interpretations of findings were made based on statistical significance, which may miss small differences due to inadequate power. Many outcomes suffered from the rareness of events where, for example, only one or two events occurred in one arm and zero in the other arm. In several other instances no events were reported in the literature base at all. It should not be assumed that a failure to find a difference means the given interventions are similar in adverse event profiles. The issue of sparse data throughout the evidence base was further complicated by the treatment phase which was being evaluated as most studies were specific to treatment of the acute phase of MDD (<12 weeks), but others evaluated only the continuation or maintenance periods. The least amount of data were available for these longer treatment periods. 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. A majority of the included RCTs, 11 of the 19 RCTs, disclosed industry sponsorship which has potential to introduce bias.\textsuperscript{89}

Most studies relied on spontaneous reporting of adverse events rather than active surveillance and it was difficult to determine if adverse outcomes were defined or pre-specified. Commonly we suspected selective outcome reporting because studies to state that certain measurements were part of the routine clinical monitoring (e.g. vitals, electrocardiogram) although none of these related outcomes were reported in the results. Little data exist regarding subgroups that are of interest in this field and although we sought to collect and analyze such data, only data regarding the impact of age and comorbidities were found.

A single, retrospective, population-based cohort study\textsuperscript{57} was the single source of data identified for some intervention/outcome combinations and suggested associated harms. Although this study was very large and methodologically sound, residual confounding after adjustment for a considerable list of patient characteristics cannot be ruled out. For example, SSRIs and SNRIs were associated with falls. Although adjustments were made for dementia, antihypertensives, sedatives and hypnotics, and prior falls other factors such as hypotension were not included. Comparator subjects had depression diagnosed at some point although differences in depression severity, concomitant medical illnesses, and prior medication history between the populations compared cannot be excluded. Authors of this cohort study also stated that further biases inherent to observational designs such as channeling bias, confounding by indication, and residual confounding could have resulted in differences in patients that informed prescribing different antidepressants which could account for some of the associations seen in the study. Effect sizes for the reported harms were not large and dose-response relationships were not adjusted for. In many cases, this study was the only source of data (e.g. mirtazapine and trazodone) thus consistency of results is unknown. Authors of this cohort study themselves suggested that results should be confirmed in a long-term trial or meta-analysis of RCTs.

**Research Gaps**

There are several research gaps to address in order to more fully understand the adverse events associated with antidepressants in older patients with MDD. Other than SSRIs and SNRIs, we found no evidence for several therapies of interest. Even within the classes of SSRIs and SNRIs, some evidence is specific to a single drug within the class because others have not been studied. There were many outcomes (e.g. SIADH) that we sought to analyze that were not reported in the eligible studies, yet these are important to clinicians and decisionmakers according to the Key Informants, Technical Expert Panelists and partners on this project who helped shape the list of outcomes of interest. Aside from subgroup data based on age and one study that looked at influence of comorbidities, there were no data to evaluate the other subgroups of interests. Again, since these subgroups were identified largely by the stakeholders involved in this review, information about their influence is highly important do the care of older depressed patients. Future studies should include these outcomes and subgroups important to the care of older adults and also account for other important factors such as nursing facility residence.

Aside from comparisons to placebo, limited data were available for direct comparisons among antidepressants. While a decision must first be made as to whether or not to treat MDD
with antidepressants, with more severe depression the more telling decision is likely to be which antidepressant to prescribe, requiring assessment of comparative harms in addition to comparative efficacy. Thus, we believe this literature base overall would benefit from additional research to further characterize comparative harms of antidepressants.

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), vortioxetine and bupropion. 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.


67. Reinlief ME. Change in cognitive functioning following acute antidepressant treatment in late-life depression. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2014;74(12-B(E)).


Appendix A. Search Strategy

Search for KQ 1 and 2 - Medline, Cochrane Central, PsychInfo and Embase all via OVID

1. major depression.mp. or major Depression/
2. major depressive.mp.
3. 1 or 2
4. elderly.mp. or Aged/
5. "Aged, 80 and over"/ or late-life.mp.
6. later-life.mp.
7. older.mp.
8. geriatric.mp.
9. 4 or 5 or 6 or 7 or 8
10. (anti-depressant or antidepressant).mp
11. Antidepressant Agents/
12. paroxetine.mp. or Paroxetine/
13. sertraline.mp. or Sertraline/
14. citalopram.mp. or Citalopram/
15. escitalopram.mp.
16. fluoxetine.mp. or Fluoxetine/
17. fluvoxamine.mp. or Fluvoxamine/
18. selective serotonin reuptake inhibitor.mp. or Serotonin Uptake Inhibitors/
19. venlafaxine.mp. or Venlafaxine Hydrochloride/
20. desvenlafaxine.mp. or Desvenlafaxine Succinate/
21. duloxetine.mp. or Duloxetine Hydrochloride/
22. serotonin norepinephrine reuptake inhibitor.mp.
23. bupropion.mp. or Bupropion/
24. mirtazapine.mp.
25. trazodone.mp. or Trazodone/
26. vilazodone.mp. or Vilazodone Hydrochloride/
27. vortioxetine.mp.
28. milnacipran.mp.
29. levomilnacipran.mp.
30. Serotonin and Noradrenaline Reuptake Inhibitors/
31. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. 3 and 9 and 31
33. Epidemiologic studies/
34. exp cohort studies/
35. exp case controlled studies/
36. Case control.tw.
37. (cohort adj (study or studies)).tw.
38. Cohort analy$.tw.
39. (Follow up adj (study or studies)).tw.
40. (observational adj (study or studies)).tw.
41. Longitudinal.tw.
42. Retrospective.tw.
43. Cross sectional.tw.
44. Cross-sectional studies/
45. or/33-44
46. Randomized Controlled Trials as Topic/
47. randomized controlled trial/
48. Random Allocation/
49. Double Blind Method/
50. Single Blind Method/
51. clinical trial/
52. clinical trial, phase i.pt.
53. clinical trial, phase ii.pt.
54. clinical trial, phase iii.pt.
55. clinical trial, phase iv.pt.
56. controlled clinical trial.pt.
57. randomized controlled trial.pt.
58. multicenter study.pt.
59. clinical trial.pt.
60. exp Clinical Trials as topic/
61. or/46-60
63. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
64. PLACEBOS/
65. placebo$.tw.
66. randomly allocated.tw.
67. (allocated adj2 random$).tw.
68. or/62-67
69. 61 or 68
70. case report.tw.
71. letter/
72. historical article/
73. or/70-72
74. 69 not 73
75. 45 or 74
76. 75 and 32
Appendix B. Excluded Studies


37. Benedictis MRE. Randomized, double-blind comparison of venlafaxine and amitriptyline in outpatients with major depression. 1998; (Conference abstract). [Not in older adults]


56. Bosomworth D, Tollefson G. A double-blind, placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. 1997;79. PMID: 7579025 [Not in older adults]


146. Eli Lilly. Duloxetine versus placebo in the long-term treatment of patients with late-life major depression. 2006. [irretrievable]


[Not in older adults]


[Not in older adults]


172. Finkel S, Newhouse P. SSRIs in the Treatment of Depressed Out Patients Aged 70 Years and Older CONFERENCE ABSTRACT. 1995. [No outcome of interest]


202. GlaxoSmithKline. A Multi-Centre, Randomised, Double-Blind, Parallel-Group, Placebo-Controlled, Flexible Dose Study to Evaluate the Efficacy, Safety and Tolerability of Extended-release Bupropion Hydrochloride (150mg-300mg once daily) in Elderly Subjects with Major Depressive Disorder [NCT00093288; AK130940]. 2006. [duplicate]


204. GlaxoSmithKline. Two Combined Multi-Center, Doxepin-Controlled, Double-Blind Studies of Paroxetine in Geriatric Outpatients with Major Depressive Disorder. 1988. [Not in older adults]


B-24


283. Ko G, Newhouse P. Comparison of Sertraline and Fluoxetine in Depressed Geriatric Outpatients: Plasma Levels and Efficacy CONFERENCE ABSTRACT. 1996. [No outcome of interest]


333. Lundbeck A/S. Randomised, Double-blind, Parallel-group, Placebo-controlled, Duloxetine-referenced, Fixed Dose Study Comparing the Efficacy and Safety of Lu AA21004 in Acute Treatment of Major Depressive Disorder in Elderly Patients [Lundbeck 12541A; NCT00811252]. 2009


416. PMID: 12884889 [Not in older adults]


429. Pollock BG, Mulsant BH. A randomized double-blind comparison of nortriptyline and paroxetine in older depressed patients conference abstract. 1998; [Acute care setting]


460. Rouillon F, et al. A double-blind, multicentre study comparing increasing doses of paroxetine (20-50mg) and clomipramine (50-150mg) in elderly patients with major depression. Poster 29060/069. 1991. [Not a human study]


472. Sanofi-Aventis. An Eight-week, Multinational, Multicenter, Randomized, Double-blind, Placebo-controlled Study, With Escitalopram as an Active Control, to Evaluate the Efficacy, Safety and Tolerability of a Saredutant 100 mg Dose Once Daily, in Elderly Patients With Major Depressive Disorder. 2006. [NCT00415142]. [Not in older adults]


Smeraldi E, Rizzo F, Crespi G. Double-blind, randomized study of venlafaxine, clomipramine and trazodone in geriatric patients with major depression. Primary Care Psychiatry. 1998;4(4):189-195. [Acute care setting]


554. Tourigny Rivard MNN. Fluvoxamine versus desipramine in elderly patients with major depression: A double-blind comparison. 1996; (Conference abstract). [Not in older adults]

555. Tourigny-Rivard MNN. Fluvoxamine versus desipramine in elderly patients with major depression: A double-blind comparison. 1996. [Not in older adults]


557. Trick L, Stanley N, Rigney U, et al. A double-blind, randomized, 26-week study comparing the cognitive and psychomotor effects and efficacy of 75 mg (37.5 mg b.i.d.) venlafaxine and 75 mg (25 mg mane, 50 mg nocte) dothiepin in elderly patients with moderate major depression being treated in general practice. J Psychopharmacol. 2004;18(2):205-214. PMID: 15260909 [No comparator of interest]


## Appendix C. Evidence Tables

### Table C-1. Study and population characteristics, randomized controlled trials

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Study population</th>
<th>Intervention</th>
<th>Age (y) [mean (SD)]</th>
<th>Males (%)</th>
<th>MDD duration [mean (SD)]</th>
<th>Recurrent episode (%)</th>
<th>MADRS [mean (SD)]</th>
<th>HAM-D [mean (SD)]</th>
<th>MMSE [mean (SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchinson, 1991&lt;sup&gt;53&lt;/sup&gt; N=90</td>
<td>≥65y; MDD per DSM-III; HAM-D≥18. Excluded severe concurrent disease, suicidal tendencies, severe depression, drug or alcohol dependence, other psychiatric illness. No concurrent psychotropics allowed, if hypnotic needed temazepam was recommended.</td>
<td>Paroxetine 20mg daily n=58</td>
<td>72.0 (5.6)</td>
<td>20.7</td>
<td>NR</td>
<td>46.6</td>
<td>NR</td>
<td>19.5</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td>Amitriptyline 100mg daily n=32</td>
<td>71.5 (9.5)</td>
<td>71.9</td>
<td>NR</td>
<td>41.0</td>
<td>NR</td>
<td>20.8</td>
<td>NR</td>
</tr>
<tr>
<td>Schone, 1993&lt;sup&gt;42&lt;/sup&gt; N=106</td>
<td>65-85y; MDD per DSM-III-R; HAM-D-21≥18 on first 17 items. Excluded severe physical illness, senile dementia, schizophrenia, organic brain syndrome, alcohol abuse. Concomitant psychotropics prohibited; exception of temazepam 15-30mg pm sleep disturbance.</td>
<td>Paroxetine 20-40mg daily n=54</td>
<td>74.3 (NR)</td>
<td>17</td>
<td>NR</td>
<td>94</td>
<td>NR</td>
<td>29.0</td>
<td>24.2</td>
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<td></td>
<td></td>
<td>Majority (81%) received 20 or 30 mg</td>
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<td></td>
<td>Fluoxetine 20-60mg daily n=52</td>
<td>73.7 (NR)</td>
<td>90</td>
<td>NR</td>
<td>88</td>
<td>NR</td>
<td>27.9</td>
<td>26.0</td>
</tr>
<tr>
<td>Kyle, 1998&lt;sup&gt;52&lt;/sup&gt; N=365</td>
<td>≥65y; MDD per DSM-III-R; MMSE≥24; MADRS≥22. Excluded multiple concurrent diseases, psychiatric disorders, alcohol or drug abuse, other psychiatric illness, suicide risk.</td>
<td>Citalopram 20-40mg in the morning n=179</td>
<td>73.4 (NR)</td>
<td>27</td>
<td>NR</td>
<td>53</td>
<td>27.7</td>
<td>NR</td>
<td>NR</td>
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<td></td>
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<td>Majority (88%) received 20mg</td>
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<td>Amitriptyline 50-100mg in the evening n=186</td>
<td>74.1 (NR)</td>
<td>26</td>
<td>NR</td>
<td>51</td>
<td>30.5</td>
<td>NR</td>
<td>NR</td>
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<td></td>
<td></td>
<td>Majority (86%) received 50mg</td>
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<tr>
<td>Finkel, 1999&lt;sup&gt;18&lt;/sup&gt; N=75</td>
<td>≥70y; MDD per DSM-III-R; MMSE≥24; HAM-D-24≥18. Excluded any significant medical problems, Axis I psychiatric or neurologic conditions, drug abuse, Mean 72.6±25 mg/day</td>
<td>Sertraline 50-100mg daily n=42</td>
<td>74 (3.6)</td>
<td>42.8</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>24.2 (4.4)</td>
<td>28.6 (1.5)</td>
</tr>
<tr>
<td>Study, year</td>
<td>Study population</td>
<td>Intervention</td>
<td>Age (y) [mean (SD)]</td>
<td>Males (%)</td>
<td>MDD duration [mean (SD)]</td>
<td>Recurrent episode (%)</td>
<td>MADRS [mean (SD)]</td>
<td>HAM-D [mean (SD)]</td>
<td>MMSE [mean (SD)]</td>
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<tr>
<td>Finkel, 1999</td>
<td>≥70y; MDD per DSM-III-R; MMSE≥24; HAM-D-24≥18. Excluded acute, unstable medical conditions; psychiatric illness, suicidality, concomitant psychotropics, DSM-III-R organic mental disorders. Chloral hydrate or benzodiazepine hypnotics allowed on prn basis.</td>
<td>Sertraline 50-150mg in the evening</td>
<td>74 (4.4)</td>
<td>33.3</td>
<td>NR</td>
<td>49</td>
<td>NR</td>
<td>24.7 (4.4)</td>
<td>NR</td>
</tr>
<tr>
<td>Cassano, 2002</td>
<td>≥65y; MDD per ICD-10 criteria for depression; MMSE≥22; HAM-D≥18; Raskin Severity of Depression score greater than Covi Anxiety score. Excluded concomitant uncontrolled systemic diseases, high suicide risk, schizophrenia, bipolar, dementia, alcohol or drug abuse. Temazepam for occasional insomnia and short or intermediate half-life benzodiazepines PRN anxiety were allowed.</td>
<td>Paroxetine 20-40mg daily</td>
<td>75.61 (6.99)</td>
<td>39.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>23.2</td>
<td>NR</td>
</tr>
<tr>
<td>Klysner, 2002</td>
<td>≥65y; MDD per DSM-IV; MADRS≥22. Excluded severe somatic disorders, mania, schizophrenia, hypomania, epilepsy, alcohol or drug abuse, suicidality. No concomitant psychotropic medication was allowed, except benzodiazepines and other hypnotics at a constant dose after 8w of phase II.</td>
<td>Citalopram 20-40mg daily</td>
<td>74 (NR)</td>
<td>18</td>
<td>NR</td>
<td>NR</td>
<td>27 (3.4)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Study, year</td>
<td>Study population</td>
<td>Intervention Comparisons</td>
<td>Age (y) [mean (SD)]</td>
<td>Males (%)</td>
<td>MDD duration [SD]</td>
<td>Recurrent episode (%)</td>
<td>MADRS [mean (SD)]</td>
<td>HAM-D [mean (SD)]</td>
<td>MMSE [mean (SD)]</td>
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<td>Schatzberg, 2002&lt;sup&gt;19&lt;/sup&gt;&lt;br&gt;N=254&lt;br&gt;8w acute phase; 16w continuation phase&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Low</td>
<td>≥65y; MDD per DSM-IV; MMSE above 25&lt;sup&gt;th&lt;/sup&gt; percentile for age and education; HAM-D-17≥18. Excluded if HAM-D decreased by ≥20% prior to baseline, unstable or untreated clinically significant medical disease, seizures, alcohol or drug abuse, psychiatric conditions, psychotic features, suicidality. Chloral hydrate (500 mg-1000 mg) or zolpidem (5 mg-10mg) PRN needed for sleep, could continue psychotherapy that had been provided for at least 3m and was stable</td>
<td>Mirtazapine 30-45mg in the evening n=128&lt;br&gt;Mean acute 25.7 (6.7); acute+continuation 34.0 (10.7)</td>
<td>71.7 (6.7)</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>22.2 (3.5)</td>
<td>28.7 (1.2)</td>
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<tr>
<td>Allard, 2004&lt;sup&gt;56&lt;/sup&gt;&lt;br&gt;N=148&lt;br&gt;6m&lt;br&gt;Low</td>
<td>≥65y; MDD per DSM-IV; MADRS≥20; MADRS decreased by ≤2% prior to baseline; MMSE≥24. Excluded drug and alcohol abuse, psychiatric disorders, acutely suicidal, receiving antipsychotics, bipolar, dementia, mental disorders, seizures, significant cardio- or cerebrovascular or HTN. Allowed zopiclone ≤7.5mg/d, zolpidem ≤5mg/d if needed for sleep, and medications for treatment of somatic disorders provided that such medications were not expected to be associated with significant toxicity.</td>
<td>Venlafaxine ER 75-150mg daily n=73&lt;br&gt;54.7% received 150mg</td>
<td>73.6 (5.9)</td>
<td>20.5</td>
<td>NR</td>
<td>NR</td>
<td>27.6 (3.6)</td>
<td>NR</td>
<td>NR</td>
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<td>Citalopram 10-40mg daily n=84</td>
<td>Mean NR</td>
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<td>Roose, 2004&lt;sup&gt;46&lt;/sup&gt;&lt;br&gt;N=174&lt;br&gt;8w&lt;br&gt;Low</td>
<td>≥75y; MDD ≥4w per DSM-IV; HAM-D-24≥24; MMSE≥19. Excluded bipolar, OCD, psychotic disorder, drug and alcohol abuse, suicidal, possible</td>
<td>Citalopram 10-40mg daily n=84</td>
<td>79.8 (4.0)</td>
<td>46.4</td>
<td>NR</td>
<td>NR</td>
<td>24.4 (5.9)</td>
<td>24.4 (4.3)</td>
<td>28.4 (1.6)</td>
</tr>
<tr>
<td>Study, year N Duration Risk of bias</td>
<td>Study population</td>
<td>Intervention Comparisons</td>
<td>Age (y) [mean (SD)]</td>
<td>Males (%)</td>
<td>MDD duration [mean (SD)]</td>
<td>Recurrent episode (%)</td>
<td>MADRS [mean (SD)]</td>
<td>HAM-D [mean (SD)]</td>
<td>MMSE [mean (SD)]</td>
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<td>Kasper, 2005&lt;sup&gt;43&lt;/sup&gt; N=517 8w Low</td>
<td>Alzheimer’s or vascular dementia, Parkinson’s disease, acute, severe or unstable medical illness.</td>
<td>Placebo daily n=90 79.3 (4.7) Males 37.8 NR NR</td>
<td>25.0 (5.9)</td>
<td>24.2 (3.9)</td>
<td>27.6 (2.5)</td>
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<td>≥65y; MDD per DSM-IV; MMSE≥22; MADRS≥22 ≤40. Excluded DSM-IV mania or bipolar, schizophrenia, any psychotic condition, OCD, eating disorders, mental retardation, cognitive disorders, suicidal thoughts.</td>
<td>Escitalopram 10mg daily n=173 75 (7) Males 25 NR NR</td>
<td>28.2 (3.8)</td>
<td>NR</td>
<td>NR</td>
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<td>Fluoxetine 20mg daily n=164 75 (7) Males 23 NR NR</td>
<td>28.5 (3.8)</td>
<td>NR</td>
<td>NR</td>
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<td>Placebo daily n=180 75 (7) Males 24 NR NR</td>
<td>28.6 (4.2)</td>
<td>NR</td>
<td>NR</td>
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<td>Reynolds, 2006&lt;sup&gt;46&lt;/sup&gt; N=53 8w OL acute phase; 16w OL continuation phase; 2y RCT maintenance phase&lt;sup&gt;*&lt;/sup&gt; High</td>
<td>≥70y; MDD (nonpsychotic, nonbipolar) per DSM-IV SCID version 2.0; HAM-D-17≥15; MMSE≥17. 19 patients in each randomized arm received augmented therapy with bupropion, lithium or nortriptyline.</td>
<td>Paroxetine 10-40mg daily n=35 77.0 (5.9) Males 40 NR NR</td>
<td>19.5 (2.7)</td>
<td>27.5 (2.5)</td>
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<td></td>
<td>Placebo daily n=18 74.8 (4.4) Males 44 NR NR</td>
<td>39 NR</td>
<td>19.8 (2.4)</td>
<td>28.7 (1.1)</td>
<td></td>
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<tr>
<td>Schatzberg, 2006&lt;sup&gt;45&lt;/sup&gt; N=300 8w Low</td>
<td>≥65y; MDD≥4w per DSM-IV; MMSE≥19; HAM-D-21≥20 and no more than 20% decrease prior to randomization. Excluded bipolar, psychotic disorder unrelated to depression, substance abuse, suicidal intent, seizures, severe acute, or unstable medical illness. Chloral hydrate ≤1000mg, zolpidem ≤10mg PRN sleep; non-psychopharmacologic drugs with psychotropic effects if the patient was on a stable dose for ≥1m (3m for thyroid hormone medication) and psychotherapy if well established before the study were allowed.</td>
<td>Venlafaxine IR 37.5-112.5mg BID n=104 71 (NR) Males 44 NR NR</td>
<td>26 (NR)</td>
<td>24 (NR)</td>
<td>NR</td>
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<td>Fluoxetine 20-60mg daily n=100 71 (NR) Males 55 NR NR</td>
<td>27 (NR)</td>
<td>24 (NR)</td>
<td>NR</td>
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<td></td>
<td>Placebo BID n=96 71 (NR) Males 54 NR NR</td>
<td>27 (NR)</td>
<td>23 (NR)</td>
<td>NR</td>
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<tr>
<td>Study, year</td>
<td>Study population</td>
<td>Intervention Comparisons</td>
<td>Age (y) [mean (SD)]</td>
<td>Males (%)</td>
<td>MDD duration [mean (SD)]</td>
<td>Recurrent episode (%)</td>
<td>MADRS [mean (SD)]</td>
<td>HAM-D [mean (SD)]</td>
<td>MMSE [mean (SD)]</td>
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<td>Gorwood, 2007</td>
<td>≥65y; MDD≥4w per DSM-IV-TR; MMSE≥24; MADRS&gt;22. Excluded unstable serious illness, manic or hypomanic episode, schizophrenia, other psychotic disorders, mental retardation, organic mental disorders, substance abuse, neurologic or neurodegenerative disease, personality disorder.</td>
<td>Escitalopram 10-20mg daily n=152 Mean NR</td>
<td>73 (NR)</td>
<td>21.7</td>
<td>NR</td>
<td>NR</td>
<td>5.1 (4.8)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Raskin, 2008</td>
<td>≥65y; MDD per DSM-IV; MMSE≥20 with or without mild dementia; HAM-D-17≥18, ≥1 prior MDD episode. Excluded primary axis I diagnosis other than MDD or mild dementia, psychotic disorder, organic mental disorder, moderate to severe dementia, mental retardation, serious or unstable medical illness.</td>
<td>Duloxetine 60mg daily n=207</td>
<td>72.6 (5.7)</td>
<td>39.6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>22.4 (3.8)</td>
<td>NR</td>
</tr>
<tr>
<td>Fraguas, 2009</td>
<td>&gt;65y; stable HF w/LVEF&lt;50%; MOD per DSM-IV onset after cardiac symptoms; HAM-D-31≥18. Excluded hemodynamically significant vascular disease, recent cardiac surgery, other significant medical conditions, Axis 1 psychiatric conditions except anxiety, substance abuse, suicidal. Zolpidem 5mg/day was permitted.</td>
<td>Citalopram 20-40mg daily n=19 Mean NR</td>
<td>74.4 (6.0)</td>
<td>52.6</td>
<td>NR</td>
<td>NR</td>
<td>21.9 (5.6)</td>
<td>22.9 (3.0)</td>
<td>NR</td>
</tr>
<tr>
<td>Hewett, 2010</td>
<td>≥65y; MDD≥8w per DSM-IV; MMSE≥4; HAM-D-17≥18 with less than 25% change prior to randomization; CGI-S≤4. Excluded unstable medical conditions, homicidal or suicidal, anorexia nervosa or bulimia, psychotic conditions, substance abuse.</td>
<td>Bupropion XR 150-300mg daily n=211 Mean 179 mg/day</td>
<td>70.9 (5.6)</td>
<td>26</td>
<td>NR</td>
<td>65</td>
<td>29.5 (0.3)e</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = Not Reported
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Study population</th>
<th>Intervention</th>
<th>Comparisons</th>
<th>Age (y) [mean (SD)]</th>
<th>Males (%)</th>
<th>MDD duration [mean (SD)]</th>
<th>Recurrent episode (%)</th>
<th>MADRS [mean (SD)]</th>
<th>HAM-D [mean (SD)]</th>
<th>MMSE [mean (SD)]</th>
</tr>
</thead>
</table>
| Katona, 2012<sup>25</sup>  
N=452  
8w  
Low  
Risk of bias | ≥65y; MDD≥4w per DSM-IV-TR; MMSE≥24; MADRS≥26, ≥1 prior MDD episode prior to age 60y. Excluded other psychiatric conditions, manic or hypomanic, schizophrenia, mental disorders, substance abuse, clinically significant neurologic disorders, neurodegenerative disorders, suicidal. | Vortioxetine 5mg daily  
n=156 | 70.5 (4.8) | 31.4 | NR | NR | 30.7 (3.6) | 29.2 (5.0) | NR |
| | Duloxetine 60mg daily  
n=151 | 70.9 (5.5) | 33.8 | NR | NR | 30.4 (3.1) | 28.5 (4.9) | NR |
| | Placebo daily  
n=145 | 70.3 (4.4) | 37.9 | NR | NR | 30.3 (3.2) | 29.4 (5.1) | NR |
| Robinson, 2014<sup>22</sup>  
N=370  
12w RCT  
acute phase;  
10w RCT  
continuation period<sup>3</sup>  
Low  
Risk of bias | ≥65y; MDD per DSM-IV-TR; MMSE≥20; MADRS≥20. Excluded bipolar, OCD, panic disorder, Axis 1 other than MDD, suicidal risk, serious unstable medical illness or lab abnormality. | Duloxetine 60-120mg daily  
n=249 | 72.89 (6.10) | 34.5 | NR | 100 | 29.25 (5.57) | 19.42 (5.56) | 28.55 (1.83) |
| | Acute: 45% received 60mg/d; Continuation: 63% received 60 mg/d | | | | | | |
| | Placebo daily<sup>9</sup>  
n=121 | 73.02 (5.64) | 41.3 | NR | 100 | 28.46 (5.40) | 19.32 (5.78) | 28.42 (1.72) |

Abbreviations: BID=twice a day; CGI=clinical global impression; d=day; DSM-III=diagnostic and statistical manual of mental disorders, 3rd edition; DSM-III-R=diagnostic and statistical manual of mental disorders, 3rd edition, revision; DSM-IV=diagnostic and statistical manual of mental disorders, 4th edition, text revision; ER=extended release; HAM-D=Hamilton depression rating scale; HF=heart failure; HTN=hypertension; ICD-10=International statistical classification of diseases and related health problems, 10th revision; IR=instant release; LVEF=left ventricular ejection fraction; m=months; MADRS=Montgomery-Åsberg depression rating scale; MDD=major depressive disorder; Mg=milligram; MMSE=mini-mental state examination; NR=not reported; OCD=obsessive-compulsive disorder; OL=open-label; PRN=when necessary; R, DB=randomized, double-blind; RCT=randomized-controlled trial; SCID=structured clinical interview for DSM-IV-TR Axis I disorders; SD=standard deviation; w=weeks; XR=extended release; y=years

<sup>a</sup>Phase I was 8w of open, acute treatment with citalopram. Patients with MADRS ≤11 entered phase II, a 16w open continuation treatment with citalopram. Patients completing phase II with MADRS ≤11 entered phase III, a 48w double-blind treatment phase with citalopram or placebo

<sup>b</sup>8-week double-blind, randomized, comparative trial of mirtzapine and paroxetine. Responders (CGI improvement score of much or very much improved and/or HAM-D-17 total score decreases of 50% or more from baseline) were eligible to continue treatment for 16w under double-blind conditions

<sup>c</sup>Patients were initially included in a short-term (8-week) treatment phase. Patients with a clinical response (Hamilton score of 0 to 10 for 3 consecutive weeks) began 16 weeks of continued treatment, which was intended to stabilize and further improve the clinical response. Full or partial responders were then randomly assigned to a two-year maintenance-treatment program

<sup>d</sup>12-week open-label treatment phase followed by a 24-week, randomized, double-blind treatment phase only for those in remission (MADRS≤12) after the open-label phase

<sup>e</sup>Standard error

<sup>f</sup>Randomized to duloxetine or placebo for 12 weeks. During the acute phase, patients requiring dosage decrease due to safety/tolerability or increase due to efficacy reasons were discontinued. From weeks 12 until 20 (continuation phase), placebo rescue or duloxetine dose optimization was available if the patient had less than 50% improvement from baseline on the HAM-D-17 total score at week 12 or HAM-D-17 score more than 10 at weeks 16 or 20, and therapy adjustment as deemed appropriate by the investigator

<sup>g</sup>Patients received placebo for 12 weeks; From weeks 12 until 20 placebo rescue was available. Placebo-responded patients received duloxetine 30 mg/day for 1 week with an increase to 60 mg/day for the remainder of the trial
Table C-2. Study and population characteristics—observational studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Study population</th>
<th>Intervention</th>
<th>Comparisons</th>
<th>Age (y) [mean (SD)]</th>
<th>Males (%)</th>
<th>MDD duration [mean (SD)]</th>
<th>Recurrent episode (%)</th>
<th>MADRS [mean (SD)]</th>
<th>HAM-D [mean (SD)]</th>
<th>MMSE [mean (SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 200857</td>
<td>N=1976</td>
<td>Escitalopram N=459</td>
<td>73.5 (4.8)</td>
<td>44</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Retrospective, claims-based cohort</td>
<td>Other SSRI/SNRI n=1517</td>
<td>73.6 (4.9)</td>
<td>43.2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Coupland, 201156</td>
<td>N=60,746 patients; 1,398,359 prescriptions</td>
<td>SSRI n=764,659 prescriptions</td>
<td>75.0ᵃ (NR)</td>
<td>33.3ᵃ</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Retrospective, population-based cohort</td>
<td>TCA n=442,192 prescriptions</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Other antidepressantᵇ n= 189,305 prescriptions</td>
<td></td>
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<tr>
<td></td>
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<td>No antidepressant n=6,708 patients</td>
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</tbody>
</table>

Abbreviations: CESD-R=the Center for Epidemiologic Studies depression-revised; HAM-D=Hamilton depression rating scale; MADRS=Montgomery-Åsberg depression rating scale; MDD=major depressive disorder; MMSE=mini-mental state examination; NR=not reported; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; WHI=women’s health initiative; y=years

ᵃFor the full study cohort
ᵇDefined as antidepressant other than SSRI, TCA or MAOI according to the British National Formulary
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchinson, 1991</td>
<td>SSRI (paroxetine) vs TCA (amitriptyline)</td>
<td>Any ADE 20/58 vs. 20/32</td>
</tr>
<tr>
<td>N=90</td>
<td>Risk of bias: Low</td>
<td>Mortality 0/58 vs. 1/32</td>
</tr>
<tr>
<td>6w</td>
<td>Mortality due to ADE 8/58 vs. 6/32</td>
<td>Withdrawal due to ADE 8/58 vs. 6/32</td>
</tr>
<tr>
<td>Schone, 1993</td>
<td>SSRI (paroxetine) vs SSRI (fluoxetine)</td>
<td>Withdrawal due to ADE 6/54 vs. 7/52</td>
</tr>
<tr>
<td>N=106</td>
<td>Risk of bias: Unclear</td>
<td></td>
</tr>
<tr>
<td>6w</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyle, 1998</td>
<td>SSRI (citalopram) vs TCA (amitriptyline)</td>
<td>Any ADE 112/179 vs. 146/186</td>
</tr>
<tr>
<td>N=365</td>
<td>Risk of bias: Low</td>
<td>Hospitalization 0/179 vs. 1/186</td>
</tr>
<tr>
<td>8w</td>
<td>Mortality 7/179 vs. 11/186</td>
<td>Withdrawal due to ADE 31/179 vs. 48/186</td>
</tr>
<tr>
<td>Finkel, 1999</td>
<td>SSRI (sertraline) vs SSRI (fluoxetine)</td>
<td>Cognitive function: HAM-D Cognitive factor score 1.7(2.4) vs. 1.2(3)</td>
</tr>
<tr>
<td>N=75</td>
<td>Risk of bias: High</td>
<td>Cognitive function: DSST score -6(18.3) vs. -6(17.2)</td>
</tr>
<tr>
<td>12w</td>
<td>Mortality due to ADE 8/42 vs. 10/33</td>
<td>Withdrawal due to ADE 8/42 vs. 10/33</td>
</tr>
<tr>
<td>Finkel, 1999</td>
<td>SSRI (sertraline) vs TCA (nortriptyline)</td>
<td>Cognitive impairment 2/38 vs. 5/37</td>
</tr>
<tr>
<td>N=76</td>
<td>Risk of bias: High</td>
<td>Serious ADE 5/39 vs. 11/37</td>
</tr>
<tr>
<td>12w</td>
<td>Mortality due to ADE 7/39 vs. 11/37</td>
<td>Withdrawal due to ADE 7/39 vs. 11/37</td>
</tr>
<tr>
<td>Cassano, 2002</td>
<td>SSRI (paroxetine) vs SSRI (fluoxetine)</td>
<td>Any ADE 34/123 vs. 39/119</td>
</tr>
<tr>
<td>N=242</td>
<td>Risk of bias: Low</td>
<td>Mortality 2/123 vs. 2/119</td>
</tr>
<tr>
<td>12m</td>
<td>Mortality due to ADE 7/123 vs. 12/119</td>
<td>Serious ADE 0/123 vs. 1/119</td>
</tr>
<tr>
<td>Klysner, 2002</td>
<td>SSRI (citalopram) vs placebo for 48w maintenance phase</td>
<td>Blood pressure: hypertension 1/60 vs. 2/61</td>
</tr>
<tr>
<td>N=121</td>
<td>Risk of bias: High</td>
<td>Blood pressure: sitting DBP (mmHg) -3(15) vs. 1(15)</td>
</tr>
<tr>
<td>8w OL acute phase; 16w OL continuation phase; 48w RDB maintenance phase</td>
<td>Blood pressure: sitting SBP (mmHg) -3(32.9) vs. 2(30)</td>
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</tr>
<tr>
<td></td>
<td>Mortality 0/60 vs. 1/61</td>
<td>Mortality 0/60 vs. 1/61</td>
</tr>
<tr>
<td></td>
<td>Serious ADE 11/61 vs. 5/61</td>
<td>Withdrawal due to ADE 6/60 vs. 8/61</td>
</tr>
<tr>
<td>Study, year</td>
<td>Comparison</td>
<td>Outcomes</td>
</tr>
<tr>
<td>---------------------</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Schatzberg, 2002</td>
<td>Mirtazapine vs. paroxetine-8w acute phase</td>
<td>Any ADE 102/208 vs. 104/126</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood pressure: Hypotension 0/128 vs. 0/126</td>
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<tr>
<td></td>
<td></td>
<td>Hospitalization 0/128 vs. 1/126</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serious ADE 3/128 vs. 3/126</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain ≥7% 5/128 vs. 0/126</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain, patient reported 14/128 vs. 0/126</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight (kg) 1.7(21.5) vs. -0.3(20.5)</td>
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<tr>
<td></td>
<td></td>
<td>Withdrawal due to ADE 19/128 vs. 33/126</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine vs. paroxetine-16w continuation phase</td>
<td>Any ADE 40/63 vs. 28/55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain ≥7% 9/63 vs. 2/55</td>
</tr>
<tr>
<td>Allard, 2004</td>
<td>SNRI (venlafaxine ER) vs. SSRI (citalopram)-8w acute phase</td>
<td>Blood pressure: DBP (mmHg) -1.95(9.08) vs. -0.49(9.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood pressure: SBP (mmHg) -5.94(14.04) vs. -3.62(15.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight (kg): -0.4(18.8) vs. -0.6(14.6)</td>
</tr>
<tr>
<td></td>
<td>SNRI (venlafaxine ER) vs. SSRI (citalopram)-22w continuation phase</td>
<td>Blood pressure: DBP (mmHg) -0.91(9.0) vs. -0.50(7.38)</td>
</tr>
<tr>
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<td></td>
<td>Blood pressure: SBP (mmHg) -2.93(15.26) vs. -0.45(11.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Falls 0/73 vs. 1/75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fracture, hip 1/73 vs. 0/75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight (kg): -1(18.8) vs. -0.1(15)</td>
</tr>
<tr>
<td></td>
<td>SNRI (venlafaxine ER) vs. SSRI (citalopram)-6m</td>
<td>Any ADE 45/73 vs. 57/75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality 0/73 vs. 1/75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serious ADE 5/73 vs. 4/75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawal due to ADE 6/73 vs. 4/75</td>
</tr>
<tr>
<td>Roose, 2004</td>
<td>SSRI (citalopram) vs. placebo</td>
<td>Withdrawal due to ADE 9/84 vs. 1/90</td>
</tr>
<tr>
<td>Study, year</td>
<td>Comparison</td>
<td>Outcomes</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
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</tr>
</tbody>
</table>
| Kasper, 2005[^3] | SSRI (escitalopram) vs. SSRI (fluoxetine) vs. placebo | Any ADE 88/173 vs. 93/164 vs. 96/180  
Blood pressure: HTN 4/173 vs. 4/164 vs. 11/180  
Blood pressure: orthostatic hypotension 2/173 vs. 1/164 vs. 1/180  
Mortality 1/173 vs. 0/164 vs. 1/180  
Suicide 1/173 vs. 0/164 vs. 0/180  
Withdrawal due to ADE 17/173 vs. 20/164 vs. 5/180 |
| Reynolds, 2006[^4] | SSRI (paroxetine) vs. placebo -2y maintenance phase | Blood pressure: orthostatic hypotension 29/35 vs. 10/18  
Suicide 0/35 vs. 0/18  
Weight (kg) 5.91(8.94) vs. 2.71(9.77)  
Withdrawal due to ADE 1/35 vs. 0/18 |
| Schatzberg, 2006[^5] | SNRI (venlafaxine IR) vs. SSRI (fluoxetine) vs. placebo | Any ADE 96/102 vs. 94/100 vs. 83/96  
Blood pressure: HTN-SBP 5/102 vs. 4/100 vs. 5/96  
Weight loss 1/102 vs. 6/100 vs. 0/96  
Withdrawal due to ADE 27/104 vs. 19/100 vs. 9/96 |
| Gorwood, 2007[^6] | SSRI (escitalopram) vs. placebo – 24w continuation phase | Any ADE 53/130 vs. 54/91  
Withdrawal due to ADE 4/152 vs. 7/153 |

[^3]: N=517  
8w  
Low  
[^4]: N=53  
8w OL acute phase; 16w OL continuation phase; 2y RCT maintenance phase c  
High  
[^5]: N=300  
8w  
Low  
[^6]: N=305  
12w OL acute phase; 24w RCT continuation phase d  
High
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Raskin, 2008<sup>64</sup>  
N=311  
8w  
High | **SNRI (duloxetine) vs. placebo**  
Any ADE 145/207 vs. 67/104  
Blood pressure: elevated supine DBP 8/201 vs. 4/102  
Blood pressure: elevated supine SBP 32/201 vs. 14/102  
Blood pressure: sustained elevated supine DBP 1/201 vs. 0/102  
Blood pressure: sustained elevated supine SBP 0/201 vs. 1/102  
Blood pressure: standing DBP (mmHg) -0.20(9.49) vs. -0.58(9.66)  
Blood pressure: standing SBP(mmHg) -2.13(14.60) vs. -0.33(15.30)  
Blood pressure: supine DBP (mmHg) 1.59(9.45) vs. 1.07(8.25)  
Blood pressure: supine SBP (mmHg) 0.77(15.14) vs. -0.80(15.57)  
Blood pressure: orthostatic hyptension 59/201 vs. 28/102  
Blood pressure: orthostatic DBP (mmHg) -1.80(7.69) vs. -1.65(8.54)  
Blood pressure: orthostatic SBP (mmHg) -2.90(11.83) vs. 0.47(10.87)  
Cognitive function: SDST 3.78(11.62) vs. 4.03(10.94)  
Cognitive function: 2DCT -1.35(5.61) vs. -0.52(5.37)  
ECG: treatment emergent abnormal ECG 66/189 vs. 36/93  
ECG: QTc (ms) Fridericia correction -2.55(18.34) vs. -1.50(17.19)  
ECG: QTc (ms) Bazzett correction -1.12(17.05) vs. -1.71(19.46)  
Falls 5/207 vs. 3/104  
Mortality 0/207 vs. 0/104  
Serious ADE 1/207 vs. 3/104  
Sodium (mEq/L) -0.79(3.45) vs. -0.34(3.21)  
Weight gain ≥7% 2/207 vs. 0/104  
Weight loss ≥7% 3/207 vs. 2/104  
Weight (kg) -0.76(2.06) vs. -0.09(1.58)  
Withdrawal due to ADE 20/207 vs. 9/104 |  |
| Fraguas, 2009<sup>50</sup>  
N=37  
8w  
High | **SSRI (citalopram) vs. placebo**  
Blood pressure: DBP rest (mmHg) 0(21.2) vs. -1.25(19.1)  
MD 1.25 (-12.24 to 14.74)  
Blood pressure: DBP exercise (mmHg) -7.5(19.6) vs. -10(11.6)  
MD 2.5(-8.33 to 13.33)  
Blood pressure: SBP rest (mmHg) 3(41.4) vs. 1.25(27.9)  
MD 1.75(-21.95 to 25.45)  
Blood pressure: SBP exercise (mmHg) -18.75(43.5) vs. -5(36.7)  
MD -13.75 (-40.69 to 13.19)  
Withdrawal due to ADE 0/19 vs. 1/18  
RD -0.06 (-0.26 to 0.13) |  |
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Comparison</th>
<th>Outcomes&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| **Hewett, 2010**<sup>14</sup> | **Bupropion XR vs. placebo** | Any ADE 121/211 vs. 122/207  
Blood pressure: SBP, clinically significant increase 23/211 vs. 35/207  
Blood pressure: DBP, clinically significant increase 19/211 vs. 15/207  
Blood pressure: SBP, sustained increase 8/211 vs. 6/207  
Blood pressure: DBP, sustained increase 13/211 vs. 17/207  
ECG: Supraventricular arrhythmia 0/211 vs. 1/207  
Mortality 0/211 vs. 0/207  
Seizures 0/211 vs. 0/207  
Serious ADE 2/211 vs. 7/207  
Withdrawals due to serious ADE 17/211 vs. 22/207 |
| **Katona, 2012**<sup>15</sup> | **SNRI (duloxetine) vs. vortioxetine vs. placebo** | Any ADE 118/151 vs. 97/159 vs. 89/145  
Blood pressure: standing DBP (mmHg) -2(8) vs. -1(9) vs. -2(9)  
Blood pressure: standing SBP (mmHg) -5(14) vs. 0(14) vs. -2(13)  
Blood pressure: supine DBP (mmHg) -1(9) vs. -2(8) vs. -2(9)  
Blood pressure: supine SBP (mmHg) -3(14) vs. 0(12) vs. -3(13)  
Cognitive function: DSST 2.28(10.88) vs. 4.30(0.89) vs. 1.51(10.98)  
MD 0.77 (-1.76 to 3.31)  
Cognitive function: RAVLT Acquisition 3.72(4.41) vs. 3.45(0.36) vs. 2.31(4.44)  
Cognitive function: RAVLT Longer delayed memory 1.58(2.06) vs. 1.42(2.08) vs. 0.94(2.08)  
Fractures 0/151 vs. 0/156 vs. 1/145  
Serious ADE 1/151 vs. 1/156 vs. 4/145  
Sodium (mEq/L) -0.91(2.61) vs. -0.6(2.82) vs. -0.36(2.41)  
Suicidal thoughts 8/114 vs. 14/121 vs. 11/114  
Suicide 1/114 vs. 0/121 vs. 0/114  
Weight (kg) -0.7(2.1) vs. -0.3(2.2) vs. -0.1(1.8)  
Withdrawal due to ADE 9/156 vs. 9/156 vs. 4/145 |
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Duration</th>
<th>Risk of bias</th>
<th>Comparison</th>
<th>Outcomes*</th>
</tr>
</thead>
</table>
| Robinson, 2014<sup>22,81</sup> | N=370 | Low | SNRI (duloxetine) vs. placebo – 12w acute phase | Blood pressure: supine DBP (mmHg) 1.89(9.7) vs. -1.58(10)  
Blood pressure: supine SBP (mmHg) 0.19 (14.7) vs. -0.58 (15.1)  
Blood pressure: orthostatic DBP (mmHg) -0.94(8.2) vs. 2.28(8.5)  
Blood pressure: orthostatic SBP (mmHg) 0.27(10) vs. 2.29(10.4)  
Blood pressure: orthostatic hypotension 57/249 vs. 27/121  
Cognitive function: SDST 1.98(10.28) vs. 3.99(9.87)  
Cognitive function: 2DCT 0.3(6.22) vs. 0.94(5.98)  
Cognitive function: MMSE 0.12(1.64) vs. 0.24(1.50)  
MD -0.12 (-0.57 to 0.33)  
Cognitive function: composite cognitive score -0.38(5.14) vs. 0.01(4.84)  
MD -0.39 (-1.67 to 0.89)  
Cognitive function: Learning trials -0.06(1.62) vs. -0.04(1.61)  
MD -0.02 (-0.43 to 0.39)  
Cognitive function: Delayed recall score -0.65(2.84) vs. -0.59(2.66)  
MD 0.8 (0.09 to 1.51)  
Cognitive function: Trail making test -5.6(39.23) vs. -3.09(37.95)  
MD -5.6 (-2.51 to 7.33);  
Falls 40/249 vs. 12/121  
Mortality 0/249 vs. 0/121  
Weight (kg) -0.86(2.67) vs. 0.06(2.82) |
| | 12w RCT acute phase; 10w RCT continuation period<sup>e</sup> |  | SNRI (duloxetine) vs. placebo – 22w acute + continuation phase | Blood pressure: elevated supine SBP 28/119 vs. 7/58  
Blood pressure: elevated supine DBP 22/210 vs. 5/98  
Blood pressure: supine DBP (mmHg) 2.44(10.7) vs. 0.65(13.4)  
Blood pressure: supine SBP (mmHg) 2.22(17.1) vs. 0.54(21.6)  
Blood pressure: orthostatic hypotension 57/249 vs. 27/121  
Blood pressure: orthostatic DBP (mmHg) -1.53(8.9) vs. 0.84(11.7)  
Blood pressure: orthostatic SBP (mmHg) -1.92 (13.8) vs. 0.50 (18.2)  
Cognitive function: SDST 1.98(10.28) vs. 3.99(9.87)  
Cognitive function: 2DCT 0.3(6.22) vs. 0.94(5.98)  
Cognitive function: MMSE 0.29(1.65) vs. 0.35(1.52)  
MD -0.06 (-0.51 to 0.69)  
Cognitive function: composite cognitive score 0.96(5.41 vs. 0.31(5.12)  
MD 0.65 (-0.7 to 2)  
Cognitive function: Learning trials 0.34(1.76) vs. 0.06(1.71)  
MD 0.28 (-0.16 to 0.72)  
Cognitive function: Delayed recall score 0.12(2.98) vs. -0.36(2.75)  
MD 0.58 (-0.16 to 1.32);  
Cognitive function: Trail making test -1.59(38.15) vs. -6.86(36.62)  
MD 5.27 (-4.27 to 14.81);  
ECG: Arrhythmia 1/249 vs. 0/121  
ECG: QTc (ms) Fridericia correction -5.02 (20.6) vs. -5.91 (19.2)  
ECG: QTc (ms) Bazzett correction -1.38 (22.4) vs. -3.78 (21)  
Falls 59/249 vs. 17/121  
Fracture, ankle 1/249 vs. 0/121  
Fracture, hip 1/249 vs. 0/121 |
Abbreviations: 2DCT=2-digit cancellation test; ADE=adverse event; DBP=diastolic blood pressure; DSST=digit symbol substitution test; ECG=electrocardiogram; HAMD=Hamilton Depression Rating Scale; HTN=hypertension; kg=kilograms; mmHg=millimeters of mercury; MD=mean difference; MMSE=mini mental status exam; NA=not applicable; OL=open label; RAVLT=Rey’s auditory verbal learning test; SDST=symbol digit substitution test; SBP=systolic blood pressure; SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

aN/N per arm for dichotomous outcomes and mean (SD) per arm for continuous outcomes

Phase I was 8w of open, acute treatment with citalopram. Patients with MADRS ≤11 entered phase II, a 16w open continuation treatment with citalopram. Patients completing phase II with MADRS ≤11 entered phase III, a 48w double-blind treatment phase with citalopram or placebo

8-week double-blind, randomized, comparative trial of mirtazapine and paroxetine. Responders (CGI improvement score of much or very much improved and/or HAM-D-17 total score decreases of 50% or more from baseline) were eligible to continue treatment for 16w under double-blind conditions

Patients were initially included in a short-term (8-week) treatment phase. Patients with a clinical response (Hamilton score of 0 to 10 for 3 consecutive weeks) began 16 weeks of continued treatment, which was intended to stabilize and further improve the clinical response. Full or partial responders were then randomly assigned to a two-year maintenance-treatment program

12-week open-label treatment phase followed by a 24-week, randomized, double-blind treatment phase only for those in remission (MADRS≤12) after the open-label phase

Randomized to duloxetine or placebo for 12 weeks. During the acute phase, patients requiring dosage decrease due to safety/tolerability or increase due to efficacy reasons were discontinued. From weeks 12 until 20 (continuation phase), placebo rescue or duloxetine dose optimization was available if the patient had less than 50% improvement from baseline on the HAMD-17 total score at week 12 or HAMD-17 score more than 10 at weeks 16 or 20, and therapy adjustment as deemed appropriate by the investigator
# Appendix D. Risk of Bias Assessment

## Table D-1. Risk of bias assessment

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Sequence Generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants, personnel</th>
<th>Blinding of Outcome assessors</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>Other sources of bias</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchinson, 1991</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>High(^a)</td>
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<tr>
<td>Schone, 1993</td>
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<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
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<tr>
<td>Kyle, 1998(^b)</td>
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<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>High(^a)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Finkel, 1999(^c)</td>
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<td>Low</td>
<td>Unclear</td>
<td>High(^d)</td>
<td>Low</td>
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<tr>
<td>Finkel, 1999(^d)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>High(^d)</td>
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<tr>
<td>Cassano, 2002(^e)</td>
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<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>High(^d)</td>
<td>Low</td>
<td>High</td>
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<tr>
<td>Kiysner, 2002(^f)</td>
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<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>High(^e)</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Schatzberg, 2002(^g)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>High(^e)</td>
<td>Low</td>
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<tr>
<td>Allard, 2004(^h)</td>
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<td>Unclear</td>
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<td>Unclear</td>
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<tr>
<td>Roose, 2004(^i)</td>
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<td>Low</td>
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<td>Unclear</td>
<td>High(^k)</td>
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<tr>
<td>Kasper, 2005(^j)</td>
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<td>Unclear</td>
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<td>Unclear</td>
<td>Low</td>
<td>High(^j)</td>
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<tr>
<td>Reynolds, 2006(^k)</td>
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<td>Unclear</td>
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<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>High(^h)</td>
<td>High</td>
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<tr>
<td>Schatzberg, 2006(^l)</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>High(^h)</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Gorwood, 2007(^m)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High(^f)</td>
<td>High(^h)</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Raskin, 2008(^n)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>High(^f)</td>
<td>High</td>
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<tr>
<td>Fraguas, 2009(^o)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>High(^f)</td>
<td>High</td>
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<tr>
<td>Hewett, 2010(^p)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>High(^f)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Katona, 2012(^q)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Robinson, 2014(^r)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High(^f)</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Study methods indicate that blood chemistries were collected but these outcomes are not reported in the results  
\(^b\)Study methods indicate that suicide attempts and laboratory abnormalities were collected but these outcomes are not reported in the results  
\(^c\)High overall attrition (37.3\%) and unclear methods to handle dropouts  
\(^d\)Study methods indicate that supine and standing systolic and diastolic blood pressure, electrocardiograms, and weight were collected but these outcomes are not reported in the results  
\(^e\)High overall (40.8\%) and differential (15.3\%) attrition  
\(^f\)Study methods indicate that blood pressure, blood chemistries, and weight were collected but these outcomes are not reported in the results  
\(^g\)High overall (76.0\%) and differential (28.5\%) attrition  

---

D-1
Study methods indicate that vital sign measurements, laboratory assessments, and weight were collected but these outcomes are not reported in the results.

Two single-arm treatment phases through first 16 weeks prior to randomization; patients were removed due to adverse events prior to randomization.

Study methods indicate that clinically relevant changes in vitals and electrocardiograms were collected but these outcomes are not reported in the results.

Study methods indicate that electrocardiograms were collected but these outcomes were not reported in the results.

Study methods indicate that clinical lab tests, electrocardiograms, vital sings, weight, and QTc changes were collected but these outcomes are not reported in the results.

Short-term (8w) and continued treatment (16w) phases prior to randomization; patients were removed from the study based on response prior to randomization.

Study methods indicate that supine and systolic blood pressure, QTc prolongation, and arrhythmias were collected but these outcomes are not reported in the results.

High overall (28.2%) and differential (26.0%) attrition.

Study methods indicate that vital signs and body weight were collected but these outcomes are not reported in the results.

Acute treatment phase (12w) prior to randomization to screen for responders; patients were also removed due to adverse events prior to randomization.

Patients unable to tolerate treatment during the 1w run-in phase were removed from study.

Study interruption after unplanned interim analysis because of a high rate of placebo response during the double-blind phase.

Methods indicate that electrocardiograms and weight were collected but these outcomes are not reported in the results.

Patients with an adverse reaction during the first 12w randomized phase were excluded from the second randomization for the continuation phase.
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Representativeness of exposed cohort</th>
<th>Selection of non-exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Outcome of interest not present at start of study</th>
<th>Comparability of cohorts</th>
<th>Assessment of outcome</th>
<th>Follow-up long enough</th>
<th>Adequacy of follow-up of cohorts</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 2008⁵⁷</td>
<td>Truly representative</td>
<td>Drawn from same community</td>
<td>Secure record</td>
<td>NA</td>
<td>Controls for key factors</td>
<td>Record linkage</td>
<td>Yes</td>
<td>Complete follow-up</td>
<td>Low</td>
</tr>
<tr>
<td>Coupland, 2011⁵⁶</td>
<td>Truly representative</td>
<td>Drawn from same community</td>
<td>Secure record</td>
<td>NA</td>
<td>Controls for key factors</td>
<td>Record linkage</td>
<td>Yes</td>
<td>Complete follow-up</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable.
### Appendix E. Strength of Evidence Assessments

Table E-1. Strength of evidence ratings for the comparison of SSRI versus placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event-acute</td>
<td>2 RCT (713)</td>
<td>Low</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Suspected reporting bias</td>
<td>Moderate</td>
</tr>
<tr>
<td>Any adverse event-continuation</td>
<td>1 RCT (221)</td>
<td>High</td>
<td>Unknown (single study)</td>
<td>Direct</td>
<td>Precise</td>
<td>Suspected reporting bias</td>
<td>Moderate</td>
</tr>
<tr>
<td>Any adverse event-unspecified</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown (single study)</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-Arrhythmia</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-QTc prolongation</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Falls</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown (single study)</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Fractures</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown (single study)</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
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<tr>
<td>Hospitalization</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
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<tr>
<td>Mortality – acute</td>
<td>1 RCT (517)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
<td>Insufficient (1 death each in escitalopram and placebo arms)</td>
</tr>
<tr>
<td>Mortality-maintenance</td>
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<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
<td>Insufficient (1 death occurred in the placebo arm)</td>
</tr>
<tr>
<td>Mortality – Unspecified</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown (single study)</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
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<tr>
<td>Serious adverse events</td>
<td>1 RCT (122)</td>
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<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
<td>Insufficient</td>
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<tr>
<td>SIADH</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Outcome</td>
<td>N of studies (n of patients)</td>
<td>Study limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Publication or reporting bias</td>
<td>Strength of evidence</td>
</tr>
<tr>
<td>----------------------------------------------</td>
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<td>---------------</td>
<td>------------</td>
<td>---------------</td>
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</tr>
<tr>
<td>Withdrawal due to adverse event-acute</td>
<td>3 RCT (887)</td>
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<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
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<tr>
<td>Withdrawal due to adverse event-continuation</td>
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<td>High</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
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<tr>
<td>Withdrawal due to adverse event-maintenance</td>
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<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
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</tbody>
</table>

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
Table E-2. Strength of evidence ratings for the comparison of SSRI versus TCA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
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<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
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<tr>
<td>Cognitive impairment</td>
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<td>High</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
<td>Insufficient</td>
</tr>
<tr>
<td>ECG- Arrhythmia</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG- QTc prolongation</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
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<td>Falls</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Fractures</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
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<td>Hospitalization</td>
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<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
<td>Insufficient (1 event occurred in the TCA arm)</td>
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<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
<td>Insufficient (1 event occurred in the TCA arm)</td>
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<td>Serious adverse events</td>
<td>2 RCTs (441)</td>
<td>Medium</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
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<td>SIADH</td>
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<td>NA</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
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<td>3 RCTs (531)</td>
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<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
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</table>

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
Table E-3. Strength of evidence ratings for the comparison of SSRI versus SSRI

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<tr>
<th>Outcome</th>
<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
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</thead>
<tbody>
<tr>
<td>Any adverse event-acute</td>
<td>2 RCTs (412)</td>
<td>Low</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Suspected reporting bias</td>
<td>Moderate</td>
</tr>
<tr>
<td>Any adverse events-maintenance</td>
<td>1 RCT (242)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Uncetected</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-Arrhythmia</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-QTc prolongation</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Falls</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Fractures</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1 OBS (1967)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Unknown</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Mortality – acute</td>
<td>1 RCT (337)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
<td>Insufficient (1 event occurred)</td>
</tr>
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<td>Mortality – maintenance</td>
<td>1 RCT (242)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Insufficient (2 deaths occurred per arm)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 RCT (242)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
<tr>
<td>SIADH</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>3 RCTs (518)</td>
<td>Low</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
Table E-4. Strength of evidence ratings for the comparison of SNRI versus placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events- acute</td>
<td>3 RCTs (805)</td>
<td>Low</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>High</td>
</tr>
<tr>
<td>Any adverse- unspecified</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-Arrhythmia</td>
<td>1 RCT (370)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Insufficient (1 event occurred)</td>
</tr>
<tr>
<td>ECG-QTc interval, ms acute</td>
<td>1 RCT (282)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
<tr>
<td>ECG-QTc interval, ms acute + Continuation</td>
<td>1 RCT (262)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>High</td>
</tr>
<tr>
<td>Falls-acute</td>
<td>2 RCTs (681)</td>
<td>Medium</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Falls – acute + continuation</td>
<td>1 RCT (370)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
<tr>
<td>Falls- Unspecified</td>
<td>1 OBS</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Fractures – acute</td>
<td>1 RCT (298)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Insufficient (1 event occurred)</td>
</tr>
<tr>
<td>Fractures – acute + continuation</td>
<td>1 RCT (370)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Insufficient (1 event occurred)</td>
</tr>
<tr>
<td>Fractures- Unspecified</td>
<td>1 OBS</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Mortality - acute</td>
<td>1 RCT (311)</td>
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<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Insufficient (no events occurred)</td>
</tr>
<tr>
<td>Mortality – acute+continuation</td>
<td>1 RCT (370)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Insufficient (no events occurred)</td>
</tr>
<tr>
<td>Outcome</td>
<td>N of studies (n of patients)</td>
<td>Study limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Publication or reporting bias</td>
<td>Strength of evidence</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------------------------</td>
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<td>----------------------</td>
<td>------------</td>
<td>-----------</td>
<td>-------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Mortality- Unspecified</td>
<td>1 OBS</td>
<td>Low</td>
<td>Unknown (single study)</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Serious adverse event- acute</td>
<td>2 RCTs (607)</td>
<td>Medium</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Serious adverse events- acute + continuation</td>
<td>1 RCT (370)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
<tr>
<td>SIADH</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Withdrawal due to adverse events- acute</td>
<td>3 RCTs (812)</td>
<td>Low</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
<tr>
<td>Withdrawal due to adverse events- acute+continuation</td>
<td>1 RCT (370)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
Table E-5. Strength of evidence ratings for the comparison of SNRI versus SSRI

<table>
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<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
</tr>
</thead>
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<tr>
<td>Any adverse event- acute</td>
<td>1 RCT (202)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Precise</td>
<td>Suspected reporting bias</td>
<td>Moderate</td>
</tr>
<tr>
<td>Any adverse events- continuation</td>
<td>1 RCT (148)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG- Arrhythmia</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG- QTc prolongation</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Falls</td>
<td>1 RCT (148)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Insufficient (1 event occurred)</td>
</tr>
<tr>
<td>Fractures</td>
<td>1 RCT (148)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Insufficient (1 event occurred)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 RCT (148)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Insufficient (1 event occurred)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 RCT (148)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
<tr>
<td>SIADH</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Withdrawal due to adverse events-acute</td>
<td>1 RCT (204)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected reporting bias</td>
<td>Low</td>
</tr>
<tr>
<td>Withdrawal due to adverse events-continuation</td>
<td>1 RCT (148)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
Table E-6. Strength of evidence ratings for the comparison of bupropion XR versus placebo

<table>
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<tr>
<th>Outcome</th>
<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>1 RCT (418)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Precise</td>
<td>Suspected selective reporting</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-Arrhythmia</td>
<td>1 RCT (418)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected selective reporting</td>
<td>Insufficient (1 event occurred)</td>
</tr>
<tr>
<td>ECG-QTc prolongation</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Falls</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Fractures</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 RCT (418)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>NA</td>
<td>Suspected selective reporting</td>
<td>Insufficient (no events occurred)</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 RCT (418)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected selective reporting</td>
<td>Low</td>
</tr>
<tr>
<td>SIADH</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>1 RCT (418)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected selective reporting</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
Table E-7. Strength of evidence ratings for the comparison of mirtazapine versus no antidepressant use

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-Arrhythmia</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-QTc prolongation</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Falls</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Fractures</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
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<td>Serious adverse events</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>SIADH</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
Table E-8. Strength of evidence ratings for the comparison of mirtazapine versus paroxetine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events—cute</td>
<td>1 RCT (254)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Suspected selective reporting</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(single trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse events—continuation</td>
<td>1 RCT (254)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected selective reporting</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(single trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td></td>
<td>(no evidence)</td>
</tr>
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<td>0</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>(no evidence)</td>
</tr>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>(no evidence)</td>
</tr>
<tr>
<td>Falls</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(no evidence)</td>
</tr>
<tr>
<td>Fractures</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(no evidence)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1 RCT (254)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected selective reporting</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(single trial)</td>
<td></td>
<td></td>
<td></td>
<td>(1 event occurred)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(no evidence)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 RCT (254)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected selective reporting</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(single trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIADH</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(no evidence)</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>1 RCT (254)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected selective reporting</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(single trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown (single study)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-Arrhythmia</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-QTc prolongation</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Falls</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown (single study)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Fractures</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown (single study)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 OBS (60,746)</td>
<td>Low</td>
<td>Unknown (single study)</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>SIADH</td>
<td>0 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
Table E-10. Strength of evidence ratings for the comparison of vortioxetine versus placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>1 RCT (301)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>High</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG- Arrhythmia</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG- QTc prolongation</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Falls</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Fractures</td>
<td>1 RCT (301)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Insufficient (1 event occurred)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 RCT (301)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
<tr>
<td>SIADH</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>1 RCT (301)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Very imprecise</td>
<td>Undetected</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
Table E-11. Strength of evidence ratings for the comparison of vortioxetine versus duloxetine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N of studies (n of patients)</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication or reporting bias</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>1 RCT (307)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>High</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-Arrhythmia</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>ECG-QTc prolongation</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Falls</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Fractures</td>
<td>1 RCT (307)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Insufficient (no events occurred)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 RCT (307)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
<tr>
<td>SIADH</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Insufficient (no evidence)</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>1 RCT (307)</td>
<td>Low</td>
<td>Unknown (single trial)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone
Appendix F. Forest Plots

Figure F-1. SNRI vs. placebo on sustained elevated supine diastolic blood pressure, acute phase

<table>
<thead>
<tr>
<th>Source</th>
<th>Events</th>
<th>Total</th>
<th>Favoring SNRI</th>
<th>Favoring Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schatzberg, 2006</td>
<td>5</td>
<td>102</td>
<td>0.94 [0.26; 3.34]</td>
<td></td>
<td>91.4%</td>
</tr>
<tr>
<td>Raskin, 2008</td>
<td>1</td>
<td>201</td>
<td>4.52 [0.07; 285.72]</td>
<td></td>
<td>8.6%</td>
</tr>
<tr>
<td>Random effects</td>
<td>6</td>
<td>303</td>
<td>1.07 [0.32; 3.61]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: $I^2 = 0%$, $t^2 = 0$, $p = 0.48$</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; OR=odds ratio; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-2. SNRI vs. placebo on standing diastolic blood pressure, acute phase

<table>
<thead>
<tr>
<th>Source</th>
<th>Total</th>
<th>Mean</th>
<th>MD [95%-CI]</th>
<th>Favoring SNRI</th>
<th>Favoring Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin, 2008</td>
<td>201</td>
<td>-0.20</td>
<td>0.38 [-1.91; 2.67]</td>
<td>45.3%</td>
<td>54.7%</td>
<td></td>
</tr>
<tr>
<td>Katona, 2012</td>
<td>128</td>
<td>-2.00</td>
<td>0.00 [-2.08; 2.08]</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Random effects</td>
<td>329</td>
<td>231</td>
<td>0.17 [-1.37; 1.71]</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: $I^2 = 0%$, $t^2 = 0$, $p = 0.81$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-3. SNRI vs. placebo on standing systolic blood pressure, acute phase

<table>
<thead>
<tr>
<th>Source</th>
<th>Total</th>
<th>Mean</th>
<th>MD [95%-CI]</th>
<th>Favoring SNRI</th>
<th>Favoring Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin, 2008</td>
<td>201</td>
<td>-2.13</td>
<td>-1.80 [5.39; 1.79]</td>
<td>45.9%</td>
<td>54.1%</td>
<td></td>
</tr>
<tr>
<td>Katona, 2012</td>
<td>128</td>
<td>-5.00</td>
<td>-3.00 [8.30; 0.30]</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Random effects</td>
<td>329</td>
<td>231</td>
<td>-2.45 [-4.88; -0.02]</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: $I^2 = 0%$, $t^2 = 0$, $p = 0.63$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-4. SNRI vs. placebo on supine diastolic blood pressure, acute phase

<table>
<thead>
<tr>
<th>Source</th>
<th>Total</th>
<th>Mean</th>
<th>MD [95%-CI]</th>
<th>Favoring SNRI</th>
<th>Favoring Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin, 2008</td>
<td>201</td>
<td>1.59</td>
<td>0.52 [1.55; 2.50]</td>
<td>34.5%</td>
<td>65.5%</td>
<td></td>
</tr>
<tr>
<td>Katona, 2012</td>
<td>128</td>
<td>-1.00</td>
<td>-1.00 [-2.10; 3.20]</td>
<td>32.5%</td>
<td>67.5%</td>
<td></td>
</tr>
<tr>
<td>Robinson, 2014</td>
<td>246</td>
<td>1.89</td>
<td>3.47 [1.30; 5.64]</td>
<td>32.9%</td>
<td>67.1%</td>
<td></td>
</tr>
<tr>
<td>Random effects</td>
<td>575</td>
<td>349</td>
<td>1.65 [-0.14; 3.44]</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: $I^2 = 62%$, $t^2 = 1.3047$, $p = 0.12$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor
Figure F-5. SNRI vs. placebo on supine systolic blood pressure, acute phase

<table>
<thead>
<tr>
<th>Source</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>MD [95%-CI]</th>
<th>Favors SNRI</th>
<th>Favors Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin, 2008</td>
<td>201</td>
<td>0.77</td>
<td>15.1400</td>
<td>102</td>
<td>-0.60</td>
<td>15.5700</td>
<td>1.57 [2.11; 5.25]</td>
<td>35.5%</td>
<td>35.5%</td>
<td>28.7%</td>
</tr>
<tr>
<td>Kato, 2012</td>
<td>128</td>
<td>-3.00</td>
<td>14.0000</td>
<td>129</td>
<td>-3.00</td>
<td>13.0000</td>
<td>0.00 [-3.30; 3.30]</td>
<td>35.5%</td>
<td>35.5%</td>
<td>35.5%</td>
</tr>
<tr>
<td>Robinson, 2014</td>
<td>248</td>
<td>0.19</td>
<td>14.7000</td>
<td>118</td>
<td>-0.58</td>
<td>15.1000</td>
<td>0.77 [2.52; 4.08]</td>
<td>35.5%</td>
<td>35.5%</td>
<td>35.5%</td>
</tr>
</tbody>
</table>

Random effects model: 675
Heterogeneity: $\tau^2 = 0\%$, $\tau^2 = 0$, $p = 0.82$

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-6. SNRI vs. placebo on orthostatic hypotension, acute phase

<table>
<thead>
<tr>
<th>Source</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>RR [95%-CI]</th>
<th>Favors SNRI</th>
<th>Favors Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson, 2014</td>
<td>57</td>
<td>249</td>
<td>27</td>
<td>121</td>
<td>1.03 [0.69; 1.54]</td>
<td>47.2%</td>
<td>52.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Raskin, 2008</td>
<td>59</td>
<td>201</td>
<td>28</td>
<td>102</td>
<td>1.07 [0.73; 1.57]</td>
<td>47.2%</td>
<td>52.8%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Random effects model: 116
Heterogeneity: $\tau^2 = 0\%$, $\tau^2 = 0$, $p = 0.88$

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-7. SNRI vs. placebo on orthostatic diastolic blood pressure, acute phase

<table>
<thead>
<tr>
<th>Source</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>MD [95%-CI]</th>
<th>Favors SNRI</th>
<th>Favors Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin, 2008</td>
<td>201</td>
<td>-1.80</td>
<td>7.6900</td>
<td>102</td>
<td>-1.55</td>
<td>8.5400</td>
<td>-0.15 [-2.12; 1.82]</td>
<td>49.3%</td>
<td>50.7%</td>
<td>49.3%</td>
</tr>
<tr>
<td>Robinson, 2014</td>
<td>246</td>
<td>-0.94</td>
<td>8.2000</td>
<td>118</td>
<td>0.28</td>
<td>8.5000</td>
<td>-3.22 [-5.05; -1.38]</td>
<td>49.3%</td>
<td>50.7%</td>
<td>49.3%</td>
</tr>
</tbody>
</table>

Random effects model: 447
Heterogeneity: $\tau^2 = 80\%$, $\tau^2 = 3.7650$, $p = 0.03$

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-8. SNRI vs. placebo on orthostatic systolic blood pressure, acute phase

<table>
<thead>
<tr>
<th>Source</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>MD [95%-CI]</th>
<th>Favors SNRI</th>
<th>Favors Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin, 2008</td>
<td>201</td>
<td>-2.90</td>
<td>11.8300</td>
<td>102</td>
<td>0.47</td>
<td>10.8700</td>
<td>-3.37 [-6.04; -0.70]</td>
<td>41.6%</td>
<td>58.4%</td>
<td>41.6%</td>
</tr>
<tr>
<td>Robinson, 2014</td>
<td>246</td>
<td>0.27</td>
<td>10.0000</td>
<td>118</td>
<td>2.29</td>
<td>10.4000</td>
<td>-2.02 [4.27; 0.25]</td>
<td>41.6%</td>
<td>58.4%</td>
<td>41.6%</td>
</tr>
</tbody>
</table>

Random effects model: 447
Heterogeneity: $\tau^2 = 0\%$, $\tau^2 = 0$, $p = 0.46$

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor
Figure F-9. SNRI vs. placebo on SDST score, acute phase

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-10. SNRI vs. placebo on 2DCT score, acute phase

Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-11. SNRI vs. placebo on falls, acute phase

Abbreviations: CI=confidence interval; RR=relative risk; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-12. SNRI vs. placebo on weight loss 7% or greater

Abbreviations: CI=confidence interval; RR=relative risk; SNRI=serotonin norepinephrine reuptake inhibitor