Comparative Effectiveness Review
Number 215

Adverse Effects of Pharmacological Treatments of Major Depression in Older Adults

AHRQ
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Prepared by:
University of Connecticut Evidence-based Practice Center
Storrs, CT

Investigators:
Diana M. Sobieraj, Pharm.D.
William L. Baker, Pharm.D.
Brandon K. Martinez, Pharm.D.
Adrian V. Hernandez, M.D., Ph.D.
Craig I. Coleman, Pharm.D.
Joseph S. Ross, M.D., M.H.S.
Karina M. Berg, M.D., M.S.
David C. Steffens, M.D.

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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.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program website at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EPC@ahrq.hhs.gov.

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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.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

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.

Gopal Khanna, M.B.A.
Director
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Aysegul Gozu, M.D., M.P.H.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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Karina M. Berg, M.D., M.S.
Associate Professor of Medicine, Center on Aging
University of Connecticut School of Medicine
Farmington, CT

Joseph S. Ross, M.D., M.H.S.
Associate Professor of Medicine and Public Health
Yale University School of Medicine, School of Public Health
New Haven, CT

David C. Steffens, M.D.
Professor and Chair of Psychiatry
University of Connecticut School of Medicine
Farmington, CT

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

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.

The list of Key Informants who provided input to this report follows:

Iqbal Ahmed, M.D.
University of Hawaii
Honolulu, HI

Peter Ajuonuma, J.D., M.B.A., R.N.
Centers for Medicare & Medicaid Services
Baltimore, MD

Rebecca Andrews, M.D.
University of Connecticut School of Medicine
Farmington, CT

Nicole Brandt, Pharm.D., M.B.A.
University of Maryland School of Pharmacy
Baltimore, MD

Lisa Hines, Pharm.D.
Pharmacy Quality Alliance
Alexandria, VA

Jean Kim, M.D.
U.S. Food and Drug Administration
Silver Spring, MD

George Niederehe, Ph.D.
National Institute of Mental Health
Bethesda, MD

Michael Steinman, M.D.
University of California, San Francisco School of Medicine
San Francisco, CA

Technical Expert Panel

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.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:

Iqbal Ahmed, M.D.
University of Hawaii
Honolulu, HI

Rebecca Andrews, M.D.
University of Connecticut School of Medicine
Farmington, CT

Nicole Brandt, Pharm.D., M.B.A.*
University of Maryland School of Pharmacy
Baltimore, MD

George Niederehe, Ph.D.*
National Institute of Mental Health
Bethesda, MD

Michael Steinman, M.D.*
University of California, San Francisco School of Medicine
San Francisco, CA

*Provided input on Draft Report

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Shelly Gray, Pharm.D., M.S.
Shirley & Herb Bridge Endowed Professor, Department of Pharmacy Practice
Director, Plein Center for Geriatric Pharmacy Research, Education and Outreach
University of Washington School of Pharmacy
Seattle, WA

Jordan F. Karp, M.D.
Associate Professor of Psychiatry, Anesthesiology, and Clinical and Translational Science
University of Pittsburgh School of Medicine
Pittsburgh, PA

Barbara Zarowitz, Pharm.D.
Independent Consultant, Geriatric Pharmacotherapy
Curavi Health, Inc.
Pittsburgh, PA

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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Evidence Summary

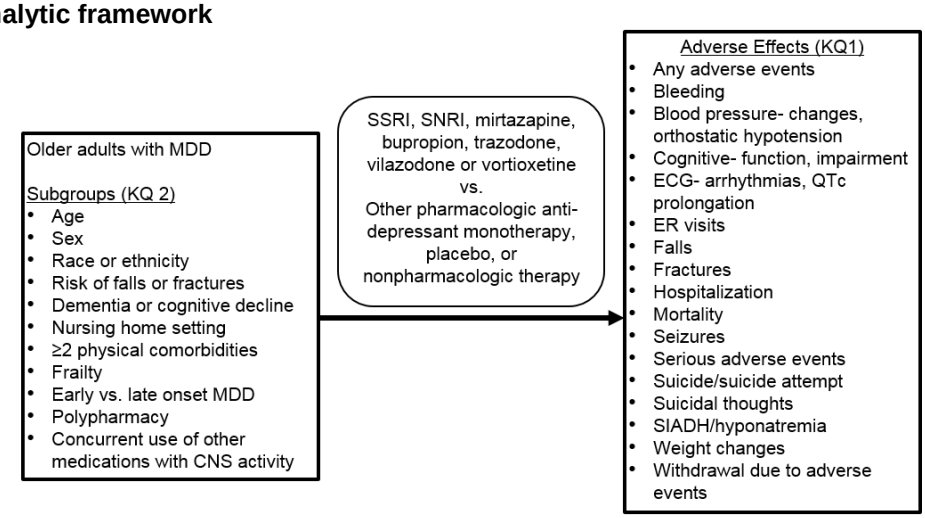
Background

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

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

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

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

Data Sources

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

Methods

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

Results

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

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

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

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

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

Adverse Effects of Antidepressants

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

Comparison/ Study design	Acute Phase (< 12 weeks) (SOE)	Continuation Phase (12 weeks to 48 weeks) (SOE)	Maintenance Phase (>48 weeks) (SOE)
SSRI vs. placebo (RCT)	**Adverse events** Similar with escitalopram, fluoxetine (++)[8,10] **Withdrawals due to adverse events** More with citalopram, escitalopram, fluoxetine (+), NNH 11 (8 to 20)[8,10,14] Insufficient evidence: mortality	**Adverse events** Fewer with escitalopram (+), NNT 5 (3 to 19)[12] Insufficient: withdrawals due to adverse events	Insufficient evidence: mortality, serious adverse events, withdrawals due to adverse events
SSRI vs. no anti-depressant use (OBS)	No data	No data	**Adverse events** Increased with SSRIs (+)[b,26] **Falls** Increased with SSRIs (+)[b,26] **Fractures** Increased with SSRIs (+)[b,26] **Mortality** Increased with SSRIs (+)[b,26]
SNRI vs. placebo (RCT)	**Adverse events** More with duloxetine and venlafaxine (+++), NNH 10 (7 to 34)[10,19,25] **Falls** Similar with duloxetine (+)[19,24] **QTc interval** Similar with duloxetine (++)[19] **Serious adverse events** Fewer with duloxetine (+), NNT 50 (25 to 1000)[19,25] **Withdrawals due to adverse events** More with duloxetine and venlafaxine (++), NNH 17 (-7 to 33)[10,19,25] Insufficient evidence : fractures, mortality	**Falls** More with duloxetine (++), NNH 10 (6 to 114)[c,24] **QTc interval** Similar with duloxetine (+++)[c,24] **Serious adverse events** Similar with duloxetine (++)[c,24] **Withdrawals due to adverse events** More with duloxetine (++), NNH 12 (7 to 33)[c,24] Insufficient evidence: arrhythmias, fractures, mortality	No data

Comparison/ Study design	Acute Phase (< 12 weeks) (SOE)	Continuation Phase (12 weeks to 48 weeks) (SOE)	Maintenance Phase (>48 weeks) (SOE)
SNRI vs. no anti-depressant use (OBS)	No data	No data	**Adverse events** Similar with venlafaxine (+)[b,26] **Falls** Increased with venlafaxine (+)[b,26] **Fractures** Increased with venlafaxine (+)[b,26] **Mortality** Increased with venlafaxine (+)[b,26]
Bupropion XR vs. placebo (RCT)	**Adverse events** Similar with bupropion XR (++)[23] **Serious adverse events** Similar with bupropion XR (+)[23] **Withdrawals due to adverse events** Similar with bupropion XR (+)[23] Insufficient evidence: arrhythmias, mortality	No data	No data
Mirtazapine vs. no anti-depressant (OBS)	No data	No data	**Adverse events** Similar with mirtazapine (+)[b,26] **Falls** Increased with mirtazapine (+)[b,26] **Fractures** Increased with mirtazapine (+)[b,26] **Mortality** Increased with mirtazapine (+)[b,26]
Trazadone vs. no anti-depressant (OBS)	No data	No data	**Adverse events** Similar with trazodone (+)[b,26] **Falls** Increased with trazodone (+)[b,26] **Fractures** Similar with trazodone (+)[b,26] **Mortality** Increased with trazodone (+)[b,26]
Vortioxetine vs. placebo (RCT)	**Adverse events** Similar with vortioxetine (+++)[25] **Serious adverse events** Similar with vortioxetine (++)[25] **Withdrawal due to adverse events** Similar with vortioxetine (+)[25] **Insufficient**: fractures	No data	No data

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

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

[b] This cohort study had a median of 364 days on treatment although whether patients were treated for an acute, continuation or maintenance period was not specified

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

Comparative Adverse Effects of Antidepressants

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

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

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

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

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

Subgroups of Interest

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

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

Discussion

Applicability of results. This review exclusively included studies that required an age of 65 years or older. The studies were consistent in excluding patients with uncontrolled/unstable comorbidities or other psychological conditions, particularly patients with high suicide risk. None of the studies were specific to nursing facility residents. Unfortunately this limits applicability of results given that older adults commonly have multiple comorbidities and are subject to taking multiple medications. Major depression was mostly diagnosed using DSM criteria. Based on scores from the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Asberg Depression Scale (MADRS) for study eligibility, the population represents those with moderate severity depression. The doses of antidepressants studied were rarely reflective of the full range cited in guideless as the usual dose range for older adults, and were

more often reflective of the lower half of that range. The data in this report does not reflect higher usual antidepressant doses.

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

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

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

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

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

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

Conclusions

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

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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 2010[2] 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,[12,15] bupropion XR,[16] and vortioxetine[17] 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.[18,19] 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.[20] 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).[21] 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[22] and citalopram[23] 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.[9] While mirtazapine was found to have higher response and remission rates than the SSRI paroxetine,[24] trials directly comparing various SSRIs to one another have been mixed.[25] 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.[4] 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.[26,27] While trials up to a year show efficacy of SSRIs versus placebo, benefits have not been sustained beyond 1 year.[12] 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.[28] 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.[28] 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.[29] The AGS suggests that SNRIs and bupropion are alternatives to TCAs and SSRIs.[30] However, the AGS also recommended using SSRIs and SNRIs with caution due to the potential to exacerbate or cause SIADH or hyponatremia.[28]

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[31]
- Concurrent use of one other medication with central nervous system activity, defined as antipsychotics, benzodiazepines, nonbenzodiazepine hypnotics, and opioids[28]

Interventions:
We were interested in pharmacologic antidepressant treatments of MDD, as single interventions (Table 1), 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

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

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

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
    - Changes in blood pressure
    - Orthostatic blood pressure

- Cognitive measures
    - Cognitive function
    - Cognitive impairment
- Electrocardiogram related
    - Arrhythmias
    - 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.

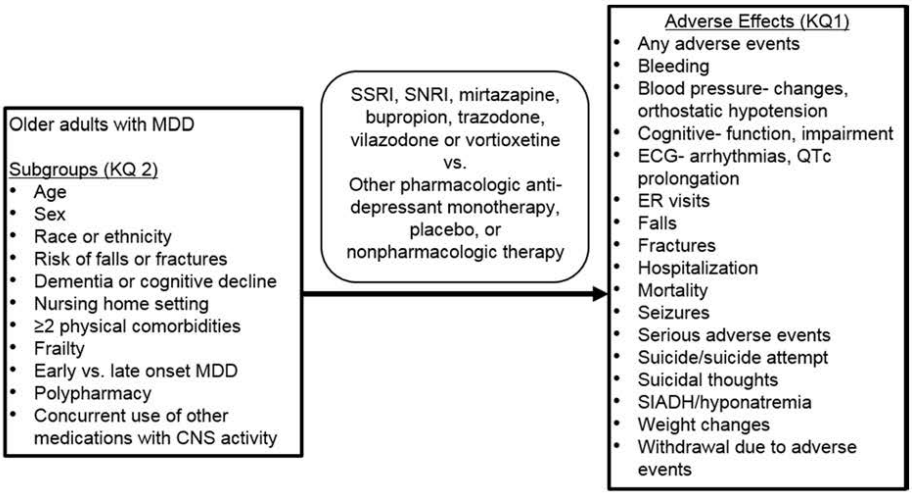
Settings:
We were interested in non-acute care settings such as specialist or generalist outpatient setting, rehabilitation facility and nursing facilities. Inpatient or urgent care settings were excluded.

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 (Table 2). 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 2. Inclusion and exclusion criteria for Key Questions

Category	Inclusion Criteria	Exclusion Criteria
Population	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.	Patients <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
Intervention	SSRI, SNRI, bupropion, mirtazapine, trazodone, vilazodone or vortioxetine (Table 1) as a single intervention	Other pharmacologic therapies, nonpharmacologic therapies, complementary alternative medicines, or combinations of therapies
Comparator	A pharmacologic antidepressant for MDD (Table 1, or TCA or MAOI), as a single intervention, including within class comparisons of SSRIs and SNRIs; placebo; nonpharmacologic interventions as specified in PICOTS	Other pharmacologic therapies, invasive nonpharmacologic interventions, complementary alternative medicines, combinations of therapies
Outcomes	As defined in the PICOTS criteria	Studies without at least one outcome listed in the PICOTS
Timing	All study durations and follow-up lengths will be included	None
Setting	Non-acute care setting (i.e. specialist or generalist outpatient setting, rehabilitation or nursing facility)	Hospital or urgent care setting
Study Design	RCTs, nonrandomized controlled trials, prospective or retrospective controlled cohort studies, case-controlled studies	Case series, case reports, studies without an active comparator or non-active control group
Publication Language and Dates	No limits on publication date or language[b]	Abstracts without published study manuscripts; non-English publications that do not have an English language abstract.

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" (Table 1) 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,[4] 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.[35] 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.[36] For outcomes with zero events in one study arm continuity correction was used,[37] except when a Peto's OR was calculated which does not utilize continuity correction.[38] 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 I^2 statistic which represents the percentage (0-100 percent) of variability in the treatment estimate that is attributable to heterogeneity.[39] 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),[31] concurrent use of one other medication with central nervous system activity,[28] 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.[40] 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.[41] 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").

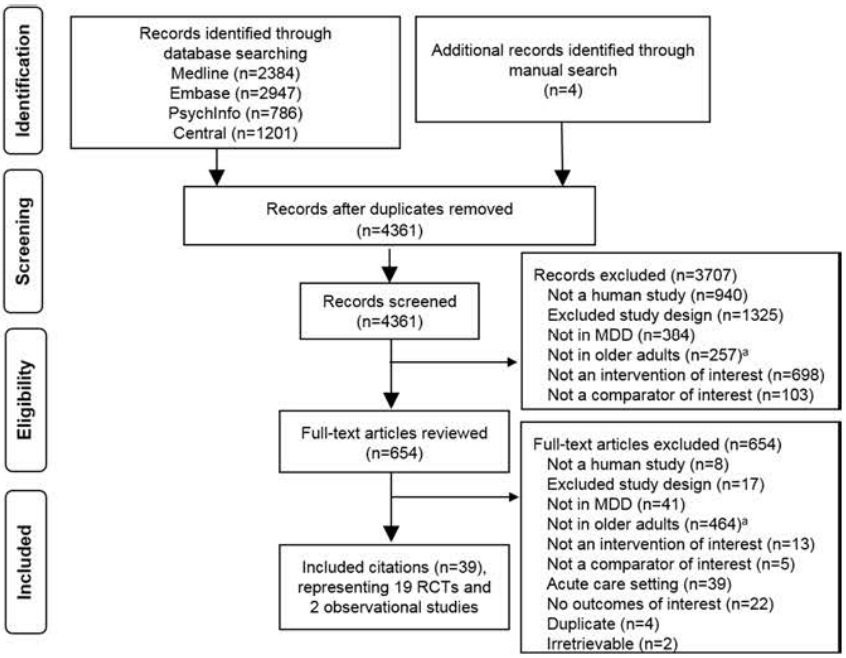
The first overview table at the start of each results section provides a list of analyzed outcomes for which we graded SOE. When two or more trials reported a given outcome, the result listed is based on meta-analysis. In cases when only 1 study was available for a given outcome, the result is reported 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[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[76-78] to supplement publications. In addition, we received additional outcomes data from authors of three included studies.[17,46,50]

Figure 2. Literature flow for Key Questions 1 and 2



Abbreviations: MDD=major depressive disorder; RCT=randomized controlled trial
[a]Studies that did not include patients at least 65 years of age and older (per study inclusion criteria).

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

Intervention/Comparator	Number of Studies	Outcomes Reported
SSRI vs. placebo/no antidepressant	7 RCTs[43,45-47,48-50] 1 OBS[56]	Any AE, bleed-UGI, blood pressure, cognitive function, falls, fracture, mortality, seizures, serious AEs, hyponatremia, suicide/attempt, weight, withdrawal due to AE
SSRI vs. TCA	3 RCTs[51-53]	Any AE, cognitive impairment, hospitalization, mortality, serious AE, withdrawal due to AE
SSRI vs. SSRI	4 RCTs[25,42-44] 1 OBS[57]	Any AE, blood pressure, cognitive function, hospitalization, mortality, serious AE, suicide/attempt, withdrawal due to AE
SNRI vs. placebo/no antidepressant	4 RCTs[15,17,45,54] 1 OBS[56]	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
SNRI vs. SSRI	2 RCTs[45,55]	Any AE, blood pressure, falls, fractures, mortality, serious AE, weight, withdrawal due to AE
Bupropion vs. placebo	1 RCT[16]	Any AE, blood pressure, ECG-arrhythmia, mortality, seizures, serious AE, suicidal thoughts, withdrawal due to AE
Mirtazapine vs. no antidepressant	1 OBS[56]	Any AE, bleed-UGI, falls, fractures, mortality, seizures, hyponatremia, suicide attempt
Mirtazapine vs. SSRI	1 RCT[24]	Any AE, blood pressure, hospitalization, serious AE, weight, withdrawal due to AE
Trazodone vs. no antidepressant	1 OBS[56]	Any AE, bleed-UGI, falls, fractures, mortality, seizures, hyponatremia, suicide attempt
Vortioxetine vs. placebo	1 RCT[17]	Any AE, blood pressure, cognitive function, ECG-QTc, fractures, serious AE, sodium, suicidal thoughts, suicide/attempt, weight, withdrawal due to AE
Vortioxetine vs. SNRI	1 RCT[17]	Any AE, blood pressure, cognitive function, ECG-QTc, fractures, serious AE, sodium, suicidal thoughts, suicide/attempt, weight, withdrawal due to AE

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

Key Question (KQ) 1. 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 (10-40mg/day),[48-50] two trials[43,45] studied fluoxetine (20-60mg/day), two trials[43,47] studied escitalopram (10-20mg/day), and one trial[46] studied paroxetine (10-40mg/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[43,45,49,50] 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

Outcome	Treatment Phase	Quantity and Type of Evidence (n)	Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)[a]	Strength of Evidence
Any adverse events	Acute	2 RCTs[43,45] (713)	RR 1.07 (0.98 to 1.16) No difference with escitalopram and fluoxetine	Moderate (suspected selective reporting)
	Continuation (24 weeks)	1 RCT[47] (221)	RR 0.69 (0.53 to 0.90) NNT 5 (3 to 19) Lower risk with escitalopram	Low (high ROB, suspected selective reporting)
	Unspecified	1 OBS[b,56] (60,746)	HR 1.20 (1.02 to 1.42) Increased risk with SSRI	Low
Falls	Unspecified	1 OBS[b,56] (60,746)	HR 1.66 (1.58 to 1.73) Increased risk with SSRI	Low
Fractures	Unspecified	1 OBS[b,56] (60,746)	HR 1.58 (1.48 to 1.68) Increased risk with SSRI	Low
Mortality	Acute	1 RCT[43] (517)	Escitalopram: RD 0.00 (-0.046 to 0.027) Fluoxetine: RD -0.01 (-0.05 to 0.02) Insufficient	Insufficient (imprecise, suspected selective reporting, 2 events occurred)
	Maintenance (48 weeks)	1 RCT[48] (121)	RD 0.02 (-0.05 to 0.09) Insufficient with citalopram	Insufficient (high ROB, imprecise, suspected selective reporting)
	Unspecified	1 OBS[b,56] (60,746)	HR 1.54 (1.48 to 1.59) Increased risk with SSRI	Low
Serious adverse events	Maintenance (48 weeks)	1 RCT[48] (122)	RR 2.20 (0.81 to 5.96) Insufficient with citalopram	Insufficient (high ROB, imprecise, suspected selective reporting)
Withdrawals due to adverse events	Acute	3 RCTs[43,45,49] (887)	RR 2.90 (1.16 to 5.06) NNH 11 (8 to 20) Increased risk with SSRIs citalopram, escitalopram, fluoxetine	Low (imprecise, suspected selective reporting)
	Continuation (24 weeks)	1 RCT[47] (305)	RR 0.58 (0.17 to 1.92) Insufficient with escitalopram	Insufficient (high ROB, imprecise, suspected selective reporting)
	Maintenance (48 weeks to 2 years)	2 RCTs[46,48] (174)	RR 0.81 (0.31 to 2.11) Insufficient with citalopram and paroxetine	Insufficient (high ROB, imprecise, suspected selective reporting)

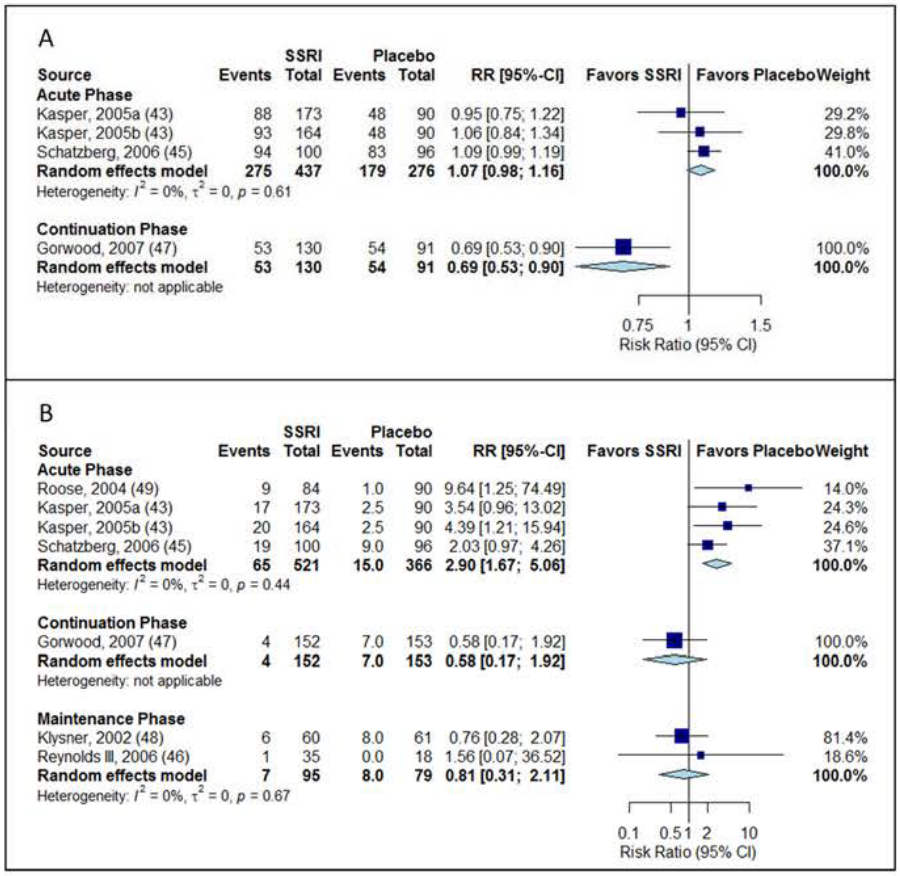
Abbreviations: CI=confidence interval; n=patient sample size; NNH=number needed to harm; NNT=number needed to treat; OBS=observational; RCT=randomized controlled trial; RD=risk difference; ROB=risk of bias; RR=risk ratio

[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[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[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



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

In the single trial[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[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[46] studying paroxetine and reporting suicide, no events occurred. In the single trial[48] studying citalopram and reporting mortality, one death occurred in the control arm (1.6 percent). 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[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

Outcome	Treatment Phase	Quantity and Type of Evidence (n)	Findings- Effect Estimate (95 Percent CI)
Bleed- UGIB	Unspecified	1 OBS[a,56] (60,746)	SSRIs: HR 1.22 (1.07 to 1.40)
Blood pressure-DBP, mmHg	Maintenance (48 weeks)	1 RCT[48] (121)	Citalopram: MD -4.0 (-9.4 to 1.4)
Blood pressure-SBP, mmHg	Maintenance (48 weeks)	1 RCT[48] (121)	Citalopram: MD -5.0 (-16.33 to 6.33)
Blood pressure-HTN	Acute	1 RCT[43] (517)	Escitalopram: RR 0.38 (0.11 to 1.34) Fluoxetine: RR 0.40 (0.11 to 1.41)
	Maintenance (48 weeks)	1 RCT[48] (121)	Citalopram: RR 0.51 (0.05 to 5.46)
Blood pressure-BP increase[b]	Acute	1 RCT[45] (196)	Fluoxetine: RR 0.77 (0.21 to 2.78)
Blood pressure-Orthostatic hypotension	Acute	1 RCT[43] (517)	Escitalopram: RR 2.08 (0.09 to 45.66) Fluoxetine: RR 1.10 (0.04 to 32.40)
	Maintenance (2 years)	1 RCT[46] (53)	Paroxetine: RR 1.49 (0.96 to 2.32)
Cognitive function	Acute	1 RCT[49,66] (174)	Citalopram: MMSE MD -0.07 (-0.93 to 0.79) Digital symbol MD -0.66 (-7.91 to 6.59) Stroop MD 0.00 (-0.26 to 0.26) CRT MD 0.05 (-0.10 to 0.20) JoLO MD 1.32 (-1.19 to 3.83) Buschke SRT MD -2.62 (-7.15 to 1.91)
Seizure/ epilepsy	Unspecified	1 OBS[a,56] (60,746)	SSRIs: HR 1.98 (1.62 to 2.43)
Hyponatremia	Unspecified	1 OBS[a,56] (60,746)	SSRIs: HR 1.62 (1.42 to 1.86)
Suicide	Acute	1 RCT[43] (517)	Escitalopram: RD 0.01 (-0.07 to 0.03) Fluoxetine: No events occurred
	Maintenance (2 years)	1 RCT[46] (53)	Paroxetine: No events occurred
Suicide attempt/self-harm	Unspecified	1 OBS[a,56] (60,746)	SSRIs: HR 2.16 (1.71 to 2.71)
Weight, kg	Maintenance (2 years)	1 RCT[46] (52)	Paroxetine: MD 3.20 (-2.27 to 8.67)
Weight loss	Acute	1 RCT[45] (196)	Fluoxetine: RD 0.06 (0.010 to 0.125)

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

[a]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.
[b]Treatment emergent elevation from baseline in supine DBP of 10 or more mmHg to an on therapy value of 90 or greater mmHg for at least 3 consecutive visit

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,[53] 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.

Results

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

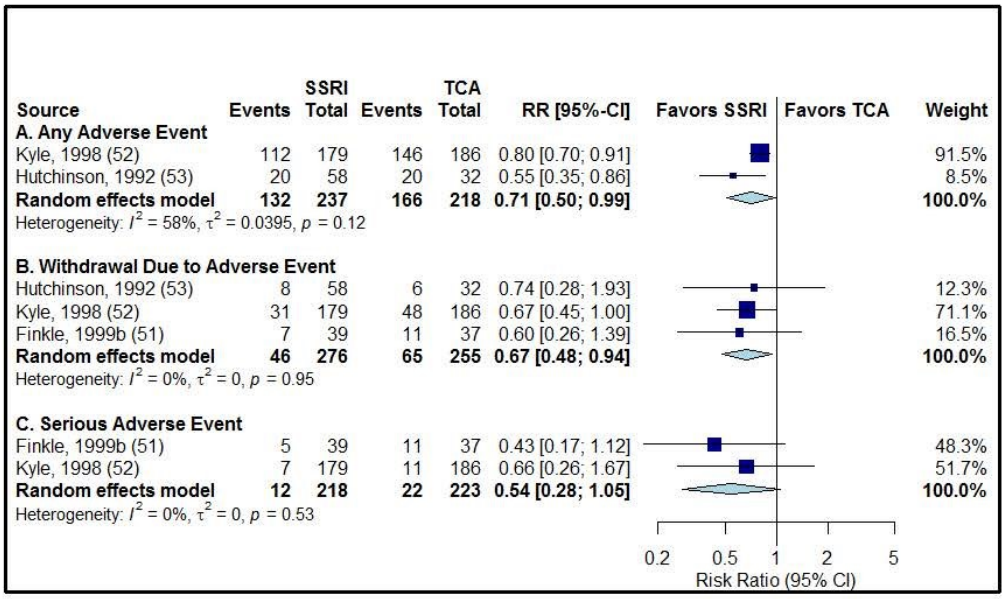
Outcome	Treatment Phase	Quantity and Type of Evidence (n)	Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)[a]	Strength of Evidence
Any adverse events	Acute	2 RCTs[52,53] (455)	RR 0.71 (0.50 to 0.99) NNT 6 (4 to 11) Decreased risk with SSRIs paroxetine, citalopram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

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 studies[52,53] 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 trial[52] reporting hospitalization, one occurred in the TCA (amitriptyline) arm (0.5 percent). One trial[53] 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 trials[25,42-44] (n=760) compared one SSRI with another SSRI (Table 7-8). A single observational study[57] 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 MDD[25,42,43] and one evaluated maintenance therapy.[44] Risk of bias was low in two trials,[43,44] high in one trial[25] and unclear in one trial.[42] Two trials[42,44] reported industry sponsorship.

Results

Main Outcomes

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

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

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

[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 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[43] reported one death in the escitalopram arm (0.6 percent) which was a suicide (0.6 percent). The single maintenance treatment trial[44] 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)[57] 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

Outcome	Treatment Phase	Quantity and Type of Evidence (n)	Findings Effect Estimate (95 Percent CI)
Blood pressure-HTN	Acute	1 RCT[43] (337)	Escitalopram vs. fluoxetine RR 0.95 (0.24 to 3.73)
Blood pressure-orthostatic Hypotension	Acute	1 RCT[43] (337)	Escitalopram vs. fluoxetine RR 1.90 (0.17 to 20.71)
Cognitive function	Acute	1 RCT[25] (75)	Sertraline vs. fluoxetine HamD Cognitive Factor MD 0.50 (-0.74 to 1.74) DSST MD 0 (-8.26 to 8.26)
Suicide	Acute	1 RCT[43] (337)	Escitalopram vs. fluoxetine RD 0.01 (-0.02 to 0.03)
	Maintenance	1 RCT[44] (242)	Paroxetine vs. fluoxetine RD -0.01 (-0.05 to 0.03)

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 trials[15,17,45,54] (n=1177) compared an SNRI to placebo (Tables 9-10). Three trials[15,17,54] studied the SNRI duloxetine (60-120mg/day), one trial[45] 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 trial[54] 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

Outcome	Treatment Phase	Quantity and Type of Evidence (n)	Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)[a]	Strength of Evidence
Any adverse events	Acute	3 RCTs[17,45,54] (805)	RR 1.14 (1.03 to 1.25) NNH 10 (7 to 34) Increased risk with duloxetine, venlafaxine	High
	Unspecified	1 OBS[56] (60,746)	HR 0.89 (0.55 to 1.46) No difference with venlafaxine	Low
ECG-Arrhythmia	Acute + Continuation	1 RCT[15] (370)	RD 0.002 (-0.03 to 0.02) Insufficient with duloxetine	Insufficient (imprecise, 1 event occurred)
ECG-QTc, ms	Acute	1 RCT[54] (282)	Bazzett correction MD 0.59 (-3.87 to 5.05); Fridericia correction MD -1.05 (-5.53 to 3.43) No difference with duloxetine	Moderate (high ROB)
	Acute + Continuation	1 RCT[15] (262)	Bazzett correction MD 2.40 (-3.72 to 8.52); Fridericia correction MD 0.89 (-4.73 to 6.51) No difference with duloxetine	High
Falls	Acute	2 RCTs[15,54] (681)	RR 1.46 (0.84 to 2.55) No difference with duloxetine	Low (moderate ROB, imprecise)
	Acute + Continuation	1 RCT[15] (370)	RR 1.69 (1.03 to 2.76) NNH 10 (6 to 114) Increased risk with duloxetine	Moderate (imprecise)
	Unspecified	1 OBS[56] (60,746)	HR 1.67 (1.48 to 1.88) Increased risk with venlafaxine	Low
Fractures	Acute	1 RCT[17] (298)	RD -0.007 (-0.04 to 0.02) Insufficient with duloxetine	Insufficient (imprecise, 1 event occurred)
	Acute + Continuation	1 RCT[15] (370)	Ankle fractures RD 0.002 (-0.03 to 0.02); Hip fractures RD 0.002 (-0.03 to 0.02) Insufficient with duloxetine	Insufficient (imprecise, 1 event occurred)
	Unspecified	1 OBS[56] (60,746)	HR 1.85 (1.58 to 2.18) Increased risk with venlafaxine	Low
Mortality	Acute	2 RCT[15,54] (681)	No events occurred Insufficient with duloxetine	Insufficient (moderate ROB, no events)
	Acute + Continuation	1 RCT[15] (370)	No events occurred Insufficient with duloxetine	Insufficient (no events)
	Unspecified	1 OBS[56] (60,746)	HR 1.65 (1.50 to 1.82) Increased risk with venlafaxine	Low
Serious AE	Acute	2 RCTs[17,54] (607)	RR 0.20 (0.04 to 0.97) NNT 50 (25 to 1000) Decreased risk with duloxetine	Low (moderate ROB, imprecise)
	Acute + Continuation	1 RCT[15] (370)	RR 1.58 (0.53 to 4.74) No difference with duloxetine	Moderate (imprecise)
Withdrawals due to adverse events	Acute	3 RCTs[17,45,54] (812)	RR 1.85 (1.05 to 3.27) NNH 17 (-7 to 33) Increased risk with duloxetine and venlafaxine	Moderate (imprecise)
	Acute + Continuation	1 RCT[15] (370)	RR 2.64 (1.21 to 5.73) NNH 12 (7 to 33) Increased risk with duloxetine	Moderate (imprecise)

Abbreviations: CI=confidence interval; HR=hazard ratio; ms=miliseconds; 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

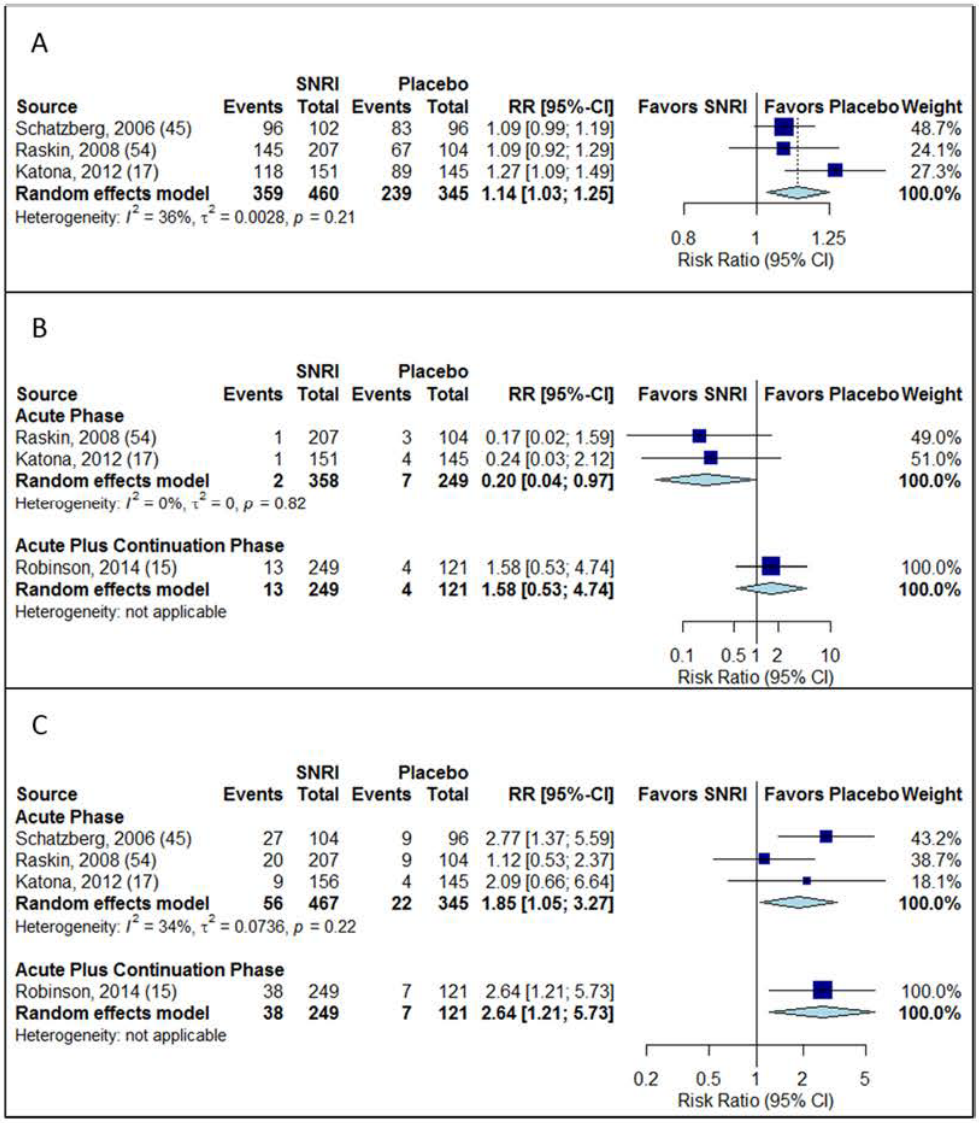
[a] Interpretation of effect estimate based on statistical significance. May overestimate estimates of no difference due to inadequate sample size and type II error.

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[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)].[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[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[15] employed active surveillance for falls and did not rely solely on patient reported falls as was done in the second trial[54] reporting this outcome during the acute treatment period. 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[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

Outcome	Treatment Phase	Quantity and Type of Evidence (n)	Findings Effect Estimate (95 Percent CI)
Bleed-UGIB	Unspecified	1 OBS[56] (60,746)	Venlafaxine: HR 1.70 (1.22 to 2.36)
Blood pressure- elevated supine DBP[a]	Acute	1 RCT[54] (303)	Duloxetine: RR 1.01 (0.31 to 3.29)
	Acute + Continuation	1 RCT[15] (308)	Duloxetine: RR 2.05 (0.80 to 5.26)
Blood pressure- elevated supine SBP[b]	Acute	1 RCT[54] (303)	Duloxetine: RR 2.29 (1.30 to 4.02)

Outcome	Treatment Phase	Quantity and Type of Evidence (n)	Findings Effect Estimate (95 Percent CI)
	Acute + Continuation	1 RCT[15] (177)	Duloxetine: RR 1.95 (0.91 to 4.20)
Blood pressure- sustained elevated supine DBP	Acute	2 RCTs[45,54] (501)	Duloxetine and venlafaxine: OR 1.07 (0.32 to 3.61)
Blood pressure - sustained elevated supine SBP	Acute	1 RCT[54] (303)	Duloxetine; RD -0.01 (-0.06 to 0.01)
Blood pressure- standing DBP, mmHg	Acute	2 RCTs[17,54] (560)	Duloxetine; MD 0.17 (-1.37 to 1.71)
Blood pressure- standing SBP, mmHg	Acute	2 RCTs[17,54] (560)	Duloxetine; MD -2.45 (-4.88 to -0.02)
Blood pressure- supine DBP, mmHg	Acute	3 RCTs[15,17,54] (924)	Duloxetine; MD 1.65 (-0.14 to 3.44)
Blood pressure- supine SBP, mmHg	Acute	3 RCTs[15,17,54] (924)	Duloxetine; MD 0.73 (-1.24 to 2.69)
Blood pressure- orthostatic hypotension	Acute	2 RCTs[15,54] (667)	Duloxetine; RR 1.05 (0.79 to 1.38)
Blood pressure- orthostatic DBP, mmHg	Acute	2 RCTs[15,54] (667)	Duloxetine; MD -1.71 (-4.71 to 1.30)
Blood pressure- orthostatic SBP, mmHg	Acute	2 RCTs[15,54] (667)	Duloxetine; MD -2.58 (-4.30 to -0.86)
Cognitive function	Acute	3 RCTs[15,17,54] (856)	Duloxetine: RAVLT-acquisition 1.41 (0.38 to 2.43) and RAVLT-longer delayed memory 0.64 (0.16 to 1.12)
	Acute + Continuation	1 RCT[15] (273)	No statistically significant difference with duloxetine according to 6 of 6 measures of cognitive function[c]
ECG- treatment emergent abnormal ECG	Acute	1 RCT[54] (282)	Duloxetine; RR 0.90 (0.65 to 1.24)
Seizures/epilepsy	Unspecified	1 OBS[56] (60,746)	Venlafaxine: HR 2.94 (1.93 to 4.58)
Sodium, mEq/L	Acute	2 RCTs[17,54] (551)	Duloxetine: MD -0.51 (-1.00 to -0.03)
Hyponatremia	Unspecified	1 OBS[56] (60,746)	Venlafaxine: HR 1.51 (1.07 to 2.13)
Suicidal thoughts	Acute	1 RCT[17] (228)	Duloxetine: RR 0.73 (0.30 to 1.74)
	Acute + Continuation	1 RCT[15] (370)	Duloxetine: RD 0.006 (-0.03 to 0.03)
Suicide	Acute	1 RCT[17] (228)	Duloxetine: RD 0.009 (-0.03 to 0.05)
Suicide attempt/self-harm	Unspecified	1 OBS[56] (60,746)	Venlafaxine: HR 4.56 (3.02 to 6.79)
Weight, kg	Acute	3 RCTs[15,17,54] (929)	Duloxetine: MD -0.70 (-0.98 to -0.42)
Weight gain ≥7 percent	Acute	1 RCT[54] (311)	Duloxetine: RD 0.007 (-0.03 to 0.03)
	Acute + Continuation	1 RCT[15] (369)	Duloxetine: RR 2.68 (0.60 to 11.92)
Weight loss ≥7 percent	Acute	2 RCTs[45,54] (509)	Duloxetine and venlafaxine: RR 1.03 (0.22 to 4.85)
	Acute + Continuation	1 RCT[15] (369)	Duloxetine: RR 1.22 (0.49 to 3.07)

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

size; RAVLT=Rey auditory verbal learning test; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; SBP=systolic blood pressure; UGIB=upper gastrointestinal bleed

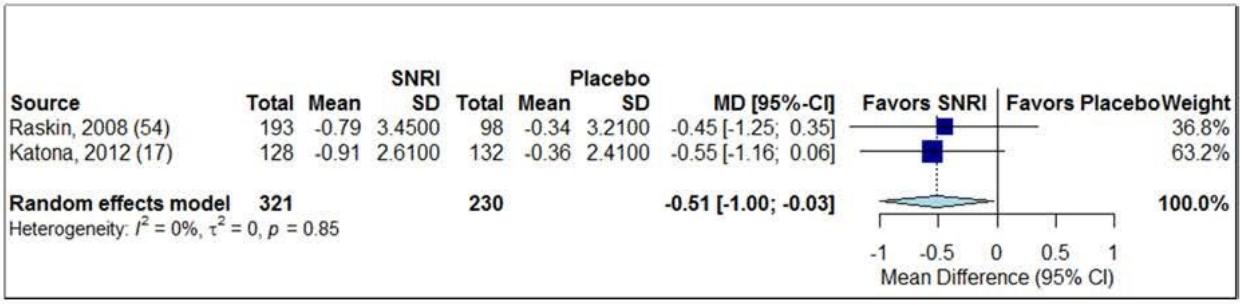
[a]Acute- 1 time elevation in supine DBP; continuation- treatment emergent elevated supine DBP 90 or greater with an increase of at least 10 from baseline

[b]Acute- 1 time elevation in supine SBP; continuation- treatment emergent elevated supine SBP 140 or more with an increase of at least 10 from baseline

[c]Data presented in Appendix C Table C-3

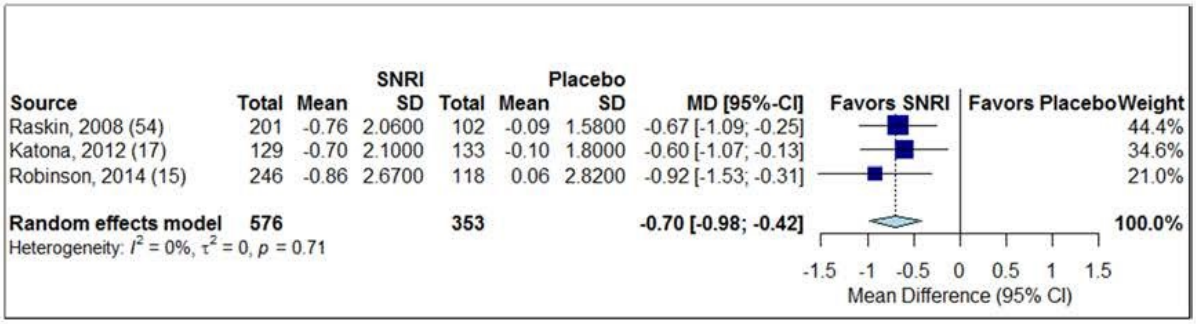
Outcomes of blood pressure were inconsistent when duloxetine was compared with placebo (Table 10). One trial[54] found the risk of elevation in supine systolic blood pressure (SBP) to be increased with duloxetine [RR 2.29 (1.30 to 4.02)], but duloxetine decreased standing SBP compared with placebo [MD -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[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[55] used citalopram 20-30mg/day and the other fluoxetine 20-60mg/day[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[45] reported industry sponsorship.

Results

Main Outcomes

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

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

Abbreviations: CI=confidence interval; n=patient sample size; RCT=randomized controlled trial; 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 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,[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

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

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[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

Outcome	Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)[a]	Strength of Evidence
Any adverse events	RR 0.97 (0.83 to 1.14) No difference	Moderate (suspected selective reporting)
ECG- supraventricular arrhythmia	RD -0.01 (-0.03 to 0.02) Insufficient	Insufficient (imprecise, 1 event occurred)
Mortality	No events occurred Insufficient	Insufficient (no events occurred)
Serious adverse events	RR 0.28 (0.06 to 1.33) No difference	Low (imprecise, suspected selective reporting)
Withdrawals due to adverse events	RR 0.76 (0.41 to 1.39) No difference	Low (imprecise, suspected selective reporting)

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

[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

Outcome	Findings Effect Estimate (95 Percent CI)
Blood pressure-clinically significant increase in DBP[a]	RR 1.24 (0.65 to 2.38)
Blood pressure-clinically significant increase in SBP[a]	RR 0.64 (0.40 to 1.05)
Blood pressure-HTN DBP[b]	RR 0.75 (0.37 to 1.51)
Blood pressure-HTN SBP[b]	RR 1.31 (0.46 to 3.70)
Seizures	No events occurred
Suicidal thoughts	RD -0.01 (-0.03 to 0.02)

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

[a]DBP increase of ≥15 mmHg; SBP increase of ≥ 20 mmHg
[b]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[56] 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[24] (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 15. Summary of findings and strength of evidence for adverse effects with mirtazapine versus paroxetine

Outcome	Treatment Phase	Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)[a]	Strength of Evidence
Any adverse events	Acute	RR 0.97 (0.86 to 1.09) No difference	Moderate (suspected selective reporting)
	Continuation	RR 1.23 (0.91 to 1.72) No difference	Low (imprecise, suspected selective reporting)

Outcome	Treatment Phase	Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)[a]	Strength of Evidence
Hospitalization	Acute	RD -0.01 (-0.05 to 0.03) Insufficient	Insufficient (imprecise, 1 event occurred)
Serious adverse drug events	Acute	RR 0.98 (0.20 to 4.79) No difference	Low (imprecise, suspected selective reporting)
Withdrawals due to adverse events	Acute	RR 0.57 (0.34 to 0.94) NNT 9 (5 to 72) Decreased risk with mirtazapine	Low (imprecise, suspected selective reporting)

Abbreviations: CI=confidence interval; kg=kilogram; MD=mean difference; NNT=number needed to treat; 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.

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[56] 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[17] (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

Outcome	Treatment Phase	Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)[a]	Strength of Evidence
Any adverse events	Acute	RR 1.01 (0.85 to 1.21) No difference	High
Hip fracture	Acute	RD -0.01 (-0.04 to 0.02) Insufficient	Insufficient (imprecise, 1 event occurred)
Serious adverse events	Acute	RR 0.23 (0.03 to 2.05) No difference	Moderate (imprecise)
Withdrawals due to adverse events	Acute	RR 2.09 (0.66 to 6.64) No difference	Low (very imprecise)

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 neuropshychological 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

Outcome	Treatment Phase	Findings Effect Estimate (95 Percent CI)
Blood pressure-standing DBP, mmHg	Acute	MD 1 (-1.17 to 3.17)
Blood pressure- standing SBP, mmHg	Acute	MD 2 (-1.27 to 5.27)
Blood pressure-supine DBP, mmHg	Acute	MD 0 (-2.05 to 2.05)

Outcome	Treatment Phase	Findings Effect Estimate (95 Percent CI)
Blood pressure-supine SBP, mmHg	Acute	MD 3 (-0.02 to 6.02)
Cognitive function	Acute	DSST MD 2.79 (0.28 to 5.30); RAVLT-acquisition MD 1.14 (0.12 to 2.16)
ECG- QTc, msec	Acute	MD 2 (-3.36 to 7.36)
Sodium, mEq/L	Acute	MD -0.24 (-0.87 to 0.39)
Suicidal ideation or behavior	Acute	RR 1.20 (0.57 to 2.53)
Suicide	Acute	No events occurred
Weight, kg	Acute	MD -0.2 (-0.68 to 0.28)

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 Versus Duloxetine

Study Characteristics

One trial[17] (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

Outcome	Treatment Phase	Findings – Effect Estimate (95 Percent CI) Interpretation (Based on Statistical Significance)[a]	Strength of Evidence
Any adverse events	Acute	RR 0.80 (0.69 to 0.92) NNT 6 (4 to 17) Decreased risk with vortioxetine	High
Hip fracture	Acute	No events occurred Insufficient	Insufficient (no events occurred)
Serious adverse events	Acute	RR 1.03 (0.07 to 16.37) No difference	Moderate (imprecise)
Withdrawals due to adverse events	Acute	RR 0.58 (0.26 to 1.29) No difference	Moderate (imprecise)

Abbreviations: CI=confidence interval; n=patient sample size; NNT=number needed to treat; RCT=randomized controlled trial; RR=risk ratio; SNRI=serotonin–norepinephrine reuptake inhibitor

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

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

Outcome	Treatment Phase	Findings Effect Estimate (95 Percent CI)
Blood pressure- standing DBP, mmHg	Acute	MD 1 (-1.07 to 3.07)
Blood pressure-standing SBP, mmHg	Acute	MD 5 (1.61 to 8.39)
Blood pressure-supine DBP, mmHg	Acute	MD -1 (-3.06 to 1.06)
Blood pressure-supine SBP, mmHg	Acute	MD 3 (-0.15 to 6.15)
Cognitive function	Acute	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)
ECG- QTc, msec	Acute	MD 5 (-0.66 to 10.66)
Sodium, mEq/L	Acute	MD 0.31 (-0.35 to 0.97)
Suicidal ideation or behavior	Acute	RR 1.65 (0.72 to 3.78)
Suicide	Acute	RD -0.009 (-0.05 to 0.03)
Weight, kg	Acute	MD 0.4 (-0.12 to 0.92)

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[58] of a trial by Gorwood et al.[47] 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 to74 years old; 7.9 percent vs. 2.0 percent, p=0.008.

An included trial by Raskin et al.[54] compared duloxetine to placebo for 8 weeks of treatment (acute MDD phase) and compared age subgroups of those 65 to 74 years to those ≥75 years. Frequency of any adverse event was similar in both age groups and between duloxetine and placebo [<75 years duloxetine (70.6 percent) vs. placebo (65.2 percent), p=0.433; ≥75 years duloxetine (68.8 percent) vs. placebo (62.9 percent), p=0.656; p=0.98 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 years duloxetine (7.7 percent) vs. placebo (7.2 percent), p=1.00; ≥75 years duloxetine (14.1 percent) vs. placebo (11.4 percent), p=1.00. 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 years of age but a mean decrease in duloxetine vs. placebo (-2.95 vs. 1.09 mmHg, p=0.368) in patients ≥75 years.

Lastly, a post-hoc analysis[61] of an included study by Robinson et al.[15] 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 years (OR 1.7) vs. those ages ≥75 years (OR 1.6, p=0.92).

Risk Factors for Falling, Comorbidities, and Concurrent Medications

The post hoc analysis[61] of Robinson et. al.[15] 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 reviews[12,27] 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-analysis[9] 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 indications[79,80] 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 review[82] 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 falls[87] 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[2] or regulatory documents[88] 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 the this dosage range. Therefore, the data in this report does not reflect higher usual antidepressant doses that may be clinical 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.[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[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 descisionmakers 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 doe 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.

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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
62. (clinical adj trial$).tw.
63. ((singl$ 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

1. A double-blind multi-centre trial of fluoxetine and dothiepin in major depressive illness. South Wales Antidepressant Drug Trial Group. Int Clin Psychopharmacol. 1988;3(1):75-81. PMID: 3282004 [Not in older adults]
2. Ackerman DL, Greenland S, Bystritsky A, et al. Characteristics of fluoxetine versus placebo responders in a randomized trial of geriatric depression. Psychopharmacol Bull. 1997;33(4):707-714. PMID: 9493483 [No outcome of interest]
3. Ackerman DL, Greenland S, Bystritsky A, et al. Side effects and time course of response in a placebo-controlled trial of fluoxetine for the treatment of geriatric depression. J Clin Psychopharmacol. 2000;20(6):658-665. PMID: 11106138 [Not in older adults]
4. Adeoye OM, Sweet RA, Pollock BG, et al. Bupropion plasma concentration and antidepressant response in elderly patients: A prospective, randomized, double-blind study International Journal of Geriatric Psychopharmacology. 2000;2(3):132-136. [Not in older adults]
5. Aguglia E, Casacchia M, Cassano GB, et al. Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. Int Clin Psychopharmacol. 1993;8(3):197-202. PMID: 8263318 [Not in older adults]
6. Alam MY, Jacobsen PL, Chen Y, et al. Safety, tolerability, and efficacy of vortioxetine (Lu AA21004) in major depressive disorder: results of an open-label, flexible-dose, 52-week extension study. Int Clin Psychopharmacol. 2014;29(1):36-44. PMID: 24169027 [Not in older adults]
7. Allard J, Artero S, Ritchie K. Consumption of psychotropic medication in the elderly: a re-evaluation of its effect on cognitive performance. Int J Geriatr Psychiatry. 2003 Oct;18(10):874-878. PMID: 14533119 [Not in MDD]
8. Altamura AC, Mauri MC, Colacurcio F, et al. Trazodone in late life depressive states: a double-blind multicenter study versus amitriptyline and mianserin. Psychopharmacology (Berl). 1988;95 Suppl:S34-6. PMID: 3133712 [Not in older adults]
9. Altamura AC, Mauri MC, Colacurcio F, et al. Trazodone in late life depressive states: A double-blind muticenter study versus amitriptyline and mianserin. Psychopharmacology (Berl). 1988;95 Suppl:34-36. PMID: 3133712 [Not in older adults]
10. Altamura AC, Mauri MC, Rudas N, et al. Clinical activity and tolerability of trazodone, mianserin, and amitriptyline in elderly subjects with major depression: a controlled multicenter trial. Clin Neuropharmacol. 1989;12 Suppl 1:S25-7. PMID: 2663151 [Not in older adults]

11. Altamura AC, Novellis FD, Guercetti G, et al. Fluoxetine compared with amitriptyline in elderly depression: a controlled clinical trial. Int J Clin Pharmacol Res. 1989;9(6):391-6. PMID: 2699465 [Acute care setting]

12. Altamura AC, Percudani M, Guercetti G, et al. Efficacy and tolerability of fluoxetine in the elderly: A double-blind study versus amitryptiline. Int Clin Psychopharmacol. 1989;4(Suppl 1):103-106. PMID: 2783697 [Acute care setting]

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14. Amsterdam JD, Brunswick DJ. Site variability in treatment outcome in antidepressant trials. Prog Neuropsychopharmacol Biol Psychiatry. 2002;26(5):989-93. PMID: 12369275 [Not in older adults]

15. Amsterdam JD, Shults J. Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. Am J Psychiatry. 2010 Jul;167(7):792-800. PMID: 20360317 [Not in MDD]

16. An H, Choi B, Park KW, et al. The Effect of Escitalopram on Mood and Cognition in Depressive Alzheimer's Disease Subjects J Alzheimers Dis. 2017;55(2):727-735. PMID: 27716660 [Not in older adults]

17. Andjelkovic M, Jovanovic DB, Zdravkovic N, et al. Gallbladder emptying in patients with major depression: a case series. Pharmacopsychiatry. 2011 Jul;44(5):165-8. PMID: 21751125 [Excluded study design]

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Appendix C. Evidence Tables

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

Study, year N Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	MDD duration [mean (SD)]	Recurrent episode (%)	MADRS [mean (SD)]	HAM-D [mean (SD)]	MMSE [mean (SD)]
Hutchinson, 1991[53] N=90 6w Low	≥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.	Paroxetine 20mg daily n=58	72.0 (5.6)	20.7	NR	46.6	NR	19.5	NR
		Amitriptyline 100mg daily n=32	71.5 (9.5)	71.9	NR	41.0	NR	20.8	NR
Schone, 1993[42] N=106 6w Unclear	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 prn sleep disturbance.	Paroxetine 20-40mg daily n=54 Majority (81%) received 20 or 30 mg	74.3 (NR)	17	NR	94	NR	29.0	24.2
		Fluoxetine 20-60mg daily n=52 Majority (64%) received 20 or 40 mg	73.7 (NR)	90	NR	88	NR	27.9	26.0
Kyle, 1998[52] N=365 8w Low	≥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.	Citalopram 20-40mg in the morning n=179 Majority (88%) received 20mg	73.4 (NR)	27	NR	53	27.7	NR	NR
		Amitriptyline 50-100mg in the evening n=186 Majority (86%) received 50mg	74.1 (NR)	26	NR	51	30.5	NR	NR
Finkel, 1999[18] N=75 12w High	≥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,	Sertraline 50-100mg daily n=42 Mean 72.6±25 mg/day	74 (3.6)	42.8	NR	NR	NR	24.2 (4.4)	28.6 (1.5)

Study, year N Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	MDD duration [mean (SD)]	Recurrent episode (%)	MADRS [mean (SD)]	HAM-D [mean (SD)]	MMSE [mean (SD)]
	suicide risk. Required to discontinue other psychotropics except chloral hydrate or temazepam used sparingly for sleep	Fluoxetine 20-40mg[f] daily n=33 Mean 28.5±10 mg/d	75 (5.3)	51.5	NR	NR	NR	25.4 (5.0)	28.5 (1.7)
Finkel, 1999[51] N=76 12w High	≥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.	Sertraline 50-150mg in the evening n=39 Mean 102±44 mg/d	74 (4.4)	33.3	NR	49	NR	24.7 (4.4)	NR
		Nortriptyline 25-100mg in the evening n=37 Mean 68±31 mg/d	75 (4.8)	32.4	NR	46	NR	24.3 (5.4)	NR
Cassano, 2002[44] N=242 12m Low	≥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.	Paroxetine 20-40mg daily n=123 Mean NR	75.61 (6.99)	39.0	NR	NR	NR	23.2	NR
		Fluoxetine 20-60mg daily n=119 Mean NR	74.85 (6.67)	49.6	NR	NR	NR	23.5	NR
Klysner, 2002[48] N=121 8w OL acute phase; 16w OL continuation phase; 48w RDB maintenance phase[a] High	≥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 benxodiazepines and other hypnotics at a constant dose after 8w of phase II.	Citalopram 20-40mg daily n=60 20mg (10%), 30mg (41.7%), 40mg (48.3%)	74 (NR)	18	NR	NR	27 (3.4)	NR	NR
		Placebo daily n=61	75 (NR)	28	NR	NR	26.7 (3.1)	NR	NR

Study, year N Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	MDD duration [mean (SD)]	Recurrent episode (%)	MADRS [mean (SD)]	HAM-D [mean (SD)]	MMSE [mean (SD)]
Schatzberg, 2002[19] N=254 8w acute phase; 16w continuation phase[b] Low	≥65y; MDD per DSM-IV; MMSE above 25th 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	Mirtazapine 30-45mg in the evening n=128 Mean acute 25.7 (6.7); acute+continuation 34.0 (10.7)	71.7 (5.7)	50	NR	NR	NR	22.2 (3.5)	28.7 (1.2)
		Paroxetine 20-40mg in the evening n=126 Mean acute 26.5(5.5); acute+continuation 33.6 (7.8)	72.0 (5.1)	46.7	NR	NR	NR	22.4 (3.5)	28.7 (1.2)
Allard, 2004[55] N=148 6m Low	≥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 zopliclone ≤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.	Venlafaxine ER 75-150mg daily n=73 54.7% received 150mg	73.6 (5.9)	20.5	NR	NR	27.6 (3.6)	NR	NR
		Citalopram 20-30mg daily n=75 55.3% received 30mg/d	72.5 (5.7)	20	NR	NR	27.0 (3.6)	NR	NR
Roose, 2004[49] N=174 8w Low	≥75y; MDD ≥4w per DSM-IV; HAM-D-24≥24; MMSE≥19. Excluded bipolar, OCD, psychotic disorder, drug and alcohol abuse, suicidal, possible	Citalopram 10-40mg daily n=84 Mean NR	79.8 (4.0)	46.4	NR	NR	24.4 (5.9)	24.4 (4.3)	28.4 (1.6)

Study, year N Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	MDD duration [mean (SD)]	Recurrent episode (%)	MADRS [mean (SD)]	HAM-D [mean (SD)]	MMSE [mean (SD)]
	Alzheimer's or vascular dementia, Parkinson's disease, acute, severe or unstable medical illness.	Placebo daily n=90	79.3 (4.7)	37.8	NR	NR	25.0 (5.9)	24.2 (3.9)	27.6 (2.5)
Kasper, 2005[43] N=517 8w Low	≥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.	Escitalopram 10mg daily n=173	75 (7)	25	NR	NR	28.2 (3.8)	NR	NR
		Fluoxetine 20mg daily n=164	75 (7)	23	NR	NR	28.5 (3.8)	NR	NR
		Placebo daily n=180	75 (7)	24	NR	NR	28.6 (4.2)	NR	NR
Reynolds, 2006[46] N=53 8w OL acute phase; 16w OL continuation phase; 2y RCT maintenance phase[c] High	≥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.	Paroxetine 10-40mg daily n=35 Mean NR	77.0 (5.9)	40	NR	40	NR	19.5 (2.7)	27.5 (2.5)
		Placebo daily n=18	74.8 (4.4)	44	NR	39	NR	19.8 (2.4)	28.7 (1.1)
Schatzberg, 2006[45] N=300 8w Low	≥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.	Venlafaxine IR 37.5-112.5mg BID n=104 Mean NR	71 (NR)	44	NR	NR	26 (NR)	24 (NR)	NR
		Fluoxetine 20-60mg daily n=100 Mean NR	71 (NR)	55	NR	NR	27 (NR)	24 (NR)	NR
		Placebo BID n=96	71 (NR)	54	NR	NR	27 (NR)	23 (NR)	NR

Study, year N Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	MDD duration [mean (SD)]	Recurrent episode (%)	MADRS [mean (SD)]	HAM-D [mean (SD)]	MMSE [mean (SD)]
Gorwood, 2007[47] N=305 12w OL acute phase; 24w RCT continuation phase[d] High	≥65y; MDD≥4w per DSM-IV-TR; MMSE≥24; MADRS≥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.	Escitalopram 10-20mg daily n=152 Mean NR	73 (NR)	21.7	NR	NR	5.1 (4.8)	NR	NR
		Placebo daily n=153	72 (NR)	20.9	NR	NR	5.1 (4.8)	NR	NR
Raskin, 2008[54] N=311 8w High	≥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.	Duloxetine 60mg daily n=207	72.6 (5.7)	39.6	NR	NR	NR	22.4 (3.8)	NR
		Placebo daily n=104	73.3 (5.7)	42.3	NR	NR	NR	22.0 (2.6)	NR
Fraguas, 2009[50] N=37 8w High	>65y; stable HF w/LVEF<50%; MDD 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.	Citalopram 20-40mg daily n=19 Mean NR	74.4 (6.0)	52.6	NR	NR	21.9 (5.6)	22.9 (3.0)	NR
		Placebo daily n=18	72.6 (4.6)	44.5	NR	NR	20.1 (4.6)	23.9 (3.4)	NR
Hewett, 2010[14] N=418 10w Low	≥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 nervousa or bulimia, psychotic conditions, substance abuse.	Bupropion XR 150-300mg daily n=211 Mean 179 mg/day	70.9 (5.6)	26	NR	65	29.5 (0.3)[e]	NR	NR
		Placebo daily n=207	71.3 (5.9)	30	NR	69	29.8 (0.3)	NR	NR

Study, year N Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	MDD duration [mean (SD)]	Recurrent episode (%)	MADRS [mean (SD)]	HAM-D [mean (SD)]	MMSE [mean (SD)]
Katona, 2012[15] N=452 8w Low	≥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[22] N=370 12w RCT acute phase; 10w RCT continuation peroid[f] Low	≥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 Acute: 45% received 60mg/d; Continuation: 63% received 60 mg/d	72.89 (6.10)	34.5	NR	100	29.25 (5.57)	19.42 (5.56)	28.55 (1.83)
		Placebo daily[g] 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; DSM-IV-TR= 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

[a]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

[b]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

[c]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

[d]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

[e]Standard error

[f]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

[g]Patients received placebo for 12 weeks; From weeks 12 until 20 placebo rescue was available. Placebo-rescued 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

Study, year N Duration Risk of bias	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males (%)	MDD duration [mean (SD)]	Recurrent episode (%)	MADRS [mean (SD)]	HAM-D [mean (SD)]	MMSE [mean (SD)]
Wu, 2008[57] N=1976 Retrospective, claims-based cohort Low	≥65y at index date; ≥1 inpatient claim or 2 medical claims with different service dates associated with MDD diagnosis; fill at least one SSRI or SNRI prescription; continuous 12m enrollment; 6m washout prior to index	Escitalopram N=459	73.5 (4.8)	44	NR	NR	NR	NR	NR
		Other SSRI/SNRI n=1517	73.6 (4.9)	43.2	NR	NR	NR	NR	NR
Coupland, 2011[56] N=60,746 patients; 1,398,359 prescriptions Retrospective, population-based cohort Low	≥65y, computer-recorded diagnosis codes for depression. Excluded diagnosis of bipolar, schizophrenia or other psychiatric conditions.	SSRI n=764,659 prescriptions	75.0[a] (NR)	33.3[a]	NR	NR	NR	NR	NR
		TCA n=442,192 prescriptions							
		Other antidepressant[b] n= 189,305 prescriptions							
		No antidepressant n=6,708 patients							

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

[a]For the full study cohort

[b]Defined as antidepressant other than SSRI, TCA or MAOI according to the British National Formulary

Table C-3. Study level outcomes

Study, year N Duration Risk of bias	Comparison Outcomes[a]
Hutchinson, 1991[53] N=90 6w Low	**SSRI (paroxetine) vs TCA (amitriptyline)** Any ADE 20/58 vs. 20/32 Mortality 0/58 vs. 1/32 Withdrawal due to ADE 8/58 vs. 6/32
Schone, 1993[42] N=106 6w Unclear	**SSRI (paroxetine) vs. SSRI (fluoxetine)** Withdrawal due to ADE 6/54 vs. 7/52
Kyle, 1998[52] N=365 8w Low	**SSRI (citalopram) vs. TCA (amitriptyline)** Any ADE 112/179 vs.146/186 Hospitalization 0/179 vs. 1/186 Serious ADE 7/179 vs. 11/186 Withdrawal due to ADE 31/179 vs. 48/186
Finkel, 1999[18] N=75 12w High	**SSRI (sertraline) vs. SSRI (fluoxetine)** Any ADE 39/42 vs. 31/33 Cognitive function: HAM-D Cognitive factor score 1.7(2.4) vs. 1.2(3) Cognitive function: DSST score -6(18.3) vs. -6(17.2) Withdrawal due to ADE 8/42 vs. 10/33
Finkel, 1999[51] N=76 12w High	**SSRI (sertraline) vs. TCA (nortriptyline)** Cognitive impairment 2/38 vs. 5/37 Serious ADE 5/39 vs. 11/37 Withdrawal due to ADE 7/39 vs. 11/37
Cassano, 2002[44] N=242 12m Low	**SSRI (paroxetine) vs. SSRI (fluoxetine)** Any ADE 34/123 vs. 39/119 Mortality 2/123 vs. 2/119 Serious ADE 7/123 vs. 12/119 Suicide 0/123 vs. 1/119
Klysner, 2002[48] N=121 8w OL acute phase; 16w OL continuation phase; 48w RDB maintenance phase[a] High	**SSRI (citalopram) vs. placebo for 48w maintenance phase** Blood pressure: hypertension 1/60 vs. 2/61 Blood pressure: sitting DBP (mmHg) -3(15) vs. 1(15) Blood pressure: sitting SBP (mmHg) -3(32.9) vs. 2(30) Mortality 0/60 vs. 1/61 Serious ADE 11/61 vs. 5/61 Withdrawal due to ADE 6/60 vs. 8/61

Study, year N Duration Risk of bias	Comparison Outcomes[a]
Schatzberg, 2002[19] N=254 8w acute phase; 16w continuation phase[b] Low	**Mirtazapine vs. paroxetine-8w acute phase** Any ADE 102/208 vs. 104/126 Blood pressure: Hypotension 0/128 vs. 0/126 Hospitalization 0/128 vs. 1/126 Serious ADE 3/128 vs. 3/126 Weight gain ≥7% 5/128 vs. 0/126 Weight gain, patient reported 14/128 vs. 0/126 Weight (kg) 1.7(21.5) vs. -0.3(20.5) Withdrawal due to ADE 19/128 vs. 33/126 **Mirtazapine vs. paroxetine-16w continuation phase** Any ADE 40/63 vs. 28/55 Weight gain ≥7% 9/63 vs. 2/55
Allard, 2004[55] N=148 6m Low	**SNRI (venlafaxine ER) vs. SSRI (citalopram)- 8w acute phase** Blood pressure: DBP (mmHg) -1.95(9.08) vs. -0.49(9.04) Blood pressure: SBP (mmHg) -5.94(14.04) vs. -3.62(15.22) Weight (kg): -0.4(18.8) vs. -0.6(14.6) **SNRI (venlafaxine ER) vs. SSRI (citalopram)- 22w continuation phase** Blood pressure: DBP (mmHg) -0.91(9.0) vs. -0.50(7.38) Blood pressure: SBP (mmHg) -2.93(15.26) vs. -0.45(11.20) Falls 0/73 vs. 1/75 Fracture, hip 1/73 vs. 0/75 Weight (kg): -1(18.8) vs. -0.1(15) **SNRI (venlafaxine ER) vs. SSRI (citalopram)- 6m** Any ADE 45/73 vs. 57/75 Mortality 0/73 vs. 1/75 Serious ADE 5/73 vs. 4/75 Withdrawal due to ADE 6/73 vs. 4/75
Roose, 2004[49] N=174 8w Low	**SSRI (citalopram) vs. placebo** Withdrawal due to ADE 9/84 vs. 1/90

Study, year **N** **Duration** **Risk of bias**	**Comparison** **Outcomes[a]**
Kasper, 2005[43] N=517 8w Low	**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[46] N=53 8w OL acute phase; 16w OL continuation phase; 2y RCT maintenance phase[c] High	**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[45] N=300 8w Low	**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[47] N=305 12w OL acute phase; 24w RCT continuation phase[d] High	**SSRI (escitalopram) vs. placebo – 24w continuation phase** Any ADE 53/130 vs. 54/91 Withdrawal due to ADE 4/152 vs. 7/153

Study, year N Duration Risk of bias	Comparison Outcomes[a]
Raskin, 2008[54] 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 hypotension 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[50] 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)

Study, year N Duration Risk of bias	Comparison Outcomes[a]
Hewett, 2010[14] N=418 10w Low	**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[15] N=452 8w Low	**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

Study, year N Duration Risk of bias	Comparison Outcomes[a]
Robinson, 2014[22,61] N=370 12w RCT acute phase; 10w RCT continuation peroid[e] 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) **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; HAM-D=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

[a]n/N per arm for dichotomous outcomes and mean (SD) per arm for continuous outcomes

[a]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

[b]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

[c]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

[d]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

[e]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

Study, Year	Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Risk of bias
Hutchinson, 1991[53]	Unclear	Unclear	Low	Unclear	Low	High[a]	Low	Low
Schone, 1993[42]	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	Unclear
Kyle, 1998[52]	Unclear	Unclear	Low	Unclear	Low	High[b]	Low	Low
Finkel, 1999[18]	Low	Low	Low	Unclear	High[c]	High[d]	Low	High
Finkel, 1999[51]	Unclear	Unclear	Low	Unclear	High[e]	High[f]	Low	High
Cassano, 2002[44]	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Klysner, 2002[48]	Unclear	Unclear	Low	Unclear	High[g]	High[h]	High[i]	High
Schatzberg, 2002[19]	Unclear	Unclear	Low	Unclear	Low	High[j]	Low	Low
Allard, 2004[55]	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Roose, 2004[49]	Low	Low	Low	Unclear	Low	High[k]	Low	Low
Kasper, 2005[43]	Unclear	Unclear	Low	Unclear	Low	High[l]	Low	Low
Reynolds, 2006[46]	Low	Unclear	Low	Low	Low	Low	High[m]	High
Schatzberg, 2006[45]	Low	Unclear	Low	Unclear	Low	High[n]	Low	Low
Gorwood, 2007[47]	Low	Low	Low	Low	High[o]	High[p]	High[q]	High
Raskin, 2008[54]	Unclear	Unclear	Low	Unclear	Low	Low	High[r]	High
Fraguas, 2009[50]	Unclear	Unclear	Low	Unclear	Low	Low	High[s]	High
Hewett, 2010[14]	Low	Low	Low	Unclear	Low	High[t]	Low	Low
Katona, 2012[15]	Low	Low	Low	Low	Low	Low	Low	Low
Robinson, 2014[22]	Low	Low	Low	Low	Low	Low	High[u]	Low

[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

[h]Study methods indicate that vital sign measurements, laboratory assessments, and weight were collected but these outcomes are not reported in the results
[i]Two single-arm treatment phases through first 16 weeks prior to randomization; patients were removed due to adverse events prior to randomization
[j]Study methods indicate that clinically relevant changes in vitals and electrocardiograms were collected but these outcomes are not reported in the results
[k]Study methods indicate that electrocardiograms were collected but these outcomes were not reported in the results
[l]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
[m]Short-term (8w) and continued treatment (16w) phases prior to randomization; patients were removed from the study based on response prior to randomization
[n]Study methods indicate that supine and systolic blood pressure, QTc prolongation, and arrhythmias were collected but these outcomes are not reported in the results
[o]High overall (28.2%) and differential (26.0%) attrition
[p]Study methods indicate that vital signs and body weight were collected but these outcomes are not reported in the results
[q]Acute treatment phase (12w) prior to randomization to screen for responders; patients were also removed due to adverse events prior to randomization
[r]Patients unable to tolerate treatment during the 1w run-in phase were removed from study
[s]Study interruption after unplanned interim analysis because of a high rate of placebo response during the double-blind phase
[t]Methods indicate that electrocardiograms and weight were collected but these outcomes are not reported in the results
[u]Patients with an adverse reaction during the first 12w randomized phase were excluded from the second randomization for the continuation phase

Table D-2. Risk of bias assessment- observational studies

Study, Year	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough	Adequacy of follow-up of cohorts	Risk of Bias
Wu, 2008[57]	Truly representative	Drawn from same community	Secure record	NA	Controls for key factors	Record linkage	Yes	Complete follow-up	Low
Coupland, 2011[56]	Truly representative	Drawn from same community	Secure record	NA	Controls for key factors	Record linkage	Yes	Complete follow-up	Low

Abbreviations: NA=not applicable.

Appendix E. Strength of Evidence Assessments

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

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication or reporting bias	Strength of evidence
Any adverse event-acute	2 RCT (713)	Low	Consistent	Direct	Precise	Suspected reporting bias	Moderate
Any adverse event-continuation	1 RCT (221)	High	Unknown (single study)	Direct	Precise	Suspected reporting bias	Moderate
Any adverse event-unspecified	1 OBS (60,746)	Low	Unknown (single study)	Direct	Precise	Undetected	Low
Cognitive impairment	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ECG-Arrhythmia	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ECG-QTc prolongation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Falls	1 OBS (60,746)	Low	Unknown (single study)	Direct	Precise	Undetected	Low
Fractures	1 OBS (60,746)	Low	Unknown (single study)	Direct	Precise	Undetected	Low
Hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Mortality – acute	1 RCT (517)	Low	Unknown (single trial)	Direct	Imprecise	Suspected reporting bias	Insufficient (1 death each in escitalopram and placebo arms)
Mortality-maintenance	1 RCT (121)	High	Unknown (single trial)	Direct	Imprecise	Suspected reporting bias	Insufficient (1 death occurred in the placebo arm)
Mortality – Unspecified	1 OBS (60,746)	Low	Unknown (single study)	Direct	Precise	Undetected	Low
Serious adverse events	1 RCT (122)	High	Unknown (single trial)	Direct	Imprecise	Suspected reporting bias	Insufficient
SIADH	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication or reporting bias	Strength of evidence
Withdrawal due to adverse event-acute	3 RCT (887)	Low	Consistent	Direct	Imprecise	Suspected reporting bias	Low
Withdrawal due to adverse event-continuation	1 RCT (305)	High	Unknown (single trial)	Direct	Imprecise	Suspected reporting bias	Insufficient
Withdrawal due to adverse event-maintenance	2 RCT (174)	High	Consistent	Direct	Imprecise	Suspected reporting bias	Insufficient

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

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication or reporting bias	Strength of evidence
Any adverse event	2 RCTs (455)	Low	Consistent	Direct	Imprecise	Suspected reporting bias	Low
Cognitive impairment	1 RCT (75)	High	Unknown (single trial)	Direct	Imprecise	Suspected reporting bias	Insufficient
ECG-Arrhythmia	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ECG-QTc prolongation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Falls	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Fractures	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Hospitalization	1 RCT (365)	Low	Unknown (single trial)	Direct	Imprecise	Suspected reporting bias	Insufficient (1 event occurred in the TCA arm)
Mortality	1 (90)	Low	Unknown (single trial)	Direct	Imprecise	Suspected reporting bias	Insufficient (1 event occurred in the TCA arm)
Serious adverse events	2 RCTs (441)	Medium	Consistent	Direct	Imprecise	Suspected reporting bias	Insufficient
SIADH	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Withdrawal due to adverse events	3 RCTs (531)	Low	Consistent	Direct	Imprecise	Suspected reporting bias	Low

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

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

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

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

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication or reporting bias	Strength of evidence
Mortality-Unspecified	1 OBS	Low	Unknown (single study)	Direct	Precise	Undetected	Low
Serious adverse event-acute	2 RCTs (607)	Medium	Consistent	Direct	Imprecise	Undetected	Low
Serious adverse events- acute + continuation	1 RCT (370)	Low	Unknown (single trial)	Direct	Imprecise	Undetected	Moderate
SIADH	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Withdrawal due to adverse events-acute	3 RCTs (812)	Low	Consistent	Direct	Imprecise	Undetected	Moderate
Withdrawal due to adverse events-acute+continuation	1 RCT (370)	Low	Unknown (single trial)	Direct	Imprecise	Undetected	Moderate

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

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

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

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

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

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

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

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication or reporting bias	Strength of evidence
Any adverse events—cute	1 RCT (254)	Low	Unknown (single trial)	Direct	Precise	Suspected selective reporting	Moderate
Any adverse events-continuation	1 RCT (254)	Low	Unknown (single trial)	Direct	Imprecise	Suspected selective reporting	Low
Cognitive impairment	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ECG-Arrhythmia	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ECG-QTc prolongation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Falls	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Fractures	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Hospitalization	1 RCT (254)	Low	Unknown (single trial)	Direct	Imprecise	Suspected selective reporting	Insufficient (1 event occurred)
Mortality	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Serious adverse events	1 RCT (254)	Low	Unknown (single trial)	Direct	Imprecise	Suspected selective reporting	Low
SIADH	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Withdrawal due to adverse events	1 RCT (254)	Low	Unknown (single trial)	Direct	Imprecise	Suspected selective reporting	Low

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone

Table E-9. Strength of evidence ratings for the comparison of trazodone versus no antidepressant use

Outcome	N of studies (n of patients)	Study limitations	Consistency	Directness	Precision	Publication or reporting bias	Strength of evidence
Any adverse events	1 OBS (60,746)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low
Cognitive impairment	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ECG-Arrhythmia	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
ECG-QTc prolongation	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Falls	1 OBS (60,746)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low
Fractures	1 OBS (60,746)	Low	Unknown (single study)	Direct	Imprecise	Undetected	Low
Hospitalization	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
Mortality	1 OBS (60,746)	Low	Unknown (single study)	Direct	Precise	Undetected	Low
Serious adverse events	0	NA	NA	NA	NA	NA	Insufficient (no evidence)
SIADH	0	NA	NA	NA	NA	NA	Insufficient (no evidence)

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

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

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone

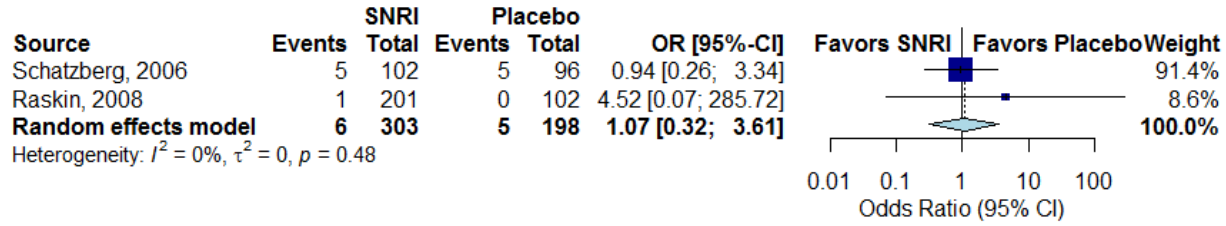
Table E-11. Strength of evidence ratings for the comparison of vortioxetine versus duloxetine

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

Abbreviations: NA=not applicable; RCT=randomized controlled trial; SIADH=syndrome of inappropriate antidiuretic hormone

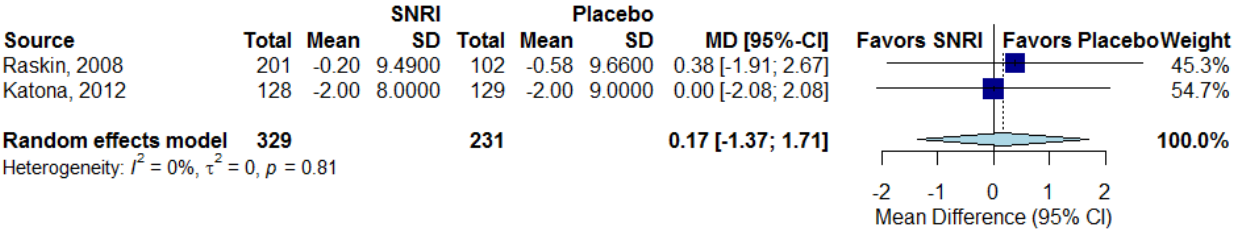
Appendix F. Forest Plots

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



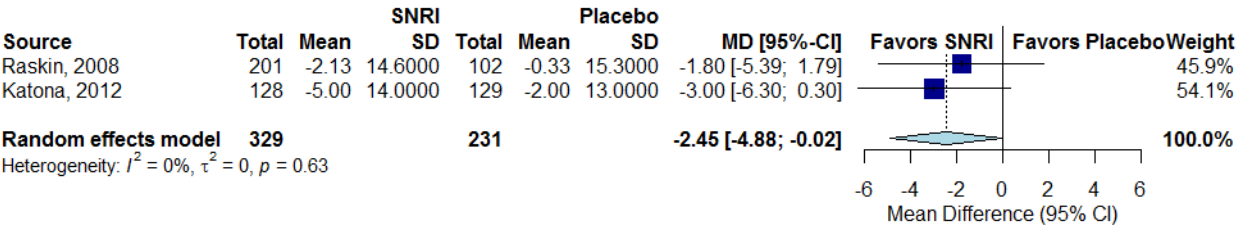
Abbreviations: CI=confidence interval; OR=odds ratio; SNRI=serotonin norepinephrine reuptake inhibitor

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



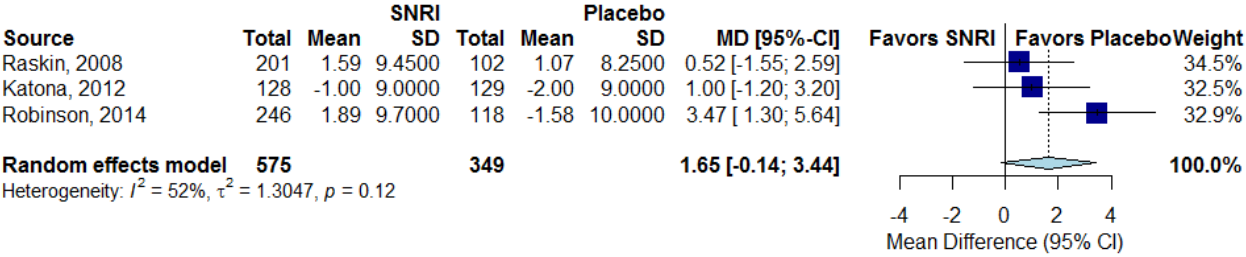
Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

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



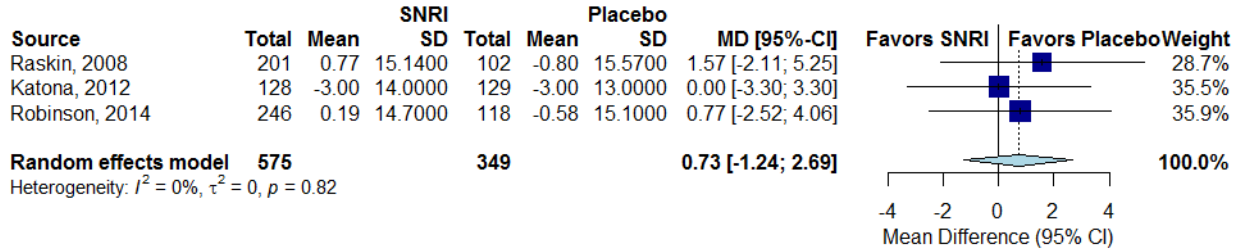
Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

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



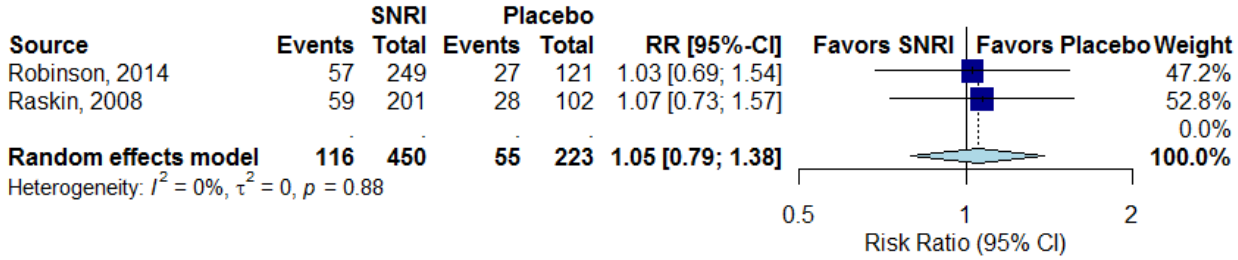
Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-5. SNRI vs. placebo on supine systolic blood pressure, acute phase



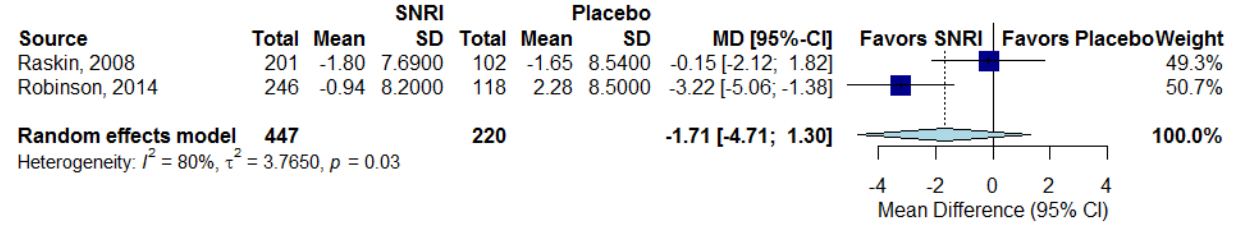
Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

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



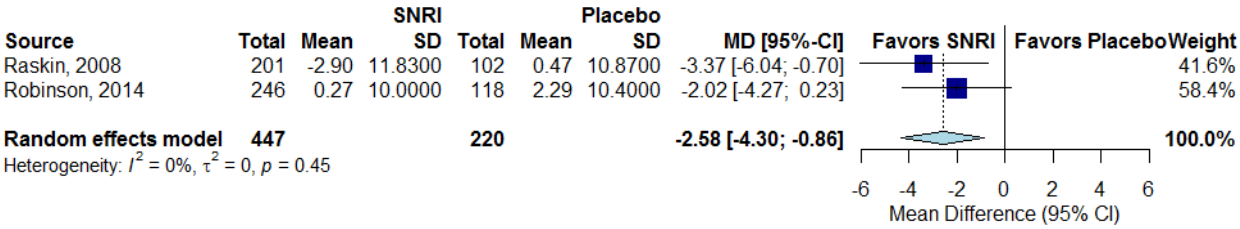
Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

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



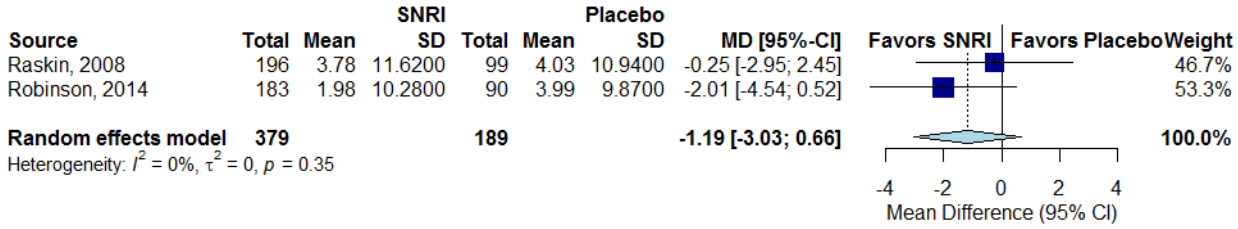
Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

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



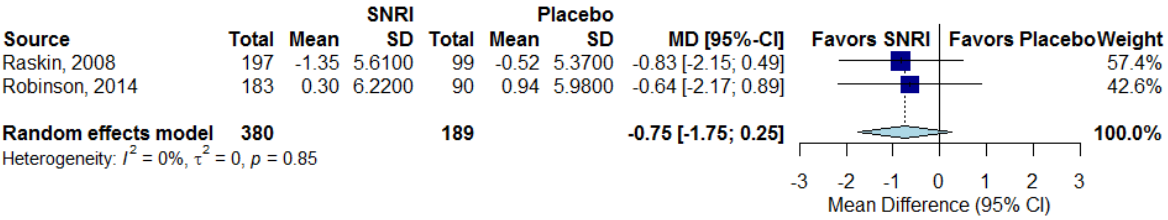
Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

Figure F-9. SNRI vs. placebo on SDST score, acute phase



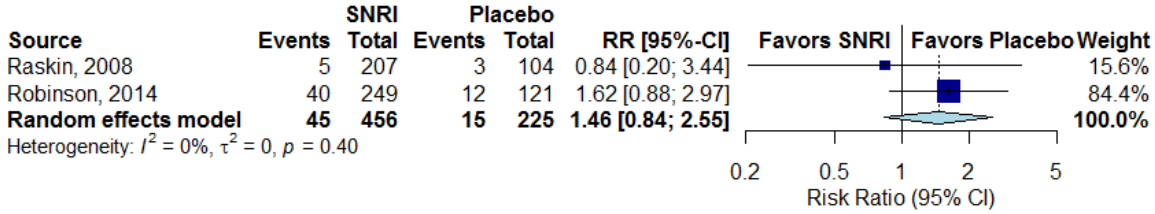
Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

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



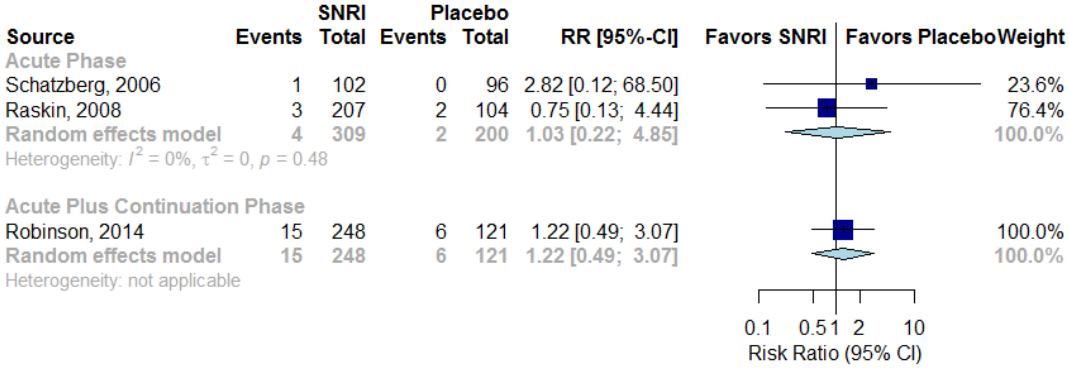
Abbreviations: CI=confidence interval; MD=mean difference; SD=standard deviation; SNRI=serotonin norepinephrine reuptake inhibitor

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