Effective Health Care Program

Comparative Effectiveness Review
Number 46

Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression:

An Update of the 2007 Comparative Effectiveness Review

Agency for Healthcare Research and Quality
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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10056-I

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AHRQ Publication No. 12-EHC012-EF
December 2011

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

Suggested citation:
Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux LJ, Van Noord M, Mager U, Gaynes BN, Thieda P, Strobelberger M, Lloyd S, Reichenpfader U, Lohr KN. Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center, Contract No. 290-2007-10056-I.) AHRQ Publication No. 12-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

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 are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

We extend our appreciation to our Technical Expert Panel (TEP): James H. Bray, Ph.D., President of the American Psychological Association; Susan G. Kornstein, M.D., Professor of Psychiatry at the Virginia Commonwealth University; John Santa, M.D. of the American Consumers Union; Gregory Simon, M.D., M.P.H. of Group Health; and John Williams, M.D., primary care physician and former Director of the Duke Evidence-based Practice Center. All provided thoughtful advice and input during our research process.

The investigators deeply appreciate the considerable support, commitment, and contributions of the EPC team staff at RTI International and the University of North Carolina. We express our gratitude to Visali Peravali, M.Sc., Tania Wilkins, M.Sc. and Shrikant Bandiwala, Ph.D. for their statistical programming for the indirect comparisons analysis; Tammeka Swinson Evans, Andrea Yuen, Shannon Brode and Audrey Holland, Research Analysts; and Loraine Monroe, our EPC publications specialist.

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Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review

Structured Abstract

Background. Depressive disorders such as major depressive disorder (MDD), dysthymia, and subsyndromal depression may be serious disabling illnesses. MDD affects more than 16 percent of adults at some point during their lifetimes. Second-generation antidepressants dominate the medical management of depressive disorders. These drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other drugs with related mechanisms of action that selectively target neurotransmitters.

Objectives. The objective of this report was to compare the benefits and harms of bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine for the treatment of depressive disorders, including variations of effects in patients with accompanying symptoms and patient subgroups.

Data Sources. We updated a comparative effectiveness review published in 2007 by the Agency for Healthcare Research and Quality searching PubMed, Embase, The Cochrane Library, and International Pharmaceutical Abstracts up to January 2011.

Review Methods. Two people independently reviewed the literature, abstracted data, and rated the risk of bias. If data were sufficient, we conducted meta-analyses of head-to-head trials of the relative benefit of response to treatment. In addition, we conducted mixed treatment comparisons to derive indirect estimates of the comparative efficacy among all second-generation antidepressants.

Results. From a total of 3,722 citations, we identified 248 studies of good or fair quality. Overall, no substantial differences in efficacy could be detected among second-generation antidepressants for the treatment of acute-phase MDD. Statistically significant differences in response rates between some drugs are small and likely not clinically relevant. No differences in efficacy were apparent in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbidities, although evidence within these subpopulations was limited.

Differences exist in the incidence of specific adverse events and the onset of action. Venlafaxine leads to higher rates of nausea and vomiting, sertraline to higher rates of diarrhea, and mirtazapine to higher rates of weight gain than comparator drugs. Bupropion causes lower rates of sexual dysfunction than other antidepressants. The evidence is insufficient to draw conclusions about the comparative efficacy and effectiveness for the treatment of dysthymia and subsyndromal depression.

Conclusions. Our findings indicate that the existing evidence does not warrant the choice of one second-generation antidepressant over another based on greater efficacy and effectiveness. Differences with respect to onset of action and adverse events may be taken into consideration for the choice of a medication.

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Executive Summary

Background

Depressive disorders such as major depressive disorder (MDD), dysthymia, and subsyndromal depression (including minor depression) may be serious disabling illnesses. MDD is the most prevalent, affecting more than 16 percent (lifetime) of U.S. adults. In 2000, the U.S. economic burden of depressive disorders was estimated to be $83.1 billion. Likely, this number has increased during the past 10 years. More than 30 percent of these costs are attributable to direct medical expenses.

Pharmacotherapy dominates the medical management of depressive disorders and may include first-generation antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors) and more recently developed second-generation antidepressants. These second-generation treatments include selective serotonin reuptake inhibitors (SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), selective serotonin and norepinephrine reuptake inhibitors (SSNRIs: duloxetine), serotonin and norepinephrine reuptake inhibitors (SNRIs: desvenlafaxine, mirtazapine, venlafaxine), and other second-generation antidepressants (bupropion, nefazodone, trazodone). The mechanism of action of most of these agents is poorly understood. These drugs work, at least in part, through their effects on neurotransmitters such as serotonin, norepinephrine, or dopamine in the central nervous system.

In general, the efficacy of first- and second-generation antidepressant medications is similar. However, first-generation antidepressants often produce multiple side effects that many patients find intolerable, and the risk for harm when taken in overdose or in combination with certain medications is high. Because of their relatively favorable side-effect profile, the second-generation antidepressants play a prominent role in the management of patients with MDD and are the focus of this review.

Objectives

This report is an update by RTI–UNC (Research Triangle Institute International–University of North Carolina) Evidence-based Practice Center of the 2007 Comparative Effectiveness Review of second-generation antidepressants. It summarizes the available evidence on the comparative efficacy, effectiveness, and harms of 13 second-generation antidepressants—bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine—in treating patients with MDD, dysthymia, and subsyndromal depression. It also evaluates the comparative efficacy and effectiveness for maintaining remission and treating accompanying symptoms such as anxiety, insomnia, or neurovegetative symptoms.

Specifically, we address the following Key Questions (KQs) in this report:

1a. For adults with major depressive disorder (MDD), dysthymia, or subsyndromal depressive disorders, do commonly used medications for depression differ in efficacy or effectiveness in treating depressive symptoms?

1b. If a patient has responded to one agent in the past, is that agent better than current alternatives at treating depressive symptoms?

1c. Are there any differences in efficacy or effectiveness between immediate-release and extended-release formulations of second-generation antidepressants?

2a. For adults with a depressive syndrome that has responded to antidepressant treatment, do second-generation antidepressants differ in their efficacy or effectiveness for preventing relapse (i.e., continuation phase) or recurrence (i.e., maintenance phase) when a patient
   - Continues the drug they initially responded to, or
   - Switches to a different antidepressant?

2b. For adults with a depressive syndrome that has not responded to acute antidepressant treatment or has relapsed (continuation phase) or recurred (maintenance phase), do alternative second-generation antidepressants differ in their efficacy or effectiveness?

3. In depressed patients with accompanying symptoms such as anxiety, insomnia, and neurovegetative symptoms, do medications or combinations of medications (including tricyclics in combination) differ in their efficacy or effectiveness for treating the depressive episode or for treating the accompanying symptoms?

4a. For adults with a depressive syndrome, do commonly used antidepressants differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to nausea, diarrhea, headache, tremor, daytime sedation, decreased libido, failure to achieve orgasm, nervousness, insomnia, and more serious events including suicide.

4b. Are there any differences in safety, adverse events, or adherence between immediate-release and extended-release formulations of second-generation antidepressants?

5. How do the efficacy, effectiveness, or harms of treatment with antidepressants for a depressive syndrome differ for the following subpopulations?
   - Elderly or very elderly patients
   - Other demographic groups (defined by age, ethnic or racial groups, and sex)
   - Patients with medical comorbidities (e.g., ischemic heart disease, cancer)
   - Patients with psychiatric and behavioral comorbidities (e.g., substance abuse disorders)
   - Patients taking other medications

Methods

The topic of this report and preliminary KQs arose through a public process involving the public, the Scientific Resource Center (SRC), and various stakeholder groups (www.effectivehealthcare.ahrq.gov/index.cfm/who-is-involved-in-the-effective-health-care-program1/about-the-stakeholder-group/).

To identify articles relevant to each KQ, we searched PubMed, Embase, the Cochrane Library, PsycInfo, and International Pharmaceutical Abstracts. We used either Medical Subject Headings (MeSH or MH) as search terms when available or keywords when appropriate. We combined terms for selected indications (major depressive disorder, dysthymia, minor depression, subsyndromal depressive disorder), drug interactions, and adverse events with a list of 13 specific second-generation antidepressants (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine). We limited electronic searches to “human” and “English language.” We searched sources from 1980 to January 2011 to capture literature relevant to the scope of our topic. The SRC contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations. We received dossiers from five pharmaceutical companies

(AstraZeneca, Eli Lilly, GlaxoSmithKline, Warner Chilcott Pharmaceuticals, and Wyeth). The SRC also searched various sources for grey literature.

For this review, results from well-conducted, valid head-to-head trials provide the strongest evidence to compare drugs with respect to efficacy, effectiveness, and harms. Randomized controlled trials (RCTs) of at least 6 weeks' duration and in adult study populations were eligible for inclusion. For quantitative analyses, we included all eligible studies without sample size limitations. In addition to head-to-head studies, we included placebo-controlled trials for mixed treatment comparisons or if no head-to-head trials were available for a particular KQ. If we concluded that we could not conduct any quantitative analyses, then we included studies only if they had sample sizes of 40 or larger.

For harms (i.e., evidence pertaining to safety, tolerability, and adverse events), we examined data from both experimental and observational studies. We included observational studies that had large sample sizes (1,000 patients or more), lasted at least 3 months, and reported an outcome of interest. Two people independently reviewed abstracts and full-text articles. If both reviewers agreed that the trial did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles and used the same eligibility criteria to determine which, if any, to exclude at this stage.

To assess the quality (internal validity) of studies, we used predefined criteria based on those developed by the U.S. Preventive Services Task Force (ratings: good, fair, poor) and the National Health Service Centre for Reviews and Dissemination. Two people independently rated the quality of each included study.

We assessed statistically each of the 78 possible drug comparisons of second-generation antidepressants for the treatment of acute-phase MDD. We conducted meta-analyses of 6 direct comparisons; the remaining 72 analyses employed mixed treatment comparison meta-analyses to derive indirect comparisons.

We evaluated the strength of evidence based on methods guidance for the Evidence-based Practice Center program of the Agency for Healthcare Research and Quality. Strength of evidence is graded only for major comparisons and major outcomes for the topic at hand. The strength of evidence for each outcome or comparison that we graded incorporates scores on four domains: risk of bias, consistency, directness, and precision.

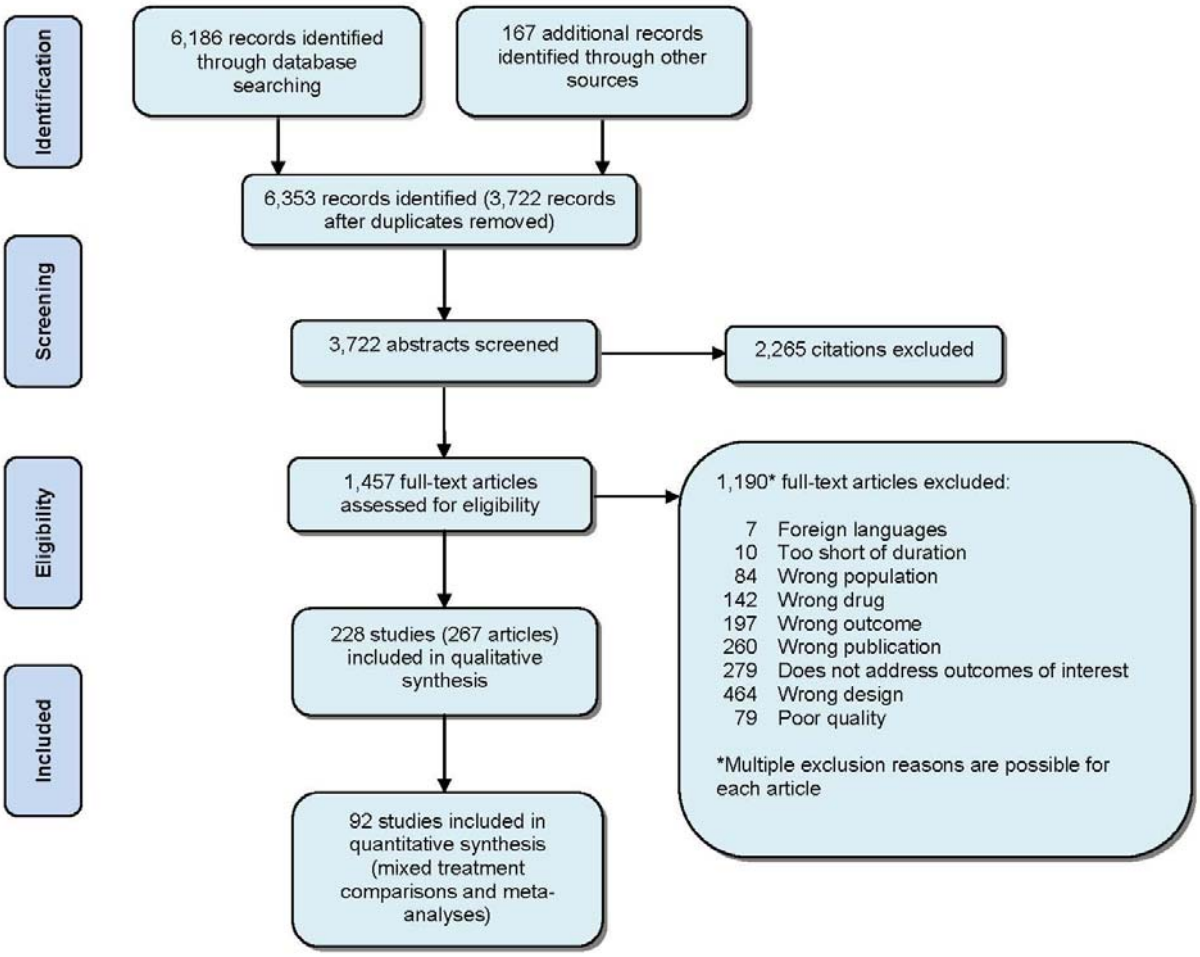
Results

Overall, the new evidence (78 new studies, 87 articles) we found during the update of the 2007 report did not lead to changes in our main conclusion from that review—namely, that no substantial differences in efficacy exist among second-generation antidepressants for the treatment of MDD. Some results are now supported by better evidence than in 2007, which is reflected in a higher grade for the strength of the evidence for some outcomes. Our summary of evidence findings are presented in Tables A through I by KQ. The strength of evidence ratings for the main outcomes of each KQ are detailed in Appendix G.

Efficacy and Effectiveness

We identified 3,722 citations from searches and reviews of reference lists. Figure A documents the disposition of the 267 included articles in this review, working from 1,457 articles retrieved for full-text review and 1,190 excluded at this stage.

Figure A. Results of literature search (PRISMA diagram)



Treatment of Major Depressive Disorder (KQ 1a)

Overall, 37 percent of patients did not respond during 6 to 12 weeks of treatment with second-generation antidepressants; 53 percent did not achieve remission. The evidence is insufficient to determine factors that can reliably predict response or nonresponse in individual patients.

Ninety-one head-to-head trials (i.e., comparisons between medications conducted within trials) provided data on 40 of the potential comparisons between the 13 second-generation antidepressants addressed in this report. Eight trials directly compared any non-SSRI second-generation antidepressant with any other; of these, only two comparisons were evaluated in more than one trial. Many efficacy trials were not powered to detect statistically or clinically significant differences, leading to inconclusive results.

Direct evidence from head-to-head trials was considered sufficient to conduct meta-analyses on the response to treatment (at least 50 percent improvement from baseline) for six drug–drug comparisons. Differences in efficacy reflected in some of these meta-analyses are of modest magnitude, and clinical implications remain to be determined.

- Citalopram versus escitalopram (5 published studies; 1,802 patients): For patients on escitalopram the odds ratio (OR) of response was statistically significantly higher than for

patients on citalopram (OR, 1.47; 95% confidence interval [CI], 1.07 to 2.01). The number needed to treat (NNT) to gain 1 additional responder at week 8 with escitalopram compared with citalopram was 13 (95% CI, 8 to 39). These results are based on meta-analyses of head-to-head trials. Results of mixed-treatment comparisons, taking the entire evidence base on second-generation antidepressants into consideration, did not confirm these findings (OR, 0.51; 95% credible interval, 0.13 to 4.14).

- Fluoxetine versus paroxetine (5 studies; 690 patients): We did not find any statistically significant differences in response rates (OR, 1.08; 95% CI, 0.79 to 1.47) between fluoxetine and paroxetine.
- Fluoxetine versus sertraline (4 studies; 940 patients): The odds ratio of response was statistically significantly higher for sertraline than for fluoxetine (OR, 1.42; 95% CI, 1.08 to 1.85). The NNT to gain 1 additional responder at 6 to 12 weeks with sertraline was 13 (95% CI, 8 to 58).
- Fluoxetine versus venlafaxine (6 studies; 1,197 patients): The odds ratio of response was statistically significantly higher for patients on venlafaxine than on fluoxetine (OR, 1.47; 95% CI, 1.16 to 1.86).
- Paroxetine versus duloxetine (3 studies; 849 patients): Pooled response rates were similar for patients on paroxetine or duloxetine (OR, 0.84; 95% CI, 0.63 to 1.12).
- Sertraline versus venlafaxine (3 studies; 470 patients): Pooled response rates were similar for patients on sertraline or venlafaxine (OR, 1.18; 95% CI, 0.81 to 1.72).

Most trials were efficacy RCTs conducted in carefully selected populations under carefully controlled conditions. Only three trials met criteria for being an effectiveness trial, which is intended to have greater applicability to typical practice. Of these trials, two were conducted in French primary-care settings and one in primary-care clinics in the United States. Findings were generally consistent with efficacy trials and did not reflect any substantial differences in comparative effectiveness in adults.

Findings from indirect comparisons yielded some statistically significant differences in response rates. The magnitudes of these differences, however, were small and are likely not to be clinically significant. Overall, we graded the strength of the evidence supporting no substantial differences in efficacy and effectiveness among second-generation antidepressants for the treatment of MDD in adults as moderate.

Quality of Life

Quality of life or functional capacity was infrequently assessed, usually as a secondary outcome. Seventeen studies (3,960 patients), mostly of fair quality, indicated no statistical differences in efficacy with respect to health-related quality of life. The strength of evidence is moderate.

Speed of Response

Seven studies, all of fair quality and funded by the maker of mirtazapine, reported that mirtazapine had a significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline. The pooled NNT to yield one additional responder after 1 or 2 weeks of treatment is seven (95% CI, 5 to 12); after 4 weeks of treatment, however, most response rates were similar. The strength of evidence is moderate.

Treatment of Dysthymia (KQ 1a)

Efficacy and Effectiveness

We identified no head-to-head trial comparing different medications in a population with dysthymia. One good-quality and four fair-quality placebo-controlled trials provide mixed evidence on the general efficacy and effectiveness of fluoxetine, paroxetine, and sertraline for the treatment of dysthymia. A fair-quality effectiveness study provides mixed evidence on the effectiveness of paroxetine compared with placebo. A subgroup of patients older than 60 years old showed a significantly greater improvement than those on placebo; a subgroup of patients younger than 60 years old did not show any difference in effectiveness between paroxetine and placebo. The strength of evidence is insufficient.

Treatment of Subsyndromal Depression (KQ 1a)

Efficacy and Effectiveness

The only head-to-head evidence for treating patients with subsyndromal depression came from a nonrandomized, open-label trial comparing citalopram with sertraline. This study did not detect any differences in efficacy. Findings from two placebo-controlled trials (both fair quality) were insufficient to draw any conclusions about the comparative efficacy and effectiveness of second-generation antidepressants for the treatment of subsyndromal depression. The strength of evidence is low.

Response to Antidepressant Agents After Successful Response in the Past (KQ 1b)

We did not find any evidence to answer this KQ.

Difference in Efficacy Between Immediate- and Extended-Release Formulations (KQ 1c)

Four RCTs and one pooled analysis of two identical RCTs provide mixed results about differences in efficacy between immediate- and extended-release formulations of various drugs.

Two RCTs reported similar rates of maintenance of response and relapse for patients treated with fluoxetine daily or fluoxetine weekly during the continuation phase. Similarly, one RCT and a pooled analysis of two identical RCTs did not find any differences in response rates in patients treated with paroxetine IR (immediate release) or paroxetine CR (controlled release) for acute-phase MDD. The strength of evidence is moderate.

By contrast, one RCT reported higher response rates for patients on venlafaxine IR than venlafaxine XR (extended release).

We could not find any studies on other medications, such as bupropion or fluvoxamine, that are available as both immediate- and extended-release formulations.

Maintenance of Response or Remission (KQ 2a)

Efficacy and Effectiveness

Six head-to-head RCTs suggest that no substantial differences exist between escitalopram and desvenlafaxine, escitalopram and paroxetine, fluoxetine and sertraline, fluoxetine and venlafaxine, fluvoxamine and sertraline, or trazodone and venlafaxine for maintaining response or remission (i.e., preventing relapse or recurrence of MDD). One naturalistic study provides fair-quality evidence that rehospitalization rates do not differ between groups of patients continuing fluoxetine versus venlafaxine. The strength of the evidence is moderate. Thirty-one placebo-controlled trials support the general efficacy and effectiveness of most second-generation antidepressants for preventing relapse or recurrence. The overall strength of this evidence is moderate.

No evidence addressed how second-generation antidepressants compare when a patient responds to one agent and then is required to switch to a different agent (e.g., because of changes in insurance benefit).

Achieving Response in Unresponsive or Recurrent Disease (KQ 2b)

Efficacy and Effectiveness

Four head-to-head studies and two effectiveness studies provide conflicting evidence on differences among second-generation antidepressants in treatment-resistant depression. A good-quality effectiveness study suggests that no substantial differences exist among bupropion SR (sustained release), sertraline, and venlafaxine XR, but a fair-quality effectiveness study suggests that venlafaxine is modestly more effective than citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline. Three of four efficacy studies (all fair quality) suggest that venlafaxine trended toward being more effective than citalopram, fluoxetine, and paroxetine, although only the comparison with paroxetine was statistically significant. Given the conflicting results, the overall strength of the evidence is low.

Although several comparative studies included patients who had relapsed or who were experiencing a recurrent depressive episode, no study specifically compared one second-generation antidepressant with another as a second-step treatment in such patients.

Treatment of Depression in Patients With Accompanying Symptom Clusters (KQ 3)

Anxiety

Evidence from seven head-to-head trials (all fair quality) suggests that antidepressant medications do not differ substantially in antidepressive efficacy for patients with MDD and anxiety symptoms. The trials found no substantial differences in efficacy among fluoxetine, paroxetine, and sertraline or between citalopram and sertraline, bupropion and sertraline, or venlafaxine and sertraline. One trial found statistically significant superiority of venlafaxine over fluoxetine. Two trials provided inconsistent evidence regarding the superiority of escitalopram over paroxetine. The strength of evidence is moderate.

Insomnia

One head-to-head study provided evidence regarding comparative efficacy of medications for treatment of depression in patients with accompanying insomnia. The study showed no statistically significant differences in depressive outcomes for fluoxetine compared with paroxetine and sertraline. One trial of fluoxetine supplemented with eszopiclone compared with fluoxetine alone showed no statistically significant difference between the groups for depression scores when the sleep items were excluded from the analysis. The strength of evidence is low.

Low Energy

One placebo-controlled RCT showed that bupropion XR is superior to placebo for treating depression in patients with low energy. The strength of evidence is insufficient.

Melancholia

Two head-to-head trials provide limited evidence on the comparative effects of medication for treating depression in patients with melancholia. In one, depression response rates for sertraline were superior to those for fluoxetine; in another, depression scores improved similarly for venlafaxine and fluoxetine. The strength of evidence is insufficient.

Pain

Two fair-quality trials that required baseline pain for inclusion produced conflicting evidence regarding the superiority of duloxetine compared with placebo for treating depression in patients with pain of at least mild intensity. The strength of evidence is insufficient.

Psychomotor Changes

One fair-quality head-to-head trial reported no statistically significant difference between fluoxetine and sertraline for treating depression in patients with psychomotor retardation. The same study found that sertraline was more efficacious than fluoxetine for treating depression in patients with psychomotor agitation. The strength of evidence is insufficient.

Somatization

We identified no relevant studies.

Treatment of Symptom Clusters in Patients With Accompanying Depression (KQ 3)

Anxiety

Twelve head-to-head trials and two placebo-controlled trials (all fair quality) provide evidence that antidepressant medications do not differ substantially in efficacy for treatment of anxiety associated with MDD. Trials found no substantial differences in efficacy for the following: fluoxetine, paroxetine, and sertraline; sertraline and bupropion; sertraline and venlafaxine; citalopram and mirtazapine; escitalopram and fluoxetine; and paroxetine and nefazodone. One trial found that venlafaxine was statistically significantly superior to fluoxetine and one trial found that escitalopram was superior to paroxetine. The strength of evidence is moderate.

Insomnia

Six head-to-head trials (all fair quality) and one placebo-controlled trial provide limited evidence about comparative effects of antidepressants on insomnia in patients with depression. Three trials indicated similar efficacy for improving sleep for the following comparisons: fluoxetine, paroxetine, and sertraline; escitalopram and fluoxetine; and fluoxetine and mirtazapine. One trial suggested that trazodone was superior to fluoxetine and one trial suggested that trazodone is superior to venlafaxine in improving sleep scores in depressed patients. One trial showed that supplementing fluoxetine therapy with eszopiclone leads to improved sleep. The strength of evidence is low.

Low Energy

One placebo-controlled RCT showed that bupropion XR is superior to placebo for treating low energy in depressed patients. The strength of evidence is insufficient.

Melancholia

We identified no relevant study.

Pain

One fair-quality systematic review showed that improvement in pain scores was similar for duloxetine and paroxetine. Six studies provided mixed evidence for the superiority of duloxetine or paroxetine compared with placebo for treatment of accompanying pain. The strength of evidence is moderate.

Psychomotor Changes

We identified no relevant study.

Somatization

One head-to-head trial of escitalopram and fluoxetine and one open-label effectiveness trial of fluoxetine, paroxetine, and setraline found no statistically significant difference for treating somatization in patients with depression. The strength of evidence is insufficient.

Differences in Harms (Adverse Events) (KQ 4a)

We analyzed adverse-events data from 92 head-to-head efficacy studies on 22,586 patients, along with data from 48 additional studies of both experimental and observational design**.** Only five RCTs were designed primarily to detect differences in adverse events. Methods of adverse-events assessment in efficacy trials differed greatly. Few studies used objective scales. Determining whether assessment methods were unbiased and adequate was often difficult.

General Tolerability

Constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence were commonly and consistently reported adverse events. On average, 63 percent of patients in efficacy trials experienced at least one adverse event. Nausea and vomiting were found to be the most common reasons for discontinuation in efficacy studies. Overall, second-generation antidepressants have similar adverse-events profiles, and the strength of evidence is high.

However, some differences in the incidence of specific adverse events exist as follows:

- Venlafaxine was associated with an approximately 52 percent (95% CI, 25 to 84 percent) higher incidence of nausea and vomiting than SSRIs as a class. The strength of evidence is high.
- Mirtazapine led to higher weight gains than comparator drugs. Mean weight gains relative to pretreatment weights ranged from 0.8 kg to 3.0 kg after 6–8 weeks of treatment. The strength of evidence for higher risks of weight gain with mirtazapine than with other antidepressants is high.
- Sertraline led to higher rates of diarrhea than comparator drugs (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine) in most studies. The incidence was 8 percent (95% CI, 3 to 11 percent) higher than with comparator drugs. Whether this finding can be extrapolated to comparisons of sertraline with other second-generation antidepressants remains unclear. The strength of evidence that sertraline has a higher risk of diarrhea than other antidepressants is moderate.
- Trazodone was associated with an approximately 16 percent (3 percent less to 36 percent higher) higher incidence of somnolence than comparator drugs (bupropion, fluoxetine, mirtazapine, paroxetine, venlafaxine). Whether this finding can be extrapolated to comparisons of trazodone with other second-generation antidepressants remains unclear. The strength of evidence that trazodone leads to higher rates of somnolence than comparator drugs is moderate.

Discontinuation Rates

Overall discontinuation rates were similar between SSRIs as a class and other second-generation antidepressants. The strength of evidence is high.

Discontinuation rates because of adverse events were also similar between SSRIs as a class and bupropion, mirtazapine, nefazodone, and trazodone. The strength of evidence is high. Duloxetine had a 67 percent (95% CI, 17 to 139) higher and venlafaxine an approximately 40 percent (95% CI, 16 to 73) higher risk for discontinuation because of adverse events than SSRIs as a class. The strength of evidence is high.

Discontinuation rates because of lack of efficacy were similar between SSRIs as a class and bupropion, duloxetine, mirtazapine, nefazodone, and trazodone. Venlafaxine had a 34 percent (95% CI, 47 to 93) lower risk of discontinuation because of lack of efficacy than SSRIs as a class. The strength of evidence is high.

Severe Adverse Events

The strength of the evidence on the comparative risks of second-generation antidepressants on most serious adverse events is insufficient to draw firm conclusions. In general, trials and observational studies were too small and study durations too short to assess the comparative risks of rare but serious adverse events such as suicidality, seizures, cardiovascular adverse events, serotonin syndrome, hyponatremia, or hepatotoxicity. Long-term observational evidence is often lacking or prone to bias.

Sexual Dysfunction

Six trials and a pooled analysis of two identical RCTs provide evidence that bupropion causes lower rates of sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline.

The NNT to yield one additional person with a high overall satisfaction of sexual functioning is seven. This treatment effect was consistent across all studies. The strength of evidence that bupropion has lower rates of sexual dysfunction than comparator drugs is high.

Compared with other second-generation antidepressants (fluoxetine, fluvoxamine, nefazodone, and sertraline), paroxetine frequently led to higher rates of sexual dysfunction (16 percent vs. 6 percent). The strength of evidence is moderate.

Other Severe Adverse Events

The existing evidence on the comparative risk for rare but severe adverse events such as suicidality, seizures, cardiovascular events, hyponatremia, hepatotoxicity, and serotonin syndrome is insufficient to draw firm conclusions. The strength of evidence is insufficient. Clinicians should keep in mind the risk of such harms during any course of treatment with a second-generation antidepressant.

Adherence

Efficacy studies do not indicate any substantial differences in adherence among second-generation antidepressants. The strength of evidence is moderate.

To what extent findings from highly controlled efficacy trials can be extrapolated to "real-world" settings remains uncertain. The evidence is insufficient to reach any conclusions about differences in adherence in effectiveness studies.

Comparative Harms and Adherence of Immediate- Versus Extended-Release Formulations (KQ 4b)

Overall, adverse-event rates were similar between fluoxetine daily and fluoxetine weekly dosing regimens. Likewise, adverse-event rates were similar between paroxetine IR and paroxetine CR, as well as venlafaxine IR and venlafaxine XR, except for higher rates of nausea in patients treated with paroxetine IR than paroxetine CR.

We could not find any studies on bupropion and fluvoxamine immediate- and extended-release formulations.

The strength of evidence is moderate that no differences in adverse events exist between daily and weekly formulations of fluoxetine. The strength of evidence is low that paroxetine IR leads to higher rates of nausea than paroxetine CR.

Based on one double-blinded RCT, no differences in adherence between patients treated with paroxetine IR and paroxetine CR (93 percent vs. 96 percent) appear to exist. The strength of evidence is moderate.

A retrospective cohort study, based on U.S. prescription data, showed higher refill adherence for prescriptions of bupropion XL (extended release) than bupropion SR. The strength of evidence is low.

Based on an open-label RCT, adherence to fluoxetine weekly was higher than to fluoxetine daily. The strength of evidence is low.

Efficacy, Effectiveness, and Harms for Selected Populations (KQ 5)

Age

Eleven head-to-head trials in older adult patients with MDD indicate that efficacy does not differ substantially among second-generation antidepressants. The strength of the evidence is moderate. We found no head-to-head studies addressing differences in efficacy or harms in older patients with dysthymia or subsyndromal depression.

Head-to-head trials suggest some differences in adverse events among older adults. The strength of the evidence is low.

Sex

We found no head-to-head trials comparing the efficacy of antidepressants in men and women; the strength of evidence is insufficient. Evidence from one RCT comparing paroxetine with sertraline and one RCT comparing paroxetine with bupropion SR suggests differences in sexual side effects between men and women. The strength of evidence is low.

Race or Ethnicity

We found no head-to-head trials comparing the efficacy of second-generation antidepressants in different racial or ethnic groups. One fair-quality trial found no significant differences in efficacy or quality of life between sertraline and placebo in low-income Latino and black patients. The remaining evidence is limited to a handful of poor-quality studies assessing the general efficacy of duloxetine or fluoxetine. The strength of the evidence is insufficient.

Comorbidities

The evidence for various comorbidities (e.g., alcohol and substance abuse, Alzheimer's disease or other dementia, arthritis, cancer, coronary artery disease, diabetes, or stroke) is limited to subgroup analyses of head-to head studies in MDD patients with co-occurring generalized anxiety disorder, a number of placebo-controlled trials across various comorbidities, and one systematic review of SSRIs for depression and comorbid myocardial infarction. These trials provide inadequate comparative evidence on the efficacy of second-generation antidepressants in subgroups with different coexisting conditions. The strength of the evidence is insufficient.

Discussion

Overall, the new evidence (78 new studies, 87 articles) we found during the update of our 2007 report did not lead to changes in our main conclusion from that review—namely, that no substantial differences in efficacy exist among second-generation antidepressants for the treatment of MDD. Some results are now supported by better evidence than in 2007, which is reflected in a higher grade for the strength of the evidence for some outcomes. In addition, the more advanced statistical analysis that we were able to do for indirect comparisons of second-generation antidepressants when no or only insufficient head-to-head evidence was available also confirmed that conclusion.

Therefore, our findings indicate that the existing evidence does not warrant the choice of one second-generation antidepressant over another based on either greater efficacy or greater effectiveness. Some of the comparisons rendered statistically significant results; the magnitudes of the differences, however, are small and likely not clinically significant. Furthermore, because

we had 78 pairwise comparisons, some are expected to be statistically significant by chance alone.

Although second-generation antidepressants are similar in efficacy, they cannot be considered identical drugs. Evidence of high and moderate strength supports some differences among individual drugs with respect to onset of action, adverse events, and some measures of health-related quality of life; these differences are of modest magnitude but statistically significant. Specifically, consistent evidence from multiple trials demonstrates that mirtazapine has a faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline and that bupropion has fewer sexual side effects than escitalopram, fluoxetine, paroxetine, and sertraline.

Some of these differences are small and might be offset by adverse events. For example, a faster onset of mirtazapine must be weighed against possible decreased adherence because of long-term weight gain. Nonetheless, some of these differences may be clinically significant and influence the choice of a medication for specific patients.

The evidence is sparse (strength of evidence for comparative efficacy is insufficient for dysthymia and subsyndromal depression). No conclusions can be drawn about comparative efficacy or effectiveness.

A considerable limitation of our conclusions is that they have been derived primarily from efficacy trials. For example, for acute-phase MDD we found only 3 effectiveness studies out of 92 head-to-head RCTs. Two of these effectiveness studies were conducted in Europe, and the applicability to the U.S. health care system might be limited. Although findings from effectiveness studies are generally consistent with those from efficacy trials, the evidence is limited to a few comparisons. Whether, for acute-phase MDD, such findings can be further extrapolated to other second-generation antidepressants remains unclear.

Given that almost two in five patients do not respond to initial treatment and that several other systematic reviews have concluded that no one antidepressant performs better than any other, an important future pharmacologic research agenda item is to focus on making the initial treatment strategy more effective. Potential approaches include looking at ways to better predict the treatment response to optimize initial treatment selections (e.g., through genetic analysis) and to explore whether combinations of antidepressants at treatment initiation would improve response rates. Furthermore, studies need to explore patient preferences about dosing regimens and the level of acceptance that individual patients have for various adverse events.

In addition, more evidence is needed regarding the most appropriate duration of antidepressant treatment for maintaining response and remission. Such studies should also evaluate further whether different formulations (i.e., controlled release vs. immediate release) lead to differences in adherence and subsequently to differences in relapse or recurrence. Additionally, although most trials maintained the dose used in acute-phase treatment throughout continuation and maintenance treatment, little is known about the effect of drug dose on the risk of relapse or recurrence.

More research is also needed to evaluate whether the benefits or harms of second-generation antidepressants differ in populations with accompanying symptoms such as anxiety, insomnia, pain, or fatigue. This research should identify and use a common core of accurate measures to identify these subgroups. Likewise, future research has to clarify differences of second-generation antidepressants in subgroups based on age, sex, race or ethnicity, and common comorbidities.

Finally, no evidence addressed how second-generation antidepressants compare when a patient responds to one agent and then is required to switch to a different agent (e.g., because of

changes in insurance benefit). Because these circumstances may be relevant for many patients, future studies should consider this question.

Table A. Summary of findings with strength of evidence, Key Question 1a: Comparative efficacy and effectiveness of second-generation antidepressants

Disorder, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Major depressive disorder Comparative efficacy	Moderate	Results from direct and indirect comparisons based on 61 head-to head trials and 31 placebo-controlled trials indicate that no substantial differences in efficacy exist among second-generation antidepressants.
Comparative effectiveness	Moderate	Direct evidence from three effectiveness trials (one good) and indirect evidence from efficacy trials indicate that no substantial differences in effectiveness exist among second-generation antidepressants.
Quality of life	Moderate	Consistent results from 18 trials indicate that the efficacy of second-generation antidepressants with respect to quality of life does not differ among drugs.
Onset of action	Moderate	Consistent results from seven trials suggest that mirtazapine has a significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline. Whether this difference can be extrapolated to other second-generation antidepressants is unclear. Most other trials do not indicate a faster onset of action of one second-generation antidepressant compared with another.
Dysthymia Comparative efficacy	Insufficient	No head-to-head evidence exists. Results from five placebo-controlled trials were insufficient to draw conclusions about comparative efficacy.
Comparative effectiveness	Insufficient	No head-to-head evidence exists. One effectiveness trial provides mixed evidence about paroxetine versus placebo; patients older than 60 showed greater improvement on paroxetine; those younger than 50 did not show any difference.
Quality of life	Insufficient	No evidence
Onset of action	Insufficient	No evidence
Subsyndromal depression Comparative efficacy	Low	One nonrandomized, open-label trial did not detect any difference between citalopram and sertraline. Results from two placebo-controlled trials were insufficient to draw conclusions.
Comparative effectiveness	Insufficient	No evidence
Quality of life	Insufficient	No evidence
Onset of action	Insufficient	No evidence

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.
[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table B. Summary of findings with strength of evidence, Key Question 1b: Greater efficacy and effectiveness with previously effective medications

Disorder, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Major depressive disorder	Insufficient	No evidence
Dysthymia	Insufficient	No evidence
Subsyndromal depression	Insufficient	No evidence

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.
[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table C. Summary of findings with strength of evidence, Key Question 1c: Differences in efficacy and effectiveness between immediate- and extended-release formulations

Disorder, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Major depressive disorder	Moderate	Results from two trials indicate that no differences in response to treatment exist between paroxetine IR and paroxetine CR. Two trials did not detect significant differences in maintenance of response and remission between fluoxetine daily and fluoxetine weekly.
	Low	One trial reported higher response rates for venlafaxine XR than venlafaxine IR.
Dysthymia	Insufficient	No evidence
Subsyndromal depression	Insufficient	No evidence

CR = controlled release; IR = immediate release; XR = extended release

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b] Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table D. Summary of findings with strength of evidence, Key Question 2a: Efficacy and effectiveness of second-generation antidepressants for maintaining response or remission (i.e., preventing relapse or recurrence)

Outcome of Interest	Strength of Evidence[a]	Findings[b]
Continuing initial medications Comparative efficacy	Moderate	Based on results from six efficacy trials and one naturalistic study, no significant differences exist between escitalopram and desvenlafaxine, escitalopram and paroxetine, fluoxetine and sertraline, fluoxetine and venlafaxine, fluvoxamine and sertraline, and trazodone and venlafaxine for preventing relapse or recurrence.
Comparative effectiveness	Insufficient	No evidence
Switching medications Comparative efficacy	Insufficient	No evidence
Comparative effectiveness	Insufficient	No evidence

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b] Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table E. Summary of findings with strength of evidence, Key Question 2b: Efficacy and effectiveness of second-generation antidepressants in managing treatment-resistant depression syndrome or treating recurrent depression

Outcome of Interest	Strength of Evidence[a]	Findings[b]
Comparative efficacy	Low	Results from four trials suggest no differences or only modest differences between SSRIs and venlafaxine. Numerical trends favored venlafaxine over comparator drugs in three of these trials, but differences were statistically significant in only one trial, which compared venlafaxine with paroxetine.
Comparative effectiveness	Low	Results from two effectiveness studies are conflicting. Based on one trial rated good, no significant differences in effectiveness exist among bupropion SR, sertraline, and venlafaxine XR. One effectiveness trial found venlafaxine to be modestly superior to citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline.

SR = slow release; SSRI = selective serotonin reuptake inhibitor; XR = extended release
[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.
[b] Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table F. Summary of findings with strength of evidence, Key Question 3: Comparative efficacy and effectiveness of second-generation antidepressants for treatment of depression in patients with accompanying symptom clusters

Accompanying Symptom, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Anxiety Comparative efficacy for depression	Moderate	Results from five head-to-head trials suggest that efficacy does not differ substantially for treatment of depression in patients with accompanying anxiety.
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for anxiety	Moderate	Results from eight head-to-head trials and three placebo-controlled trials suggest that no substantial differences in efficacy exist among second-generation antidepressants for treatment of accompanying anxiety symptoms.
Comparative effectiveness for anxiety	Insufficient	No evidence
Insomnia Comparative efficacy for depression	Insufficient	Results from one head-to-head study are insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting insomnia.
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for insomnia	Low	Results from five head-to-head trials suggest that no substantial differences in efficacy exist among second-generation antidepressants for treatment of accompanying insomnia. Results are limited by study design; differences in outcomes are of unknown clinical significance.
Comparative effectiveness for insomnia	Insufficient	No evidence
Low energy Comparative efficacy for depression	Insufficient	Results from one placebo-controlled trial of bupropion XL are insufficient to draw conclusions about treating depression in patients with coexisting low energy. Results from head-to-head trials are not available.
Comparative effectiveness for depression	Insufficient	No evidence

Table F. Summary of findings with strength of evidence, Key Question 3: Comparative efficacy and effectiveness of second-generation antidepressants for treatment of depression in patients with accompanying symptom clusters (continued)

Accompanying Symptom, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Comparative efficacy for low energy	Insufficient	Results from one placebo-controlled trial of bupropion XL are insufficient to draw conclusions about treating low energy in depressed patients. Results from head-to-head trials are not available.
Comparative effectiveness for low energy	Insufficient	No evidence
Melancholia Comparative efficacy for depression	Insufficient	Results from two head-to-head trials are insufficient to draw conclusions about treating depression in patients with coexisting melancholia. Results are inconsistent across studies.
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for melancholia	Insufficient	No evidence
Comparative effectiveness for melancholia	Insufficient	No evidence
Pain Comparative efficacy for depression	Insufficient	Results from two placebo-controlled trials are conflicting regarding the superiority of duloxetine over placebo. Results from head-to-head trials are not available.
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for pain	Moderate	Evidence from one systematic review, two head-to-head trials (one poor), and five placebo-controlled trials indicate no difference in efficacy between paroxetine and duloxetine.
Comparative effectiveness for pain	Insufficient	No evidence
Psychomotor change Comparative efficacy for depression	Insufficient	Results from one head-to-head trial are insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting psychomotor change.
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for psychomotor change	Insufficient	No evidence
Comparative effectiveness for psychomotor change	Insufficient	No evidence
Somatization Comparative efficacy for depression	Insufficient	No evidence
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for somatization	Insufficient	Results from one head-to-head trial are insufficient to draw conclusions about the comparative efficacy for treating somatization in depressed patients. Results indicate similar improvement in somatization.
Comparative effectiveness for somatization	Insufficient	Evidence from one open-label head-to-head trial is insufficient to draw conclusions about the comparative efficacy for treating coexisting somatization in depressed patients. Results indicate no difference in effectiveness.

XL = extended release

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b] Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table G. Summary of findings with strength of evidence, Key Question 4a: Comparative risk of harms (safety, adverse events), adherence, and persistence

Outcome of Interest	Strength of Evidence[a]	Findings[b]
General tolerability Adverse-events profiles	High	Adverse-events profiles, based on 92 efficacy trials and 48 studies of experimental or observational design, are similar among second-generation antidepressants. The incidence of specific adverse events differs across antidepressants
Comparative risk of nausea and vomiting	High	Meta-analysis of 15 studies indicates that venlafaxine has a higher rate of nausea and vomiting than SSRIs as a class.
Comparative risk of weight change	High	Results from seven trials indicate that mirtazapine leads to higher weight gains than citalopram, fluoxetine, paroxetine, and sertraline.
Comparative risk of gastrointestinal adverse events	Moderate	Results from 15 studies indicate that sertraline has a higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine. Results from one systematic review confirm some of these findings.
Comparative risk of somnolence	Moderate	Results from six trials indicate that trazodone has a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine.
Comparative risk of discontinuation syndrome	Moderate	A good systematic review indicates that paroxetine and venlafaxine have the highest rates of discontinuation syndrome; fluoxetine has the lowest.
Comparative risk of discontinuation of treatment	High	Meta-analyses of numerous efficacy trials indicate that overall discontinuation rates are similar. Duloxetine and venlafaxine have a higher rate of discontinuations because of adverse events than SSRIs as a class. Venlafaxine has a lower rate of discontinuations because of lack of efficacy than SSRIs as a class.
Severe adverse events Comparative risk of suicidality (suicidal thoughts and behavior)	Insufficient	Results from 11 observational studies (two good quality), five meta-analyses or systematic reviews (four good), and one systematic review yield conflicting information about the comparative risk of suicidality.
Comparative risk of sexual dysfunction	High	Results from six trials indicate that bupropion causes significantly less sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline.
	Moderate	Among SSRIs, paroxetine has the highest rates of sexual dysfunction.
Comparative risk of seizures	Insufficient	Results from three studies (one good observational design) yield conflicting information about the comparative risk of seizures.
Cardiovascular events	Insufficient	Results from one good observational study and one pooled analysis yield noncomparative or conflicting information about the comparative risk of cardiovascular events.
Comparative risk of hyponatremia	Insufficient	No trials or observational studies assessing hyponatremia met criteria for inclusion in this review. One cohort study not meeting inclusion criteria suggested that hyponatremia was more common in elderly patients treated with various antidepressants than in placebo-treated patients.
Comparative risk of hepatotoxicity	Insufficient	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of hepatotoxicity. Weak evidence indicates that nefazodone might have an increased risk of hepatotoxicity.
Comparative risk of serotonin syndrome	Insufficient	No trials or observational studies assessing serotonin syndrome were included in this review. Numerous case reports of this syndrome exist but were not included in this review.
Adherence Comparative adherence in efficacy studies	Moderate	Efficacy studies indicate no differences in adherence.

Table G. Summary of findings with strength of evidence, Key Question 4a: Comparative risk of harms (safety, adverse events), adherence, and persistence (continued)

Outcome of Interest	Strength of Evidence[a]	Findings[b]
Comparative adherence in effectiveness studies	Insufficient	Evidence from existing studies is insufficient to draw conclusions about adherence in real-world settings.
Comparative persistence	Insufficient	No evidence

SSRI = selective serotonin reuptake inhibitor

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b] Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table H. Summary of findings with strength of evidence, Key Question 4b: Differences in harms, adherence, and persistence between immediate- and extended-release formulations

Disorder, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Major depressive disorder Comparative risk of harms	Moderate	Findings from one trial each indicate that no differences in harms exist between fluoxetine daily and fluoxetine weekly or between venlafaxine IR and venlafaxine XR.
	Low	One trial provides evidence that paroxetine IR leads to higher rates of nausea than paroxetine CR.
Comparative adherence	Low	One trial provides evidence that fluoxetine weekly has better adherence rates than fluoxetine daily.
Comparative persistence	Low	Evidence from one observational study indicates that prescription refills are more common with the extended-release than the immediate-release formulation of bupropion.
Dysthymia	Insufficient	No evidence
Subsyndromal depression	Insufficient	No evidence

CR = controlled release; IR = immediate release; XR = extended release

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b] Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table I. Summary of findings with strength of evidence, Key Question 5: Subgroups

Subpopulation of Interest, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Age Comparative efficacy	Moderate	Evidence from 11 trials indicates that efficacy does not differ substantially among second-generation antidepressants for treating MDD in patients age 60 years or older.
	Insufficient	No head-to-head evidence found for dysthymia or subsyndromal depression. Results from one good placebo-controlled trial showed no difference between fluoxetine and placebo.
Comparative effectiveness	Insufficient	No evidence in older patients with MDD.
	Insufficient	One effectiveness study showed greater improvement with paroxetine versus placebo in dysthymia patients older than 60 years; insufficient evidence to draw conclusions on comparative effectiveness.
Comparative harms	Low	Results from six studies indicate that adverse events may differ somewhat across second-generation antidepressants in older adults.
	Insufficient	No head-to-head studies were found for dysthymia or subsyndromal depression.
Sex Comparative efficacy	Insufficient	No evidence
Comparative effectiveness	Insufficient	No evidence
Comparative harms	Low	Two trials suggest differences between men and women in sexual side effects.
Race or ethnicity Comparative efficacy	Insufficient	No evidence
Comparative effectiveness	Insufficient	No evidence
Comparative harms	Insufficient	No evidence
Comorbidities Comparative efficacy	Low	Results from a subgroup analysis of one trial indicate significantly greater response with venlafaxine XR than fluoxetine in patients with MDD and comorbid generalized anxiety disorder.
	Insufficient	Placebo-controlled trials assessed efficacy in patients with the following comorbidities: alcohol/substance abuse, Alzheimer's disease/dementia, arthritis, diabetes, HIV/AIDS, multiple sclerosis, stroke, and vascular disease. No head-to-head evidence exists on comparative efficacy.
Comparative effectiveness	Insufficient	No evidence
Comparative harms	Insufficient	No evidence

MDD = major depressive disorder; XR = extended release

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b] Good or fair designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Glossary

CI	Confidence interval
CR	Controlled release
KQ	Key Question
IR	Immediate release
MDD	Major depressive disorder
NNT	Number needed to treat
RCT	Randomized controlled trial
SRC	Scientific Resource Center
SR	Sustained release
SSNRI	Selective serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
OR	Odds ratio
XR	Extended release

Introduction

Background

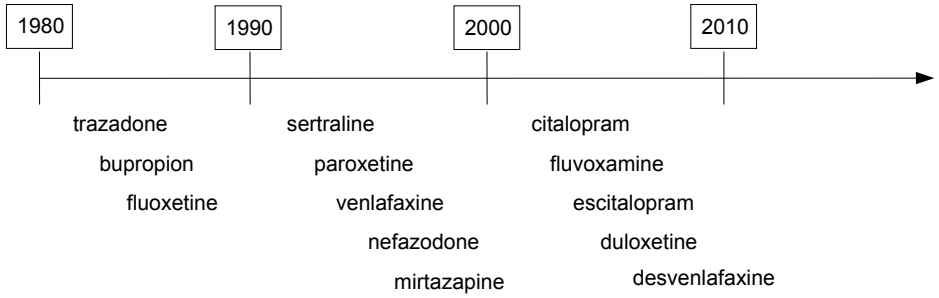
Axis I psychiatric disorders such as depressive disorder can be serious disabling illnesses.[1] Combined, they affect approximately one in five Americans.[2] Major depressive disorder (MDD) is the most prevalent, affecting more than 16 percent (lifetime) of U.S. adults.[3] The U.S. economic burden of depressive disorders is estimated to be more than $83 billion annually.[4] More than 30 percent of these costs were attributable to direct medical expenses. Projected depression-related U.S. workforce productivity losses are estimated to be $24 billion annually.[5]

Pharmacotherapy is the primary treatment for the medical management of depression. As of 2005, an estimated 27 million Americans were treated with antidepressants.[6] Antidepressants include first-generation drugs such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs); they also include newer drugs referred to here as second-generation antidepressants. Compared with the first-generation antidepressants, the second-generation antidepressant have similar efficacy.[7, 8] However, first-generation drugs often are accompanied by multiple side effects that many patients find intolerable. For example, TCAs tend to cause anticholinergic effects including dry mouth and eyes, urinary hesitancy, and sometimes retention and constipation. In addition, TCAs have a high rate of lethality when overdose occurs. MAOIs can produce a potentially lethal hypertensive crisis if taken along with particular medications or with certain foods or dietary supplements containing excessive amounts of tyramine. Thus, first-generation antidepressants are no longer agents of choice in many circumstances.

Second-generation antidepressants now account for the majority of antidepressant prescribing. These drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other drugs with related mechanisms of action that selectively target neurotransmitters. In 2009, these drugs accounted for $9.9 billion in sales in the United States, ranking as the fourth top-selling therapeutic class of prescription drugs.[9]

Many second-generation drugs are now available generically, although newer agents such as desvenlafaxine (2008), duloxetine (2004), and escitalopram (2002) have remaining patent protection. Figure 1 illustrates the timing of approvals for second-generation antidepressant drug by the U.S. Food and Drug Administration (FDA) for the United States over the past three decades.

Figure 1. Second-generation antidepressant approvals



Except for fluvoxamine (which is approved only for the treatment of obsessive-compulsive disorder), all second-generation antidepressants are approved for the treatment of MDD. Table 1 summarizes the second-generation antidepressants that are available in the United States by mechanism of action; it shows names, all dosage forms, therapeutic class, and FDA-approved (labeled) uses.

Table 1. Second-generation antidepressants approved for use in the United States

Generic Name	U.S. Trade Name [a]	Dosage Forms	Therapeutic Classification	Labeled Uses [b]
Bupropion [c]	Wellbutrin®; Wellbutrin SR®; Wellbutrin XL®	75, 100 mg tabs; 100, 150, 200 mg SR tabs 150, 300 mg XL tabs	Other	MDD; Seasonal affective disorder
Citalopram [c]	Celexa®	10, 20, 40 mg tabs; 2 mg/ml solution	SSRI	MDD
Desvenlafaxine	Pristiq®	50, 100 mg tabs	SNRI	MDD
Duloxetine	Cymbalta®	20, 30, 60 mg caps	SSNRI	MDD; GAD; Neuropathic pain; Fibromyalgia
Escitalopram	Lexapro®	5, 10, 20 mg tabs 1 mg/ml solution	SSRI	MDD; GAD
Fluoxetine [c]	Prozac®; Prozac Weekly®	10, 20, 40 mg caps; 4mg/ml solution 90 mg caps	SSRI	MDD; OCD; PMDD; Panic disorder; Bulimia nervosa
Fluvoxamine [c]	Luvox®	25, 50, 100 mg tabs	SSRI	OCD
Mirtazapine [c]	Remer on® Remer on Sol tab®	15, 30, 45 mg tabs; 15, 30, 45 mg orally disintegrating tabs	SNRI [d]	MDD
Nefazodone [c]	Serzone® [e]	50, 100, 150, 200, 250 mg tabs	Other	MDD
Paroxetine [c]	Paxil®; Paxil CR® [f]	10, 20, 30, 40 mg tabs; 2 mg/ml solution; 12.5, 25, 37.5 mg CR tabs	SSRI	MDD; OCD; Panic disorder; Social anxiety disorder; GAD; PTSD; PMDD [f]
Sertraline [c]	Zoloft®	25, 50, 100 mg tabs; 20 mg/ml solution	SSRI	MDD; OCD; Panic disorder; PTSD; PMDD; Social anxiety disorder
Trazodone [c]	Desyrel®	50, 100, 150, 300 mg tabs	Other	MDD
Venlafaxine [c]	Effexor®; Effexor XR®	25, 37.5, 50, 75, 100 mg tabs; 37.5, 75, 150 mg XR caps	SNRI	MDD; GAD;[g] Panic disorder; [g] Social anxiety disorder [g]

tabs = tablets; caps = capsules

[a]CR, SR, XL, and XR are registered trademarks referring to controlled, sustained, or extended-release dosage forms, respectively.

[b]GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PMDD, premenstrual dysphoric disorder; PTSD, post-traumatic stress disorder.

[c]Generic available for some dosage forms.

[d]Mirtazapine's mechanism of action is not clearly an SNRI, but it was grouped in this class owing to similarities.

[e]Only generic nefazodone is available in the United States.

[f]Only Paxil CR (not Paxil) is approved for the treatment of PMDD.

[g]Only Effexor XR (not Effexor) is approved for the treatment of GAD and social anxiety disorder.

The mechanism of action of most second-generation antidepressants is poorly understood. In general, these drugs work through their effect on prominent neurotransmitters in the central nervous system. Although the drugs can be grouped as SSRIs, SNRIs, SSNRIs (selective serotonin norepinephrine reuptake inhibitors), and "other" antidepressants because of their primary mechanism of action, drugs within these groups are not homogenous, and the specific activity may differ among them.

The six SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) act by selectively inhibiting the reuptake of serotonin 5-HT at the presynaptic neuronal membrane. Reuptake inhibition has the effect of increasing the levels of serotonin made available to improve the transmission of neural signals at the synapse. The three SNRIs (desvenlafaxine, mirtazapine, and venlafaxine) are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Mirtazapine differs from desvenlafaxine and venlafaxine in that it is believed to enhance central noradrenergic and serotonergic activity as a 5-HT2 and 5-HT3 receptor antagonist. However, we classify them together because of overlap in the affected neurotransmitters. Duloxetine selectively inhibits serotonin and norepinephrine; we refer to it as an SSNRI although it also could be grouped with the SNRIs.

The three remaining drugs, classified as other, are believed to work in related ways through their effects on serotonin, norepinephrine, and dopamine. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine; its primary mechanism of action is believed to be dopaminergic and noradrenergic. Nefazodone is believed to inhibit neuronal uptake of serotonin and norepinephrine. Trazodone appears to produce its primary effect by selectively inhibiting serotonin reuptake, but it also causes adrenoreceptor subsensitivity and induces significant changes in 5-hydroxytryptamine (5-HT) presynaptic receptor adrenoreceptors. At low doses, it appears to act as a serotonin antagonist and at higher doses as an agonist.[10, 11]

Purpose of This Report

The purpose of this review is to help policymakers, clinicians, and patients make informed choices about the use of second-generation antidepressants. Given the prominent role of drug therapy in psychiatric disease and the prevalent use of these drugs, our goal is to summarize comparative data on the efficacy, effectiveness, and harms of 13 newer antidepressants: bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine. We evaluate evidence for these agents in treating patients with depressive syndrome, including MDD, dysthymic disorder, and subsyndromal depressive disorders, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[1] We focus this review on these disorders in adults 18 years of age and older, including the elderly.

This report updates our previous report (January 2007)[12] by including new evidence published since the latest date of publications in the original review. We have included one new medication (desvenlafaxine). In addition to reviewing new comparative evidence, we extend our prior analyses by comparing different formulations of the same chemical entity (Table 2). We also examine whether switching medications after a successful response to an initial medication increases the risk of relapse or recurrence. This question is especially relevant to patients who face changes in their insurance benefit when their insurers no longer cover the medication they are currently taking.

Table 2. Usual dosing range and frequency of administration for adults

Generic Name	U.S. Trade Name [a]	Usual Daily Dosing Range	Frequency
Bupropion	Wellbutrin®	200-450 mg	Three times daily
	Wellbutrin SR®	150-400 mg	Twice daily
	Wellbutrin XL®	150-450 mg	Once daily
Citalopram	Celexa®	20-40 mg	Once daily
Desvenlafaxine	Pristiq®	50 mg	Once daily
Duloxetine	Cymbalta®	40-60 mg [b]	Once or twice daily
Escitalopram	Lexapro®	10-20 mg	Once daily
Fluoxetine	Prozac®	10-80 mg	Once or twice daily
	Prozac Weekly®	90 mg (weekly)	Once weekly
Fluvoxamine	Luvox®	50-300 mg	Once or twice daily
Mirtazapine	Remeron®	15-45 mg	Once daily
	Remeron Sol tab®	15-45 mg	Once daily
Nefazodone	Serzone®	200-600 mg	Twice daily
Paroxetine	Paxil®	20-60 mg	Once daily
	Paxil CR®	12.5-75 mg	Once daily
Sertraline	Zoloft®	50-200 mg	Once daily
Trazodone	Desyrel®	150-400 mg	Three times daily
Venlafaxine	Effexor®	75-375 mg	Two to three times daily
	Effexor XR®	75-225 mg	Once daily

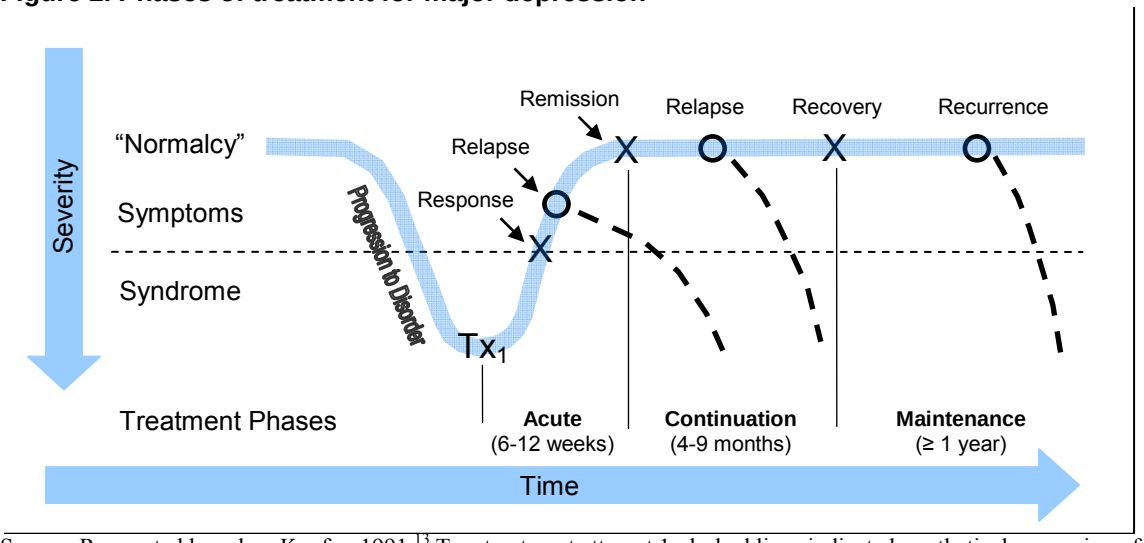
[a] CR, SR, XL, and XR are registered trademarks referring to controlled-, sustained-, or extended-release dosage forms, respectively.
[b] Doses of duloxetine up to 120 mg were studied in clinical trials, although doses above 60 mg are not believed to have additional efficacy.

We address several areas that are relevant for clinicians and policymakers that previous reports have not covered. First, we consider whether differences exist when comparing efficacy, effectiveness, or adverse events for immediate-release products with those factors for extended-release products. The distinction in immediate-release versus extended-release has implications for the number of times per day (or per week) patients need to take the medication. This factor influences dosing and medication adherence, which could be related to differences in effectiveness or tolerability. This question is particularly relevant to bupropion, fluoxetine, fluvoxamine, mirtazapine, paroxetine, and venlafaxine because these products come in multiple formulations.

Second, we consider treatment in the continuation and maintenance phases of depression, not simply the acute phase of treatment (see Figure 2). Among patients who have already responded to acute-phase treatment or who have maintained a response through continuation-phase treatment, we consider how treatments compare for preventing relapse or recurrence. We consider this question for patients who continue on the drug they initially responded to, as well as for patients who switch to a different antidepressant during the continuation or maintenance phase. The latter question may apply to patients who experience a change in insurance benefit and have to switch treatment because a drug is no longer covered by insurance or the cost is now

prohibitive. These considerations are especially important to the initial treatment selection and the ongoing management of depression for several reasons.

Figure 2. Phases of treatment for major depression



Source: Re-created based on Kupfer, 1991.[13] Tx_1=treatment attempt 1; dashed lines indicate hypothetical worsening of depressive severity.

First, clinical decisions will differ depending on where patients are in the trajectory of their treatment. The American College of Physicians (ACP) recommends that when clinicians are initially treating patients with acute major depressive disorders, they should first select an antidepressant on the basis of adverse-event profiles, cost, and patient preferences.[14] Once an initial medication is selected, the ACP guidelines recommend that clinicians assess the patients' status, therapeutic response, and adverse effects on a regular basis, beginning 1 to 2 weeks after initiation of therapy. If patients do not have an adequate response to pharmacotherapy within 6 to 8 weeks, then clinicians should modify the treatment. If an adequate response is achieved, then patients should remain on the same antidepressant during a continuation phase that lasts at least 4 to 9 months. Finally, clinicians should consider a maintenance phase lasting an additional 1 or more years for patients who have had two or more previous episodes of depression.[14-16]

We consider all three phases of depression management (Figure 2):

- Acute phase, first phase of depression management, usually 6 to 12 weeks;
- Continuation phase, second phase of depression management, during which the treatment goal is ongoing absence of depressive symptoms for an additional 4 to 9 months such that the patient's episode can be considered completely resolved (i.e., relapse prevention); and
- Maintenance phase, third phase of depression management, frequently a multiyear period during which the treatment goal is preventing the recurrence of a new, distinct episode (i.e., recurrence prevention).

Following this categorization allows us to make the clinically relevant distinction between relapse and recurrence. We define relapse as the return of depressive symptoms during the acute or continuation phases, so it is considered part of the same depressive episode. We define recurrence as the return of depressive symptoms during the maintenance phase, so it is considered a new, distinct episode.

This distinction is critical to determining long-term treatment plans. If an individual has a single episode of MDD that has resolved, treatment recommendations may or may not include

continued medication treatment. If, however, an individual has a diagnosis of recurrent MDD, the recommendation for continued treatment may be years.[15, 16] In addition, this categorization can frame decisions about depression management into best treatments for immediate resolution of depressive symptoms (acute phase) and those best for ongoing management once symptoms have resolved (continuation and maintenance phases). Of note, the latter two phases involve a treatment period that is much longer than that for the first phase.

Finally, we review the data addressing whether the presence of accompanying symptoms, such as anxiety and insomnia, might affect outcomes. For example, MDD is frequently associated with concurrent anxiety. If certain antidepressants can treat such a depression more successfully than other agents, or if they can mitigate the specific concurrent anxiety symptoms, these agents might be preferred choices. Such data could guide clinicians on how better to target antidepressant selection and steer policymakers toward the best available agents.

Scope and Key Questions

This review compares the efficacy, effectiveness, and harms of second-generation antidepressant medications. To that end, we address the following Key Questions:

1a. For adults with major depressive disorder (MDD), dysthymia, or subsyndromal depressive disorders, do commonly used medications for depression differ in efficacy or effectiveness in treating depressive symptoms?

1b. If a patient has responded to one agent in the past, is that agent better than current alternatives at treating depressive symptoms?

1c. Are there any differences in efficacy or effectiveness between immediate-release and extended-release formulations of second-generation antidepressants?

2a. For adults with a depressive syndrome that has responded to antidepressant treatment, do second-generation antidepressants differ in their efficacy or effectiveness for preventing relapse (i.e., continuation phase) or recurrence (i.e., maintenance phase) when a patient
- Continues the drug to which they initially responded, or
- Switches to a different antidepressant?

2b. For adults with a depressive syndrome that has not responded to acute antidepressant treatment or has relapsed (continuation phase) or recurred (maintenance phase), do alternative second-generation antidepressants differ in their efficacy or effectiveness?

3. In depressed patients with accompanying symptoms such as anxiety, insomnia, and neurovegetative symptoms, do medications or combinations of medications (including a tricyclic in combination with a second-generation antidepressant) differ in their efficacy or effectiveness for treating the depressive episode or for treating an accompanying symptoms?

4a. For adults with a depressive syndrome, do commonly used antidepressants differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to nausea, diarrhea, headache, tremor, daytime sedation, decreased libido, failure to achieve orgasm, nervousness, insomnia, and more serious events including suicide.

4b. Are there any differences in safety, adverse events, or adherence between immediate-release and extended-release formulations of second-generation antidepressants?

5. How do the efficacy, effectiveness, or harms of treatment with antidepressants for a depressive syndrome differ for the following subpopulations?

- Elderly or very elderly patients
- Other demographic groups (defined by age, ethnic or racial groups, and sex)
- Patients with medical comorbidities (e.g., ischemic heart disease, cancer)
- Patients with psychiatric and behavioral comorbidities (e.g., substance abuse disorders)
- Patients taking other medications

Throughout this report, we highlight effectiveness studies conducted in primary-care or office-based settings that use less-stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most efficacy studies.[17] We deemed studies that met at least six of seven predefined criteria as effectiveness studies (Table 3).[18] Their results are more applicable to the average patient than are results from highly selected populations in efficacy studies.

Table 3. Criteria for effectiveness studies

Criteria	Relevance to Treatment of Depressive Disorders
Study population	Primary care population
Less-stringent eligibility criteria	Determine case by case
Health outcomes	Response, remission, quality of life, functional capacity, hospitalization
Clinically relevant treatment modalities	≥8 weeks study duration; flexible dose design; physician diagnosis
Assessment of adverse events	Always
Adequate sample size to assess a minimally important difference from a patient perspective	n>150
Intention-to-treat analysis	Reflects treatment effects in a real world setting

For each Key Question, we evaluated specific outcome measures (where appropriate), as reported in Table 4. For efficacy and effectiveness, we focused on head-to-head trials comparing one second-generation antidepressant with another. This kind of information constitutes "direct" evidence. When sufficient head-to-head evidence was unavailable, we evaluated placebo-controlled evidence. Comparisons made using this kind of information constitute "indirect" evidence. Finally, we included observational studies to assess relapse or recurrence prevention, second-line treatment, and safety and tolerability.

Table 4. Outcome measures and study eligibility criteria

Key Question Outcomes of Interest and Specific Measures	Study Eligibility Criteria
Key Questions 1, 3, and 5: **Efficacy and effectiveness** Response Remission Speed of response/remission Relapse Quality of life Functional capacity Hospitalization	**Study design** Head-to-head, double-blind RCTs High-quality meta-analyses When sufficient evidence is not available for direct head-to-head comparisons: double-blind, placebo-controlled RCTs **Minimum study duration** For all studies: 6 weeks **Sample size** For quantitative analysis: no minimum For qualitative analysis: n ≥40

Table 4. Outcome measures and study eligibility criteria (continued)

Key Question Outcomes of Interest and Specific Measures	Study Eligibility Criteria
Key Question 2a: **Maintenance of remission**	**Study design** Head-to-head, double-blind RCTs High-quality meta-analyses When sufficient evidence is not available for direct head-to-head comparisons: double-blind, placebo-controlled RCTs or high-quality controlled observational studies **Minimum study duration** For all studies: 3 months **Sample size** For RCTs: no minimum For observational studies: n ≥100
Key Question 2b: **Response and remission for recurrent depression**	**Study design** Head-to-head, double-blind RCTs High-quality meta-analyses When sufficient evidence is not available for direct head-to-head comparisons: double-blind, placebo-controlled RCTs or high-quality controlled observational studies **Minimum study duration** For RCTs: 6 weeks For observational studies: 3 months **Study population** Adult inpatients and outpatients with recurrent depression **Sample size** For RCTs: For quantitative analysis: no minimum For qualitative analysis: n ≥40 For observational studies: n ≥100
Key Question 4: **Safety and tolerability:** Overall adverse events Withdrawals because of adverse events Serious adverse events Specific adverse events or withdrawals because of specific adverse events, including: hyponatremia seizures suicide hepatoxicity weight gain gastrointestinal symptoms sexual side effects others	**Study design** Head-to-head, double-blind, RCTs High-quality meta-analyses Observational studies (cohort studies, case-control studies, large database reviews) Pooled data analyses **Minimum study duration** For RCTs: 6 weeks For observational studies: 3 months **Study population** Adult inpatients and outpatients with major depressive disorder, dysthymia, or subsyndromal depression **Sample size** For RCTs: For quantitative analysis: no minimum For qualitative analysis: n ≥40 For observational studies: n ≥1000

n = number; RCT = randomized controlled trial

To evaluate comparative evidence, we compared a large range of doses within and across studies. Because a reference standard does not exist for making dose comparisons across drugs, we use a comparative dose classification system to identify gross inequities in drug-dose comparisons.[19] This classification provides a rough mechanism to determine whether doses are relatively similar when making head-to-head comparisons. The dose classification is rooted primarily in the dosing range suggested in the FDA-approved labeling; we also made some adjustments to this range to reflect clinical practice patterns that might not have been considered

in the FDA-reviewed studies. The usual dosing range is divided by the upper and lower quartile to create three levels (Table 5).

Table 5. Comparative dose classification of second-generation antidepressants

Generic	U.S. Trade Name [a]	Usual Range [b]	Three-Level Dose Classification		
			Low	Medium	High
Bupropion	Wellbutrin®	200–450 mg	<262.5	262.5-387.5	>387.5
	Wellbutrin SR®	150–400 mg	<212.5	212.5-337.5	>337.5
	Wellbutrin XL®	150–450 mg	<225	225-375	>375
Citalopram	Celexa®	20–40 mg	<25	25-35	>35
Desvenlafaxine	Pristiq®	50mg	<50	50	>50
Duloxetine	Cymbalta®	40–60 mg	<45	45-55	>55
Escitalopram	Lexapro®	10–20 mg	<12.5	13-17.5	>17.5
Fluoxetine	Prozac®	10–80 mg	<27.5	28-62.5	>62.5
	Prozac Weekly®	90 mg (weekly)	<90	90	>90
Fluvoxamine	Luvox®	50–300 mg	<112.5	113-237.5	>237.5
Mirtazapine	Remeron®	15–45 mg	<22.5	22.5-37.5	>37.5
	Remeron Sol tab®	15–45 mg	<22.5	22.5-37.5	>37.5
Nefazodone [d]	Serzone® [c]	200–600 mg	<300	300-500	>500
Paroxetine	Paxil®	20–60 mg	<30	30-50	>50
	Paxil CR®	12.5–75 mg	<28.125	28.125-59.375	>59.375
Sertraline	Zoloft®	50–200 mg	<87.5	87.5-162.5	>162.5
Trazodone [d]	Desyrel®	150–400 mg	<212.5	212.5-337.5	>337.5
Venlafaxine	Effexor®	75–375 mg	<150	150-300	>300
	Effexor XR®	75–225 mg	<112.5	112.5-187.5	>187.5

[a]CR, SR, XL, and XR are registered trademarks referring to controlled-, sustained-, or extended-release dosage forms.
[b]Dose classification is rooted primarily in the dosing range suggested in the FDA-approved labeling; we also made some adjustments to this range to reflect clinical practice patterns that might not have been considered in the FDA-reviewed studies.
[c]Generic product no longer marketed in the United States.

Organization of the Report

The remainder of this comparative effectiveness review describes our methods to review and synthesize this literature, presents our results by Key Question, and discusses the implications of those results for clinical applications and future research. Appendix A describes our search strategy; Appendix B lists excluded studies; Appendix C presents evidence tables; Appendix D provides characteristics of studies with poor internal validity; Appendix E contains studies included in our mixed-treatment comparison; Appendix F contains a bibliography of articles by database searched; Appendix G exhibits evidence profiles for grading the strength of evidence for main outcomes for each Key Question. Appendix H presents our review and abstraction forms, including the quality assessment criteria.

Methods

This chapter documents all the methods used to conduct and produce this updated comparative effectiveness review (CER) on second-generation antidepressants for the Agency for Healthcare Research and Quality (AHRQ) through its Effective Health Care Program (www.effectivehealthcare.ahrq.gov). Because it is an update, we begin with an overview of the main changes to or differences in methods since we produced the initial report in 2007.[12]

Summary of Methodological Changes Since the 2007 Report

We have made only a few changes to the methods used for the CER published in 2007. They involve drugs, approaches to the literature searches, articles included or excluded, techniques for quantitative synthesis, and grading strength of evidence for the overall body of evidence. Specific changes are noted here; longer documentation will be found in later parts of this methods chapter.

We added one drug—desvenlafaxine—to the literature searches and analyses (we used the same search strategy in electronic databases as for the original report). For manual literature searches, we changed the process to semi-automatic searches using the Scopus™ abstraction and citation database (www.scopus.com/home.url). The method is described below in the section on Literature Searches. We did not make any changes to the eligibility criteria (Table 4 in the Introduction). We used the same approach as in the 2007 report to select literature, assess the quality of individual studies (i.e., appraise their risk for bias), and extract relevant data.

Despite using identical methods to select relevant evidence, however, we removed some studies in the 2007 report from the current update. These studies had not met eligibility criteria in the 2007 report to begin with, but because they represented the only available evidence to answer a particular question at the time we had retained them. In the 2007 report we also had briefly summarized findings of such studies to provide a synopsis of the best available evidence (best-evidence approach). When, for this update, we have identified newer evidence that meets our eligibility criteria, we excluded the other "ineligible" studies from the current update.

For indirect comparisons we changed our statistical methods. Specifically, we now use a Bayesian mixed-treatment comparisons approach rather than meta-regressions and network meta-analyses. A detailed description of this approach appears in the section below on Data Synthesis.

We changed our method for rating the strength of evidence. In 2007 we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. For this update, we follow the principles outlined for use by the AHRQ Evidence-based Practice Centers in AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews[20] (www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318). Details are summarized below in Grading Strength of a Body of Evidence.

Topic Development

The topic of the first comparative effectiveness review report and preliminary Key Questions arose through an internal process within the AHRQ Evidence-based Practice Center Program in early 2005. Investigators from the RTI International–University of North Carolina Evidence-based Practice Center (RTI–UNC EPC) then refined the questions in consultation with AHRQ and a Technical Expert Panel (TEP). We addressed the refined questions in the 2007 published

report. For this report we added three new Key Questions (1c, 2a, 4b) to address input from the current TEP for the update review.

Literature Search

To identify articles relevant to each Key Question, we searched PubMed, Embase, the Cochrane Library, PsycInfo, and International Pharmaceutical Abstracts. We used either Medical Subject Headings (MeSH or MH) as search terms when available or keywords when appropriate. We combined terms for selected indications (major depressive disorder, dysthymia, minor depression, subsyndromal depressive disorder), drug interactions, and adverse events with a list of 13 specific second-generation antidepressants (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine). We limited the electronic searches to "human" and "English language." We searched sources from 1980 to January 2011 to capture literature relevant to the scope of our topic. We used the National Library of Medicine (NLM) publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses. The search strategy is outlined in Appendix A.

We also used semi-automatic manual searches of reference lists of pertinent review articles and letters to the editor employing Scopus.[21] We imported all citations into an electronic database (EndNote X.04).

The Scientific Resource Center (SRC) contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations. We received dossiers from five pharmaceutical companies (AstraZeneca, Eli Lilly, GlaxoSmithKline, Warner Chilcott Pharmaceuticals, and Wyeth). The SRC also searched the following sources for grey literature: the U.S. Food and Drug Administration (FDA) Web site, Health Canada, Authorized Medicines for the European Union, ClinicalTrial.gov, Current Controlled Trials, Clinical Study Results, WHO (World Health Organization) Clinical Trials, Conference Papers Index, NIH RePORTER, HSRProj (a service of the NLM), Hayes, Inc. Health Technology Assessment, and the New York Academy of Medicine's Grey Literature Index. One person reviewed the grey literature found through these searches to detect potentially relevant unpublished data and studies and ongoing trials.

Study Selection

We developed eligibility criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons to antidepressant medications within our scope of interest, as described in Table 4 (in the Introduction). Two people independently reviewed abstracts. If both reviewers agreed that the trial did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles and used the same eligibility criteria to determine which, if any, to exclude at this stage.

For this review, results from well-conducted, valid head-to-head trials provide the strongest evidence to compare drugs with respect to efficacy, effectiveness, and harms. We defined head-to-head trials as those comparing one second-generation antidepressant with another. RCTs of at least 6 weeks' duration and in adult study population were eligible for inclusion. For quantitative analyses we included all eligible studies without sample size limitations. In addition to head-to-head studies we included placebo-controlled trials for mixed treatment comparisons or if no head-to-head trials were available for a particular Key Question. If we concluded that we could not conduct any quantitative analyses, then we included studies only if they had sample sizes of 40 or larger.

For harms (i.e., evidence pertaining to safety, tolerability, and adverse events), we examined data from both experimental and observational studies. (Throughout this report we use "harms" as a summary term for adverse events and unwanted effects, as suggested by the CONSORT [Consolidated Standards of Reporting Trials] statement).[22] We included observational studies that had large sample sizes (1,000 patients or more), lasted at least 3 months, and reported an outcome of interest.

Initially, we reviewed studies with health outcomes as primary outcomes. Such outcomes, for example, were quality of life, relapse, functional capacity, and hospitalization. We reviewed response and remission when based on changes in depression scores as proxies for health outcomes (e.g., for response, a 50 percent improvement of depression scores). For harms, we looked for both overall and specific outcomes ranging in severity (e.g., suicide, sexual side effects, hyponatremia, weight change, seizures, gastrointestinal symptoms, discontinuation syndrome) and for withdrawals attributed by the investigators to adverse events.

We included meta-analyses in this CER if we found them to be relevant for a Key Question and of good or fair methodological quality.[23] We did not review individual studies if they had already been included in a high-quality meta-analysis. We excluded meta-analyses that were not based on a comprehensive systematic literature search or did not maintain the units of the studies in their statistical analyses. We checked our database to guarantee that our literature search had detected trials included in any meta-analyses that we discarded, and we then obtained any missing articles.

Data Extraction

We designed and used a structured data abstraction form to ensure consistency of appraisal for each study. Trained reviewers initially abstracted data from each study and assigned an initial quality rating. A senior reviewer then read each abstracted article, evaluated the completeness and accuracy of the data abstraction, and confirmed the quality rating. We resolved discrepancies by consensus or by the involvement of a third, senior reviewer.

We abstracted the following data from included trials: study design, eligibility criteria, intervention (drugs, dose, duration), additional medications allowed, methods of outcome assessment, population characteristics (such as age, sex, race or ethnicity, or comorbid anxiety), sample size, loss to followup, withdrawals because of adverse events, results, and adverse events reported. We recorded intention-to-treat results (ITT; i.e., all patients are analyzed as randomized with missing values imputed) if available. For studies eligible for quantitative analyses, we contacted authors if reported data were incomplete or missing. All data abstraction employed SRS 4.0, Möbius Analytics.

Quality Assessment

To assess the quality (internal validity) of studies, we used predefined criteria based on those developed by the U.S. Preventive Services Task Force (ratings: good, fair, poor)[24] and the National Health Service Centre for Reviews and Dissemination.[25] Elements of quality assessment included, among others, randomization and allocation concealment, similarity of compared groups at baseline, use of ITT analysis, and overall and differential loss to followup. To assess the quality of observational studies, we used criteria outlined by Deeks et al.[26] Items assessed included selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of followup, and statistical analysis.

In general terms, a "good" study has the least risk of bias and results are considered to be valid. A "fair" study is susceptible to some bias, but probably not sufficient to invalidate its results. The fair quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A "poor" rating indicates significant risk of bias (stemming from, e.g., serious errors in design, analysis reporting large amounts of missing information, or discrepancies in reporting) that may invalidate the study's results. We generally excluded studies with a poor rating from our analyses. If no other evidence on an outcome of interest was available, however, we may comment on findings from poor studies.

Ratings of the internal validity of studies are not comparable across study designs. That is, a good observational study does not necessarily equal a good RCT. We take limitations of certain study designs into consideration when we grade the strength of the evidence.

Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting a third, independent party. Time constraints precluded our contacting study authors for clarification of methodological questions.

In addition to internal validity, we assessed the comparability of dosages. To evaluate comparative evidence, we considered a large range of doses within and across studies. Because a reference standard does not exist for making dose comparisons across drugs, we had previously created and then used in this CER a comparative dose classification system to identify gross inequities in drug-dose comparisons.[19]

This classification provides a rough mechanism to determine whether doses are relatively similar when making head-to-head comparisons. The dose classification is rooted primarily in the dosing range suggested in FDA-approved labeling for these medications. We also made some adjustments to this range to reflect clinical practice patterns that might not have been considered in the FDA-reviewed studies. As shown in Table 5, the usual dosing range (middle column) is divided by the upper and lower quartile to create three levels (right-hand columns).

Applicability Assessment

Throughout this report, we highlight effectiveness studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods than most efficacy studies. The results of effectiveness studies are more applicable to the spectrum of patients who will use a drug, have a test, or undergo a procedure than results from highly selected populations in efficacy studies. We used criteria proposed by Gartlehner et al. to distinguish effectiveness from efficacy trials.[18] These criteria assess seven categories: primary care population, eligibility criteria, outcome measures, study duration and intervention modalities, adverse events assessment, sample size, and ITT analysis.

Grading Strength of a Body of Evidence

We evaluated the strength of evidence based on methods guidance for the EPC program.[20] Strength of evidence is graded only for major comparisons and major outcomes for the topic at hand. The strength of evidence for each outcome or comparison that we graded incorporates scores on four domains: risk of bias, consistency, directness, and precision; it can also reflect ratings for other domains that can be factored in when relevant (e.g., dose-response relationships).

As described in Owens et al., evaluating risk of bias includes assessment of study design and aggregate quality of studies.[20] We judged good quality studies to yield evidence with low risk of bias. We graded evidence as consistent when effect sizes across studies were in the same

direction. When the evidence linked the interventions directly to health outcomes, we graded the evidence as being direct. We graded evidence as being precise when results had a low degree of uncertainty. A precise estimate is one that would allow a clinically useful conclusion; an imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions.[20]

As shown in Table 6, we used four grades to designate strength of evidence: high, moderate, low, and insufficient. Grades reflect the strength of the body of evidence to answer Key Questions on the comparative efficacy, effectiveness, and harms of second-generation antidepressants. They do not refer to the general efficacy or effectiveness.

Table 6. Definitions of the grades of the overall strength of evidence

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

This approach does not incorporate other factors that might be relevant to assess reliably the comparative efficacy, effectiveness, and harms; such considerations can include funding sources and comparable dosing. For this CER, we reported these additional factors and highlighted any problems that could potentially bias our assessments (e.g., all studies funded by the same manufacturer).

We dually evaluated the overall strength of evidence for each major outcome based on a qualitative assessment of strength of evidence for each domain. We reconciled all disagreements in grades through consensus discussion.

Data Synthesis

Overall Approaches and Meta-analyses for Direct Comparisons

Throughout this CER we synthesized the literature qualitatively. These are the results presented first (by Key Question) in Results.

When data were sufficient, we augmented findings with quantitative analyses. We conducted meta-analyses of data for head-to-head comparisons for trials that were fairly homogenous in study populations and outcome assessments. For efficacy, we used two outcome measures:

1. The odds ratio (OR) of being a responder (more than 50 percent improvement from baseline) on the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS) at study endpoint.
2. The weighted mean difference of changes on a specific depression rating scale (HAM-D or MADRS). We chose this outcome measure to have an estimate of the actual difference in effect sizes between treatments.

For each meta-analysis, we conducted a test of heterogeneity (I^2 index) and applied both a random and a fixed effects model. We report the results from random effects models because, in all our meta-analyses, the results from random and fixed effects models were very similar. If the OR was statistically significant, we then conducted a meta-analysis of the risk differences to

calculate the number needed to treat (NNT). All meta-analyses were conducted using StatsDirect Ltd. version 2.4.5.

We assessed publication bias using funnel plots and Kendell's tests. However, given the small number of component studies in our meta-analyses, these tests have low sensitivity to detect publication bias.

Indirect Comparisons With Mixed Treatment Comparisons Techniques

If fewer than three head-to-head trials were available for any drug comparison, we computed indirect comparisons employing mixed treatment comparisons (MTC) using Bayesian methods.[27, 28] Evidence suggests that indirect comparisons agree with head-to-head trials if component studies are similar and treatment effects are expected to be consistent in patients in different trials.[29] Nevertheless, results have to be interpreted cautiously.

To conduct MTC analyses, we included all placebo- and active-controlled double-blinded RCTs of good or fair quality that were fairly homogenous in study populations and outcome assessments. For this analysis, we excluded studies conducted exclusively in subjects who were older than 65 years of age or who had depressive disorders other than MDD or treatment-resistant depression.

Our outcome measure of choice was the rate of response on the HAM-D (defined as a 50 percent improvement of scores from baseline). We recalculated response rates for each study using the number of all randomized patients as the denominator to reflect a true ITT analysis. With this approach we attempted to correct variations in results of modified ITT analyses encountered in individual studies.

We used a random effects logistic regression model that adjusted for correlations between arms within each study, developed by the Multi-Parameter Evidence Synthesis (MPES) Research Group.[28]

The analysis was performed using WinBUGS Version 1.4, a Bayesian software package that uses Markov chain Monte Carlo (MCMC) techniques.[30] For our analysis, study effect and treatment effect parameters were modeled by flat prior distributions that were Normal (0, 10000). For the heterogeneity of the random-effects model, a vague uniform prior distribution with large range was used. The first 20,000 simulations were discarded to allow for model convergence and then a further 80,000 simulations were used in estimating the posterior probabilities. Satisfactory convergence was verified by trace plots and calculation of the Monte Carlo error for each parameter.

We calculated odds ratios and 95 percent credible intervals for all possible comparisons among our drugs of interest.

Peer Review

Individuals who were experts in psychiatry and individuals representing various stakeholder and user communities were invited to provide an external peer review of this CER. The Task Order Officer and the SRC oversaw the peer review process. Peer reviewers were charged with commenting on the content, structure, and format of the evidence report, providing additional relevant citations, and pointing out issues related to how we had conceptualized and defined the topic and Key Questions. Our peer reviewers (listed in the front matter of the report) gave us permission to acknowledge their review of the draft. In addition to AHRQ staff, an Associate

Editor reviewed the report, and the Eisenberg Center placed the draft report on the AHRQ Web site (http://effectivehealthcare.ahrq.gov) for 4 weeks to elicit public comment.

We compiled comments from all these sources and addressed each one individually, revising the text as appropriate. We documented all of this in a peer review disposition report delivered to AHRQ. For purposes of transparency of the entire EPC process, AHRQ makes this report available to the public at about 3 months after the Agency posts the final CER on the AHRQ Web site.

Results

This chapter is organized as follows: first by Key Question (KQ), second by subquestion or subpopulation, and third by intervention comparison. In addition, according to the specifications from the Agency for Healthcare Research and Quality (AHRQ) for comparative effectiveness reviews (CER), within each KQ section we present an overview, then key points, and finally detailed analyses. Finally, as explained in Methods, we graded the strength of evidence for all major comparisons and outcomes in the key points. Table 7 summarizes the main issues that we address here.

Table 7. Key Questions about the comparative efficacy and safety of second-generation antidepressants

Key Questions
KQ 1. Efficacy or effectiveness in treating depressive disorders and symptoms
KQ 2. Efficacy or effectiveness for maintaining remission or for treating patients with unresponsive or recurrent disease
KQ 3. Efficacy or effectiveness for treating depression with accompanying symptoms
KQ 4. Comparative harms and adherence for second-generation antidepressants
KQ 5. Efficacy, effectiveness, and harms for selected populations

KQ = Key Question.

We focus on randomized controlled trials (RCTs) for all questions; for KQ 2 on maintaining remission and treating unresponsive or recurrent disease, and KQ 4 on harms, we also include observational studies. Evidence tables for all included studies, by Key Question, are presented in Appendix C.

Reasons for exclusion were based on eligibility criteria or methodological criteria. We excluded 77 studies that originally met eligibility criteria but were later rated as poor quality for internal validity (Appendix D). The two main reasons for rating RCTs as poor were high loss to followup (more than 40 percent overall) and lack of intention-to-treat (ITT) analysis. Among meta-analyses, lack of a systematic literature search was the main reason for exclusion; this problem leads to a selected spectrum of trials and subsequently to biased results.

Studies reviewed for this report employed a notable array of diagnostic scales and health status or quality-of-life instruments. Most were pertinent to depressive and other disorders considered in this report, but some are considered more generic instruments that assess, for example, health-related quality of life. Table 8 lists abbreviations of diagnostic scales and health status or quality-of-life instruments encountered in this literature.

Table 8. Abbreviations and full names of diagnostic scales and other instruments

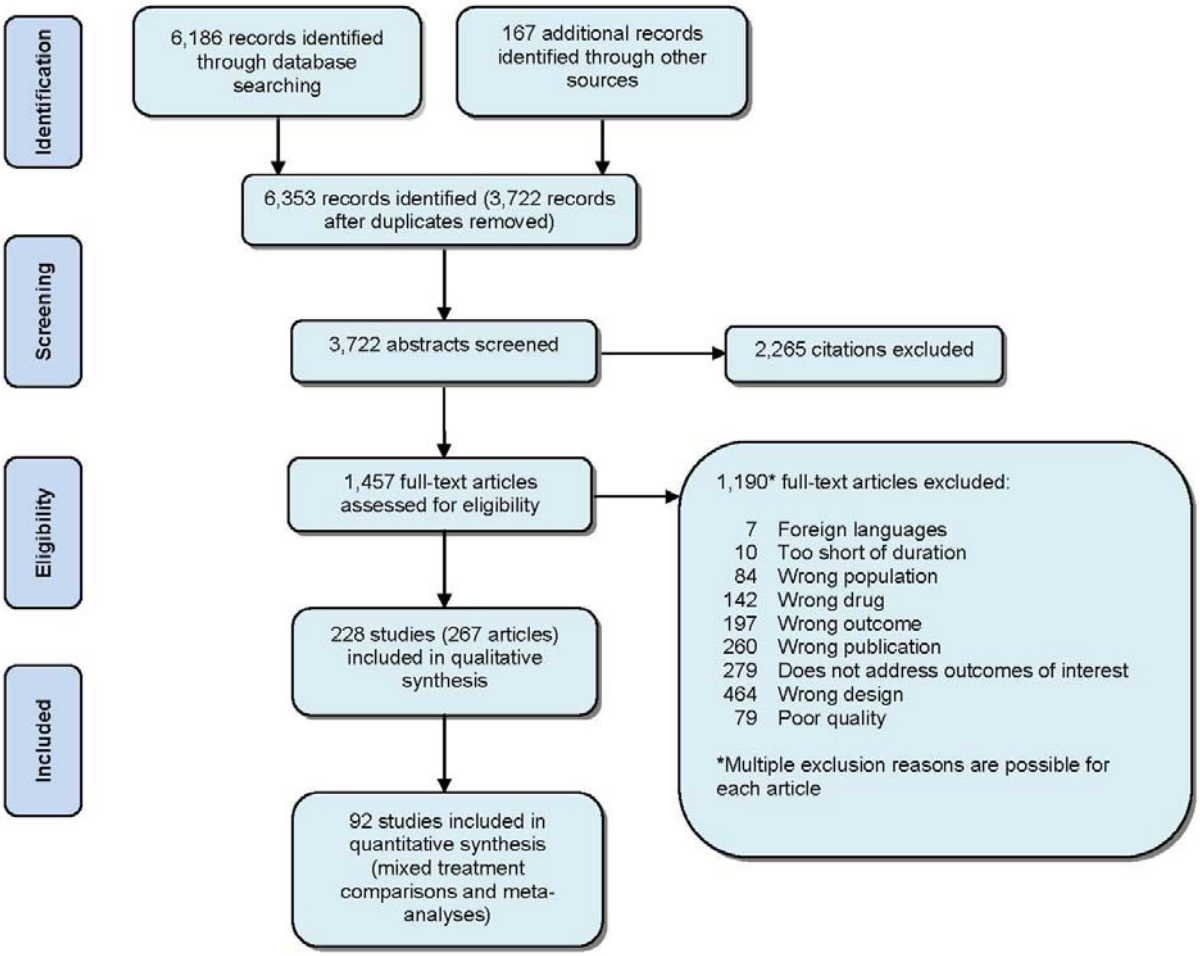
Abbreviation	Full Name of Instrument
BDI	Beck Depression Inventory
Beck's SSI	Beck's Scale for Suicide Ideation
BIMT	Blessed Information and Memory Test
BPI	Brief Pain Inventory
BQOL	Battelle Quality of Life Measure
BQOLS	Battelle Quality of Life Scale
CAS	Clinical Anxiety Scale
CES-D	Center for Epidemiological Studies-Depression Scale
CGI	Clinical Global Impressions
CGI–I	Clinical Global Impressions Improvement Scale
CGI–S	Clinical Global Impressions Severity Scale
DESS	Discontinuation Emergent Signs and Symptoms Checklist
FSQ	Functional Status Questionnaire
HAD-A	Hospital Anxiety and Depression Rating Scale
HAM–A	Hamilton Rating Scale for Anxiety
HAM–D	Hamilton Rating Scale for Depression
HSCL-D20	Hopkins Symptom Checklist - Depression
IDAS	Irritability, Depression, and Anxiety Scale
IDS-C	Inventory for Depressive Symptomatology - Clinician Rated
IDS-SR	Inventory for Depressive Symptomatology - Self Rated
MADRS	Montgomery-Asberg Depression Rating Scale
MMSE	Mini Mental State Examination
PGI-I	Patient Global Impression of Improvement
PRSexDQ	Psychotropic-Related Sexual Dysfunction Questionnaire
QLDS	Quality of Life in Depression Scale
Q-LES-Q, QLSQ	Quality of Life Enjoyment and Satisfaction Questionnaire
HSCL 56	Hopkins Symptom Checklist- 56 item version
SF-36	Medical Outcomes Study Health Survey – Short Form 36
SIP	Sickness Impact Profile
SLT	Shopping List Task
VAS	Visual Analogue Scale
UKU-SES	Utvalg for Kliniske Undersogelse Side Effect Scale

Because this report is an update of the original CER on second-generation antidepressants,[12] we identify all new studies in the summary tables of included studies in each detailed analysis section.

Overview of all Key Questions

We identified 3,722 citations from searches and reviews of reference lists. Figure 3 documents the disposition of the 267 included articles in this review, working from 1,457 articles retrieved for full text review and 1,190 excluded at this stage.

Figure 3. Results of literature search (PRISMA diagram)



We included 264 articles reporting on 248 studies of good or fair quality: 104 head-to-head randomized controlled trials (RCTs), 84 placebo-controlled RCTs, 46 meta-analyses or systematic reviews, observational studies, and studies of other design. We incorporated data from 14 additional placebo-controlled studies for indirect comparisons only. We attempted to contact 26 authors. We sent emails soliciting HAM-D response rates to 21 authors (current contact information for 5 authors could not be found). Fourteen authors responded to our query, but most could not provide data as it is no longer available. In the end, only two authors were able to provide us with HAM-D response rates from their studies. We were able to use the HAM-D data provided by Boulenger, 2006[31] in our mixed-treatment comparison; Blumenthal, 2007[32] HAM-D data is used in our sensitivity analysis.

Key Question 1a: Efficacy or Effectiveness in Treating Depressive Disorders and Symptoms

Major Depressive Disorder: Overview

In all, 91 RCTs (reported in 93 articles) compared the efficacy or effectiveness of one second-generation antidepressant with that for another for treating patients with MDD. Details can be found in the evidence tables in Appendix C.

Tables 9 through 14 provide selected information on all these studies. Studies are grouped according to the main drug classes compared—SSRIs versus SSRIs (Table 9); SSRIs versus SSNRIs and SNRIs (Table 10); and SSRIs versus other second-generation antidepressants (Table 11); SNRIs versus SSNRIs and SNRIs (Table 12); SNRIs versus other second-generation antidepressants (Table 13); and other second-generation antidepressants versus other second-generation antidepressants (Table 14). They are then listed alphabetically by the specific drugs compared.

Most subjects were younger than 60 years; 11 trials were conducted in populations of 55 years or older. We discuss these 11 studies in more detail in KQ 5 on subgroups. In the text below, studies are of fair quality unless otherwise specified.

In general, studies enrolled patients according to a criteria-based diagnosis of MDD relating to the Diagnostic and Statistical Manual of Mental Disorders (DSM, either revised third edition or fourth edition [DSM-III-R, DSM-IV]) and a predefined cutoff point of a widely used depression scale (i.e., Hamilton Rating Scale for Depression [HAM-D]=18 or Montgomery-Asberg Depression Rating Scale [MADRS]=19). Most patients had moderate to severe depression as measured by a variety of scales. Most studies excluded patients who had additional Axis I disorders, high suicidal risk, or progressive medical diseases or who used psychotherapy, electroconvulsive therapy, or psychotropic medications.

Of 78 possible comparisons of included second-generation antidepressants, we found direct head-to-head evidence for only 40 comparisons. Table 9 and Table 10 depict possible comparisons and the numbers of available head-to-head trials for each comparison. For those with fewer than three head-to-head trials, we conducted indirect comparisons. Appendix E presents studies included in our mixed-treatment comparisons.

Study investigators rarely assessed quality of life and functional capacity; if they did, they typically considered these as only secondary outcomes. Most studies employed both physician-rated scales; these included, for instance, HAM-D, MADRS, Clinical Global Impressions Scale (CGI) and patient-rated scales (e.g., Hospital Anxiety and Depression Rating Scale [HAD-A], Battelle Quality of Life Scale [BQOLS]).

In the majority of studies, the primary endpoints were either changes from baseline or rates of response or remission on investigator-rated diagnostic depression scales such as the HAM-D or MADRS. Changes on such diagnostic depression scales are generally viewed as intermediate outcomes rather than health outcomes, and they are not always reliably related to changes in health outcomes. Response or remission, even when deducted from such a scale (e.g., response is defined as a 50 percent improvement of scores on HAM-D or MADRS), can be seen as proxies to health outcomes. Therefore, we focused on differences in response or remission rates rather than differences in changes of scores.

Table 9. SSRIs versus SSRIs study characteristics, response and remission rates, and quality ratings of studies in adults with major depressive disorder

Study	N	Duration	Comparison and Dose (mg/day)	Response[a] (percent) and Significance Level	Remission[a] (percent) and Significance Level	Quality Rating
SSRIs vs. SSRIs Burke et al., 2002[33]	369	8 weeks	Citalopram 40 Escitalopram 20	46 vs. 51[b] *P*=NR (ns)	NR	Fair
		8 weeks	Citalopram 40 Escitalopram 10	46 vs. 50[b] *P*=NR (ns)	NR	
Colonna et al., 2005[34]	357	8 weeks	Citalopram 20 Escitalopram 10	55 vs. 63[b] *P*<0.05	45 vs. 55[b] *P*=NR	Fair
		24 weeks	Citalopram 20 Escitalopram 10	78 vs. 80[b] *P*=NR (ns)	71 vs. 76[b] *P*=NR	
Lepola et al., 2003[35]	315	8 weeks	Citalopram 20-40 Escitalopram 10-20	53 vs. 64[b] *P*=0.021	43 vs. 52[b] *P*=0.036	Fair
Moore et al., 2005[36]	294	8 weeks	Citalopram 40 Escitalopram 20	61 vs. 76[b] *P*=0.008	43 vs. 54[b] *P*=0.04	Fair
Unpublished Study SCT MD-02[37]	248	8 weeks	Citalopram 10-20 Escitalopram 20-40	51 vs. 46[b] *P*=NR	NR	Fair
Yevtushenko et al., 2007[38] *	330	6 weeks	Citalopram 10 Citalopram 20 Escitalopram 20	44 vs. 83 vs.95[b] *P*<0.001	26 vs. 61 vs.90[b] *P*<0.001	Fair
Patris et al., 1996[39]	357	8 weeks	Citalopram 20 Fluoxetine 20	78 vs. 76[b] *P*=NR (ns)	75 vs. 68[b] *P*=0.26	Fair
Haffmans et al., 1996[40]	217	6 weeks	Citalopram 20-40 Fluvoxamine 100-200	30 vs. 28 *P*=NR	14 vs. 8 *P*=NR (ns)	Fair
Ekselius et al., 1997[41]	400	24 weeks	Citalopram 20-60 Sertraline 50-150	81 vs. 76[c] *P*=NR (ns)	NR	Good
Kasper et al., 2005[42]	518	8 weeks	Escitalopram 10 Fluoxetine 20	46 vs. 37[b] *P*=NR (ns)	40 vs. 30[b] *P*=NR (ns)	Fair
Mao et al., 2008[43] *	240	8 weeks	Escitalopram 10 Fluoxetine 20	80 vs. 79 *P*>0.05	46 vs. 55 *P*=NR	Fair
Baldwin et al., 2006[44] *	325	8 weeks	Escitalopram 10-20 Paroxetine 20-40	68 vs. 71[b] *P*=NR	56 vs. 62[b]	Fair
Boulenger et al., 2006[31] *	459	24 weeks	Escitalopram 20 Paroxetine 40	82 vs. 77[b] *P*=NR (ns)	75 vs. 67[b] *P*<0.05	Fair
Ventura et al., 2007[45] *	215	8 weeks	Escitalopram 10 Sertraline 50-200	72 vs. 69 *P*=NR (ns)	49 vs. 53 *P*=NR (ns)	Fair
Dalery and Honig, 2003[46]	184	6 weeks	Fluoxetine 20 Fluvoxamine 100	NR *P*=NR (ns)	NR	Fair
Rapaport et al., 1996[47]	100	7 weeks	Fluoxetine 20-80 Fluvoxamine 100-150	NR	NR	Fair
Cassano et al., 2002[48]	242	52 weeks	Fluoxetine 20-60 Paroxetine 20-40	NR	NR	Fair
Chouinard et al., 1999[49]	203	12 weeks	Fluoxetine 20-80 Paroxetine 20-50	68 vs. 67 *P*=0.93	59 vs. 58 *P*=0.84	Fair
De Wilde et al., 1993[50]	100	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	62 vs. 67 *P*=NR	NR	Fair
Fava et al., 1998[51]	109	12 weeks	Fluoxetine 20-80 Paroxetine 20-50	57 vs. 58 *P*=NR (ns)	NR	Fair

Table 9. SSRIs versus SSRIs study characteristics, response and remission rates, and quality ratings of studies in adults with major depressive disorder (continued)

Study	N	Duration	Comparison and Dose (mg/day)	Response[a] (percent) and Significance Level	Remission[a] (percent) and Significance Level	Quality Rating
Gagiano et al., 1993[52]	90	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	63 vs. 70 *P*=NR	NR	Fair
Schöne and Ludwig, 1993[53]	106	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	Data NR *P*=0.03	NR	Fair
Tignol, 1993[54]	178	6 weeks	Fluoxetine 20 Paroxetine 20	78 vs. 75[b] *P*=NR (ns)	NR	Fair
Fava et al., 2002[55]	284	10-16 weeks	Fluoxetine 20-60 Paroxetine 20-60 Sertraline 50-200	65 vs. 69 vs. 73 *P*=0.49	54 vs. 57 vs. 59 *P*=0.80	Fair
Bennie et al., 1995[56]	286	6 weeks	Fluoxetine 20-40 Sertraline 50-100	51 vs. 59 *P*=NR	NR	Fair
Boyer et al., 1998[57]	242	≈ 26 weeks	Fluoxetine 50-150 Sertraline 20-60	43 vs. 47[b] *P*=NR (ns)	NR	Fair
Newhouse et al., 2000[58, 59]	236	12 weeks	Fluoxetine 20-40 Sertraline 50-100	71 vs. 73 *P*=NR (ns)	46 vs. 45 *P*=NR	Fair
Sechter et al., 1999[60]	238	24 weeks	Fluoxetine 20-60 Sertraline 50-150	64 vs. 74 *P*=0.11	NR	Fair
Van Moffaert et al., 1995[61]	165	8 weeks	Fluoxetine 20 Sertraline 50	NR	NR	Fair
Kiev and Feiger, 1997[62]	60	7 weeks	Fluvoxamine 50-150 Paroxetine 20-50	NR	NR	Fair
Ushiroyama et al., 2004[63]*	105	12 weeks	Fluvoxamine 50-150 Paroxetine 20-50	NR	NR	Fair
Nemeroff et al., 1995[64]	95	7 weeks	Fluvoxamine 50-150 Sertraline 50-200	NR	NR	Fair
Rossini et al., 2005[65]	93	7 weeks	Fluvoxamine 150 Sertraline 200	72 vs. 56 *P*=0.12	NR	Fair
Aberg-Wistedt et al., 2000[66]	353	8 weeks	Paroxetine 20-40 Sertraline 50-150	63 vs. 63[c] *P*=NR (ns)	57 vs. 52[b] *P*=NR (ns)	Fair
	353	24 weeks	Paroxetine 20-40 Sertraline 50-150	69 vs. 72 *P*=NR (ns)	NR[b] *P*=NR (ns)	

mg/d = milligram per day; NR = not reported; ns = not significant; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus; XR = extended release

Note: Drug names not otherwise specified refer to the immediate-release formulations, extended-release formulation are indicated as CR, XL, or XR.

*New study added during update.

[a]Response and remission (as defined by authors of the individual studies) are measured on the Hamilton Depression Rating Scale (HAM-D) unless indicated otherwise.

[b]Measured on the Montgomery – Asberg Depression Rating Scale (MADRS)

[c]Measured on a combination of scales

Table 10. SSRIs versus SSNRIs and SNRIs study characteristics, response and remission rates, and quality ratings of studies in adults with major depressive disorder

Study	N	Duration	Comparison and Dose (mg/day)	Response[a] (percent) and Significance Level	Remission[a] (percent) and Significance Level	Quality Rating
Leinonen et al., 1999[67]	270	8 weeks	Citalopram 20-60 Mirtazapine 15-60	88 vs. 85[b] *P*=0.54	NR	Fair
Allard et al., 2004[68]	151	22 weeks	Citalopram 10-30 Venlafaxine XR 75-150	93 vs. 93[b] *P*=NR (ns)	23 vs. 19[b] *P*=NR (ns)	Fair
Khan et al., 2007[69] *	278	8 weeks	Escitalopram 10-20 Duloxetine 60	61 vs. 52 *P*=NR	41 vs. 35 *P*=NR	Fair
Nierenberg et al., 2007[70] *	547	8 weeks	Escitalopram 10 Duloxetine 60	41 vs. 43 *P*=NR	32 vs. 37 *P*=NR	Fair
Wade et al., 2007[71] *	295	24 weeks	Escitalopram 20 Duloxetine 60	77 vs. 73 *P*=NR (ns)	67 vs. 60 *P*=NR (ns)	Fair
Bielski et al., 2004[72]	198	8 weeks	Escitalopram 20 Venlafaxine XR 225	61 vs. 48 *P*=NR (ns)	36 vs. 32 *P*=NR (ns)	Fair
Montgomery et al., 2004[73]	293	8 weeks	Escitalopram 10-20 Venlafaxine XR 75-150	77 vs. 80[b] *P*=NR (ns)	70 vs. 70[b] *P*=NR (ns)	Fair
Goldstein et al., 2002[74]	103	8 weeks	Fluoxetine 20 Duloxetine 40-120	45 vs. 49 *P*=0.39	30 vs. 43 *P*=0.82	Fair
Hong et al., 2003[75]	132	6 weeks	Fluoxetine 20-40 Mirtazapine 15-45	51 vs. 58 *P*=NR (ns)	27 vs. 35 *P*=NR (ns)	Fair
Versiani et al., 2005[76]	299	8 weeks	Fluoxetine 20-40 Mirtazapine 15-60	Data NR *P*=NR (ns)	41. vs. 40. *P*=NR (ns)	Fair
Wheatley et al., 1998[77]	133	6 weeks	Fluoxetine 20-40 Mirtazapine 15-60	Data NR *P*=NR (ns)	25 vs. 23 *P*=NR (ns)	Fair
Alves et al., 1999[78]	87	12 weeks	Fluoxetine 20-40 Venlafaxine 75-150	74 vs. 87 *P*=NR	41 vs. 51 *P*=NR	Fair
Costa e Silva, 1998[79]	382	8 weeks	Fluoxetine 20-40 Venlafaxine 75-225	Data NR *P*=0.15	60 vs. 60 *P*=NR	Fair
De Nayer et al., 2002[80]	146	12 weeks	Fluoxetine 20-40 Venlafaxine 75-150	49 vs. 72 *P*=0.008	40 vs. 59 *P*=0.028	Fair
Dierick et al., 1996[81]	314	8 weeks	Fluoxetine 20 Venlafaxine 75-150	60 vs. 72 *P*=0.023 (at week 6)	NR	Fair
Nemeroff and Thase, 2007[82] *	206	6 weeks	Fluoxetine 20-60 Venlafaxine 75-225	45 vs. 53 *P*=NR (ns)	28 vs. 32 *P*=NR (ns)	Fair
Rudolph and Feiger, 1999[83]	203	8 weeks	Fluoxetine 20-60 Venlafaxine XR 75-225	50 vs. 57 *P*=NR	22 vs. 37 *P*≤0.05	Fair
Silverstone and Ravindran, 1999[84]	249	12 weeks	Fluoxetine 20-60 Venlafaxine XR 75-225	62 vs. 67 *P*=NR	NR	Fair
Tzanakaki et al., 2000[85]	109	6 weeks	Fluoxetine 60 Venlafaxine 225	58 vs. 65[c] *P*=NR	36 vs. 41 *P*=NR	Fair
Tylee et al., 1997[86]	341	12 weeks	Fluoxetine 20 Venlafaxine 75	63 vs. 55[c] *P*=NR (ns)	34 vs. 35 *P*=NR (ns)	Fair
Detke et al., 2004[87]	274	8 weeks	Paroxetine 20 Duloxetine 80	74 vs. 65 *P*=NR (ns)	44 vs. 46 *P*=NR (ns)	Fair
		8 weeks	Paroxetine 20 Duloxetine 120	74 vs. 71 *P*=NR (ns)	44 vs. 52 *P*=NR (ns)	

Table 10. SSRIs versus SSNRIs and SNRIs study characteristics, response and remission rates, and quality ratings of studies in adults with major depressive disorder (continued)

Study	N	Duration	Comparison and Dose (mg/day)	Response[a] (percent) and Significance Level	Remission[a] (percent) and Significance Level	Quality Rating
Perahia et al., 2006[88] *	293	8 weeks	Paroxetine 20 Duloxetine 80	61 vs. 65 *P*=NR (ns)	43 vs. 44 *P*=NR (ns)	Fair
		8 weeks	Paroxetine 20 Duloxetine 120	61 vs. 68 *P*=NR (ns)	43 vs. 40 *P*=NR (ns)	
Lee et al., 2007[89] *	478	8 weeks	Paroxetine 20 Duloxetine 60	65 vs. 60 *P*=0.296	50 vs. 49 *P*=0.855	Fair
Benkert et al., 2000[90]	275	6 weeks	Paroxetine 20-40 Mirtazapine 15-45	54 vs. 58 *P*=NR (ns)	34 vs. 41 *P*=NR (ns)	Fair
Blier et al., 2009[91] *	40	6 weeks	Paroxetine 20 Mirtazapine 30	NR [b] *P*=NR (ns)	NR [b] *P*=NR (ns)	Fair
Schatzberg et al., 2002[92]	255	8 weeks	Paroxetine 20-40 Mirtazapine 15-45	58 vs. 64[c] *P*=NR (ns)	Data NR *P*=NR (ns)	Fair
Ballus et al., 2000[93]	84	12 weeks	Paroxetine 20-40 Venlafaxine 75-150	NR *P*=NR (ns)	33 vs. 57 *P*=0.011	Fair
		24 weeks	Paroxetine 20-40 Venlafaxine 75-150	NR *P*=NR (ns)	NR[b] *P*=NR (ns)	
McPartlin et al., 1998[94]	361	12 weeks	Paroxetine 20 Venlafaxine XR 75	NR *P*=NR (ns)	52 vs. 54 *P*=NR (ns)	Fair
Owens et al., 2008[95] *	86	8 weeks	Paroxetine CR 75 Venlafaxine XR 375	65 vs. 71 [b] *P*=0.63	46 vs. 63 [b] *P*=0.17	Fair
Behnke et al., 2003[96]	346	8 weeks	Sertraline 50-150 Mirtazapine 30-45	NR *P*=NR (ns)	NR *P*=NR (ns)	Fair
Mehtonen et al., 2000[97]	147	8 weeks	Sertraline 50-100 Venlafaxine 75-150	68 vs. 83 *P*=0.05	45 vs. 68 *P*=0.008	Good
Shelton et al., 2006[98] *	160	8 weeks	Sertraline 50-150 Venlafaxine XR 75-225	55 vs. 65 *P*=0.22	38 vs. 49 *P*=0.168	Fair
Sir et al., 2005[99]	163	8 weeks	Sertraline 50-150 Venlafaxine XR 75-225	71 vs. 71 *P*=0.95	60 vs. 54 *P*=0.47	Good

mg/d = milligram per day; NR = not reported; ns = not significant; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus; XR = extended release

Note: Drug names not otherwise specified refer to the immediate-release formulations, extended-release formulation are indicated as CR, XL, or XR.

*New study added during update.

[a]Response and remission (as defined by authors of the individual studies) are measured on the Hamilton Depression Rating Scale (HAM-D) unless indicated otherwise.

[b]Measured on the Montgomery – Asberg Depression Rating Scale (MADRS).

[c]Measured on a combination of scales.

Table 11. SSRIs versus other second-generation antidepressants study characteristics, response and remission rates, and quality ratings of studies in adults with major depressive disorder

Study	N	Duration	Comparison and Dose (mg/day)	Response[a] (percent) and Significance Level	Remission[a] (percent) and Significance Level	Quality Rating
Coleman et al., 2001[100]	304	8 weeks	Fluoxetine 20-60 Bupropion SR 150-400	57 vs. 56 *P*=NR (ns)	40 vs. 47 *P*=NR (ns)	Fair
Feighner et al., 1991[101]	123	6 weeks	Fluoxetine 20-80 Bupropion 225-450	58 vs. 63 *P*=NR (ns)	NR	Fair
Gillin et al., 1997[102]	44	8 weeks	Fluoxetine 20 Nefazadone 400	NR	NR	Fair
Beasley et al., 1991[103]	126	6 weeks	Fluoxetine 20-60 Trazodone 100-400	62 vs. 69 *P*=NR (ns)	51 vs. 42 *P*=NR (ns)	Fair
Perry et al., 1989[104]	40	6 weeks	Fluoxetine 20-60 Trazodone 50-400	NR	NR	Fair
Kennedy et al., 2006[105] *	141	8 weeks	Paroxetine 20-40 Bupropion SR 150-300	56 vs. 60 *P*=NR (ns)	36 vs. 38 *P*=NR (ns)	Fair
Weihs et al., 2000[106]	100	6 weeks	Paroxetine 10-40 Bupropion SR 100-300	77 vs. 71 *P*=NR (ns)	NR	Fair
Baldwin et al., 1996[107]	206	8 weeks	Paroxetine 20-40 Nefazodone 200-600	60 vs. 58[b] *P*=NR (ns)	NR	Fair
Hicks et al., 2002[108]	40	8 weeks	Paroxetine 20-40 Nefazodone 400-600	80 vs. 55 *P*=NR (ns)	NR *P*=NR (ns)	Fair
Kasper et al., 2005[109]	108	6 weeks	Paroxetine 20-40 Trazodone 150-450	91 vs. 87 *P*=NR (ns)	68 vs. 69 *P*=NR (ns)	Fair
Coleman et al., 1999[110]	240	8 weeks	Sertraline 50-200 Bupropion SR 150-400	61 vs. 66 *P*=NR (ns)	NR	Fair
Croft et al., 1999[111]	239	8 weeks	Sertraline 50-200 Bupropion SR 150-400	68 vs. 66 *P*=NR (ns)	NR	Fair
Kavoussi et al., 1997[112] Rush et al., 2001[113]	248	16 weeks	Sertraline 50-200 Bupropion SR 100-300	74 vs. 66 *P*=NR (ns)	63 vs. 55 *P*=NR (ns)	Fair
Feiger et al., 1996[114]	160	6 weeks	Sertraline 50-200 Nefazodone 100-600	57 vs. 59 *P*=NR (ns)	NR	Fair
Munizza et al., 2006[115] *	122	6 weeks	Sertraline 50-100 Trazodone 150-450	63 vs. 74 *P*=NR (ns)	49 vs. 60 *P*=NR (ns)	Fair

mg/d, milligram per day; NR, not reported; ns, not significant; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; vs., versus; XR, extended release.

Note: Drug names not otherwise specified refer to the immediate-release formulations, extended-release formulation are indicated as CR, XL, or XR.

*New study added during update.

[a]Response and remission (as defined by authors of the individual studies) are measured on the Hamilton Depression Rating Scale (HAM-D) unless indicated otherwise.

[b]Measured on the Clinical Global Impressions (CGI) scale

Table 12. SNRIs versus SSNRIs and SNRIs study characteristics, response and remission rates, and quality ratings of studies in adults with major depressive disorder

Study	N	Duration	Comparison and Dose (mg/day)	Response[a] (percent) and Significance Level	Remission[a] (percent) and Significance Level	Quality Rating
Tourian et al.,2009[116] *	474	8 weeks	Desvanlafaxine 50 Desvenlafaxine 100 Duloxetine 60	39 vs. 49 vs. 47 *P*=NR	20 vs. 28 vs. 29 *P*=NR	Fair
Benkert et al., 2006[117] *	242	6 weeks	Mirtazapine 45 Venlafaxine XR 225	NR	NR	Fair
Guelfi et al., 2001[118]	157	8 weeks	Mirtazapine 45-60 Venlafaxine 225-375	62 vs. 52 *P*=NR (ns)	NR *P*=NR (ns)	Fair

mg/d = milligram per day; NR = not reported; ns = not significant; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus; XR = extended release

Note: Drug names not otherwise specified refer to the immediate-release formulations, extended-release formulation are indicated as CR, XL, or XR.

*New study added during update.

[a]Response and remission (as defined by authors of the individual studies) are measured on the Hamilton Depression Rating Scale (HAM-D) or indicated otherwise.

Table 13. SNRIs versus other second-generation antidepressants study characteristics, response and remission rates, and quality ratings of studies in adults with major depressive disorder

Study	N	Duration	Comparison and Dose (mg/day)	Response[a] (percent) and Significance Level	Remission[a] (percent) and Significance Level	Quality Rating
Halikas et al., 1995[119]	100	6 weeks	Mirtazapine 5-35 Trazodone 40-280	51 vs. 41 *P*=NR (ns)	NR	Fair
van Moffaert et al., 1995[120]	200	6 weeks	Mirtazapine 24-72 Trazodone 150-450	61 vs. 51 *P*=NR (ns)	NR	Fair
Hewett et al., 2009[121] *	374	8 weeks	Venlafaxine XR 75-150 Bupropion XR 150-300	65 vs. 57 [b] *P*=NR (ns)	51 vs. 47 [b] *P*=NR (ns)	Fair
Hewett et al., 2010[122] *	591	8 weeks	Venlafaxine XR 75-150 Bupropion XR 150-300	66 vs. 57 [b] *P*=NR (ns)	56 vs. 45 [b] *P*=NR (ns)	Fair
Cunningham et al., 1994[123]	225	6 weeks	Venlafaxine 75-200 Trazodone 150-400	72 vs. 60 [c] *P*=NR (ns)	NR	Fair

NR = not reported; XR = extended release

*New study added during update.

[a]Response and remission (as defined by authors of the individual studies) are measured on the Hamilton Depression Rating Scale (HAM-D) or indicated otherwise.

[b]Measured on the Montgomery – Asberg Depression Rating Scale (MADRS)

[c]Measured on the Clinical Global Impressions (CGI) scale

Table 14. Response and remission rates, and quality ratings of studies in adults with major depressive disorder

Study	N	Duration	Comparison and Dose (mg/day)	Response[a] (percent) and Significance Level	Remission[a] (percent) and Significance Level	Quality Rating
Weisler et al., 1994[124]	124	6 weeks	Bupropion 225-450 Trazodone 150-400	56 vs. 40 *P*=NR	46 vs. 31 *P*=NR	Fair

mg/d = milligram per day; NR = not reported; ns = not significant; vs. = versus

Note: Drug names not otherwise specified refer to the immediate-release formulations; extended-release formulation are indicated as CR, XL, or XR.

[a]Response and remission (as defined by authors of individual studies) are measured on the Hamilton Depression Rating Scale (HAM-D) or indicated otherwise.

We rated the quality of most studies as fair for internal validity. Most trials (68 percent) were of either short (6 weeks to 8 weeks) or medium (9 weeks to 11 weeks) duration; 32 percent reported followup of 12 weeks or more. Short-term studies may be limited in their ability to account appropriately for response rates and long-term adverse events. In addition, reviewed studies were conducted over a time span of more than 2 decades. Therefore, study populations differ with respect to cotreatment, prior exposures to other second-generation antidepressants, and other factors.

Trial reporting was often incomplete. Most articles did not report the method of randomization or allocation concealment. Last-observation-carried-forward methods (or LOCF analysis, which means that the last observed measurement serves as the substitute for missing values because patients drop out at different time points), were a frequent approach to ITT analysis. Few authors, however, reported the overall number of patients lost to followup from the point of randomization to the end of the trial.

Loss to followup (number of patients randomized who did not proceed to endpoint), a potential source of bias, was a frequent problem for internal validity. The high rates of loss to followup for many studies may be attributable to specific characteristics of a psychiatric outpatient population and a high rate of adverse events in the examined drug classes.

Major Depressive Disorder: Key Points

Ninety-one head-to-head studies (Tables 9 to 14) were included for a total of 40 comparisons (Tables 15 to 17) between the 13 second-generation antidepressants addressed in this report. Of these, only nine trials[116-124] directly compared any non-SSRI second-generation antidepressant with any other non-SSRI agent (Table 18); of these, only three comparisons were evaluated in more than one trial.

Table 15. Number of head-to-head trials of selective serotonin reuptake inhibitors for treating major depressive disorders: SSRIs versus SSRIs

Comparison	Number of Studies
Citalopram vs. Escitalopram	5
Citalopram vs. Fluoxetine	1
Citalopram vs. Fluvoxamine	1
Citalopram vs. Paroxetine	0
Citalopram vs. Sertraline	1
Escitalopram vs. Fluoxetine	2
Escitalopram vs. Fluvoxamine	0
Escitalopram vs. Paroxetine	2
Escitalopram vs. Sertraline	1
Fluoxetine vs. Fluvoxamine	2
Fluoxetine vs. Paroxetine	9
Fluoxetine vs. Sertraline	7
Fluvoxamine vs. Paroxetine	2
Fluvoxamine vs. Sertraline	2
Paroxetine vs. Sertraline	2

Note: The total number of studies might be different from the number of included articles because some studies are published in more than one article.

Table 16. Number of head-to-head trials of selective serotonin reuptake inhibitors for treating major depressive disorders: SSRIs versus SNRIs

Comparison	Number of Studies
Citalopram vs. Duloxetine	0
Escitalopram vs. Duloxetine	3
Fluoxetine vs. Duloxetine	1
Fluvoxamine vs. Duloxetine	0
Paroxetine vs. Duloxetine	3
Sertraline vs. Duloxetine	0
Citalopram vs. Desvenlafaxine	0
Citalopram vs. Mirtazapine	1
Citalopram vs. Venlafaxine	1
Escitalopram vs. Desvenlafaxine	0
Escitalopram vs. Mirtazapine	0
Escitalopram vs. Venlafaxine	2
Fluoxetine vs. Desvenlafaxine	0
Fluoxetine vs. Mirtazapine	3
Fluoxetine vs. Venlafaxine	9
Fluvoxamine vs. Desvenlafaxine	0
Fluvoxamine vs. Mirtazapine	0
Fluvoxamine vs. Venlafaxine	0
Paroxetine vs. Desvenlafaxine	0
Paroxetine vs. Mirtazapine	3
Paroxetine vs. Venlafaxine	3
Sertraline vs. Desvenlafaxine	0
Sertraline vs. Mirtazapine	1
Sertraline vs. Venlafaxine	3

Note: The total number of studies might be different from the number of included articles because some studies are published in more than one article.

Table 17. Number of head-to-head trials of selective serotonin reuptake inhibitors for treating major depressive disorders: SSRIs versus other second-generation antidepressants

Comparison	Number of Studies
Citalopram vs. Bupropion	0
Citalopram vs. Nefazodone	0
Citalopram vs. Trazodone	0
Escitalopram vs. Bupropion	0
Escitalopram vs. Nefazodone	0
Escitalopram vs. Trazodone	0
Fluoxetine vs. Bupropion	2
Fluoxetine vs. Nefazodone	1
Fluoxetine vs. Trazodone	2
Fluvoxamine vs. Bupropion	0
Fluvoxamine vs. Nefazodone	0
Fluvoxamine vs. Trazodone	0
Paroxetine vs. Bupropion	2
Paroxetine vs. Nefazodone	2
Paroxetine vs. Trazodone	1
Sertraline vs. Bupropion	3
Sertraline vs. Nefazodone	1
Sertraline vs. Trazodone	1

Note: The total number of studies might be different from the number of included articles because some studies are published in more than one article.

Table 18. Number of head-to-head trials of selective serotonin norepinephrine reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and other antidepressants for treating major depressive disorders

Comparison	Number of Studies
SSNRIs and SNRIs vs. SNRIs:	
Duloxetine vs. Desvenlafaxine	1
Duloxetine vs. Venlafaxine	0
Duloxetine vs. Mirtazapine	0
Desvenlafaxine vs. Mirtazapine	0
Desvenlafaxine vs. Venlafaxine	0
Mirtazapine vs. Venlafaxine	2
SSNRIs vs. Other Second-Generation Antidepressants:	
Duloxetine vs. Bupropion	0
Duloxetine vs. Nefazadone	0
Duloxetine vs. Trazodone	0
SNRIs vs. Other Second-Generation Antidepressants:	
Desvenlafaxine vs. Bupropion	0
Desvenlafaxine vs. Nefazodone	0
Desvenlafaxine vs. Trazodone	0
Mirtazapine vs. Bupropion	0
Mirtazapine vs. Nefazodone	0
Mirtazapine vs. Trazodone	2
Venlafaxine vs. Bupropion	2
Venlafaxine vs. Nefazadone	0
Venlafaxine vs. Trazodone	1
Other Second-Generation Antidepressants vs. Other Second-Generation Antidepressants:	
Bupropion vs. Nefazadone	0
Bupropion vs. Trazodone	1
Nefazadone vs. Trazodone	0

Note: The total number of studies might be different from the number of included articles because some studies are published in more than one article.

Overall, 37 percent of patients did not achieve a treatment response during 6 weeks to 12 weeks of treatment with second-generation antidepressants; 53 percent did not achieve remission.

Based on our meta-analyses of head-to-head trials and our mixed treatment comparisons, second-generation antidepressants had similar efficacy. Statistically significant differences for some comparisons are likely not to be clinically relevant. The overall strength of evidence for the comparative efficacy was rated moderate.

Direct evidence was considered sufficient to conduct meta-analyses for six drug-drug comparisons:

- Citalopram versus escitalopram (5 published studies[33-36, 38] and 1 FDA review;[37] 1,802 patients): For patients on escitalopram the odds ratio (OR) of response was statistically significantly higher than for patients on citalopram (OR, 1.47; 95% CI, 1.07 to 2.01). The number needed to treat (NNT) to gain 1 additional responder at week 8 with escitalopram compared with citalopram was 13 (95% CI, 8 to 39). These results are based on meta-analyses of head-to-head trials. Results of mixed-treatment comparisons, taking the entire evidence base on second-generation antidepressants into consideration, did not confirm these findings. (OR, 0.51; 95% credible interval [CrI], 0.13 to 4.14).
- Fluoxetine versus paroxetine (5 studies;[49-52, 55, 82] 690 patients): Pooled response rates between fluoxetine and paroxetine were similar (OR, 1.08; 95% CI, 0.79 to 1.47).

- Fluoxetine versus sertraline (4 studies;[55, 56, 58, 60] 940 patients): The odds ratio of response was statistically significantly higher for sertraline than for fluoxetine (OR, 1.42; 95% CI, 1.08 to 1.85). The NNT to gain 1 additional responder at 6 to 12 weeks with sertraline was 13 (95% CI, 8 to 58).
- Fluoxetine versus venlafaxine (six studies;[78, 80-84] 1,197 patients): The odds ratio of response was statistically significantly higher for patients on venlafaxine than on fluoxetine (OR, 1.47; 95% CI, 1.16 to 1.86).
- Paroxetine versus duloxetine (three studies;[87-89] 849 patients). Pooled response rates were similar between patients on paroxetine and duloxetine (OR, 0.84; 95% CI, 0.63 to 1.12).
- Sertraline versus venlafaxine (three studies;[97-99] 470 patients). Pooled response rates were similar between patients on sertraline or venlafaxine (OR, 1.18; 95% CI, 0.81 to 1.72).

Seventeen studies (n=3,960) comparing one second-generation antidepressant with another indicated no differences in health-related quality of life.[33, 57, 58, 60, 66, 67, 72, 76, 77, 82, 94, 99, 103, 106, 118, 125, 126] Quality of life, however, was rarely assessed as a primary outcome measure. The strength of evidence is moderate.

Seven studies, all funded by the maker of mirtazapine, reported that mirtazapine has a statistically significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline (Table 19).[67, 75-77, 90, 92, 96] The pooled NNT to yield one additional responder after 1 or 2 weeks of treatment is seven (95% CI, 5 to 12). This treatment effect was consistent across all studies. The strength of evidence is moderate.

Table 19. Characteristics of trials comparing mirtazapine to SSRIs on onset of action (response rate)

Study	Sample Size	Comparison	Effect Size [a]	*P*-value	Comments
Leinonen et al., 1999[67]	270	Citalopram	Significantly greater reduction of MADRS scores with mirtazapine at day 14 (difference: -2.3)	*P*=0.002	No statistically significant differences in response rates at endpoint
Hong et al., 2003[75]	132	Fluoxetine	At day 28 significantly more responders with mirtazapine (53.3% vs. 39.0%) RRR, 0.23[b] RD: 0.14 [b] NNT: 7 [b]	*P*=NR (ns)	No statistically significant differences in overall response rate at week 6; more responders in the mirtazapine group (58% vs. 51%)
Versiani et al., 2005[76]	299	Fluoxetine	Significantly more responders at day 7 with mirtazapine (data NR) Higher rate of remitters for mirtazapine at days 14 (6.2 % vs. 2.0%), 28 (18.6% vs. 12.9%), and 42 (29.0% vs. 21.1%)	*P*=0.002 *P*=NR (ns)	No statistically significant differences in response and remission at endpoint (day 56)
Wheatley et al., 1998[77]	133	Fluoxetine	Significantly more responders at day 28 with mirtazapine (data NR)	*P*=0.006	Statistically significantly greater decrease of HAM-D scores for mirtazapine at days 21 and 28. No statistically significant differences in response and remission at endpoint (day 42)
Benkert et al., 2000[90]	275	Paroxetine	Significantly more responders (23.2% vs. 8.9%) and remitters (8.8% vs. 2.4%) at day 7 with mirtazapine. RRR, 0.15 [b] RD: 0.14 [b] NNT: 8 [b]	Response: *P*=0.002 Remission: *P*=0.03	More responders and remitters in the mirtazapine group throughout the study. No statistically significant difference at endpoint (response: 58% vs. 53.7%; remission: 41% vs. 35%)
Schatzberg et al., 2002[92]	255	Paroxetine	Significantly more responders at day 14 with mirtazapine (27.8% vs. 13.3%) RRR, 0.17 [b] RD: 0.14 [b] NNT: 7 [b] Significantly greater decrease of HAM-D scores at days 7, 14, 21, and 42 with mirtazapine Median time to response: Mirtazapine: 26 days Paroxetine: 40 days	*P*=0.005 *P*=0.01 (day 7) *P*=0.006 (day 14) *P*=0.024 (day 21) *P*=0.042 Kaplan-Mayer: *P*=0.016	No statistically significant differences in response or remission rates at endpoint
Behnke et al., 2003[96]	346	Sertraline	Significantly higher response rates at days 7, 10, and 14 with mirtazapine (data NR)	*P*<0.05 (day 7) *P*<0.01 (day 10) *P*<0.05 (day 14)	No statistically significant differences in response and remission at endpoint (day 56)

HAM-D = Hamilton Rating Scale for Depression; NNT = number needed to treat; NR = not reported; ns = not significant; RD = risk difference; RRR = relative risk reduction

Note: Drug names not otherwise specified refer to the immediate-release formulations, extended-release formulation are indicated as CR, XL, or XR.

[a]Response and remission are measured on the Hamilton Depression Rating Scale (HAM-D) or indicated otherwise.

[b]Estimates were calculated by authors of report.

Major Depressive Disorder: Detailed Analysis

Head-to-Head Evidence: SSRIs Versus SSRIs

Citalopram Versus Escitalopram

Citalopram and escitalopram are produced by the same manufacturer, which funded all available studies. Generic brands of citalopram are available in the United States; escitalopram is still under patent protection.

Five published trials[33-36, 38] and one unpublished trial[37] compared the efficacy of citalopram and escitalopram (Table 20). Five studies were conducted over 6 to 8 weeks[33, 35-38] and one over 24 weeks.[34] One study was a flexible dose trial.[35] Table 20 summarizes study characteristics and differences in effect sizes of studies comparing citalopram with escitalopram.

Overall, results of individual studies favored escitalopram over citalopram. In four studies, differences in response rates reached statistical significance at 8 weeks.[34-36, 38] The flexible dose trial was a European-Canadian study that compared efficacy and harms of citalopram (20-40 mg/day), escitalopram (10-20 mg/day) in 315 depressed outpatients attending primary care centers.[35] ITT results showed that the escitalopram group had significantly more patients responding (63.7 percent vs. 52.6 percent; P=0.021) and achieving remission (52.1 percent vs. 42.8 percent; P=0.036) than the citalopram group. Escitalopram was numerically better at all time points on three scales (MADRS, Clinical Global Impressions Improvement Scale [CGI-I], Clinical Global Impressions Severity Scale [CGI-S]). The study did not assess health outcomes.

The 24-week study was a fixed-dose trial (escitalopram 10 mg/day, citalopram 20 mg/day) of 357 European primary care patients over 24 weeks.[34] Escitalopram patients had significantly higher response rates at week 8 (63 percent vs. 55 percent; P<0.05) but not at week 24 (80 percent vs. 78 percent; P=NR). Escitalopram had significantly lower CGI-S scores (1.75 vs. 2.00) and significantly fewer withdrawals (12.7 percent vs. 22.4 percent) than citalopram at week 24.

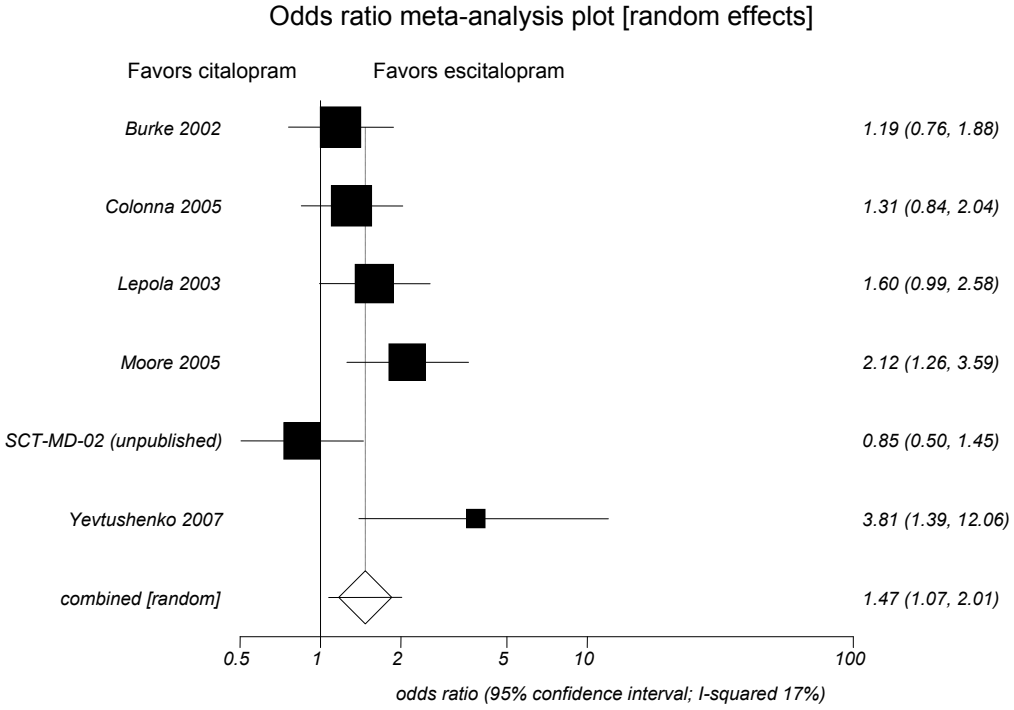
We conducted two meta-analyses of these studies comparing the effects of citalopram with those of escitalopram on MADRS scores at weeks 6-8. The outcome of the first meta-analysis was the odds ratio of being a responder on the MADRS scale after 6–8 weeks of treatment (Figure 4). In addition to the five published trials, we included data from one unpublished study from the FDA Center for Drug Evaluation and Research (CDER) database.[37] A "response" was defined as an improvement of 50 percent or more on the MADRS. Pooled results included 1,802 patients and yielded a statistically significant additional treatment effect for escitalopram. The odds ratio that a patient would respond was 1.47 (95% CI, 1.07 to 2.01) for escitalopram relative to citalopram. The NNT to gain one additional responder based on the pooled risk difference is 13 (95% CI, 8 to 39). As mentioned above, all available head-to-head trials have been funded by the manufacturer of citalopram and escitalopram. Publication bias, therefore, is conceivable.

Table 20. Characteristics and effect sizes of studies comparing citalopram with escitalopram

Study	N	Duration	Dosage CIT vs ESC mg/day	Response[a] (percent)	Remission[a] (percent)	Quality Rating
Burke et al., 2002[33]	369	8 weeks	40 vs. 20	46 vs. 51 *P*=NR (ns)	NR	Fair
			40 vs. 10	46 vs. 50 *P*=NR (ns)	NR	
Colonna et al., 2005[34]	357	8 weeks	20 vs. 10	55 vs. 63 *P*<0.05	NR	Fair
		24 weeks	20 vs. 10	78 vs. 80 *P*=NR (ns)	NR	
Lepola et al., 2003[35]	315	8 weeks	20-40 vs. 10-20	53 vs. 64 *P*=0.021	43 vs. 52 *P*=0.036	Fair
Moore et al., 2005[36]	294	8 weeks	40 vs. 20	61 vs. 76 *P*=0.008	43 vs. 54 *P*=0.04	Fair
Unpublished Study SCT MD-02[37]	248	8 weeks	20-40 vs. 10-20	51 vs. 46 *P*=NR	NR	Fair
Yevtushenko et al., 2007[38]*	330	6 weeks	10 vs. 20	44 vs. 95 *P*<0.001	26 vs. 90 *P*<0.001	Fair
			20 vs. 20	83 vs. 95 *P*<0.001	51 vs. 90 *P*<0.001	

CIT = citalopram; ESC = escitalopram; NR = not reported; ns = not significant
*New study added during update.
[a]Measured on the Montgomery-Asberg Depression Rating Scale (MADRS).

Figure 4. Odds ratio meta-analysis of MADRS response rates comparing citalopram with escitalopram



Results of mixed treatment comparisons of good or fair studies, taking comparisons of each drug with other second-generation antidepressants into consideration, revealed no statistically significant difference of response rates on HAM-D between the two medications (OR, 0.51; 95%

CrI, 0.13 to 4.14). Although not statistically significant, the point estimate of MTC results was in favor of citalopram over escitalopram.

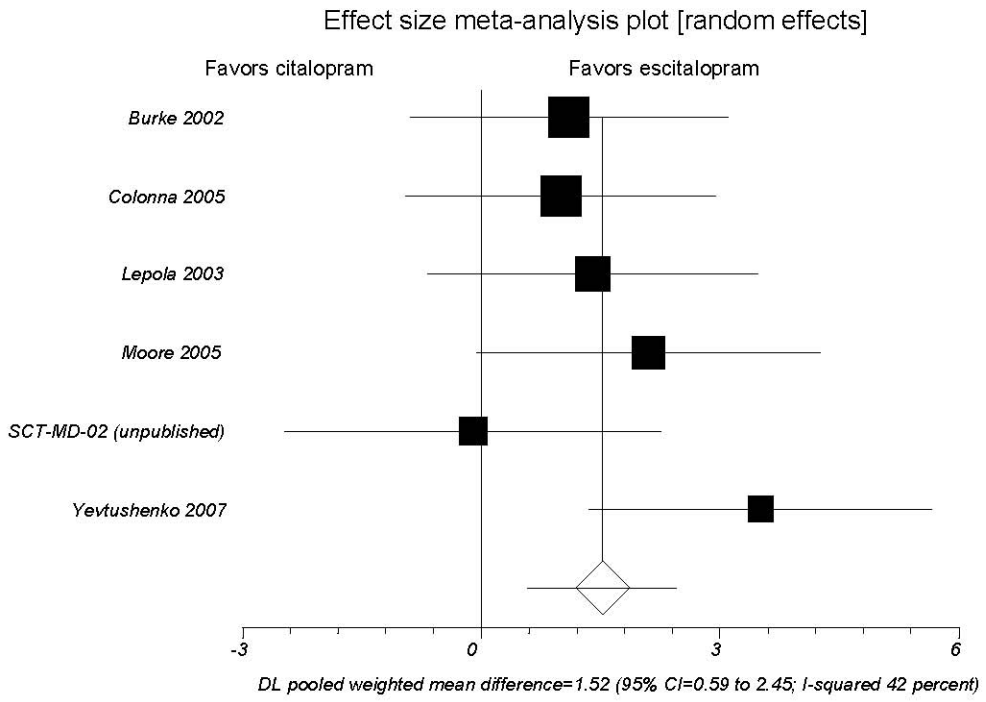
In a sensitivity analysis we extended the evidence base to all available studies (i.e. including studies that were rated poor because of high risk of bias). Results increased the precision of estimates and yielded similar response rates between citalopram and escitalopram (OR, 1.04; 95% CrI, 0.57 to 2.12).

The second meta-analysis was an effect size meta-analysis of all six studies (1,802 patients) assessing the pooled difference of points on the MADRS (Figure 5). The weighted mean difference (WMD) presented an additional treatment effect of a 1.52 point reduction (95% CI, 0.59 to 2.45) for escitalopram compared with citalopram.

Citalopram Versus Fluoxetine

In a French trial, 357 outpatients with MDD attending general practices were randomly assigned to citalopram (20 mg/day) or fluoxetine (20 mg/day) over 8 weeks.[39] Citalopram had a faster onset of efficacy than fluoxetine; significantly more patients were rated as responding (35 percent vs. 24 percent; *P*=0.048) or completely recovered (27 percent vs. 16 percent; *P*=0.034) on the MADRS after 2 weeks. At 8 weeks, however, response rates for the citalopram and the fluoxetine group were similar (78 percent vs. 76 percent; *P*=NR).

Figure 5. Effect size meta-analysis comparing citalopram with escitalopram on the MADRS



Citalopram Versus Fluvoxamine

A Dutch study (n=217) did not find any differences in efficacy (HAM-D, CGI, Zung self-rating depression scale at 6 weeks) between citalopram (20-40 mg/day) and fluvoxamine (100–200 mg/day).[40] Remission rates did not differ significantly between citalopram and fluvoxamine treatments (14 percent vs. 8 percent; *P*=NR).

Citalopram Versus Sertraline

A Swedish study rated good quality assessed the effectiveness of citalopram (20-60 mg/day) and sertraline (50-150 mg/day) in 400 patients in general practice during 24 weeks of treatment.[41] The majority of patients suffered recurrent depression (citalopram, 65 percent; sertraline, 56 percent) and used other medications for medical illnesses (citalopram, 44.5 percent; sertraline, 55 percent). The investigators found no significant differences between treatment groups in any outcome measures at any point in time (MADRS, CGI-S, CGI-I). Also, subgroup analyses of patients with recurrent depression or single episode depression did not report any differences in effectiveness between drugs. Response rates (defined as a 50 percent or greater in MADRS from baseline, CGI-S score of 1-3 and CGI-I score rated "much" or "very much" improved) were similar at week 24 (citalopram, 81.0 percent; sertraline, 75.5 percent; *P*=NR). This study was one of only a few trials not funded by the pharmaceutical industry; it can be considered an effectiveness trial.

Escitalopram Versus Fluoxetine

Two RCTs assessed the comparative efficacy of escitalopram and fluoxetine.[42, 43] One study (n=240) was conducted in a Chinese population[43] and the other (n=518) in European patients older than 65 years.[42] Both trials had a fixed-dose design (escitalopram 10 mg/day, fluoxetine 20 mg/day) and lasted 8 weeks.

In both studies, patients showed similar treatment effects. The Chinese study found no significant difference between groups in HAM-D response (80 percent vs. 79 percent, *P*>0.05) or remission (46 percent vs. 55 percent, *P*=NR) rates at week 8. MADRS response and remission rates were similar.[43]

In the European trial, neither escitalopram nor fluoxetine achieved statistically significantly different MADRS response (46 percent vs. 37 percent) or remission rates (40 percent vs. 30 percent) compared with placebo (response: 47 percent, remission: 42 percent). We discuss this study in more detail for KQ 5 (subgroups).[42]

Escitalopram Versus Paroxetine

Two RCTs provided mixed results about the comparative efficacy of escitalopram and paroxetine.[31, 44] Both studies were funded by the producer of escitalopram.

A double-blind, flexible-dose RCT compared the efficacy of escitalopram (10-20 mg/day) and paroxetine (20–40 mg/day) during the acute and maintenance phases of the treatment of 325 patients with MDD.[44] After 8 weeks both groups achieved similar MADRS response (67.9 vs. 71.2 percent and remission [56 vs. 62 percent]) rates. Similarly, no differences in response and remission could be observed during the maintenance period (8–27 weeks).

The second study was a fixed-dose RCT of 459 patients undergoing treatment with escitalopram 20 mg/day or paroxetine 40 mg/day.[31] After 24 weeks of treatment, patients on escitalopram achieved higher MADRS remission rates than patients treated with paroxetine (75 percent vs. 67 percent; P<0.05). No statistically significant differences in response rates could be detected (82.0 percent vs. 76.7 percent), however.

Escitalopram Versus Sertraline

An 8-week, multicenter study randomized 215 patients to fixed-dose escitalopram (10 mg/day) or flexible-dose sertraline (50-200 mg/day).[45]At study endpoint no substantial differences in efficacy between patients in both treatment arms could be detected. Overall, 72

percent of patients on escitalopram and 69 percent of patients treated with sertraline achieved a HAM-D response. Remission rates were also similar between treatment groups (49 percent vs. 53 percent; *P*=NR).

Fluoxetine Versus Fluvoxamine

Two studies evaluated the comparative efficacy and safety of fluoxetine and fluvoxamine in 284 outpatients with MDD.[46, 47] A 7-week flexible-dose study (fluoxetine: 20-80 mg/day; fluvoxamine 100-150 mg/day) did not identify any statistically or clinically significant differences in efficacy between the two treatment groups (HAM-D, HAM-A, CGI-S, Raskin-Covi Scale, Hopkins Symptoms Checklist [HSCL-D20]).[47] Both treatment regimens significantly improved scores on assessment scales over 7 weeks.

In a 6-week fixed-dose European trial (fluoxetine 20 mg/day; fluvoxamine 100 mg/day) in 184 outpatients with MDD,[46] results are consistent with those of the flexible-dose study; scores on the primary outcome measure (HAM-D) were not significantly different at any time. At endpoint, the drugs were equally effective for secondary outcome measures such as suicidal ideation, sleep, anxiety, and severity of illness (CGI, Clinical Anxiety Scale [CAS], the Irritability, Depression, and Anxiety Scale [IDAS], Beck's Scale for Suicide Ideation [Beck's SSI]). Fluvoxamine had significantly more responders on the CGI-S (29 percent vs. 16 percent; $P<0.05$) and a greater reduction of CGI-S scores ($P<0.05$) at week 2 but not at weeks 4 or 6.

Fluoxetine Versus Paroxetine

Nine studies compared fluoxetine with paroxetine.[48-55] Two trials were conducted in populations older than 60 years of age,[48, 53] which we discuss for KQ 5 (subgroups).

Most studies lasted from 6 to 12 weeks. Efficacy measures included HAM-D, HAM-A, MADRS, CGI-S, CGI-I, Covi Anxiety Scale, and others. Overall, these studies did not indicate substantial differences in outcome measures between fluoxetine and paroxetine. The largest study was a Canadian RCT (n=203) with a study duration of 12 weeks.[49] At study endpoint, fluoxetine (20-80 mg/day) and paroxetine (20-50 mg/day) presented similar response (68 percent vs. 67 percent; $P=0.93$) and remission rates (59 percent vs. 58 percent; $P=0.84$).

One study was conducted in an inpatient population.[54] Results were consistent with findings of the other studies.

We conducted a meta-analysis of five studies using HAM-D scores at the end of followup;[49-52, 55] i.e., we excluded the three studies that did not report data on HAM-D or had been conducted in elderly populations.[48, 53, 54, 82] We defined "response" as an improvement of 50 percent or more on the HAM-D. The meta-analysis included 690 patients. The pooled estimate of the random effects model, presented in Figure 6, indicates that fluoxetine and paroxetine do not differ significantly in efficacy (OR, 1.08; 95% CI, 0.79 to 1.47). An effect size meta-analysis (Figure 7) also did not detect a statistically significant difference between fluoxetine and paroxetine (0.52; 95% CI, -0.42 to +1.47).

Four studies did not detect differences between fluoxetine and paroxetine in improvement of anxiety in patients with depression (HAM-A, Covi Anxiety Scale).[49, 51, 52, 55]

Figure 6. Odds ratio meta-analysis of response rates comparing fluoxetine with paroxetine on the HAM-D

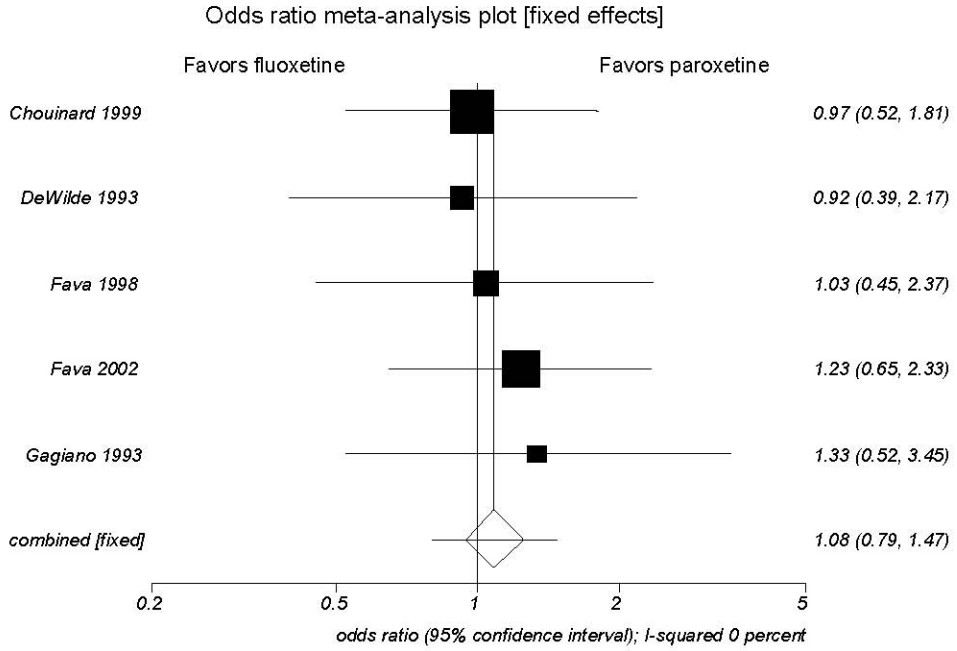
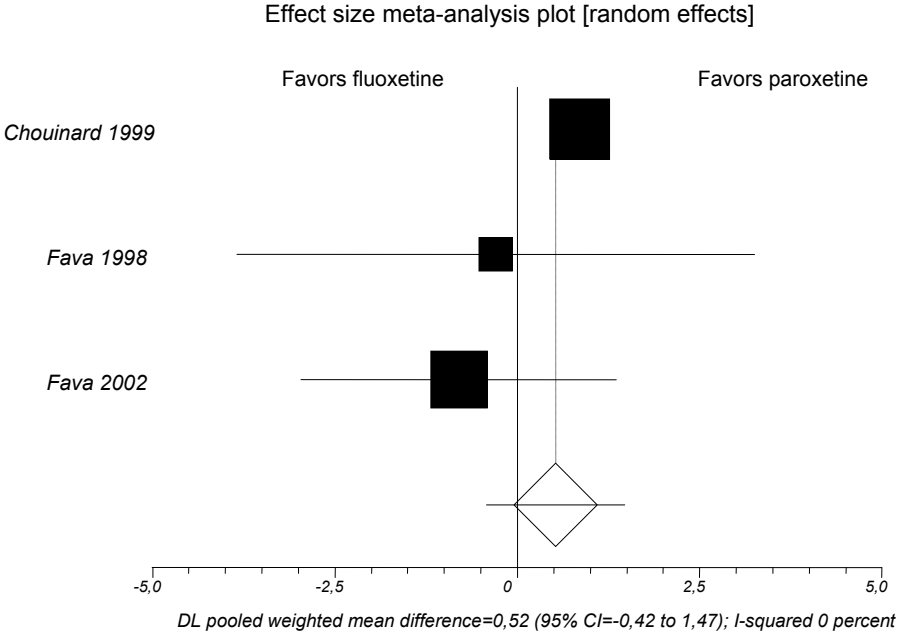


Figure 7. Effect size meta-analysis comparing fluoxetine with paroxetine on the HAM-D



Fluoxetine Versus Sertraline

Seven studies compared fluoxetine with sertraline.[55-61, 127] The best evidence consisted of one effectiveness[60] and one efficacy trial[57] with long periods of followup.

Two multicenter trials in France comparing fluoxetine (20-60 mg/day) and sertraline (50–150 mg/day) were conducted in office settings (private psychiatrists and general physicians [GPs]).[57, 60] The psychiatrist study[60] randomized 238 patients for 24 weeks; the GP study[57] randomized 242 patients for nearly 26 weeks (180 days). The majority of patients had concomitant medical conditions. Both studies assessed quality of life as a secondary outcome measure (Sickness Impact Profile [SIP], Functional Status Questionnaire [FSQ]). Exclusion criteria were less stringent in the GP trial than the psychiatrist trial. Loss to followup was 4.5 percent in the GP trial and 29.8 percent in the psychiatrist trial. In the GP trial, researchers conducted outcome assessments only at day 120 and day 180, but patients could choose to consult the physician at any time. ITT analyses in both studies did not reveal any statistically significant differences in any primary (MADRS, HAM-D, CGI) or secondary (Covi Anxiety Scale, HAD, SIP, Leeds Sleep Evaluation) efficacy measures or in the incidence of adverse events.

The ARTIST (A Randomized Trial Investigating SSRI Treatment) trial was an open-label RCT designed as an effectiveness study and carried out in primary care physician settings over 9 months.[128] This study did not meet our eligibility criteria because of lack of blinding; we present it because it is one of only a few effectiveness trials. This study enrolled 601 patients at 76 sites. Initial diagnosis for enrollment was not based on diagnostic criteria but rather on the judgment of the treating physician. Criteria-based evaluation classified 74 percent of patients as having MDD, 18 percent dysthymia, and 8 percent minor depression. Patients' treatments could be switched among study drugs or to other antidepressive medications as needed. ITT analysis maintained the original randomization. Outcome measures assessing changes in depression and health-related quality of life measures (work, social, and physical functioning, concentration and memory, and sexual functioning) were administered over the telephone by a blinded third party. Range of dosage and loss to followup were incompletely reported.

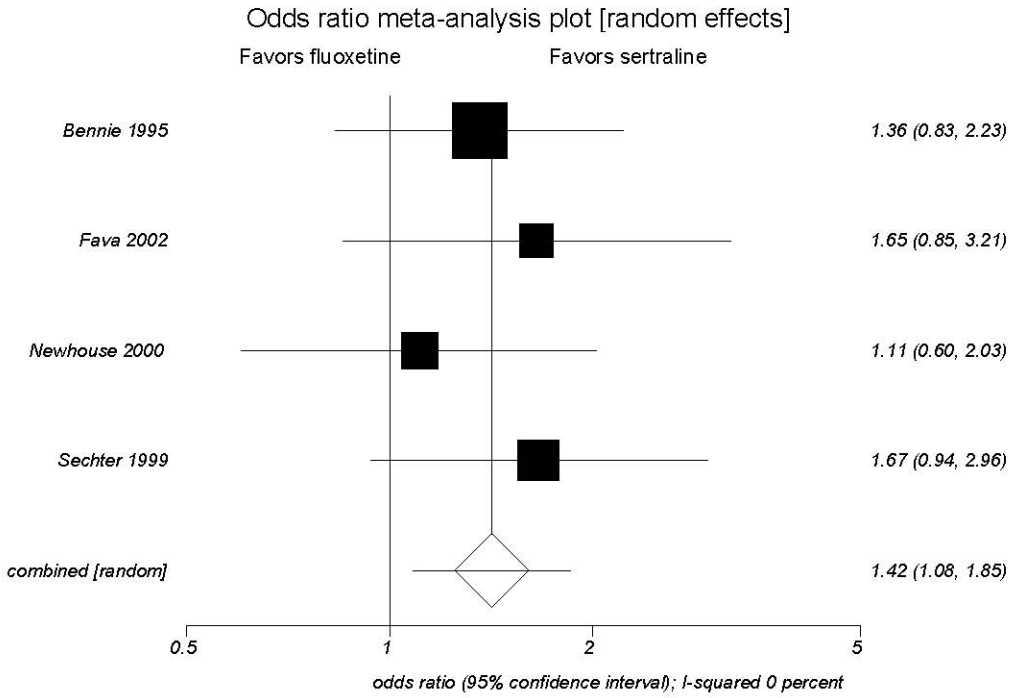
Results of the ARTIST trial did not reveal any significant differences among drugs in any outcome measures at either 3 or 9 months.[128] Compared with baseline measures, all treatment groups significantly improved during the study. Subgroup analyses did not show different effectiveness for patients with MDD or for those older than 60 years.

Four additional trials did not find any significant differences in primary outcome measures (HAM-D, MADRS, CGI-S).[55, 56, 58, 59, 61] Studies lasted from 6 weeks to 16 weeks.

One study was conducted in 236 participants older than 60 years.[58] and will be discussed in more detail in KQ5 (subgroups). Briefly, in this RCT, outcome measures also included quality of life (Q-LES-Q) and cognitive assessments (Shopping List Task [SLT], MMSE, Digital Symbol Substitution Test). Results on these health outcome measures were similar for both drugs.

We conducted two meta-analyses of four studies[55, 56, 58, 60] comparing the effects of fluoxetine and sertraline at study endpoint. The outcome of the first meta-analysis was the odds ratio of being a responder on the HAM-D (improvement of 50 percent or more) at study endpoint (Figure 8).

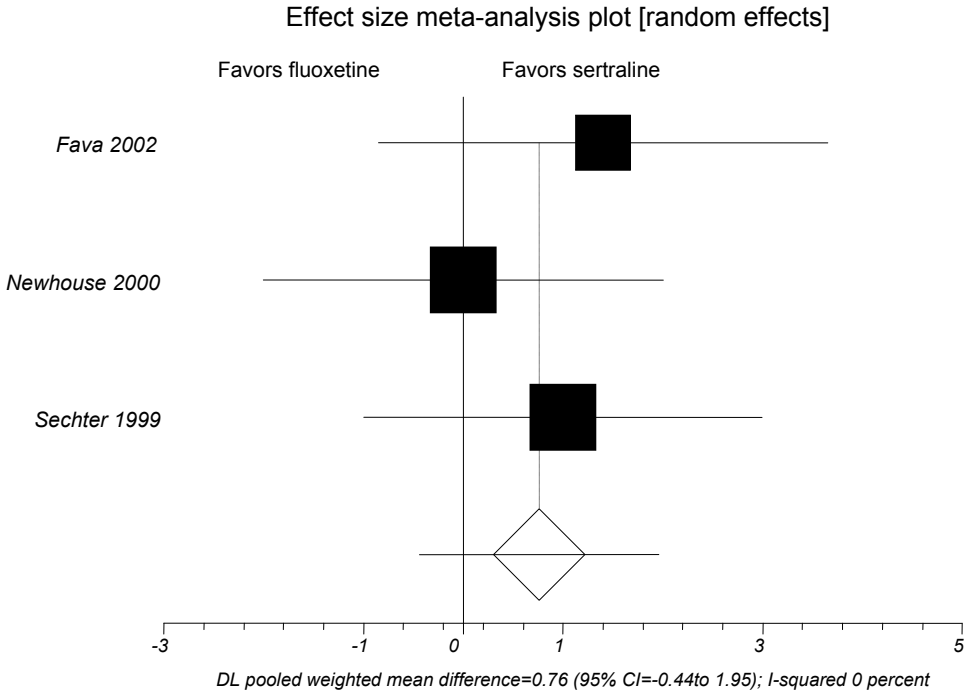
Figure 8. Odds ratio meta-analysis of response rates comparing fluoxetine with sertraline on the HAM-D



Pooled results including 940 patients yielded a statistically significant additional treatment effect for sertraline (OR, 1.42; 95% CI, 1.08 to 1.85). Both random effects and fixed effects models presented similar, statistically significant results. The NNT to gain one additional responder based on the pooled risk difference was 13 (95% CI, 8 to 58).

The second, effect size meta-analysis assessed the pooled difference of points on the HAM-D scale (Figure 9). Because of lack of reported data, we limited the analysis to three studies.[55, 58, 60] We found no statistically significant difference in points on the HAM-D scale between fluoxetine and sertraline. Relative to fluoxetine, sertraline had an additional treatment effect of a 0.76 point reduction in HAM-D (95% CI, -0.44 to +1.95).

Figure 9. Effect size meta-analysis comparing fluoxetine with sertraline on the HAM-D



Fluvoxamine Versus Paroxetine

Two RCTs, one flexible-dose[62] and one fixed-dose,[63] compared the efficacy and safety of fluvoxamine and paroxetine. The flexible-dose trial was a 7-week RCT comparing the efficacy and safety of fluvoxamine (50–150 mg/day) and paroxetine (20–50 mg/day) in 60 outpatients with MDD.[62] Loss to followup was 30 percent. Results presented no statistically significant differences on HAM-D, HAM-A, CGI, and HSCL-56. The fixed-dose trial enrolled 105 perimenopausal women with MDD and provided consistent findings with the flexible-dose trial.[63] Neither trial assessed response or remission rates.

Fluvoxamine Versus Sertraline

Two 7-week trials compared the depression scores and harms of fluvoxamine (50–150 mg/day) and sertraline (50–200 mg/day).[64, 65] One trial was conducted in a mixed (84 percent unipolar, 16 percent bipolar depression) inpatient population.[65] In both trials, efficacy did not differ significantly between treatment groups. Both regimens led to significant improvements in depression scores from baseline (HAM-D, CGI).

Paroxetine Versus Sertraline

Two studies assessed the comparative efficacy of paroxetine and sertraline.[55, 66] A Swedish RCT compared paroxetine (20–40 mg/day) with sertraline (50–150 mg/day) in a 24-week study involving 353 patients.[66] Outcome measures included MADRS, CGI, and Battelle Quality of Life Measure (BQOL). LOCF analysis yielded no significant differences in primary outcome measures (MADRS, CGI) at any point in time. Clinically significant improvement occurred over baseline among all quality of life factors. Treatment groups did not differ significantly on BQOL factors. Likewise, the second study yielded similar response rates between paroxetine and sertraline.[55]

Head-to-Head Evidence: SSRIs Versus SSNRIs and SNRIs

Citalopram Versus Mirtazapine

An 8-week European study (n=270) determined the comparative efficacy of citalopram (20-60 mg/day) and mirtazapine (15–60 mg/day) on depression and anxiety symptoms in a mixed inpatient and outpatient population.[67] At study endpoint, results on efficacy measures (MADRS, HAM-A, CGI-S, Leeds Sleep Evaluation Questionnaire) and a quality of life measure (Q-LES-Q) were similar between treatment groups. Response rates on MADRS reached 88 percent in the citalopram and 85 percent in the mirtazapine group (P=0.54). Mirtazapine, however, had a faster onset of action with significantly greater response rates on MADRS, HAM-A, CGI-S, and Q-LES-Q at day 14. Overall discontinuation rates because of adverse events did not differ significantly between the two groups.

Citalopram Versus Venlafaxine

A 6-month European study compared citalopram (10–30 mg/day) with venlafaxine XR (75–150 mg/day) for the treatment of depression in elderly outpatients (mean age 73 years) found no statistical differences in any outcome measures (MADRS, CGI-S, CGI-I) at study endpoint.[68] We discuss these results in more detail for KQ 5 (subgroups).

Escitalopram Versus Duloxetine

Three RCTs compared the efficacy and safety of escitalopram and duloxetine in 1,257 patients with MDD.[69-71] Two of these trials were funded by the maker of escitalopram,[69, 71] the third by the manufacturer of duloxetine.[70] Two studies compared fixed-dose regimens of escitalopram (10 and 20 mg/day) and duloxetine (60 mg/day).[70, 71] The third trial assessed the efficacy and safety of a flexible dose escitalopram (10–20 mg/day) treatment with a fixed dose regimen of duloxetine (60 mg/day).[69] Overall, results rendered similar response and remission rates between patients on escitalopram and duloxetine.

Escitalopram Versus Venlafaxine

Two 8-week trials assessed the comparative effectiveness of escitalopram and venlafaxine XR.[72, 73] One assigned 293 patients to escitalopram (10–20 mg/day) or venlafaxine XR (75–150 mg/day).[73] The groups did not differ significantly in response (escitalopram, 77.4 percent; venlafaxine XR, 79.6 percent; P=NR) or remission (escitalopram, 69.9 percent; venlafaxine XR, 69.7 percent; P=NR). Survival analysis of the ITT population indicated that escitalopram-treated patients achieved sustained remission 6.6 days earlier than patients on venlafaxine XR (P<0.01).

The second trial also reported that no statistically significant differences were apparent between escitalopram (20 mg/day) and venlafaxine XR (225 mg/day) in response (61 percent vs. 48 percent; P=NR) and remission rates.[72]

Fluoxetine Versus Duloxetine

An 8-week RCT assigned 173 patients to duloxetine (40–120 mg/day), fluoxetine (20 mg/day), or placebo.[74] Results revealed no statistically significant differences between fluoxetine and duloxetine in response rates (45 percent vs. 49 percent; P=0.39). Remission rates at study endpoint favored duloxetine but did not reach statistical significance (43 percent vs. 30 percent; P=0.82). However, the fixed-dose design for fluoxetine but not for duloxetine introduces equivalency issues and reduces the validity of this direct comparison.

Fluoxetine Versus Mirtazapine

Three trials compared the efficacy of fluoxetine and mirtazapine.[75-77] Two studies enrolled either exclusively[76] or a large percentage[77] of inpatients and outpatients with severe depression (HAM-D>25). In both of these trials, treatments did not differ on any efficacy measures (MADRS, HAM-D, CGI) or quality of life measures (Q-LES-Q) at endpoint (6 and 8 weeks). Both trials reported a faster onset of mirtazapine but no differences in remission rates at endpoint. These findings are consistent with results from the third study, which was conducted in Taiwanese outpatients with moderate depression.[75]

In all three studies, patients treated with mirtazapine gained weight; by contrast, those treated with fluoxetine lost weight. In two studies, the differences reached statistical significance.[76, 77] In one trial, 10.3 percent of patients in the mirtazapine group experienced an increase in body weight of more than 7 percent from baseline as did 0.9 percent of patients on fluoxetine.[76]

Fluoxetine Versus Venlafaxine

Nine studies compared the efficacy of fluoxetine to venlafaxine.[78-86] One study was conducted in inpatient populations.[85] One trial was conducted in outpatients with concomitant anxiety (minimum score of 8 on Covi Anxiety Scale).[80] The studies lasted from 6 weeks to 12 weeks. Except in one study,[86] results consistently presented greater efficacy of venlafaxine than fluoxetine; in three studies, this difference reached statistical significance.[78, 80, 81]

We conducted a meta-analysis of seven studies comparing fluoxetine with venlafaxine,[78, 80-85] all supported by the manufacturer of venlafaxine. The main outcome measure was the odds ratio of being a responder on the HAM-D scale at study endpoint.

Results (Figure 10), based on 1,197 patients, reflect higher response rates of venlafaxine than fluoxetine (OR, 1.47; 95% CI, 1.16 to 1.86). A meta-analysis of changes on the HAM-D rendered a significantly greater reduction of points for venlafaxine than fluoxetine.

These findings are consistent with results of a meta-analysis reported by Smith et al.[129] Compared with fluoxetine, venlafaxine yielded a modest but significantly greater standardized effect size (-0.14; 95% CI, -0.22 to -0.06) and a significantly greater odds ratio for remission (OR, 1.42; 95% CI, 1.17 to 1.73). The odds ratio for response was numerically greater for venlafaxine but not statistically significant (OR, 1.17; 95% CI, 0.99 to 1.38).

Paroxetine Versus Duloxetine

Three 8-week, fixed-dose trials assessed the comparative efficacy of duloxetine (60, 80, and 120 mg/day) and paroxetine (20 mg/day).[87-89] In all three trials, efficacy outcomes were similar for duloxetine and paroxetine regimens, although dosages were not always equivalent. In the largest study (n=478), 60 percent of patients on duloxetine (60 mg/day) achieved response and 49 percent remission as did 65 percent and 50 percent, respectively, of patients on paroxetine.[89]

We pooled response rates on the HAM-D from low-dose paroxetine (20 mg/day) and low-dose duloxetine arms (60 and 80 mg/day) (Figure 11). Results indicate that the two drugs have similar efficacy (OR, 0.84; 95% CI, 0.63 to 1.12). Data were too heterogeneous to achieve a meaningful pooled estimate of the mean change of scores on the HAM-D (I^2, 99 percent).

Figure 10. Odds ratio meta-analysis of response rates comparing fluoxetine with venlafaxine on the HAM-D

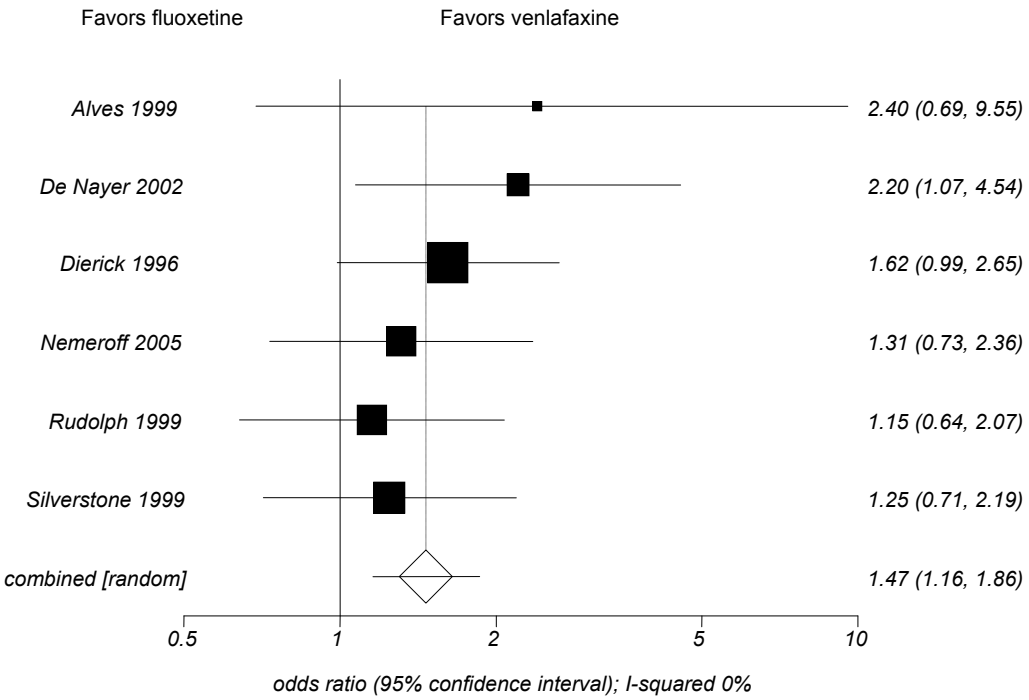
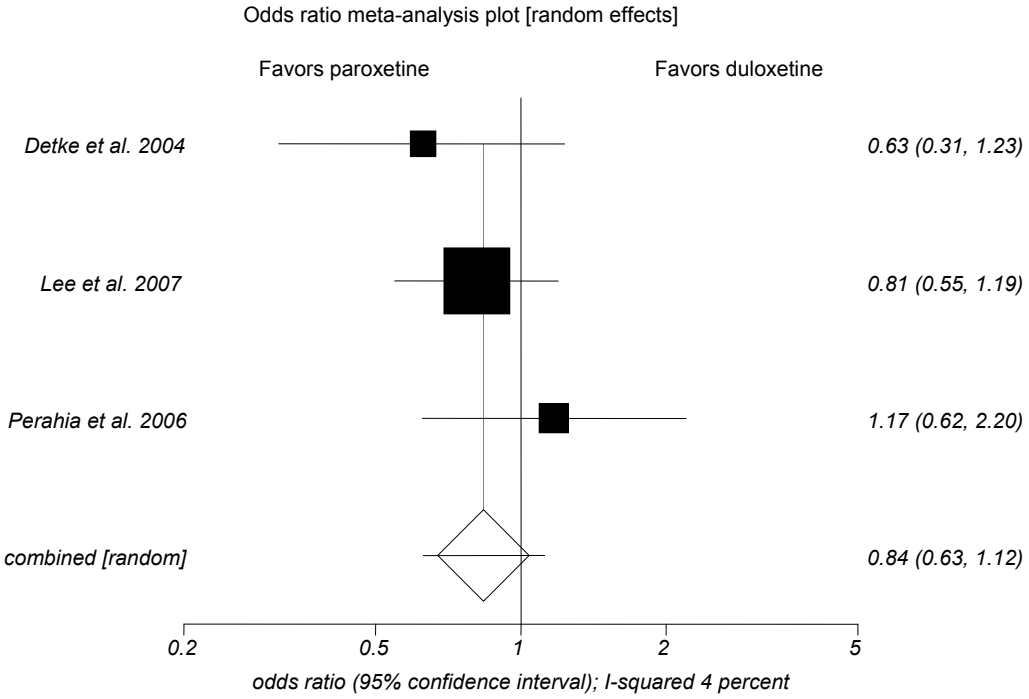


Figure 11. Odds ratio meta-analysis of response rates comparing paroxetine with duloxetine on the HAM-D



Paroxetine Versus Mirtazapine

Three trials assessed the efficacy of paroxetine (20–40 mg/day) and mirtazapine (15–45 mg/day).[90-92] One study among depressed patients 65 years or older[92] is discussed in more detail for KQ 5.

In all three trials, paroxetine and mirtazapine were equally effective in reducing HAM-D and MADRS scores at the endpoint. Mirtazapine led to a faster response in two trials.[90, 92] For example, in a German study, 23.2 percent of mirtazapine-treated patients and 8.9 percent of paroxetine-treated patients responded to the treatment at week 1 ($P<0.002$).[90] A Kaplan-Meier analysis in the other trial also showed a significantly faster time to response for mirtazapine than for paroxetine (mean 26 days vs. mean 40 days; $P=0.016$).[92] The NNT to yield one additional patient responding with mirtazapine at weeks 1 or 2 is seven. No significant difference in response rates on the CGI scale was noted. All three trials reported weight gain in significantly more patients treated with mirtazapine than with paroxetine ($P<0.05$).

Paroxetine Versus Venlafaxine

Three studies compared paroxetine with venlafaxine.[93-95] A Spanish study compared the effects of paroxetine (20-40 mg/day) with venlafaxine (75–150 mg/day) in outpatients (n=84) with either MDD or dysthymia over 24 weeks.[93] The majority of patients (88 percent) were female. The percentage of dysthymic patients was not reported, and the authors did not differentiate between dysthymia and mild or moderate depression. Loss to followup was 32 percent, with a substantially higher loss to followup in the venlafaxine group (39 percent vs. 26 percent). Response and remission rates favored venlafaxine at all time points. The difference in remission rates reached statistical significance at week 12 (57 percent vs. 33 percent; $P=0.011$). ITT analysis yielded no significant differences between treatment groups on any primary outcome measures (HAM-D, MADRS, CGI) at 24 weeks.

A British fixed-dose trial lasting 12 weeks randomized 361 mainly moderately ill patients (based on CGI severity score) treated in 43 general practices to either paroxetine (20 mg/day) or venlafaxine XR (75 mg/day).[94] Study groups did not differ significantly in efficacy measures, quality of life scores, or adverse events.

Similarly, a trial comparing extended-release formulations of paroxetine and venlafaxine (paroxetine CR 75 mg/day; venlafaxine XR 375 mg/day) yielded similar treatment effects between the two medications.[95]

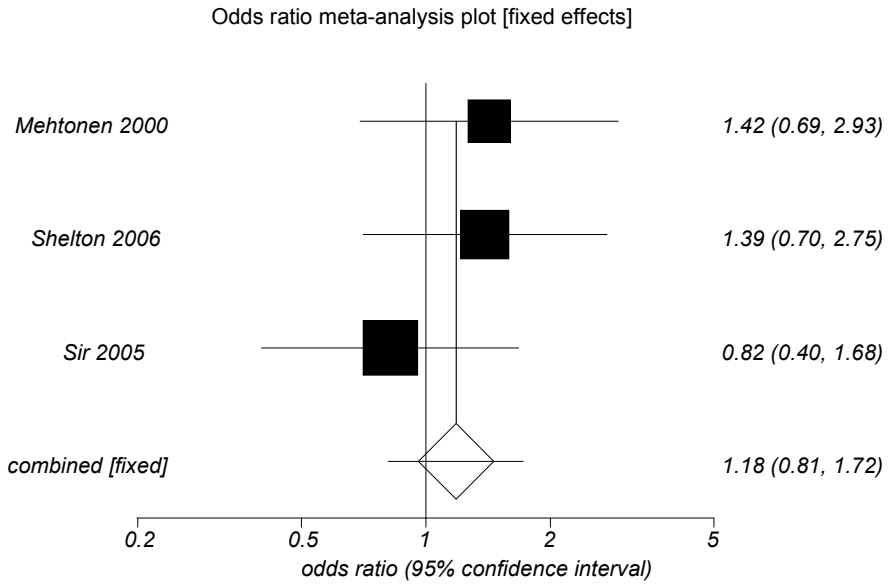
Sertraline Versus Mirtazapine

One European study examined the onset of efficacy of sertraline (50-150 mg/day) compared with that of mirtazapine (30-45 mg/day) in 346 outpatients.[96] Onset of action was faster for the mirtazapine group than for the sertraline group on HAM-D and MADRS. Significantly more patients achieved response and remission on mirtazapine than on sertraline after the first 2 weeks (data not reported in the article; $P<0.05$) No significant difference could be detected at endpoint. Subgroup analysis in patients with severe depression (HAM-D>25) led to similar findings. A significantly higher number of patients withdrew because of adverse events in the mirtazapine group (12.5 percent vs. 3 percent; P=NR), and significantly more patients on mirtazapine than on sertraline had an increase in body weight of more than 7 percent (14.6 percent vs. 0 percent; $P=0.01$).

Sertraline Versus Venlafaxine

Three 8-week trials, two rated good[97, 99] and one rated fair,[98] compared sertraline with venlafaxine or venlafaxine XR;[98] all three studies were funded by the makers of venlafaxine. In a Scandinavian study (n=147), venlafaxine (75–150 mg/day) was significantly more efficacious than sertraline (50–100 mg/day) with respect to remissions achieved on the HAM-D (68 percent vs. 45 percent; P=0.008).[97] We pooled response rates of these three studies on the HAM-D rating scale for 470 patients (Figure 12); fluoxetine and venlafaxine had similar treatment effects (OR, 1.18; 95% CI, 0.81 to 1.72).

Figure 12. Odds ratio meta-analysis of response rates comparing sertraline with venlafaxine on the HAM-D



Head-to-Head Evidence: SSRIs Versus Other Second-Generation Antidepressants

Fluoxetine Versus Bupropion

Two trials compared the efficacy and harms of fluoxetine and bupropion.[100, 101] Both trials reported similar response rates at endpoint; efficacy measures (changes of HAM-D, HAM-A, CGI-S, CGI-I scores) did not differ significantly. In the larger trial (n=456), bupropion SR (150-400 mg/day) treatment yielded a higher rate than fluoxetine (20-60 mg/day) of patients achieving remission, but this difference was not significant (47 percent vs. 40 percent; P=NR).[100] From week 1 until endpoint (week 8), significantly more patients on fluoxetine than on bupropion SR were dissatisfied with their overall sexual function (data not reported; P<0.05).

Fluoxetine Versus Nefazodone

One trial (n=44) compared the efficacy of fluoxetine (20 mg/day) and nefazodone (400 mg/day) in patients with MDD and insomnia.[102] After 8 weeks both groups had similar reductions in HAM-D scores. Authors did not report on response or remission rates. A pooled data analysis that did not meet our eligibility criteria combined results of this trial with two other

trials with identical protocols.[130] Fluoxetine and nefazodone were similarly efficacious in producing response on the HAM-D scale (45 percent vs. 47 percent; *P*=NR).

Fluoxetine Versus Trazodone

Two 6-week trials compared the efficacy and harms of fluoxetine (20-60 mg/day) and trazodone (50-400 mg/day).[103, 104] The groups did not differ significantly in any outcome measures (HAM-D, CGI-I, CGI-S, PGI-I). Remission rates in the larger study (n=126), however, favored fluoxetine over trazodone at study endpoint (51 percent vs. 42 percent; *P*=NR).[103] Moreover, significantly fewer patients on fluoxetine than on trazodone experienced sedation or adverse events associated with sedation (22 percent vs. 43 percent; *P*=0.11)

Paroxetine Versus Bupropion

A 6-week, flexible-dose RCT compared paroxetine (20–40 mg/day) with bupropion SR (150-300 mg/day).[105] The main objectives of the study were to assess comparative efficacy and to evaluate sexual functioning. Response rates on HAM-D were similar for patients treated with paroxetine or with bupropion SR (52 percent vs. 56 percent; *P*=NR). Men treated with paroxetine reported a greater worsening of sexual functioning than men on bupropion SR. Sexual functioning did not appear to differ for women.

A second RCT examined the efficacy of paroxetine (10–40 mg/day) and bupropion SR (100-300 mg/day) in 100 outpatients ages 60 years or older (range 60–88 years) over 6 weeks;[106] it is discussed in more detail in KQ5 (subgroups). Briefly, relative to baseline, both groups significantly improved in all outcome measures (HAM-D, HAM-A, CGI-I, CGI-S), but the treatment groups did not differ significantly. Response rates were similar in both groups (paroxetine, 77 percent; bupropion SR, 71 percent; *P*=NR).

Paroxetine Versus Nefazodone

Two studies determined the comparative efficacy of paroxetine and nefazodone on depression and sleep improvement.[107, 108] The larger trial enrolled 206 moderately depressed patients to an 8-week, acute-phase trial comparing nefazodone (200–600 mg/day) with paroxetine (20–40 mg/day).[107] Both groups showed significant improvements from baseline HAM-A, HAM-D, and MADRS scores. Response rates were similar for paroxetine and nefazodone (60 percent vs. 58 percent; *P*=NR). The second trial provided similar results for the comparative antidepressive efficacy.[108] Nefazodone, however, led to significantly greater improvements than paroxetine in objective sleep measures.

Paroxetine Versus Trazodone

A European study compared paroxetine (20–40 mg/day) with trazodone (150–400 mg/day) in 108 outpatients with MDD.[109] Study duration was 6 weeks. No differences in any efficacy outcome measures could be detected (HAM-D, CGI-S, CGI-I, MADRS). Response rates (91 percent vs. 87 percent; *P*=NR) and remission rates (68 percent vs. 69 percent; *P*=NR) did not differ significantly between paroxetine and trazodone.

Sertraline Versus Bupropion

Three studies compared the efficacy and harms of sertraline and bupropion.[110-113] Studies lasted from 8 weeks to 16 weeks. All three studies reported no statistically significant differences

in efficacy on any outcome measure (HAM-D, CGI-I, CGI-S, HAM-A). Response rates in the largest trial (n=364) were 61 percent for sertraline and 66 percent for bupropion SR (*P*=NR).[110]

In all three studies, patients on sertraline had statistically significantly higher rates of sexual dysfunction than patients on bupropion. Two RCTs assessed the incidence of sexual dysfunction during 8 weeks of treatment with sertraline (50–200 mg/day), bupropion SR (150–400 mg/day), or placebo as primary outcome measures using DSM-IV definitions for sexual dysfunction disorders.[110, 111] In another study, discontinuation rates because of sexual adverse events were significantly higher in the sertraline group than the bupropion SR group (13.5 percent vs. 3.3 percent, *P*=0.004).[112] In addition, in this study some adverse events (nausea, diarrhea, somnolence, sweating) were significantly more common among patients treated with sertraline than among those on bupropion SR (*P*<0.05).

Sertraline Versus Nefazodone

A multicenter European study assessed the efficacy and harms of sertraline (50–200 mg/day) and nefazodone (100–600 mg/day) among 160 outpatients with moderate to severe depression.[114] ITT analysis in this 6-week trial did not yield significant differences in efficacy between treatment groups. Response rates were similar between patients treated with sertraline and those treated with nefazodone (57 percent vs. 59 percent; *P*=NR). Additional outcome measures assessed by questionnaire were sexual function and satisfaction under antidepressant treatment. Overall satisfaction with sexual function was significantly higher in the nefazodone group (*P*<0.01). Among men, 67 percent in the sertraline group and 19 percent in the nefazodone group reported difficulty with ejaculation (*P*<0.01). Other adverse events did not differ significantly between the two groups.

Sertraline Versus Trazodone

A 6-week Italian trial (n=122) randomized outpatients with MDD to sertraline (50-100 mg/day) or trazodone prolonged release (150–450 mg/day).[115] At study endpoint sertraline and trazodone did not differ significantly in efficacy (HAM-D, MADRS, CGI-I, CGI-S). Overall, response rates were lower for sertraline than trazodone (HAM-D, 63 percent vs. 74 percent; MADRS: 66 percent vs. 78 percent). The mean changes of HAM-D and MADRS scores from baseline, however, were similar for sertraline- and trazodone- treated patients (-11.5 vs. -12.9 and -15.0 vs. -16.5, respectively).

Head-to-Head Evidence: SNRIs Versus SSNRIs or SNRIs

Desvenlafaxine Versus Duloxetine

An 8-week, fixed-dose RCT compared desvenlafaxine 50 and 100 mg/day with duloxetine 60 mg/day in 638 outpatients with MDD.[116] At study endpoint no significant differences in efficacy could be detected among treatment arms (HAM-D, MADRS, CGI-I, CGI-S, HAM-A). Overall, response rates were numerically lower for patients on desvenlafaxine 50 mg/day than for patients on desvenlafaxine 100 mg/day or duloxetine 60 mg/day (39 percent vs. 49 percent vs. 47 percent; *P*=NR). Similarly, the percentage of patients on desvenlafaxine 50 mg/day who achieved remission was lower than the figure for patients in the other treatment arms (20 percent vs. 28 percent vs. 29 percent). The differences, however, did not reach statistical significance.

Mirtazapine Versus Venlafaxine

Two European trials compared the efficacy of mirtazapine and venlafaxine.[117, 118] One 8-week trial evaluated efficacy and harms in hospitalized, severely depressed patients (mean HAM-D 29.3) with melancholic features.[118] At study endpoint, no significant differences in any efficacy or quality of life measures were apparent (HAM-D, MADRS, CGI-S, Q-LES-Q, QLDS); however, response rates favored mirtazapine over venlafaxine (62 percent vs. 52 percent; *P*=NR). During the study, significantly fewer patients on mirtazapine than on venlafaxine dropped out because of adverse events (5.1 percent vs. 15.3 percent; *P*=0.037). Mirtazapine led to weight gain in significantly more patients than did venlafaxine (10.3 percent vs. 5.1 percent; *P*<0.05). Venlafaxine had significantly lower rates of constipation (17.1 percent vs. 31.1 percent; *P*=0.056) and sweating (15.8 percent vs. 35.1 percent; *P*≤0.05) than venlafaxine.

The other study enrolled 242 outpatients treated at private practices in Germany.[117] Like the trial described above, mirtazapine ODT (orally disintegrated tablets; 45 mg/day) had a faster onset of action than venlafaxine XR (225mg/day). At day 8, 19.7 percent of patients on mirtazapine and 6.1 percent of patients on venlafaxine XR (*P*=0.002) had responded to treatment. At study endpoint, mirtazapine and venlafaxine XR did not differ significantly in efficacy measures (data not reported).

Venlafaxine Versus Duloxetine

A pooled data analysis of two RCTs that have not been published individually provides the only available head-to-head evidence comparing venlafaxine with duloxetine;[131] both RCTs were funded by the makers of duloxetine This study did not meet our eligibility criteria; however, because it is the only available direct evidence on the comparative efficacy of venlafaxine and duloxetine, we briefly summarize its results.

The two RCTs used a 6-week fixed-dose period comparing venlafaxine XR (150 mg/day) with duloxetine (60 mg/day) followed by a 6-week flexible dose period in 667 patients with MDD. Overall, response rates (69.1 percent vs. 62.6 percent) and remission rates (50.3 vs. 48.1 percent) did not differ significantly between the two groups. Discontinuation rates, however, were significantly lower in the venlafaxine group than in the duloxetine group (25 percent vs. 35 percent; *P*=0.006).

Head-to-Head Evidence: SNRIs Versus Other Second-Generation Antidepressants

Mirtazapine Versus Trazodone

Two studies compared mirtazapine with trazodone in patients with MDD.[119, 120] One trial was conducted in depressed patients 55 years of age and older;[119] the other was done in hospitalized patients with MDD.[120] Efficacy measures in both trials favored mirtazapine, but differences did not reach statistical significance. In the hospitalized patients, response rates at endpoint were 61 percent for mirtazapine and 51 percent for trazodone (*P*=NR).[120]

Venlafaxine Versus Bupropion

Two 8-week RCTs compared the efficacy and safety of venlafaxine XR and bupropion XR.[121, 122] Both studies were flexible-dose trials treating patients with venlafaxine XR (75–150 mg/day), bupropion XR (150–300 mg/day), or placebo. After 8 weeks of treatment, response and

remission rates for patients treated with venlafaxine XR or bupropion XR were similar. For example, in one study, MADRS response (65 percent vs. 57 percent; *P*=NR) and remission rates (51 percent vs. 47 percent; *P*=NR) did not differ significantly between patients on venlafaxine XR and bupropion XR. Likewise, no substantial differences in health outcomes (Q-LES-Q-SF, Shehan Disability Scale) were apparent at study endpoint.[121]

Venlafaxine Versus Trazodone

A 6-week study enrolled 225 patients to assess efficacy and harms of venlafaxine (150-400 mg/day), trazodone (75-200 mg/day), and placebo.[123] Efficacy outcomes (HAM-D, MADRS, CGI-S) did not differ significantly between active treatment groups. Response rates at endpoint, however, favored venlafaxine over trazodone (72 percent vs. 60 percent; *P*=NR). Trazodone led to improvements in sleep disturbance that were statistically significantly superior to those with venlafaxine. Significantly more patients on venlafaxine than on trazodone suffered from nausea (44 percent vs. 19 percent; $P<0.05$); however, trazodone led to a significantly higher rate of dizziness than venlafaxine (36 percent vs. 17 percent; $P<0.05$).

Head-to-Head Evidence: Other Second-Generation Antidepressants Versus Other Second-Generation Antidepressants

Bupropion Versus Trazodone

In a two-center study, 124 outpatients were randomly assigned to bupropion (225–450 mg/day) or trazodone (150–450 mg/day).[124] Because of a statistically significant treatment-by-center interaction, the article reported results separately for each center. Overall, in both centers, efficacy results did not differ significantly between the two treatment groups.

Mixed Treatment Comparisons

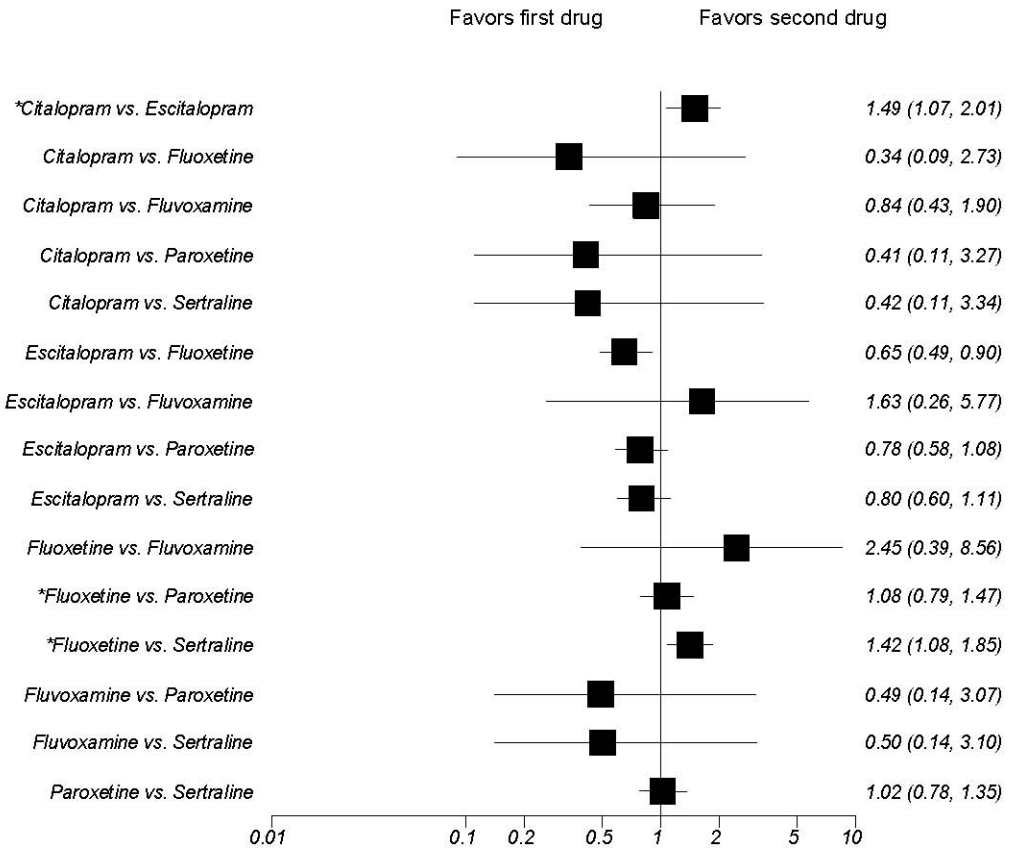
Of 78 possible comparisons, the evidence was sufficient to pool data in meta-analyses for only six comparisons for MDD (those documented in Figures 4 through Figure 12). For the remaining 72 MDD comparisons, we conducted mixed treatment comparisons, as outlined in the Methods chapter. Studies used for the mixed treatment comparisons can be found in Appendix E; those excluded are listed in Appendix B.

We assessed the odds ratio of response to treatment on the HAM-D scale. The majority of comparisons did not reflect statistically significant differences in response rates among compared antidepressants. For those comparisons that reached statistical significance in favor of one drug, differences in treatment effects were small and are likely not to be clinically significant.

In general, findings from mixed treatment comparisons were consistent with available head-to-head studies. Results of direct (denoted by an asterisk) and indirect comparisons are depicted in Figures 13 to 15.

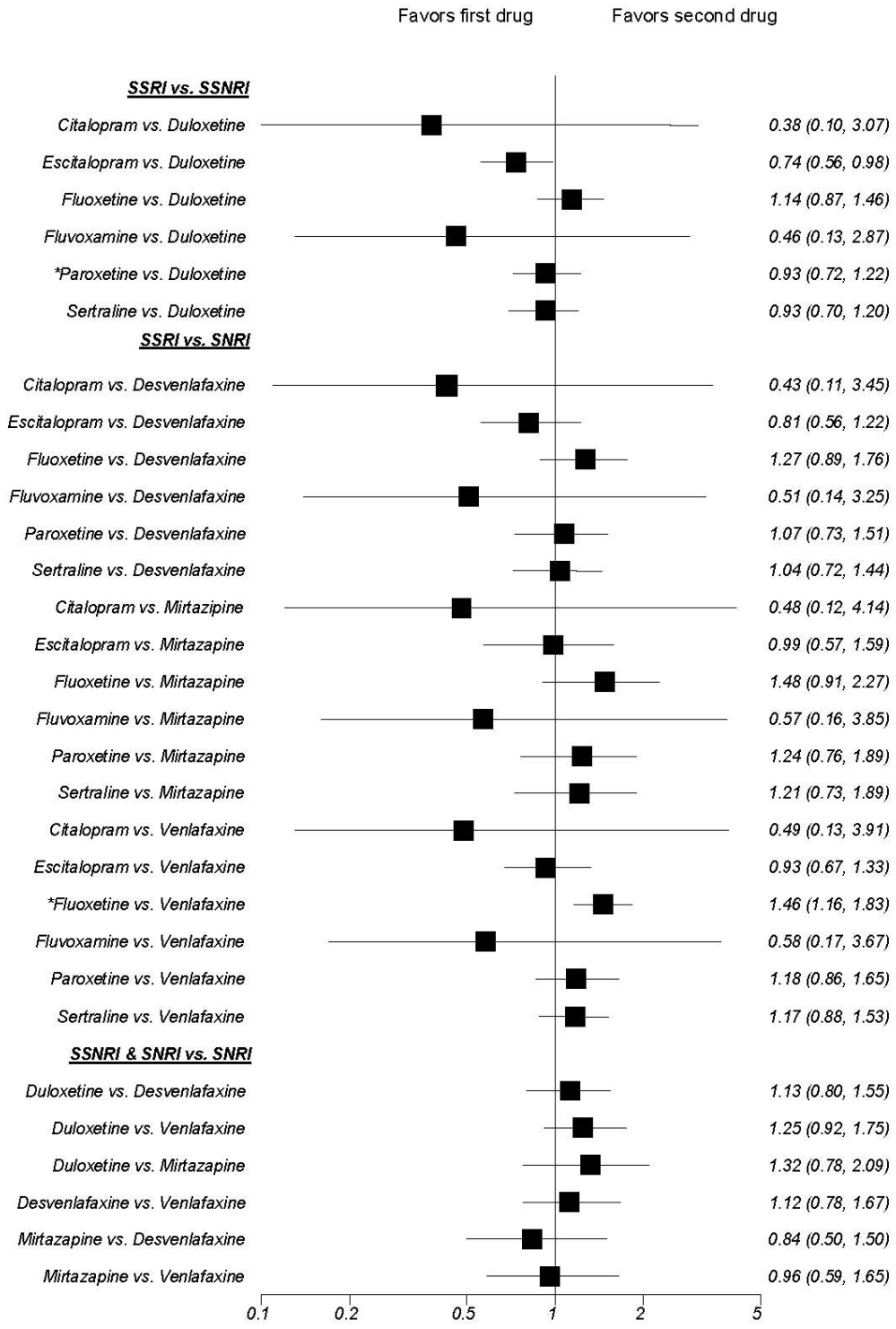
Sensitivity analyses including studies with high risk of bias increased the precision of the estimates and confirmed the overall conclusion that no substantial differences in response rates exist among second-generation antidepressants. In most cases, broadening the body of evidence to all available studies moved the point estimates towards the null.

Figure 13. Odds ratios of response rates comparing SSRIs with SSRIs



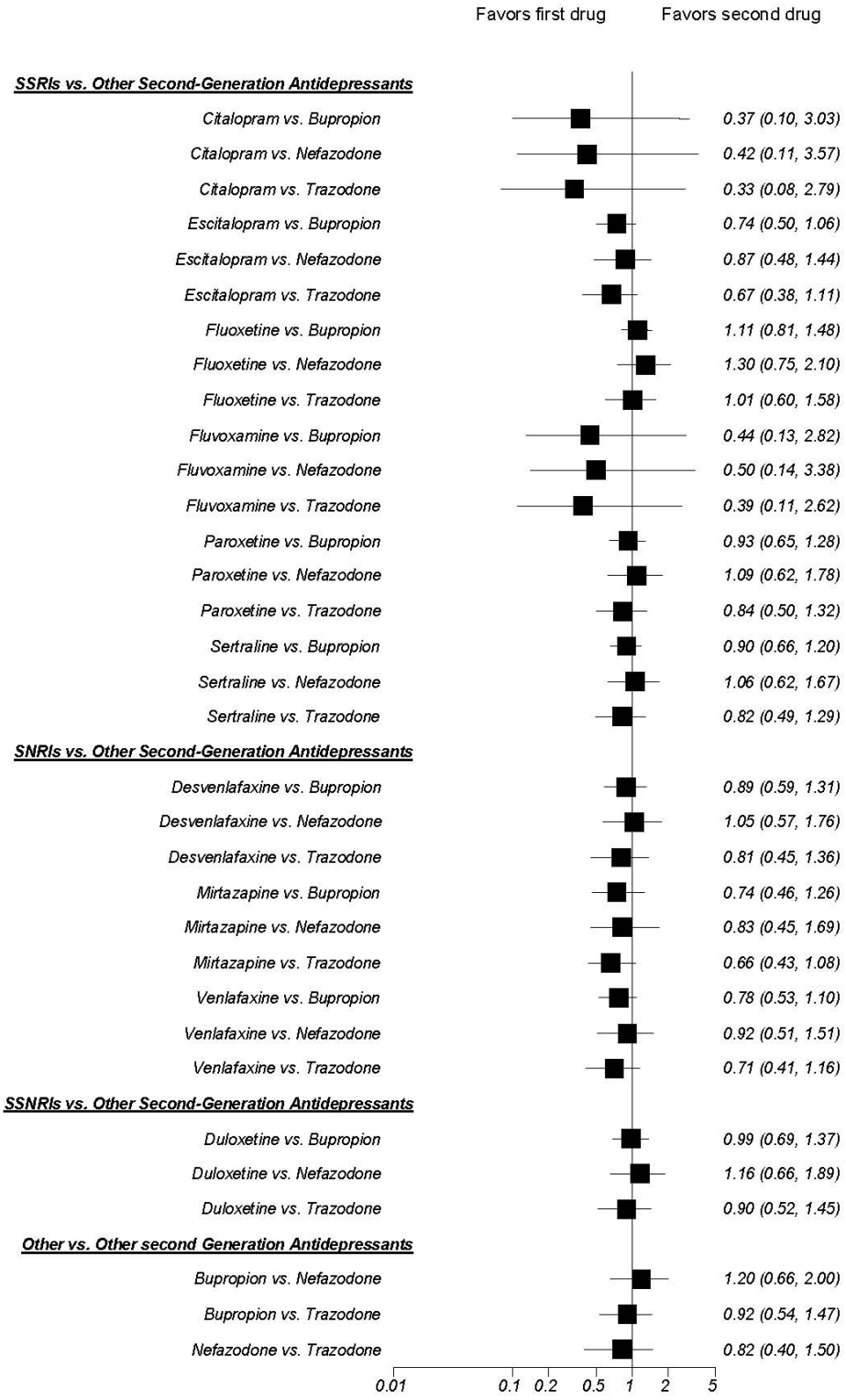
*Based on meta-analysis of head-to-head trials.

Figure 14. Odds ratios of response rates comparing SSRIs and SNRIs with SNRIs and SSNRIs



*Based on meta-analysis of head-to-head trials.

Figure 15. Odds ratios of response rates comparing SSRIs, SNRIs, SSNRIs and other second-generation antidepressants with other second-generation antidepressants



*Based on meta-analysis of head-to-head trials.

Dysthymia: Overview

We did not find any head-to-head trials on patients with dysthymia. Five placebo-controlled trials (Table 21) assessed effectiveness, efficacy, and harms of fluoxetine, paroxetine, and sertraline in populations with dysthymia.[125, 126, 132-136] Four studies were of fair quality; the fifth was of good quality. Details can be found in the evidence tables in Appendix C.

Table 21. Interventions, numbers of patients, results, and quality ratings of studies in adults with dysthymia

Study	N	Duration	Interventions	Results	Quality Rating
Devanand et al., 2005[136]	90	12 weeks	Fluoxetine vs. placebo	No difference in response rates and quality of life	Good
Vanelle et al., 1997[126]	111	26 weeks	Fluoxetine vs. placebo	Significantly more responders for fluoxetine	Fair
Barrett et al., 2001[135] Williams et al., 2000[134]	656	11 weeks	Paroxetine vs. placebo vs. behavioral therapy	In patients older than 60 years, significantly greater improvement in symptom scores for paroxetine than for placebo; in patients younger than 60 years, no difference	Fair
Thase et al., 1996[133] Kocsis et al., 1997[132]	412	12 weeks	Sertraline vs. imipramine vs. placebo	Significantly more responders for sertraline than placebo	Fair
Ravindran et al., 2000[125]	310	12 weeks	Sertraline vs. placebo	Significantly more responders and remitters for sertraline	Fair

Dysthymia: Key Points

We identified no head-to-head trials in a population with dysthymia. The substantial differences in population characteristics in placebo-controlled trials make the evidence too inconsistent to identify differences between treatments. The strength of evidence is insufficient.

Five placebo-controlled trials (seven articles) provide conflicting evidence on the general efficacy and effectiveness of fluoxetine, paroxetine, and sertraline for the treatment of dysthymia.[125, 126, 132-136] Specifically:

- Two studies provide mixed evidence about the general efficacy of fluoxetine for the treatment of dysthymia.[126, 136]
- One effectiveness study did not detect any statistically significant difference between paroxetine and placebo.[134, 135]
- Two studies indicate that sertraline has a significantly greater efficacy in the treatment of dysthymia than placebo.[125, 132, 133]

Dysthymia: Detailed Analysis

Head-to-Head Evidence

We identified no head-to head trials.

Placebo-Controlled Evidence

Fluoxetine Versus Placebo

Two trials evaluated the efficacy of fluoxetine for treating patients with dysthymia over 12 weeks; the studies provide mixed results.[126, 136] An RCT of good quality examined the efficacy and safety of fluoxetine (20–60 mg/day) in patients 60 years of age and older;[136] we discuss this trial in more detail for KQ 5 (subgroups). Briefly, ITT analysis indicated that fluoxetine had limited efficacy. Response rates on the HAM-D favored fluoxetine over placebo, but the two groups did not differ significantly (27.3 percent vs. 19.6 percent; *P*=0.4). Likewise, the investigators found no difference in quality of life.

The other trial was conducted in patients 18 years of age and older (mean 43 years).[126] Significantly more patients on fluoxetine than on placebo were rated as responders (58 percent vs. 36 percent; *P*=0.03). Remission rates favored fluoxetine but did not reach statistical significance (44.4 percent vs. 25.6 percent; *P*=0.07).

Paroxetine Versus Placebo Versus Behavioral Therapy

A large, primary-care-based effectiveness study randomized 656 patients with dysthymia or minor depression to 11 weeks of paroxetine (10–40 mg/day), placebo, or behavioral therapy.[134, 135] Participants were stratified into patients 60 years of age and older (n=415) and patients younger than 60 years of age (n=241) for ITT analysis. We discuss the results of the subgroup analysis on older patients in more detail for KQ 5 (subgroups).

Briefly, in patients 60 years or older, paroxetine-treated patients showed a greater change in HSCL-D-20 scores than placebo-treated patients (*P*=0.004).[134] Effects were similar for patients with dysthymia and minor depression. Among the younger patients, treatment groups did not differ significantly on the HSCL-D-20.[135] For dysthymia only, the remission rate of patients with at least 4 weeks of treatment was significantly higher in the paroxetine group than in the placebo group (80 percent vs. 44 percent; *P*=0.008). Paroxetine was not more efficacious than placebo in patients with minor depression.

Sertraline Versus Placebo

Two RCTs that assessed the efficacy of sertraline (50–200 mg/day) for the treatment of dysthymia over 12 weeks provided similar results.[125, 132, 133] In both studies, only patients who had had the diagnosis of dysthymia for more than 5 years were eligible; outcomes included quality of life and measures of functional capacity. Patients on sertraline had significantly greater antidepressant responses than those on placebo (64 percent vs. 44 percent; *P*<0.001[133] and 52 percent vs. 34 percent; *P*=0.001[125]). In addition, sertraline was more efficacious than placebo on psychosocial and quality of life instruments (Global Assessment of Functioning Scale, Social Adjustment Scale [SAD], Quality of Life Enjoyment and Satisfaction Questionnaire [QLSQ], BQOLS).

Subsyndromal Depressive Disorders: Overview

We found no head-to-head RCTs on patients with subsyndromal depressive disorders. The only head-to-head evidence was a nonrandomized, single-blinded trial comparing citalopram with sertraline.[137] Because of the lack of head-to-head evidence, we briefly summarize this study, although it did not meet eligibility criteria. In addition, two placebo-controlled studies assessed

the efficacy and tolerability of fluoxetine[138] and paroxetine[134, 135] in patients with subsyndromal depression (Table 22). Details can be found in the evidence tables in Appendix C.

Table 22. Interventions, numbers of patients, results, and quality ratings of studies in adults with subsyndromal depressive disorders

Study	N	Duration	Interventions	Results	Quality Rating
Judd et al., 2004[138]	162	12 weeks	Fluoxetine vs. placebo	Greater improvements on depression scales for fluoxetine than for placebo; no difference in psychosocial outcomes	Fair
Barrett et al., 2001[135] Williams et al., 2000[134]	656	11 weeks	Paroxetine vs. placebo vs. behavioral therapy	In patients older than 60 years, significantly greater improvement in symptom scores for paroxetine than for placebo; in patients younger than 60 years, no difference	Fair

Subsyndromal Depressive Disorders: Key Points

We identified no head-to-head RCTs in a population with subsyndromal depression. A nonrandomized, open-label trial did not detect any differences in efficacy between citalopram and sertraline.[137]

In placebo-controlled trials, differences in population characteristics make the evidence insufficient to identify differences between treatments.[134, 135, 138] In one effectiveness study in a primary care setting, effectiveness did not differ significantly between paroxetine and placebo for the treatment of minor depression.[134, 135] The strength of evidence is insufficient.

Subsyndromal Depressive Disorders: Detailed Analysis

Head-to-Head Evidence

We did not find any head-to-head RCTs. A nonrandomized, single-blinded trial (n=138) lasting 1 year assessed the comparative efficacy and safety of citalopram and sertraline in patients with late-life minor depression or other subsyndromal depressive disorders.[137] Overall, both treatments improved depressive symptoms but the groups did not differ significantly at any time point. At the end of the study, remission was achieved by 53 percent of patients on citalopram and 42 percent on sertraline (P=0.25). Likewise, no differences in psychosocial functioning emerged.

Placebo-Controlled Evidence

Two studies were conducted in populations with minor depression.

Fluoxetine Versus Placebo

A 12-week trial (n=162) evaluated the efficacy of fluoxetine in patients with minor depression.[138] Improvements on depression scales (HAM-D, Beck Depression Inventory [BDI], IDS-C) were statistically significantly greater for patients receiving fluoxetine than for those receiving placebo. Likewise, the overall severity of illness (CGI-S) improved statistically significantly more in the fluoxetine than in the placebo group (P=0.002). No significant differences could be detected in psychosocial outcomes.

Paroxetine Versus Placebo

A large primary-care-based effectiveness study randomized 656 patients with dysthymia or minor depression to 11 weeks of paroxetine (10-40 mg/day), placebo, or behavioral therapy.[134, 135] Participants were stratified into patients 60 years and older (n=415) and patients younger than 60 years (n=241) for ITT analysis.

In the 60 or older subgroup, patients receiving paroxetine showed a greater change in HSCL-D-20 scores than those receiving placebo (*P*=0.004), but those on paroxetine did not demonstrate more change than patients on behavioral therapy (*P*=0.17).[134] Effects were similar for patients with dysthymia and minor depression. Paroxetine was not more efficacious than placebo in patients with minor depression in the younger subgroup.[135]

Key Question 1b: Response to Antidepressant Agents After Successful Response in the Past

We did not find any evidence that answered this Key Question.

Key Question 1c: Differences in Efficacy and Effectiveness between Immediate- and Extended-Release Formulations

Efficacy of Immediate- Versus Extended-Release Formulations: Overview

We found five head-to-head trials that investigated the comparative efficacy of daily versus weekly dosing (Table 23) and immediate- versus extended-release formulations (Table 24).[139-143] Two of these trials compared fluoxetine daily with fluoxetine weekly;[139, 140] two good-quality trials assessed paroxetine IR (immediate-release) versus paroxetine CR (controlled-release);[141, 142] and one trial compared venlafaxine IR with venlafaxine XR (extended release).[143] We could not find any studies on other medications, such as bupropion or fluvoxamine, that are available as both immediate- and extended-release formulations.

Table 23. Interventions, numbers of patients, results, and quality ratings of studies comparing daily with weekly fluoxetine regimens during continuation treatment

Study	N	Duration	Comparison and Dose (mg/day)	Relapse (percent) and Significance Level [a]	Remission (percent) and Significance Level[a]	Quality Rating
Burke et al., 2001[139]	70	7 weeks	Fluoxetine 20 Fluoxetine 60 weekly Placebo	NR	NR	Fair
Schmidt et al., 2000[140]	501	25 weeks	Fluoxetine 20 Fluoxetine 90 weekly placebo	26 vs. 37	NR	Fair

mg/d = milligram per day; NR = not reported; vs. = versus

Note: Drug names not otherwise specified refer to the immediate-release formulations; extended-release formulation are indicated as CR, XL, or XR.

[a]Response and remission (as defined by authors of individual studies) are measured on the Hamilton Depression Rating Scale (HAM-D) or indicated otherwise.

Table 24. Interventions, numbers of patients, results, and quality ratings of studies comparing immediate- with extended-release formulations

Study	N	Duration	Comparison and Dose (mg/day)	Response (percent) and Significance Level [a]	Remission (percent) and Significance Level[a]	Quality Rating
Golden et al., 2002[141]	640	12 weeks	Paroxetine CR 25-62.5 Paroxetine IR 20-50 Placebo	74 vs. 73 vs. 61 *P*=0.0004 *P*=0.036	56 vs. 53 vs. 44 *P*=0.05 vs. placebo	Good
Rapaport et al., 2003[142]	319	12 weeks	Paroxetine CR 50 Paroxetine IR 40 Placebo	72 vs. 65 vs. 52 *P*=0.002 vs. 0.06 vs. placebo	43 vs. 44 vs. 26 *P*=0.009 vs. 0.01 vs. placebo	Good
Cunningham, 1997[143]	278	12 weeks	Venlafaxine XR 75-150 Venlafaxine IR 37.5-150 Placebo	Venlafaxine XR vs. placebo (*P*=0.01 to *P*<0.001) Venlafaxine IR vs. placebo (*P*=0.05) Venlafanie XR superior to IR (*P*<0.05)	NR	Fair

mg/d = milligram per day; NR = not reported; ns = not significant; vs. = versus
Note: Drug names not otherwise specified refer to the immediate-release formulations; extended-release formulation are indicated as CR, XL, or XR.
[a]Response and remission (as defined by authors of individual studies) are measured on the Hamilton Depression Rating Scale (HAM-D) or indicated otherwise.

Efficacy of Immediate- Versus Extended-Release Formulations: Key Points

Five head-to-head trials investigated the comparative efficacy of daily versus weekly dosing and immediate- versus extended-release formulations.[139-143]

Two RCTs reported similar rates of maintenance of response and relapse for patients treated with fluoxetine daily or fluoxetine weekly during the continuation phase of MDD therapy.[139, 140] The strength of evidence is moderate.

One RCT and a pooled analysis of two identical RCTs did not find any differences in response rates in patients treated with paroxetine IR or paroxetine XR for acute phase MDD.[141, 142] The strength of evidence is moderate.

One RCT reported higher response rates for patients on venlafaxine XR than venlafaxine IR. The strength of evidence is low.

Efficacy of Immediate- Versus Extended-Release Formulations: Detailed Analysis

Head-to-Head Evidence

Fluoxetine Daily Versus Fluoxetine Weekly

No extended-release formulation of fluoxetine exists. Because of the long elimination half-lives of fluoxetine and its active metabolite norfluoxetine, investigators have explored different dosing regimens for fluoxetine during continuation treatment. Of particular interest has been weekly treatment regimens. Unlike daily treatments, the weekly treatment is administered with an enteric-coated formulation to reduce gastrointestinal adverse events.

Two double-blinded RCTs compared the efficacy of fluoxetine (20 mg/day) with fluoxetine (60 mg/week and 90 mg/week) during the continuation phase of patients with MDD who had responded to 20 mg/day of fluoxetine during the acute-treatment phases. The acute-treatment

periods in both studies were open-label and lasted between 7 and 13 weeks.[139, 140] Patients who achieved response were randomized to double-blinded continuation treatment with fluoxetine (20 mg/day) or fluoxetine (60 mg/week or 90 mg/week). Treatment durations during the continuation periods were 7 and 25 weeks, respectively.

The larger study randomized 501 patients to fluoxetine (20 mg/day), fluoxetine (90 mg/week), or placebo.[140] After 25 weeks of continuation treatment, 37 percent of patients on weekly fluoxetine weekly and 26 percent of patients on daily fluoxetine experienced a relapse (*P*=NR). Both groups (weekly vs. daily) also exhibited similar changes in CGI-S (1.0 vs. 0.9) and HAM-D (6.6 vs. 6.4) scores. The smaller study also did not detect any statistically significant differences in the main outcome measures (MADRS, Hopkins Symptom Checklist).[139]

Paroxetine IR Versus Paroxetine CR

One double-blinded RCT[142] and a pooled analysis of two identical RCTs[141] compared the efficacy and safety of paroxetine IR with paroxetine CR. The RCT enrolled 319 elderly patients with acute MDD, randomizing them to paroxetine IR (up to 40 mg/day), paroxetine CR (up to 50 mg/day), or placebo.[142] The primary outcome measure was the change of HAM-D scores after 12 weeks of treatment. Patients in both active treatment arms had similar changes on the HAM-D (paroxetine IR, -12.3; paroxetine CR, - 12.1). Likewise, response (65 percent vs. 72 percent) and remission rates (44 percent vs. 43 percent) were similar for the two groups.

The other study pooled data (n=820) of two identical RCTs conducted in adult outpatients between 18 and 65 years of age who had MDD.[141] Patients received treatment with paroxetine IR (20 to 50 mg/day), paroxetine CR (25–62.5 mg/day), or placebo. After 12 weeks of treatment, patients on the IR and CR formulations exhibited similar response rates (73 percent vs. 74 percent) and remission rates (53 percent vs. 56 percent).

Venlafaxine IR Versus Venlafaxine XR

One flexible-dose, placebo-controlled RCT compared the efficacy and safety of twice-daily venlafaxine IR (37.5–150 mg/2x per day) with once-daily venlafaxine XR (75–150 mg/day) in 293 patients with acute-phase MDD.[143] Primary outcome measures were the HAM-D, the MADRS, and the CGI scales. After 12 weeks of treatment, significantly more patients on venlafaxine XR experienced a response to treatment than patients treated with venlafaxine IR (data not reported; $P<0.05$ for response on HAM-D, MADRS, and CGI).

Key Question 2: Efficacy or Effectiveness for Maintaining Remission or for Treating Patients With Unresponsive or Recurrent Disease

This section deals with two key aspects of treating patients with major depressive disorder (MDD). KQ 2a addresses maintaining remissions and preventing relapses or recurrences for patients who have responded to antidepressant treatment; KQ 2b focuses on addressing ongoing depressive disease for those who have not responded to such therapy or who have experienced relapses or new episodes. For patients who have responded, two subquestions are important: the efficacy or effectiveness of (1) continuing the initial (existing) medication or (2) switching to a different one (KQ 2a). For patients who have not responded, the issues focus on using different antidepressants (KQ 2b).

For purposes of exposition in this section, we use the phrase "maintaining remission" to encompass preventing relapse or recurrence; we also use the phrase "achieving response" to encompass treating patients who have not responded in an acute phase of disease or who have experienced a relapse or recurrence. Detailed information on all trials reviewed for KQ 2 can be found in the evidence tables in Appendix C.

Maintaining Remission: Overview

Continuing Initial Medications

In all, we had 38 trials relating to KQ 2a about continuing existing medications (Table 25). We also identified two additional systematic reviews and meta-analyses, but we did not formally assess them because their component trials were already included in our work.[144, 145] Seven head-to-head studies (eight articles) compared the efficacy of one second-generation antidepressant with another for preventing relapse or recurrence.[44, 61, 123, 146-150] Comparisons included escitalopram versus desvenlafaxine,[148] escitalopram versus paroxetine,[44] fluoxetine versus sertraline,[61] fluoxetine versus venlafaxine,[149, 150] fluvoxamine versus sertraline,[146, 147] and trazodone versus venlafaxine.[123]

Another 31 RCTs[140, 149, 151-187] provide additional placebo-controlled evidence to support the general efficacy of bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine for maintaining remission in patients with depressive disorders (Table 26).

Using the disease treatment framework depicted in Figure 1 of the Introduction chapter, we characterized studies that assessed continuation treatment of patients who had responded or remitted with acute-phase treatment as relapse-prevention studies. Relapse-prevention studies typically included an open-label, acute-phase treatment and a double-blind, randomized, placebo-controlled continuation-phase treatment. The duration of continuation treatment in these trials ranged from 14 weeks to 72 weeks.

We further denoted studies that assessed maintenance treatment among patients who had remained in remission following acute and continuation treatment as recurrence-prevention studies. These studies usually included an open-label acute phase, then an open-label continuation phase for acute-phase responders, followed by a randomized, double-blind, placebo-controlled maintenance phase for patients who had not relapsed. The maintenance phase in these trials lasted from 36 weeks to 100 weeks.

Investigators generally determined the initial inclusion of patients on a criteria-based diagnosis (e.g., DSM-III-R, DSM-IV) and a predefined cutoff point of a universally used depression scale (e.g., HAM-D≥18 or MADRS≥19). Subsequent inclusion criteria varied. Some trials randomized patients who had demonstrated a clinically significant response to open-label treatment (e.g., ≥50 percent improvement from baseline on the HAM-D or MADRS). Others used a predefined cutoff point on a depression scale to identify and randomize those who were in remission (e.g., HAM-D≤9, MADRS≤12, CGI-I≤2). Most studies assessed relapse or recurrence using a predefined cutoff point on a depression rating scale (e.g., HAM-D>18, MADRS>19, CGI-S≥4), but the specific cutoff point varied widely.

Table 25. Number of head-to-head trials and placebo-controlled trials of second-generation antidepressants for preventing relapse, by comparison

Comparison	Number of Studies
Head-to-Head Trials—SSRIs vs. SSRIs:	
Escitalopram vs. paroxetine	1
Fluoxetine vs. sertraline	1
Escitalopram vs. desvenlafaxine	1
Fluoxetine vs. venlafaxine	1
Placebo-Controlled Trials—SSRIs:	
Citalopram vs. placebo	2
Fluoxetine vs. placebo	2
Fluvoxamine vs. placebo	0
Paroxetine vs. placebo	1[a]
Sertraline vs. placebo	2
Placebo-Controlled Trials—SSNRIs:	
Duloxetine vs. placebo	1
Placebo-Controlled Trials—SNRIs:	
Desvenlafaxine vs. placebo	1
Mirtazapine vs. placebo	1
Venlafaxine vs. placebo	1
Placebo-Controlled Trials—Other Second-Generation Antidepressants:	
Bupropion vs. placebo	1
Nefazodone vs. placebo	1
Trazodone vs. placebo	0

[a]One trial reported continuation-phase and maintenance-phase results.

Table 26. Number of head-to-head trials and placebo-controlled trials of second-generation antidepressants for recurrence of major depressive disorder, by comparison

Comparison	Number of Studies
Head-to-Head Trials—SSRIs vs. SSRIs:	
Fluvoxamine vs. sertraline	1
Head-to-Head Trials—SSRIs vs. SNRIs:	
Fluoxetine vs. venlafaxine	1
Head-to-Head Trials—NRIs v s. Other Second-Generation Antidepressants:	
Venlafaxine vs. trazodone	1
Placebo Controlled Trials—SSRIs:	
Citalopram vs. placebo	2
Fluoxetine vs. placebo	2
Fluvoxamine vs. placebo	1
Paroxetine vs. placebo	3[a]
Sertraline vs. placebo	4
Placebo Controlled Trials—SSNRIs:	
Duloxetine vs. placebo	1
Desvenlafaxine vs. placebo	0
Mirtazapine vs. placebo	0
Venlafaxine vs. placebo	3[b]
Placebo Controlled Trials—Other Second-Generation Antidepressants:	
Bupropion vs. placebo	0
Nefazodone vs. placebo	1
Trazodone vs. placebo	1[b]

[a]One trial reported continuation-phase and maintenance-phase results.
[b]Includes placebo comparison from a head-to-head trial of trazodone and venlafaxine.

Because we rated most of these trials as fair quality (internal validity), we denote quality in this section only for those rated good. Poor-quality studies are not included here; a listing of

these studies can be found in Appendix D. Trial reporting was often incomplete. Most articles did not report their methods of randomization or allocation concealment. Even though investigators frequently used intention-to-treat analysis, few authors reported the overall number of patients lost to followup from randomization to the end of the trial.

Because of heterogeneous study designs and the relatively small number of trials, we did not make indirect comparisons between drugs.

Switching Medications

No trial specifically addressed the efficacy or effectiveness of any second-generation antidepressant for preventing relapse (i.e., continuation phase) or recurrence (i.e., maintenance phase) when a patient had previously responded to one antidepressant and switched to an alternative antidepressant.

Maintaining Remission: Key Points

Continuing Initial Medications

In six head-to-head studies,[44, 61, 123, 146-150] the overall efficacy for maintaining remission does not differ between escitalopram and desvenlafaxine,[148] escitalopram and paroxetine,[44] fluoxetine and sertraline,[61] fluoxetine and venlafaxine,[149] fluvoxamine and sertraline,[146, 147] and trazodone and venlafaxine.[123] One naturalistic study provided evidence that rehospitalization rates do not differ between patients continuing fluoxetine versus continuing venlafaxine.[150] We rated the strength of head-to-head evidence as moderate.

We found 14 placebo-controlled relapse-prevention trials that provide consistent efficacy evidence favoring active treatment over placebo.[140, 151-164, 176] Seventeen placebo-controlled recurrence-prevention trials provide consistent evidence for active treatment over placebo.[149, 152, 165-175, 177-187] We rated the strength of this evidence as moderate.

Effect sizes generally were similar across drugs in placebo-controlled efficacy trials. This observation is consistent with effect sizes noted in two published meta-analyses of placebo-controlled trials: (1) relapse prevention with venlafaxine (OR, 0.37; 95% CI, 0.27 to 0.51);[145] (2) relapse prevention with second-generation antidepressants (RR, 0.54; 95% CI, 0.46 to 0.62);[144] and (3) recurrence prevention with second-generation antidepressants; (RR, 0.56; 95% CI, 0.48 to 0.66).[144]

Switching Medications

As noted, we identified no studies on this point. The strength of evidence in this case is graded insufficient. We do not comment further on this treatment option.

Maintaining Remission: Detailed Analysis

Head-to-Head Evidence on Continuing Initial Medications

Six head-to-head trials[44, 61, 123, 146-149] and one naturalistic (nonrandomized) study[150] compared one second-generation antidepressant with another for maintaining remission (Table 27). Findings for acute-phase treatment are reported in KQ 1 (above) and not replicated here, although we list acute-phase treatments and duration for context with other studies.

Table 27. Head-to-head studies of maintaining remission (preventing relapse or recurrence)

Study	Phase	Duration (Weeks)	N	Comparison and Dose (mg/day)	Relapse or Recurrence n (%)		Quality Rating
SSRIs vs SSRIs: Baldwin et al., 2006[44] *	Acute	8	165 156	Escitalopram 10-20 Paroxetine 20-40	NA NA		Fair
	Continuation	19	109 110	Escitalopram 10-20 Paroxetine 20-40	11 (10) 10 (9)	*P*=NR	
Van Moffaert et al., 1995[61]	Acute	8	82 83	Fluoxetine 20-40 Sertraline 50-100	NA NA		Fair
	Continuation	24	56 49	Fluoxetine 20-40 Sertraline 50-100	7 (13) 5 (10)	*P*=NR	
Franchini et al., 1997[146] Franchini et al., 2000[147]	Acute	NR	NR	NR	NA		Fair
	Continuation	16	NR	NR	NA		
	Maintenance (2 years)[146]	104	32	Fluvoxamine 200-300	6 (19)	*P*=0.88	
			32	Sertraline 100-200	7 (22)		
	Maintenance (4 years)[147]	208	25	Fluvoxamine 200-300	5 (20)	*P*=0.92	
			22	Sertraline 100-200	3 (14)		
SSRIs vs SNRIs: Soares et al., 2010[148] *	Acute	8	308 299	Escitalopram 10-20 Desvenlafaxine 100-200	NA NA		Fair
	Continuation	26	160 137	Escitalopram 10-20 Desvenlafaxine 100-200	32 (20) 25 (18)	*P*=0.70	
Keller et al., 2007[149] *	Acute	10	266 781	Fluoxetine 20-60 Venlafaxine XR 75-300	NA NA		Fair
	Continuation	26	177 499	Fluoxetine 20-60 Venlafaxine XR 75-300	3 (2) 5 (1)	*P*=0.44	
Lin et al., 2008[150] * [a]	Acute	NR	NR NR	Fluoxetine 20-60 Venlafaxine 75-225	NA NA		Fair
	Continuation	52	80 122	Fluoxetine 20-60 Venlafaxine 75-225	37 (46) 53 (43)	*P*=0.70	
SNRIs vs. Other Second-Generation Antidepressants Cunningham et al., 1994[123]	Acute	6	77 72 76	Trazodone 150-400 Venlafaxine 75-200 Placebo	NA NA NA		Fair
	Continuation/ Maintenance	52	30 37 29	Trazodone 150-400 Venlafaxine 75-200 Placebo	4 (13) 3 (8) 4 (14)	*P*=NR	

NA = not applicable; NR = not reported; ns = not statistically significant

*New study added during update.

[a]Acute treatment was during hospitalization, and relapse outcome was defined by rehospitalization.

SSRIs Versus SSRIs

Escitalopram Versus Paroxetine

One trial compared the acute-phase and continuation-phase efficacy of escitalopram (10–20 mg/day) with paroxetine (20–40 mg/day).[44] Although this study was designed primarily to assess discontinuation effects during treatment interruption and during tapered withdrawal, it provided data for the 19-week continuation period that followed on an 8-week acute phase. At the end of 27 weeks, response rates were similar for escitalopram and paroxetine (≥50 percent improvement in MADRS total score from baseline [85 percent vs. 79 percent; *P*=NR]). Relapse rates were not explicitly reported, but we calculated them from the sample flow data to be 10 percent and 9 percent, respectively, for escitalopram and paroxetine.

Fluoxetine Versus Sertraline

One trial compared the efficacy of fluoxetine and sertraline for preventing relapse during a 24-week continuation phase.[61] A total of 165 patients with major depression were randomized to

fluoxetine (20–40 mg/day) or sertraline (50–100 mg/day). At 8 weeks, 56 responders (≥50 percent reduction in HAM-D or MADRS) in the fluoxetine group and 49 responders in the sertraline group entered the continuation phase, continuing the same dose attained at the end of the acute phase. Relapse rates were similar in the two groups (13 percent and 10 percent, respectively; *P*=NR). This design may be prone to bias and confounding because patients had not been rerandomized at the start of the continuation phase.

Fluvoxamine Versus Sertraline

One Italian trial of 64 patients with recurrent depression compared the efficacy of fluvoxamine and sertraline for maintaining remission over 2 years[146] and 4 years.[147] After at least 4 months of remission with tricyclic antidepressants (n=49), SSRIs (n=4), monoamineoxidase inhibitors (n=2), or combination treatment (n=9), investigators randomized patients to fluvoxamine (200–300 mg/day) or sertraline (100–200 mg/day) and followed them for up to 4 years. Recurrence rates (HAM-D>15) for fluvoxamine and sertraline were similar at 2 years (19 percent vs. 22 percent, respectively; *P*=0.88) and 4 years (20 percent vs. 14 percent, respectively; *P*=0.92).

SSRIs Versus SNRIs

Escitalopram Versus Desvenlafaxine

One trial compared escitalopram (10–20 mg/day) with desvenlafaxine (100–200 mg/day) for relapse prevention during 6 months of continuation-phase treatment in postmenopausal women with MDD.[148] At 8 weeks, 160 responders (≥50 percent reduction in HAM-D_{17} total score) in the escitalopram group and 137 responders in the desvenlafaxine group entered the continuation phase, continuing the same dose attained at the end of the acute phase. Relapse rates were similar in the two groups (20 percent and 18 percent, respectively; *P*=0.7).

Fluoxetine Versus Venlafaxine

One trial[149] and a longitudinal naturalistic study[150] assessed continuation-phase treatment comparing fluoxetine with venlafaxine. One trial, the Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT), randomized patients to double-blind treatment with fluoxetine 20-60 mg/day or venlafaxine ER 75–300 mg/day for 10 weeks; it then allowed patients achieving a response (≥50 percent reduction in HAM-D_{17} or total score≤12) or remission (HAM-D_{17}≤7) to continue through 6 months of continuation treatment.[149] Continuation-phase response rates (92 percent vs. 90 percent) and remission rates (69 percent vs. 72 percent) were similar for fluoxetine and venlafaxine, respectively. Only 3 fluoxetine-treated patients (2 percent) and 5 venlafaxine-treated patients (1 percent) relapsed during continuation-phase treatment (*P*=0.44).

A naturalistic study compared time to rehospitalization in Chinese patients with major depression who had received acute treatment in an inpatient setting.[150] Patients were not randomly assigned to treatment, although patient characteristics at discharge were similar between the fluoxetine and venlafaxine groups. Patients continued the same antidepressant at the same dose as used at discharge; they were followed over 1 year to monitor clinical condition and rehospitalization status. Rehospitalization rates did not statistically significantly differ between fluoxetine and venlafaxine during this 1 year (46 percent vs. 43 percent of patients were rehospitalized, respectively; *P*=0.695).

SNRIs Versus Other Second-Generation Antidepressants

Venlafaxine Versus Trazodone

One trial of 225 patients with major depression compared the efficacy and safety of trazodone and venlafaxine over a 1-year continuation/maintenance phase.[123] Investigators randomized patients for acute treatment with venlafaxine 75–200 mg/day (n=72), trazodone 150–400 mg/day (n=77), or placebo (n=76). After 6 weeks, 37 in the venlafaxine group and 30 responders in the trazodone group (CGI-I score of 1 or 2) were allowed to continue into the long-term phase. Relapse rates were similar in the three groups (8 percent, 13 percent, and 14 percent, respectively; *P*=NR). Fewer patients treated with venlafaxine than with either trazodone or placebo withdrew from treatment for any reason; the difference between venlafaxine and trazodone reached statistical significance ($P \leq 0.05$) during the long-term phase.

Placebo-Controlled Evidence on Continuing Initial Medications

Fourteen placebo-controlled trials (16 publications) assessed relapse prevention[140, 151-164, 176] and 17 trials (24 publications) assessed recurrence prevention.[149, 152, 165-175, 177-187] Because the duration of acute, continuation, and maintenance phase treatment is not consistent in all patients, and because the definition of these treatment phases is not universal, some studies described below (Table 28) can be categorized as addressing both relapse and recurrence prevention.

SSRI: Citalopram Versus Placebo

Two trials assessed relapse prevention;[153, 188] two other trials assessed recurrence prevention.[165, 166] Both relapse-prevention trials randomized patients who had responded in the acute phase (MADRS≤12) to placebo or continuation treatment with citalopram (20-60 mg/day). Statistically significantly fewer patients on citalopram than on placebo relapsed after 24 weeks in both trials. Relapse rates were 14 percent and 24 percent, respectively ($P=0.04$), in one trial, and 11 percent (pooled) and 31 percent, respectively ($P<0.02$), in the other trial.

Both recurrence-prevention trials included open-label, acute-phase treatment with citalopram (20-60 mg/day; 6 weeks to 9 weeks), followed by 16 weeks of open-label continuation treatment at the same dose for responders (MADRS≤11).[165, 166] Patients who had not relapsed (MADRS≤22) during the continuation phase were randomized to 48 weeks of double-blind maintenance treatment with citalopram or placebo. Recurrence rates were lower for citalopram-treated patients than for placebo-treated patients in both trials (18 percent vs. 43 percent, respectively; $P<0.001$,[165] and 32 percent vs. 67 percent, respectively; *P*=NR[166]).

SSRI: Escitalopram Versus Placebo

Three trials compared escitalopram with placebo; two assessed relapse prevention[154, 163] and one recurrence prevention.[178] The two trials on relapse prevention reported that patients continuing on escitalopram had statistically significantly lower relapse rates than patients on placebo.

Table 28. Placebo-controlled studies of relapse prevention and recurrence prevention

Study	Phase	Duration (Weeks)	N	Comparison and Dose (mg/day)	Relapse or Recurrence n (%)		Quality Rating
SSRIs vs. placebo: Hochstrasser et al., 2001[165]	Acute	6-9	427	Citalopram 20-60	NA		Fair
	Continuation	16	327	Citalopram 20-60	NA		
	Maintenance	48	132	Citalopram 20-60	24 (18)	*P*<0.001	
			137	Placebo	59 (43)		
Klysner et al., 2002[166]	Acute	8	230	Citalopram 20-40	NA		Fair
	Continuation	16	172	Citalopram 20-40	NA		
	Maintenance	48	60	Citalopram 20-40	19 (32)	*P*=NR	
			61	Placebo	41 (67)		
Montgomery et al., 1992[189]	Acute	6	NR	Citalopram 20-40	NA		Fair
	Continuation	24	48	Citalopram 20	4 (8)	*P*<0.02[b]	
			57	Citalopram 40	7 (12)		
			42	Placebo	13 (31)		
Robert and Montgomery, 1995[153]	Acute	8	391	Citalopram 20-60	NA		Fair
	Continuation	24	152	Citalopram 20-60	21 (14)	*P*=0.04	
			74	Placebo	18 (24)		
Gorwood et al., 2007[163 a]	Acute	12	405	Escitalopram 10-20	NA		Fair
	Continuation	24	152	Escitalopram 10-20	13 (9)	*P*<0.001	
			153	Placebo	50 (33)		
Kornstein et al., 2006[178 a]	Acute	8	131	Citalopram 20-60	NA		Fair
			129	Fluoxetine 20-80	NA		
			128	Paroxetine 20-50	NA		
			127	Sertraline 50-200	NA		
	Continuation	16	228	Escitalopram 10-20	NA		
	Maintenance	52	73	Escitalopram 10-20	20 (27)	*P*=NR	
			65	Placebo	42 (65)		
Rapaport et al., 2004[154]	Acute	8	502	Escitalopram 10-20	NA		
	Continuation	36	181	Escitalopram 10-20	47 (26)	*P*=0.01	Fair
			93	Placebo	37 (40)		
Gilaberte et al., 2001[167]	Acute	8	253	Fluoxetine 20-40	NA		Fair
	Continuation	24	179	Fluoxetine 20-40	NA		
	Maintenance	52	70	Fluoxetine 20-40	14 (20)	*P*=0.01	
			70	Placebo	28 (40)		
McGrath et al., 2006[179 *]	Acute	12	570	Fluoxetine 10-60	NA		Fair
	Continuation	26	131	Fluoxetine 10-60	46 (35)	*P*=NR	
			131	Placebo	81 (62)		
	Maintenance	26	131	Fluoxetine 10-60	60 (46)	*P*=0.004	
			131	Placebo	94 (72)		
Reimherr et al., 1998[155, 190]	Acute	12-14	839	Fluoxetine 20	NA		Fair
	Continuation	14	299	Fluoxetine 20	77 (26)	*P*<0.001	
			95	Placebo	46 (49)		
	Continuation	38	105	Fluoxetine 20	9 (9)	*P*<0.04	
			52	Placebo	12 (23)		
	Continuation	50	28	Fluoxetine 20	3 (11)	*P*=0.54	
			34	Placebo	6 (16)		
Schmidt et al., 2000[140] Dinan, 2001[156]	Acute	13	932	Fluoxetine 20	NA		Fair
	Continuation	25	189	Fluoxetine 20	49 (26)	*P*<0.01[a]	
			190	Fluoxetine 90 mg/week	70 (37)		
			122	Placebo	61 (50)		

Table 28. Placebo-controlled studies of relapse prevention and recurrence prevention (continued)

Study	Phase	Duration (Weeks)	N	Comparison and Dose (mg/day)	Relapse or Recurrence n (%)		Quality Rating
Terra and Montgomery, 1998[168]	Acute	6	436	Fluvoxamine 100-300	NA		Fair
	Continuation	18	283	Fluvoxamine 100	NA		
	Maintenance	52	110	Fluvoxamine 100	14 (13)	*P*<0.001	
			94	Placebo	33 (35)		
Claghorn and Feighner, 1993[170]	Acute	6	240	Paroxetine 10-50	NA		Fair
			237	Imipramine 65-275			
			240	Placebo			
	Continuation	52	94	Paroxetine 10-50	11 (12)	*P*=NR	
			79	Imipramine 65-275	3 (4)		
			46	Placebo	10 (22)		
Montgomery and Dunbar, 1993[152]	Acute	8	172	Paroxetine 20-40	NA		Fair
	Continuation	16	68	Paroxetine 20-30	2 (3)	*P*<0.01	
			67	Placebo	13 (19)		
	Maintenance	36	66	Paroxetine 20-30	9 (14)	*P*<0.05	
			54	Placebo	16 (30)		
Reynolds et al., 2006[180 *]	Acute	8	195	Paroxetine10-40	NA		Fair
	Continuation	16	151	Paroxetine 10-40	NA		
	Maintenance	104	35	Paroxetine 10-40	13 (37)	*P*=0.06	
			18	Placebo	10 (58)		
Lepine et al., 2004[173]	Remission Stability	8	371	Placebo	NA		Good
	Maintenance	72	189	Sertraline 50-100	32 (17)	*P*=0.002	
			99	Placebo	33 (33)		
Doogan and Caillard, 1992[159]	Acute	8	480	Sertraline 50-200	NA		Fair
	Continuation	44	185	Sertraline 50-200	24 (13)	*P*<0.001	
			110	Placebo	48 (46)		
Kamijima et al., 2006[164 a]	Acute	8	361	Sertraline 25-200	NA		Fair
	Continuation	16	117	Sertraline 25-200	10 (9)	*P*=0.016	
			118	Placebo	23 (20)		
Keller et al., 1998[171, 172]	Acute	12	426	Sertraline 50-200	NA		Fair
	Continuation	16	209	Sertraline 50-200	NA		
	Maintenance	76	77	Sertraline 50-200	5 (6)	*P*=0.002	
			84	Placebo	19 (23)		
Lustman et al., 2006[a181]	Acute / Continuation	16	351	Sertraline 25-200	NA		Fair
	Maintenance	52	79	Sertraline 25-200	27 (34)	*P*=0.02	
			73	Placebo	38 (52)		
Wilson et al., 2003[174]	Acute	8	318	Sertraline 50-200	NA		Fair
	Continuation	16-20	254	Sertraline 50-100	NA		
	Maintenance	100	56	Sertraline 50-100	25 (45)	*P*=0.21	
			57	Placebo	31 (54)		
SSNRIs vs. Placebo: Perahia et al., 2006[161, 162 *]	Acute	12	533	Duloxetine 60	NA		Fair
	Continuation	26	136	Duloxetine 60	23 (17)	*P*≤0.05	
			142	Placebo	39 (29)		
Perahia et al., 2009[177 *]	Acute	10	514	Duloxetine 60-120	NA		Fair
	Continuation	24	413	Duloxetine 60-120	17 (4)		
	Maintenance	52	146	Duloxetine 60-120	21 (14)	*P*<0.001	
			142	Placebo	47 (33)		

Table 28. Placebo-controlled studies of relapse prevention and recurrence prevention (continued)

Study	Phase	Duration (Weeks)	N	Comparison and dose daily (mg/day)	Relapse or Recurrence n (%)		Quality Rating
SNRIs vs. Placebo: Rickels et al., 2010[176] *	Acute	12	594	Desvenlafaxine 200-400	NA		Fair
	Maintenance	26	189	Desvenlafaxine 200-400	45 (24)	*P*<0.001	
			185	Placebo	78 (42)		
Thase et al., 2001[157]	Acute	8-12	410	Mirtazapine 15-45	NA		Fair
	Continuation	40	76	Mirtazapine 15-45	15 (20)	*P*=0.001	
			80	Placebo	35 (44)		
Kocsis et al., 2007[149, 182-187] *	Acute	10	266	Fluoxetine 20-60	NA		Fair
			781	Venlafaxine 75-300			
	Continuation	26	185	Fluoxetine 20-60	3 (2)	*P*=0.438	
			530	Venlafaxine 75-300	5 (1)		
	Maintenance	52	129	Venlafaxine 75-300	30 (23)	*P*=0.005	
			129	Placebo	54 (42)		
	Maintenance	52	43	Venlafaxine 75-300	3 (8)	*P*=0.001	
			40	Placebo	18 (45)		
Montgomery et al., 2004[175]	Acute / Continuation	26	495	Venlafaxine 100-200	NA		Fair
	Maintenance	52	109	Venlafaxine 100-200	24 (22)	*P*<0.001	
			116	Placebo	64 (55)		
Simon et al., 2004[160]	Acute	8	490	Venlafaxine 75-225	NA		Fair
	Continuation	26	161	Venlafaxine 75-225	45 (28)	*P*<0.001	
			157	Placebo	82 (52)		
Other Second-Generation Antidepressants vs. Placebo: Weihs et al., 2002[151]	Acute	8	816	Bupropion SR 300	NA		Fair
	Continuation	44	210	Bupropion SR 300	78 (37)	*P*=0.004	
			213	Placebo	111 (52)		
Gelenberg et al., 2003[169]	Acute	12	681	Nefazodone 300-600	NA		Fair
	Continuation	16	269	Nefazodone 300-600	NA		
	Maintenance	52	76	Nefazodone 300-600	23 (30)	*P*=0.043	
			84	Placebo	40 (48)		
Feiger et al., 1999[158]	Acute	16	467	Nefazodone 400-600	NA		Fair
	Continuation	36	65	Nefazodone 400-600	1 (2)	*P*=0.009	
			66	Placebo	12 (18)		

NA = not applicable; NR = not reported; SR = slow release

*New study added during update.

[a]Active treatment vs. placebo.

One trial focused on 405 older patients (age≥65 years; mean age 73).[163] Participants received open-label escitalopram (10–20 mg/day) for 12 weeks; responders (MADRS total score≤12) were eligible for randomization to 24 weeks of double-blinded treatment with escitalopram (10-20 mg/day; n=152) or placebo (n=153). Significantly fewer escitalopram-treated patients (MADRS≥22 or lack of efficacy as judged by the investigator) than placebo-treated patients experienced a relapse (9 percent vs. 33 percent; *P*<0.001). The risk of relapse was 4.4 times higher for placebo- than for escitalopram-treated patients (*P*<0.001), and the time to relapse was shorter for escitalipram- than for placebo-treated patients (*P*<0.001).

Another trial openly treated 502 MDD patients with escitalopram (10–20 mg/day) for 8 weeks.[154] Patients who responded (MADRS≤12) were randomized to 36 weeks of double-blind continuation treatment with escitalopram (n=181) or placebo (n=93). Relapse rates (MADRS≥22) were statistically significantly lower for escitalopram-treated patients than for

placebo-treated patients (26 percent vs. 40 percent, respectively; P=0.01), and the time to depressive relapse was significantly longer in patients who received escitalopram than in patients who received placebo (P=0.013).

One trial assessed recurrence prevention in 515 patients with recurrent depression (two or more previous episodes) who had responded (MADRS≤12) to 8 weeks of acute open-label treatment with citalopram, fluoxetine, paroxetine, or sertraline.[178] The 234 responders were openly treated with escitalopram (10–20 mg/day) for 16 weeks. Patients who continued to respond (MADRS≤12) were randomized to 52 weeks of maintenance-phase treatment with escitalopram (n= 73) or placebo (n=65). Recurrence rates were lower for patients receiving escitalopram than for those receiving placebo (27 percent vs. 65 percent), and time to recurrence was significantly longer for patients receiving escitalopram than placebo (hazard ratio 0.26; 95% CI, 0.13 to 0.52; P<0.001).

SSRI: Fluoxetine Versus Placebo

Three trials (five publications) assessed relapse prevention.[140, 155, 156, 179, 190] One of these trials,[179] plus one additional trial,[167] assessed recurrence prevention.

Of the relapse-prevention studies, one trial sought to determine the optimal length of continuation treatment by randomizing patients who were in remission (HAM-D<7 for 3 consecutive weeks) during 12 weeks to 14 weeks of acute-phase treatment with fluoxetine (20 mg/day) to 14 weeks, 38 weeks, or 50 weeks of continuation treatment with fluoxetine or placebo.[155, 190] Relapse rates were significantly lower for fluoxetine-treated patients than for placebo-treated patients at 14 weeks (26 percent vs. 49 percent, respectively; P<0.001) and 38 weeks (9 percent vs. 23 percent, respectively; P=0.04), but not at 50 weeks (11 percent vs. 16 percent, respectively; P=0.54). The other trial openly treated 932 patients with MDD for 13 weeks with fluoxetine.[140, 156] Responders (HAM-D≤9 and CGI-I≤2) were randomized to 25 weeks of continuation treatment with fluoxetine (20 mg/day; n=189), fluoxetine (90 mg/week; n=190), or placebo (n=122). Relapse rates were statistically significantly lower for both the daily and the weekly doses of fluoxetine than for placebo (26 percent and 37 percent vs. 50 percent, respectively; P<0.01 for placebo comparisons).

Another trial assessed both relapse and recurrence rates in patients who had responded (response criteria not reported) to 12 weeks of open-label treatment with fluoxetine (10-60 mg/day).[179] Patients were randomized (n=131 fluoxetine and n=131 placebo) only at the beginning of the continuation phase, but the authors reported results for a conventional 6-month continuation phase and an additional 6-month maintenance phase; statistical tests reflected only aggregate 52-week data. After 6 months, relapse rates (relapse criteria not reported) were 35 percent for fluoxetine and 62 percent for placebo; after 1 year, relapse rates were 45.9 percent for fluoxetine and 72.0 percent for placebo (hazard ratio 1.73; 95% CI, 1.20 to 2.51; P=0.004).

A different recurrence-prevention trial randomized patients who continued to meet remission criteria (HAM-D≤8) during a 6-month continuation period to 1 year of double-blind maintenance treatment with either fluoxetine (20-40 mg/day; n=70) or placebo (n=70).[167] Recurrence rates were statistically significantly lower for fluoxetine-treated patients than for placebo-treated patients (20 percent vs. 40 percent, respectively; P=0.01).

SSRI: Fluvoxamine Versus Placebo

One trial assessed recurrence prevention with fluvoxamine (100-300 mg/day).[168] Of 436 patients with major depression treated openly with fluvoxamine for 6 weeks, 283 responders

(MADRS<10 and CGI-I≤2) entered 18 weeks of continuation treatment with fluvoxamine 100 mg/day. Patients who sustained their response (MADRS<12 and no CGI-I score>2) were randomized to 1 year of double-blind treatment with fluvoxamine (n=110) or placebo (n=94). Recurrence rates were statistically significantly lower for fluvoxamine-treated patients than for placebo-treated patients (13 percent vs. 35 percent, respectively; $P<0.001$).

SSRI: Paroxetine Versus Placebo

Three trials compared paroxetine with placebo for relapse and recurrence prevention.[152, 170, 180] One trial focused specifically on patients 70 years old and older (mean age 77.1 years), comparing recurrence rates among four groups: (1) paroxetine plus clinical management (n=35); (2) paroxetine plus psychotherapy (n=28); (3) placebo plus psychotherapy (n=35); and (4) placebo plus clinical management (n=18).[180] We focused on the comparison of paroxetine with placebo for patients receiving clinical management services, which included monthly 30-minute visits to assess symptoms and possible adverse events. Major depression recurred (HAM-D_{17}≥15) among 37 percent of the paroxetine (10-40 mg/day) group and 58 percent of the placebo group ($P=0.06$).

One U.K. trial[152] and one U.S. trial[170] assessed long-term treatment with paroxetine. Both trials randomized patients who had responded to acute-phase paroxetine therapy to 1 year of paroxetine or placebo.

The U.K. study assessed relapse prevention after 16 weeks of double-blind treatment and recurrence prevention after an additional 36 weeks of continued double-blind treatment with paroxetine 20-30 mg/day.[152] After 16 weeks, significantly fewer paroxetine-treated patients had relapsed than placebo-treated patients (3 percent vs. 19 percent, respectively; $P<0.01$). Of the patients who maintained a response through the continuation phase and entered the maintenance phase, recurrence rates were lower for paroxetine-treated patients than for placebo-treated patients (14 percent vs. 30 percent, respectively; $P<0.05$).

The U.S. study was an extension of a 6-week acute-phase trial that compared paroxetine, imipramine, and placebo.[170] Investigators invited patients who had responded in the 6-week trial to continue flexible-dose, double-blind treatment for up to 1 year. Treatment allocation in the long-term extension was not randomized; the authors reported only aggregated relapse rates. More placebo-treated patients withdrew from the long-term trial because of "lack of efficacy"[170](n=10; 22 percent) than did patients treated with either paroxetine 10-50 mg/day (n=11; 12 percent) or imipramine 65-275 mg/day (n=3; 4 percent).

SSRI: Sertraline Versus Placebo

Two studies assessed relapse prevention;[159, 164] four other studies[171, 173, 174, 181] assessed recurrence prevention. In one relapse-prevention study, 295 patients who had responded in the acute phase were randomized to 44 weeks of double-blind treatment with sertraline (50-200 mg/day; n=185) or placebo (n=110).[159] Statistically significantly fewer sertraline-treated patients than placebo-treated patients experienced a relapse (13 percent vs. 46 percent, respectively; $P<0.001$). In a Japanese relapse-prevention study, 235 patients who had responded to 8 weeks of open sertraline treatment were randomized to 16 weeks of double-blind sertraline (50-100 mg/day; n=117) or placebo (n=118).[164] The relapse rate was significantly lower for sertraline patients than for placebo patients (9 percent vs. 20 percent; $P=0.016$). Time-to-relapse also was significantly longer for sertraline- than placebo-treated patients ($P=0.026$).

The good-quality relapse/recurrence-prevention trial addressed potential methodological biases by including patients with recurrent depression who had been successfully treated for at least 4 months with any antidepressant other than sertraline.[173] Active treatment was replaced with placebo for 2 months to identify patients truly in remission; patients who continued to remain in remission were randomized to sertraline 50 mg/day; (n=95), sertraline 100 mg/day (n=94), or placebo (n=99) and followed for 18 months. Patients treated with sertraline were statistically significantly less likely to have a recurrent depressive episode than patients treated with placebo (17 percent vs. 33 percent, respectively, for the pooled comparison; P=0.002).

Two other recurrence-prevention studies found that patients treated with sertraline had fewer recurrences than did those on placebo.[171, 174] In a 76-week maintenance phase, 6 percent of sertraline-treated and 23 percent of placebo-treated patients had a recurrent depressive episode (P=0.002).[171] Differences did not reach statistical significance in a 100-week maintenance treatment of community residents 65 years of age and older with major depression; 45 percent of sertraline-treated patients and 54 percent of placebo-treated patients had a recurrent episode (P=0.21).[174] This trial is described in further detail in KQ 5.

Another recurrence-prevention trial was conducted in patients with diabetes mellitus.[181] Patients who recovered from depression (four consecutive BDI scores≤9) during 16 weeks of open-label treatment with sertraline (25–200 mg/day) were randomized to 52 weeks of maintenance sertraline (n=79) or placebo (n=73). Recurrence of major depression (defined by DSM-IV criteria) was more common among placebo- than sertraline-treated patients (52 percent vs. 34 percent; P=0.02). This trial is described in further detail in KQ 5.

SSNRI: Duloxetine Versus Placebo

One trial (two articles) compared duloxetine with placebo for preventing relapse;[161, 162] one trial compared duloxetine with placebo for preventing recurrence.[177] The relapse-prevention trial treated MDD patients (n=533) openly with duloxetine (60 mg/day) for 12 weeks and then randomized responders (HAM-D17≤9, CGI-S≤2, and did not meet DSM-IV criteria for a major depressive episode) to 26 weeks of double-blinded duloxetine (60 mg/day; n=136) or placebo (n=142).[161, 162] Duloxetine-treated patients had significantly longer time to relapse (P=0.004); the estimated probability of relapse was 38.3 percent for duloxetine and 19.7 percent for placebo (P<0.05).

The recurrence-prevention trial treated MDD patients (n=514) openly with duloxetine 60-120 mg/day for 10 weeks, and then continued patients (n=413) meeting response criteria (HAM-D_{17}≤9, CGI-S≤2, and did not meet DSM-IV criteria for a major depressive episode) openly on duloxetine 60-120 mg/day for 24 weeks.[177] Patients continuing to meet response criteria were randomized to 52 weeks of maintenance treatment with duloxetine (n=146) or placebo (n=142). Time to depressive recurrence was significantly longer for duloxetine-treated patients than for placebo-treated patients (depressive recurrence of 14 percent vs. 33 percent, respectively; P<0.001).

SNRI: Desvenlafaxine Versus Placebo

One trial compared desvenlafaxine with placebo for preventing relapse.[176] After 12 weeks of open-label treatment with desvenlafaxine 200-400 mg/day, 375 responders (HAM-D17 total score≤11 on day 84) were randomized to 6 months of double-blind treatment with desvenlafaxine (n=189) or placebo (n=185). Patients receiving desvenlafaxine had significantly longer times to relapse compared with patients receiving placebo (log-rank test, P<0.0001). The

percentage of patients relapsing were 24 percent and 42 percent in the desvenlafaxine and placebo groups, respectively (P<0.001).

SNRI: Mirtazapine Versus Placebo

One trial of relapse prevention openly treated patients with recurrent or chronic major depression (n=410) with mirtazapine 15-45 mg/day for 8 weeks to 12 weeks.[157] Those in remission (HAM-D≤7 and CGI-I≤2) were randomized to 40 weeks of continuation treatment with mirtazapine (n=76) or placebo (n=80). Relapse rates were statistically significantly lower for mirtazapine-treated patients than for placebo-treated patients (20 percent vs. 44 percent, respectively; P=0.001).

SNRI: Venlafaxine Versus Placebo

Three trials studied venlafaxine;[160, 175, 182] one of these trials, the Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study, had multiple phases and was reported in multiple publications.[149, 182-187] The PREVENT trial's head-to-head continuation-phase comparison of fluoxetine with venlafaxine has already been presented (Table 28).[149] Among completers of this part of the trial, the venlafaxine responders (HAM-D_{17} total score≤12 and≥50 percent decrease from baseline) were randomized to 12 months of continued venlafaxine 75-300 mg/day (n=129) or placebo (n=129). At month 12, the recurrence probabilities were, respectively, 23.1 percent and 42.0 percent for venlafaxine- and placebo-treated patients (P=0.005).[182] Patients taking venlafaxine who maintained their response through 12 months were then again randomly assigned to a second 12 months of venlafaxine (n=43) or placebo (n=40). At the end of this second 12 months of maintenance treatment, recurrence was more common among placebo-treated patients than venlafaxine-treated patients (45 percent vs. 8 percent; P<0.001).[183] For the 2-year combined maintenance treatment, the recurrence probability was 47 percent for placebo- and 29 percent for venlafaxine-treated patients (P=0.005).[183]

One additional study assessed relapse prevention,[160] and one study assessed recurrence prevention.[175] The relapse-prevention study openly treated 490 patients with major depression with venlafaxine XR 75–225 mg/day for 8 weeks.[160] Patients who responded (CGI-S≤3 and HAM-D≤10) were randomized to 26 weeks of double-blind treatment with venlafaxine (n=161) or placebo (n=157). Statistically significantly fewer venlafaxine-treated patients than placebo-treated patients experienced a relapse (28 percent vs. 52 percent, respectively; P<0.001).

The recurrence-prevention study openly treated 495 patients with recurrent major depression for 6 months with venlafaxine 100–200 mg/day.[175] After 6 months, those who had responded (HAM-D≤12) were randomized to 12 months of venlafaxine (n=109) or placebo (n=116). The recurrence rate was statistically significantly lower for venlafaxine-treated patients than for placebo-treated patients (22 percent vs. 55 percent, respectively; P<0.001).

Other Second-Generation Antidepressants: Bupropion Versus Placebo

One trial assessed relapse prevention with bupropion.[151] Patients with recurrent major depression (n=816) were treated openly for 8 weeks with bupropion SR 300 mg/day. Those who responded (CGI-I score of 1 or 2 during the last 3 weeks of the acute phase) were randomized to placebo (n=213) or continuation treatment with the same dose of bupropion SR (n=210). After 44 weeks, relapse rates were statistically significantly lower for patients on bupropion than for those on placebo (37 percent vs. 52 percent, respectively; P=0.004). The median time to relapse,

as defined by the need for treatment intervention after randomization into the double-blind phase, was 24 weeks for placebo and at least 44 weeks for bupropion.

Other Second-Generation Antidepressants: Nefazodone Versus Placebo

One relapse-prevention trial[158] and one recurrence-prevention trial[169] evaluated nefazodone. In the relapse-prevention study, investigators randomized patients in remission (HAM-D≤10) to 36 weeks of double-blind treatment with nefazodone 400–600 mg/day (n=65) or placebo (n=66).[158] Statistically significantly fewer nefazodone-treated than placebo-treated patients relapsed (2 percent vs. 18 percent, respectively; P=0.009). The recurrence-prevention study openly treated 681 patients with chronic or recurrent major depression for 12 weeks with nefazodone 300-600 mg/day.[169] Patients who responded (≥50 percent improvement in HAM-D score from baseline) continued open-label nefazodone for an additional 16 weeks, and patients who maintained a response after this 16 weeks of continuation treatment were randomly assigned to 1 year of double-blind treatment with nefazodone (n=76) or placebo (n=84). The rate of recurrence was statistically significantly lower for patients on nefazodone than for those on placebo (30 percent vs. 48 percent, respectively; P=0.043).

Achieving Response in Unresponsive or Recurrent Disease: Overview

Trials relating to treating depressive disorders (MDD, dysthymia, or subsyndromal depression) in patients who had not responded to any acute-phase therapy—often referred to as treatment-resistant or refractory depression—or who suffered a relapse or recurrence focus on using drugs other than any medication first tried (KQ 2b). We review head-to-head evidence for treatment-resistant patients.

Six studies assessed differences among several alternative antidepressants in patients who had either not responded or could not tolerate an acute-phase treatment;[191-197] all included venlafaxine as a comparison. This group of trials varied in design; they included two effectiveness studies[191, 198] and four efficacy trials.[192, 193, 196, 197]

Achieving Response in Unresponsive or Recurrent Disease: Key Points

Of six comparative studies, the majority of studies did not report statistically significant differences among compared treatments.[193-197] The best evidence comes from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which was a good-quality study that indicated no differences in effectiveness among venlafaxine XR, bupropion SR, and sertraline as second-line agents.[194] Similar conclusions of no differences can be drawn based on three efficacy trials; one comparing citalopram with venlafaxine XR;[196] one comparing fluoxetine with venlafaxine XR;[197] and one comparing venlafaxine, mirtazapine, and paroxetine.[193] One efficacy trial comparing venlafaxine with paroxetine[192] and one open-label Spanish effectiveness study comparing venlafaxine XR, citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline both contradict these findings.[191] However, the efficacy trial was only 4 weeks long, which could limit the ability to observe full medication effects. Further, statistically significant differences were noted on the remission but not the response outcome measure.[192] Although the effectiveness study[191] was larger and potentially more generalizable, the magnitude of differences was relatively small and may not be clinically significant.

Overall, the body of evidence suggests that meaningful differences likely do not exist among compared agents for treatment-resistant depression. However, the degree of conflicting evidence as well as the lack of consistency in statistical significance led us to rate the overall strength of the evidence as low. The body of evidence was limited to relatively few comparisons, and additional studies could influence our overall conclusions of no differences.

Achieving Response in Unresponsive or Recurrent Disease: Detailed Analysis

Six studies assessed differences among alternative antidepressants in patients who either had not responded to or could not tolerate an acute-phase treatment (Table 29).[191-197] They covered several antidepressants, but all included venlafaxine (an SNRI) as a comparison. Three efficacy trials compared an SSRI with venlafaxine (an SNRI) in patients with treatment-resistant depression; comparisons included citalopram,[196] fluoxetine,[197] and paroxetine.[192] An additional trial compared venlafaxine with paroxetine but also included a mirtazapine arm.[193] Of two effectiveness trials, one compared venlafaxine XR with citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline in patients failing venlafaxine XR 75–225 mg/day or with some other conventional antidepressant therapy.[191] A second effectiveness trial compared bupropion SR, sertraline, and venlafaxine XR in patients failing aggressive management with citalopram. This trial also included augmentation strategies that added bupropion SR or buspirone to the citalopram.[194, 195, 198] Details on these comparisons are provided here.

Table 29. Head-to-head trials of treatment-resistant and recurrent depression

Study	Duration (Weeks)	N	Comparison and Dose (mg/day)	Response n (%)		Remission n (%)		Quality Rating
Lenox-Smith and Jiang, 2008[196] [a]	12	206	Citalopram 20-60	NR	*P*=NR	56 (27)	*P*=0.95	Fair
		200	Venlafaxine XR 75-375	NR		72 (36)		
Corya et al., 2006[197] [a]	12	60	Fluoxetine 10-80	19 (34)	*P*=NR	10 (18)	*P*=NR	Fair
		59	Venlafaxine XR 75-225	29 (50)		13 (22)		
Poirier and Boyer, 1999[192]	4	62	Paroxetine 30-40	18 (36)	*P*=0.07	11 (18)	*P*=0.02	Fair
		61	Venlafaxine XR 200-300	27 (45)		22 (37)		
Fang et al., 2010[193] [a]	8	45	Paroxetine 20	30 (67)	*P*=0.664	21 (47)	*P*=0.578	Fair
		50	Venlafaxine XR 225	32 (64)		21 (42)		
		55	Mirtazapine 45	32 (58)		20 (36)		
Rush et al., 2006[195] Trivedi et al., 2006[198] [a] (STAR*D trial)	Switch [a] 12-14	239	Bupropion SR 150-400	62 (26)	*P*>0.05	51 (21)	*P*=0.16	Good
		238	Sertraline 50-200	63 (27)		42 (18)		
		250	Venlafaxine XR 37.5-375	62 (25)		62 (25)		
	Augment[a] 12-14	279	Cit + Bupropion SR 200-400	89 (32)	*P*=0.21	109 (39)	*P*=0.13	
		286	Cit + Buspirone 15-60	77 (27)		94 (33)		
Baldomero et al., 2005[191]	24 (open)	1,465	Conventional therapy (pooled)	1,034 (71)	*P*<0.001	754 (52)	*P*<0.001	Fair
		294	Citalopram 20-40	209 (71)	*P*=0.024	153 (52)	*P*=0.024	
		248	Fluoxetine 20-40	174 (70)	*P*=0.012	128 (52)	*P*=0.032	
		116	Mirtazapine 30-45	75 (65)	*P*=0.004	52 (45)	*P*=0.003	
		312	Paroxetine 20-40	226 (73)	*P*=0.078	161 (52)	*P*=0.015	
		279	Sertraline 50-150	197 (71)	*P*=0.014	147 (53)	*P*=0.042	
		1,632	Venlafaxine XR 75-225	1,262 (78)	NA	963 (59)	NA	

CIT = citalopram; NR = not reported; ns = not statistically significant; STAR*D = Sequenced Treatment Alternatives to Relieve Depression; XR = extended release

[a]Primary comparison considered in this review

Citalopram Versus Venlafaxine XR

One efficacy trial assessed differences between citalopram 20–60 mg/day and venlafaxine XR 75-300 mg/day among 406 patients from Europe and Australia who had not experienced a response to 8 weeks of monotherapy with an adequate regimen of an SSRI other than citalopram.[196] After 12 weeks, similar numbers of patients met criteria for remission (HAM-D_{21}≤7; approximately 27 percent for citalopram and 36 percent for venlafaxine; *P*=0.95).

Fluoxetine Versus Venlafaxine XR

Another efficacy trial compared fluoxetine with venlafaxine in 119 patients who had failed to achieve satisfactory response to at least 6 weeks of SSRI treatment at a therapeutic dose.[197] This trial also included treatment arms for olanzapine (an atypical antipsychotic) and olanzapine plus fluoxetine combination, although we did not consider these comparisons. After 12 weeks, a larger percentage of patients treated with venlafaxine than with fluoxetine had a response (≥50 percent improvement in MADRS total score from baseline; 50 percent vs. 34 percent) or went into remission (MADRS≤8; 22 percent vs. 18 percent); statistical significance was not reported for these comparisons.

Paroxetine Versus Venlafaxine XR

A third efficacy trial compared paroxetine with venlafaxine in patients with major depression who either had not responded to or could not tolerate at least two previous treatments for their current depressive episode.[192] Patients were to be no more than minimally improved (CGI-I≥3) with their second treatment. The investigators enrolled 123 patients in the study—61 on venlafaxine 200-300 mg/day and 62 on paroxetine 30-40 mg/day—and followed them for 4 weeks. At endpoint, statistically significantly more venlafaxine-treated patients than paroxetine-treated patients were classified as having responded to treatment (≥50 percent improvement in HAM-D from baseline; 45 percent vs. 36 percent, respectively; *P*=0.07) and being in remission (HAM-D<10; 37 percent vs. 18 percent, respectively; *P*=0.02).

Paroxetine Versus Venlafaxine XR Versus Mirtazapine

A Chinese trial randomized patients with MDD who had failed two consecutive antidepressant trials to fixed-dose treatment with venlafaxine 225 mg/day (n=50), mirtazapine 45 mg/day (n=55), or paroxetine 20 mg/day (n=45).[193] After 8 weeks, response (HAM-D_{17} reduction from baseline≥50 percent) and remission (HAM-D_{17}≤7) rates were similar across all treatment groups. For response, the figures were 64 percent, 58 percent, and 67 percent, respectively (*P*=0.664); for remission, the figures were 42 percent, 36 percent, and 47 percent, respectively (*P*=0.578).

Sertraline Versus Venlafaxine XR Versus Bupropion SR

One study, the STAR*D trial, had several different treatment comparisons. We rated the quality of this trial as good and classify it as an effectiveness trial. Aspects of this trial have been reported in multiple manuscripts; we focused on the randomized medication-switch comparisons in level 2 (i.e., following failure of open-label citalopram) because these were the only direct comparisons of antidepressants included in this review.[194, 195] However, we also briefly mention the augmentation comparisons that included second-generation antidepressants.[198]

The STAR*D trial assessed differences in effectiveness in patients with MDD who had not gone into remission (Quick Inventory of Depressive Symptomatology—Clinician version

[QIDS-C-16]≤5) or could not tolerate citalopram during acute-phase treatment.[194, 195, 198] Participants eligible for second-step treatment had the option of switching to an alternative medication, cognitive behavioral therapy, or augmentation therapy. To mimic clinical practice, patients could opt to exclude certain second-step treatment options, and they were then randomized to an acceptable treatment option. The investigators compared only the treatments for which patients had accepted randomization. The primary outcome measure was the Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR).

Of the 727 patients randomized to second-step medication switch, 239 received bupropion SR 150–400 mg/day, 238 received sertraline 50–200 mg/day, and 250 received venlafaxine XR 37.5-375 mg/day. The investigators adjusted doses based on clinical judgment and side effect rating scales. Second-step treatment was continued for up to 14 weeks. At endpoint, response and remission rates were not statistically significantly different among bupropion SR, sertraline, and venlafaxine XR. For response, the figures were 26 percent, 27 percent, and 28 percent, respectively (P>0.05); for remission, the figures were 21 percent, 18 percent, and 25 percent, respectively (P=0.16). Treatments also differed only minimally with respect to tolerability and adverse events.

Level 2 of the STAR*D trial also included a randomized comparison of patients receiving citalopram plus augmentation with either bupropion SR 200–400 mg/day or buspirone 15–60 mg/day. (Buspirone is a psychoactive medication used principally as an anxiolytics; it does not belong to the SSRI/SNRI drug classes.) After 12 to 14 weeks, the percentage of patients with a QIDS-SR response or remission was not statistically significantly different between the patients receiving bupropion SR and buspirone augmentation (P=0.21 and P=0.13, respectively).

Citalopram Versus Fluoxetine Versus Mirtazapine Versus Paroxetine Versus Sertraline Versus Venlafaxine XR

The effectiveness trial randomized 3,502 patients with major depression, dysthymia, or minor depression who had shown inadequate response or intolerance to at least 4 weeks of previous antidepressant treatment with venlafaxine XR 75–225 mg/day or with some other conventional antidepressant therapy.[191] Conventional therapy selection was at the discretion of the treating psychiatrist; it included citalopram 20–40 mg/day (n=333), fluoxetine 20–40 mg/day (n=292), mirtazapine 30–45 mg/day (n=133), paroxetine 20–40 mg/day (n=361), sertraline 50–150 mg/day (n=299), and other miscellaneous drug treatments (n=254).

After 24 weeks of treatment, venlafaxine-treated patients had a statistically significantly better rate of response and remission than patients treated with conventional therapy. (For response, the figures were 78 percent vs. 71 percent, respectively; P<0.001; for remission, the figures were 59 percent vs. 52 percent, respectively; P<0.001.) Response and remission rates for venlafaxine XR were statistically significantly better than the rates for each of the individual drugs characterized as conventional therapy except for paroxetine. The response and remission rates in this study were much higher than those reported from the good-quality (STAR*D) effectiveness trial comparing bupropion SR, sertraline, and venlafaxine XR.[194, 195] Although differences in measurement scales may partially explain response rates, the reason that remission rates differed remains unclear because both trials used a HAM-D cutoff point of 7 or less to classify persons in remission.

Finally, one systematic review and meta-analysis of five trials reported a greater odds of response (OR, 1.35; 95% CI, 1.19 to 1.52) and remission (OR, 1.35; 95% CI, 1.2 to 1.52) for venlafaxine than for bupropion, citalopram, fluoxetine, and sertraline.[145] This analysis appeared

to rely on the same data presented above, although we could not confirm which trials contributed to the meta-analysis.

Key Question 3: Efficacy or Effectiveness for Treating Symptoms Accompanying Depression

All Symptoms: Overview

For this issue, we focus on the comparative benefit of medications for patients with depression and an accompanying symptom cluster. We identified studies addressing seven symptom clusters: anxiety, insomnia, low energy, pain, psychomotor change (retardation or agitation), melancholia (a depressive subtype that is a severe form of MDD with characteristic somatic symptoms), and somatization (physical complaints that are manifestations of depression rather than of an underlying physical illness). This set does not represent a complete list of symptoms commonly accompanying depression. For example, we did not identify any studies addressing appetite change—a common accompanying symptom reported by depressed patients.[199, 200]

For each symptom cluster, we arrange our summary by how the data best addresses the Key Question. We identified 29 relevant studies (Tables 30–36). Of these, 20 studies were head-to-head trials and one was a systematic review. Seven trials were placebo-controlled.

We identified 12 head-to-head trials on anxiety,[43, 49, 52, 67, 80, 84, 99, 107, 113, 201-203] six on insomnia,[43, 55, 76, 102, 103, 123] two on melancholia,[85, 202] one on pain,[87] and one each on psychomotor changes[202] and somatization.[43] Two head-to-head trials assessed more than one symptom subgroup.[43, 202] We did not locate any head-to-head trials on low energy.

The open-label effectiveness trial addressing somatization did not meet our eligibility criteria because of the lack of double blinding.[128] However, we report on its results because it was a well-conducted randomized controlled effectiveness trial and constitutes the only available evidence on effectiveness for somatization in depressed patients.

The remaining seven studies were placebo-controlled trials. Five addressed pain,[204-208] one addressed only anxiety,[209] and one addressed anxiety, low energy, and insomnia.[210] Two studies reported on adjuvant eszoplicone for insomnia.[211, 212]

All but two studies[52, 80] either were funded by or involved authors funded by pharmaceutical companies.

We rated all studies as fair quality. The fair rating was nearly universally a result of inadequate description of randomization and allocation concealment. A second common weakness was failure to report attrition rates, which occurred in several trials.[201, 202, 204, 205, 209] Quality was rated not applicable for the effectiveness trial because it did not meet our initial selection criteria.[128] No trial was rated good quality. We excluded five studies because of poor quality: one each on melancholia,[213] anxiety,[214] and insomnia,[215] and the other two on pain.[216, 217] Generally, the poor studies suffered high attrition either between treatment groups[213] or high overall attrition.[214, 216] We rated the insomnia study as poor because the authors failed to provide essential baseline information regarding patient characteristics and did not make clear whether they used an ITT analysis.[215] Finally, we excluded a meta-analysis of studies of patients with MDD and pain because of an inadequate literature search, poor assessment of the internal validity of included studies, and poor description of included studies.[217]

We report on poor studies only if the available evidence was very limited. For any poor studies retained for use in this report, we required, at a minimum, that investigators had employed a randomization scheme and applied ITT analysis.

Detailed information on these poor quality studies can be found in the evidence tables in Appendix D. We included one systematic review and meta-analysis on depressed patients with pain.[218] Our evidence tables are presented in Appendix C and provide information on systematic reviews and meta-analyses related to treating depression and accompanying symptoms.

Anxiety: Key Points

Seven head-to-head trials investigated treatment of depression in patients with accompanying anxiety symptoms.[80, 84, 99, 113, 201-203] Eleven head-to-head trials[43, 49, 52, 67, 80, 84, 99, 107, 113, 201, 203] and two placebo-controlled trials examined treatment of accompanying anxiety symptoms in patients with MDD.[209, 210] Six of these trials addressed both treatment of depression in patients with accompanying anxiety symptoms as well as treatment of accompanying anxiety symptoms.[80, 84, 99, 113, 201, 203]

Of the 14 trials, six compared various SSRIs with each other, six compared an SSRI with an SNRI or another second-generation drug, and two compared an SSRI or another second-generation drug with placebo (Table 30). We rated the strength of evidence that antidepressants are equally efficacious in treating depression in anxious patients and in treating the accompanying anxiety as moderate.

Depression in Patients With Anxiety

Overall, seven head-to-head trials generally indicated that antidepressant medications do not differ in treatment efficacy for depressed patients with accompanying anxiety symptoms. Five trials analyzed a subgroup with identified high anxiety; only two used the same definition criteria (a HAM-D anxiety-somatization factor of 7 or more).[99, 201]

The head-to-head trials compared SSRIs with each other,[201-203] venlafaxine,[80, 84, 99] or bupropion SR.[113] Studies appeared to compare similar doses of antidepressant medications. Two studies comparing SSRIs (fluoxetine, paroxetine, and sertraline) found no statistically significant differences in depressive improvement, response rates, or remission rates.[201, 202] One study comparing escitalopram and paroxetine showed escitalopram to be superior to paroxetine in improving depressive symptoms in a subgroup of patients with high anxiety.[203] Three studies comparing an SSRI and venlafaxine showed mixed results. One found a greater decrease in depressive severity and higher response rates with venlafaxine than with fluoxetine,[80] and one found no statistically significant difference in depressive severity change, response rates, or remission rates between venlafaxine XR and sertraline,[99] and venlafaxine XR and fluoxetine.[84] One study comparing sertraline and bupropion SR found no significant differences in response or remission rates.[113]

Table 30. Studies of adults with major depressive disorders and accompanying anxiety

Study	N	Duration	Comparison and Dose	Results	Quality Rating
SSRIs vs. SSRIs: Mao et. al., 2008[43] *	240	8 weeks	Escitalopram 10 Fluoxetine 20	Improvement on anxiety items of HAM-D similar for both groups	Fair
Boulenger et al., 2010[203] *	286	24 weeks	Escitalopram 20 Paroxetine 40	Improvement in depression scores greater for escitalopram than paroxetine (P<0.05) Improvement in anxiety scores greater for escitalopram than paroxetine (P<0.05)	Fair
Chouinard et al., 1999[49]	203	12 weeks	Fluoxetine 20-80 Paroxetine 20-50	Improvement in anxiety scores similar for both groups (P=NR)	Fair
Fava et al., 2000[201]	128 (all with anxiety)	10 to 16 weeks	Fluoxetine 20-60 Paroxetine 20-60 Sertraline 50-200	Improvement in depression scores (P=0.32), depression response rates (P=0.41) and remission rates similar for all groups (P=0.59) Improvement in anxiety scores similar for all groups (P=0.20)	Fair
Gagiano et al., 1993[52]	90	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	Improvement in anxiety scores was similar for both groups (P=NR)	Fair
Flament et al., 1999[202]	286 overall; 131 with anxiety	6 weeks	Fluoxetine 20-40 Sertraline 50-100	Improvement in depression scores and depression response rates similar for both groups (P=NR)	Fair
SSRIs vs. SNRIs or other second-generation antidepressant: Rush et al., 2001[113]	248 overall; top quartile of HAM-A score with anxiety (number not provided)	16 weeks	Bupropion SR 100-300 Sertraline 20-200	Depression response and remission similar for both groups (P=NR) Improvement in anxiety scores similar for both groups (P=NR)	Fair
Leinonen et al., 1999[67]	270	8 weeks	Citalopram 20-60 Mirtazapine 15-60	Improvement in anxiety scores similar for both groups (P=0.75)	Fair
DeNayer et al., 2002[80]	146 (all with anxiety)	12 weeks	Fluoxetine 20-40 Venlafaxine 75-150	Improvement in depression scores was greater and response rates higher for venlafaxine than fluoxetine (P<0.05) Improvement in anxiety scores greater for venlafaxine than for fluoxetine (P=0.001)	Fair
Silverstone, et al., 1999[84]	368 (all with anxiety)	12 weeks	Fluoxetine 20-60 Venlafaxine XR 75-225	Improvement in depression scores and response rates similar for venlafaxine and fluoxetine Improvement in anxiety response greater for venlafaxine XR than for fluoxetine (P=0.037)	Fair
Baldwin et al.,1996[107]	206	8 weeks	Nefazodone 200-600 Paroxetine 20-40	Improvement in anxiety scores similar for both groups	Fair
Sir et al., 2005[99]	163 overall; 120 with anxiety	8 weeks	Sertraline 50-150 Venlafaxine XR 75-225	Improvement in depression scores (P=0.70), depression response rates (P=0.26), and remission rates (P=0.44) similar for both groups Improvement in anxiety scores similar for both groups (P=0.32)	Fair

Table 30. Studies of adults with major depressive disorders and accompanying anxiety (continued)

Study	N	Duration	Comparison and Dose	Results	Quality Rating
SNRIs vs. Placebo: Khan et al., 1998[209]	403 overall; 346 with anxiety	12 weeks	Venlafaxine (3 doses) 75, 150, 200 Placebo	Improvement in anxiety scores for the 3 venlafaxine groups superior to placebo group (P<0.05); improvement similar for the 3 venlafaxine dose groups	Fair
Other second-generation antidepressants vs. placebo: Jefferson et al., 2006[210] *	274	8 weeks	Bupropion XL 150-450 Placebo	Similar improvement in anxiety for both groups (P=0.16)	Fair

HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; NR = not reported; SR = slow release; SSRI = selective serotonin reuptake inhibitor; vs. = versus; XL = extended release; XR = extended release
*New study added during update.

Anxiety in Depressed Patients

Overall, results from 11 head-to-head trials and two placebo-controlled trials suggested that antidepressant medications do not differ in treatment efficacy for treating anxiety associated with MDD. Six trials analyzed a subgroup with high anxiety;[80, 99, 113, 201, 203, 209] only two used identical definitions to identify the high anxiety group.[99, 201] In addition, outcome definitions for anxiety varied. The studies compared similar doses of antidepressants.

The head-to-head trials compared SSRIs with each other, with SNRIs, and with other second-generation drugs (bupropion, nefazodone). Four studies comparing SSRIs (including escitalopram, fluoxetine, sertraline, and paroxetine) found no statistically significant differences for treatment of patients' anxiety symptoms.[43, 49, 52, 201] One trial of escitalopram versus paroxetine demonstrated a superior improvement in anxiety scores for escitalopram compared with paroxetine in a subgroup of highly anxious patients.[203] Three studies comparing an SSRI (fluoxetine, sertraline) with venlafaxine found mixed results. Two trials reported that venlafaxine produced a greater decrease in anxiety severity than fluoxetine,[80, 84] whereas the other study reported similar anxiety reduction for venlafaxine XR and sertraline.[99] One study comparing sertraline and bupropion SR found no difference in anxiety reduction.[113] Two other studies found no difference in anxiety reduction between paroxetine and nefazodone,[107] and between citalopram and mirtazapine.[67]

The two placebo-controlled trials examined two different antidepressant agents for the treatment of anxiety; they produced conflicting information about the efficacy of the active agent compared with placebo. One trial reported that venlafaxine treatment produced a statistically greater reduction in anxiety scores than placebo.[209] In contrast, a trial of bupropion XL failed to demonstrate superiority over placebo for patients with depression and reduced energy, pleasure and interest.[210]

Anxiety: Detailed Analysis

Head-to-Head Evidence

We identified 12 head-to head trials comparing the efficacy of specific medications treating depressed patients with coexisting anxiety symptoms. Of these, one trial addressed only

improvement in depression among persons with anxiety[202] and seven studies addressed only improvement in anxiety as an outcome.[43, 49, 52, 67, 107, 209, 210]

Escitalopram Versus Fluoxetine

One trial compared low-dose escitalopram (10mg/day) with low-dose fluoxetine (20mg/day) over 8 weeks in 240 Chinese patients with MDD.[43] Patients were not required to have anxiety for inclusion and no subgroup analysis of patients with anxiety was provided. Response rates for the two HAM-D items for psychological and somatic anxiety (items 10 and 11) showed no significant difference between escitalopram and fluoxetine (Anxiety: psychological 77 percent vs. 76 percent and Anxiety: somatic 75 percent vs. 79 percent, respectively).

Escitalopram Versus Paroxetine

One trial compared high-dose escitalopam (20mg /d) with high-dose paroxetine (40mg /d) over 24 weeks. The investigators retrospectively divided the patients in a larger trial into high and low anxiety subgroups (HAM-A≤20 or HAM-A>20) and the results for depression and anxiety scores were re-analyzed for each subgroup. Here we report the results for the high-anxiety subgroup (n=286). Patients randomized to escitalopram showed a statistically significant greater improvement in both anxiety (HAM-A) and depression (MADRS) scores than those randomized to paroxetine (HAM-A: -17.6 vs. -15.2, $P<0.05$; MARDS, -24.2 vs. -21.5, $P<0.05$).

Fluoxetine Versus Paroxetine

Two trials compared the efficacy of low-to-high doses of fluoxetine with similar doses of paroxetine for treatment of anxiety.[49, 52] Neither study required high anxiety for inclusion in the analysis.

One trial compared fluoxetine (20–80 mg/day) and paroxetine (20–50 mg/day) in a 12-week trial involving 203 patients with severe MDD.[49] Improvements on multiple measures of anxiety did not substantially differ between the two treatment groups.

The other trial compared fluoxetine (20–60 mg/day) and paroxetine (20–40 mg/day) over 6 weeks in 90 patients with severe MDD.[52] Mean baseline anxiety severity was similar; each group had a moderate to severe degree of anxiety. Improvements in HAM-A scores were similar for the two groups.

Fluoxetine Versus Paroxetine Versus Sertraline

One RCT compared low-to-high dose fluoxetine (20–60 mg/day), low-to-high dose paroxetine (20–60 mg/day), and low-to-high dose sertraline (50–200 mg/day) over 10 to 16 weeks in patients with MDD of at least moderate severity and high anxiety (as defined by a score on the six-item HAM-D anxiety-somatization factor≥7 [range 0–18]).[201] Analyses were performed in the subgroup with high anxiety (n=108 patients from a trial with 284 participants overall); the outcomes included both depressive measures and anxiety measures. Depression outcomes were similar for the three medications, as measured by three outcomes: (1) improvement in HAM-D total scores, (2) improvement in response rates (≥50 percent reduction in HAM-D score; fluoxetine, 73 percent, paroxetine, 77 percent; and sertraline, 86 percent, $P=0.405$); and (3) improvement in remission rates (HAM-D endpoint≤7; fluoxetine, 53 percent; paroxetine, 50 percent; and sertraline, 62 percent; $P=0.588$). Authors reported no difference among the three groups with respect to anxiety outcomes (measured by overall change on HAM-D anxiety-somatization factor score).

Fluoxetine Versus Sertraline

One trial compared low-to-medium doses of fluoxetine (20–40 mg/day) and sertraline (50–100 mg/day) over 6 weeks in patients with MDD of at least moderate severity who also had high anxiety as defined by a Covi Anxiety Score≥7.[202] The outcome was depression response. Authors reported that response rates (defined by≥50 percent reduction in HAM-D total score) did not differ between the fluoxetine-treated group (48 percent) and the sertraline-treated group (47 percent).

Citalopram Versus Mirtazapine

One trial compared the efficacy of low-to-high dose citalopram (20–60 mg/day) and low-to-high dose mirtazapine (15–60 mg/day) over 8 weeks in 270 patients with MDD of at least moderate severity.[67] The outcome was treatment effect on anxiety as measured by HAM-A scores. However, patients were not categorized by anxiety level, and the analysis included all patients with MDD, not merely those with anxiety. The improvement in anxiety symptoms did not differ between citalopram and mirtazapine (mean HAM-A change in both groups was approximately -13 points).

Fluoxetine Versus Venlafaxine

Two trials compared fluoxetine and venlafaxine.[80, 84] One trial compared low-to-medium doses of fluoxetine (20–40 mg/day) with low doses of venlafaxine (75-150 mg/day) over 12 weeks in 146 moderately depressed patients with MDD who had a Covi Anxiety Scale score of 8 or higher (consistent with clinically relevant anxiety).[80] The other trial compared low-to-high doeses of fluoxetine (20–60mg/d) with low-to-high doses of venlafaxine XR (75–225 mg/d) over 12 weeks in 386 patients with MDD and anxiety (Covi score≥8). Both trials reported depression and anxiety outcomes. The results for depression were conflicting. In the smaller trial, the improvement in depressive severity on the HAM-D was significantly greater in the venlafaxine-treated group than the fluoxetine-treated group (-14.4 points vs. -10.4 points, P=0.0048). In the larger trial no significant difference in depression response or remission was reported. In contrast, venlafaxine was superior to fluoxetine for anxiety response in both trials. In the larger trial there were significantly more HAM-A responders at week 12 in the venlafaxine group compared with the fluoxetine group (P=0.037) and in the smaller trial the mean reduction on the Covi Anxiety Scale was greater for venlafaxine than for fluoxetine (-5.7 points vs. -3.9 points, P=0.001).

Sertraline Versus Bupropion SR

One efficacy trial compared low-to-high dose sertraline with low-dose buproprion SR over 16 weeks in 248 patients with MDD of moderate severity.[113] High anxiety patients were defined as those with scores in the top quartile on HAM-A (≥19, consistent with at least moderate anxiety). Outcomes included both depression ($HAM\text{-}D_{21}$) and anxiety (HAM-A) measures. For the subgroup with high anxiety, depression response rates (≥50 percent reduction in total score, approximately 70 percent in each group) and remission rates (endpoint≤8, approximately 70 percent in each group) were similar. Likewise, in the high-anxiety subgroup, authors reported no difference in anxiety reduction (measured by mean change in HAM-A) between patients treated with sertraline (-10.0) and bupropion (-9.7).

Sertraline Versus Venlafaxine XR

One efficacy trial compared low-to-high dose sertraline (50–150 mg/day) with low-to-high dose venlafaxine XR (75–225 mg/day) over 8 weeks in a subgroup of 120 patients with MDD of at least moderate severity and accompanying anxiety, defined as a HAM-D anxiety-somatization score of≥7.[99] Outcomes included both depressive ($HAM\text{-}D_{17}$) and anxiety (HAM-A) measures. Authors reported no difference between treatment groups in mean depressive severity reduction (-17.3 for sertraline vs. -14.8 for venlafaxine XR, P=0.7), depression response rates (≥50 percent reduction in total score, 80 percent for sertraline vs. 69 percent for venlafaxine XR, P=0.26), or depression remission rates (endpoint≤7, 63.0 percent for sertraline vs. 54.1 percent with venlafaxine XR, P=0.44).

Anxiety symptom outcomes did not differ between treatment groups for the overall study population (n=163) or for the high anxiety subgroup (n=120). In the overall study population, the mean reduction in HAM-A was -14.1 for the sertraline-treated group and -12.9 for the venlafaxine XR-treated group (P=0.32). In the high anxiety subgroup, response on the HAM-D anxiety-somatization subscale (criteria not described) was similar for both treatment arms (83.3 percent for sertraline vs. 70.5 percent for venlafaxine XR, P=0.12).

Paroxetine Versus Nefazodone

One RCT compared the low-to-medium dose paroxetine (20–40 mg/day) with low-to-high dose nefazodone (200–600 mg/day) for treatment of accompanying anxiety symptoms over 8 weeks in patients with moderate to severe MDD.[107] Inclusion in the analysis did not require high anxiety, and patients were not categorized based on anxiety level; the outcome was the mean difference between treatment groups in HAM-A improvement. Authors reported similar improvement in HAM-A for the treatment groups (-8.0 for paroxetine versus -6.5 for nefazodone, P=NS, 95% CI for difference between groups, -0.7-3.8).

Placebo-Controlled Evidence

Two trials examined the efficacy of a second-generation antidepressant only against placebo.

Venlafaxine Versus Placebo

One 12-week study randomly assigned patients with severe MDD to one of three doses of immediate-release venlafaxine or to placebo.[209] Inclusion did not require a high anxiety score. Treatment effects on anxiety were analyzed in a subgroup of 346 patients with accompanying anxiety (defined as a score of≥2 [at least moderate] on the HAM-D anxiety-psychological item, range 0–4). Each treatment arm had an equivalent number of patients with high anxiety. All four treatment arms experienced a reduction in anxiety. Patients in all three venlafaxine groups had statistically significant greater improvement in HAM-D anxiety-psychological and anxiety-somatization scores compared with the placebo group. The three venlafaxine groups did not differ from each other in anxiety outcomes.

Bupropion XL Versus Placebo

One placebo-controlled trial randomized 274 patients with depression and reduced energy, pleasure, and interest to 8 weeks of 150 mg/day to 450 mg/day of bupropion XL or placebo.[210] Investigators measured anxiety using the anxiety subset of the 30-item Inventory of Depressive Symptomatology- (Interactive Voice Response) Self Report scale (IDS-IVR-30). After 8 weeks

study investigators did not see any difference in improvement in anxiety between the bupropion XL and placebo groups: bupropion XL -2.4 compared with placebo -2.1, P=0.16.

Insomnia: Key Points

We identified six head-to-head studies that compared the effects of medications on treatment of depression and accompanying insomnia (Table 31)[43, 55, 76, 102, 103, 123] and one placebo-controlled trial.[210] Three of these trials required insomnia for inclusion in the analysis.[55, 102, 211] Five other trials did not require insomnia for inclusion but rather assessed sleep for all subjects.[43, 76, 103, 123, 210] The studies that identified an insomnia group provided data addressing both effects on depressive symptoms and effects on insomnia.[55, 102, 211] The other studies provided information solely on insomnia outcomes. Generally, antidepressants were equally efficacious for accompanying insomnia; however, two trials demonstrated that treatment with trazodone produced greater improvement in sleep scores than fluoxetine and venlafaxine[103, 123]and one trial showed that fluoxetine led to a worsening in sleep parameters and nefzodone to a slight improvement.[102, 212] In addition, two trials showed fluoxetine plus eszopiclone to be superior to fluoxetine alone.[211, 212] We rated the strength of evidence for depression outcomes in patients with accompanying insomnia as insufficient and for insomnia outcomes in patients with depression as low.

Depressive Episode in Patients With Insomnia

Two head-to-head studies provided evidence regarding comparative efficacy of medications for treatment of depression in patients with accompanying insomnia.[55, 102] The studies showed no statistically significant differences in depressive outcomes for fluoxetine compared with paroxetine and sertraline[55] or fluoxetine compared with nefazodone.[102] Two trials of fluoxetine supplemented with eszopiclone compared with fluoxetine alone showed mixed results for the difference between the groups for depression scores when the sleep items were excluded from the analysis.[211, 212]

Insomnia in Depressed Patients

Six head-to-head trials provided mixed evidence about the effects of antidepressants on insomnia in patients with depression. Two trials reported greater improvement in sleep scores for trazodone than for fluoxetine[103] and venlafaxine;[123] however, neither of these analyzed a subgroup of patients with insomnia. One trial found that sleep scores worsened with fluoxetine treatment but not with nefazodone.[102] One trial each found no statistically significant differences for patients on the following medications: escitalopram or fluoxetine;[43] fluoxetine, paroxetine, or sertaline;[55] and fluoxetine or mirtazapine.[76] Two trials of fluoxetine supplemented with eszopiclone compared with fluoxetine alone in depressed patients with insomnia showed an improvement in sleep for those receiving concomitant eszopiclone.[211, 212] A placebo-controlled study of bupropion XL found a small, statistically significant improvement in insomnia in those taking bupropion.[210]

Table 31. Trials of adults with major depressive disorders and accompanying insomnia

Study	N	Duration	Interventions	Results	Quality Rating
SSRIs vs. SSRIs: Mao et. al., 2008[43] *	240	8 weeks	Escitalopram 10 Fluoxetine 20	Improvement in HAM-D Insomnia items similar for both groups	Fair
Fava et al., 2002[55]	284 overall; 125 with insomnia	10 to 16 weeks	Fluoxetine 20-60 Paroxetine 20-60 Sertraline 50-200	Improvement in depression scores similar for all groups (*P*=0.853) Improvement in sleep similar for all groups (*P*=0.852)	Fair
SSRIs or SNRIs vs. other second-generation antidepressant: Versiani et al., 2005[76]	299	8 weeks	Fluoxetine 20-40 Mirtazapine 15-60	Improvement in sleep quality similar for both groups (overall score not reported)	Fair
Gillen et al., 1997[102]	44	8 weeks	Fluoxetine 20-40 Nefazodone 200-500	Improvement in depression scores similar for both groups Worsening in sleep scores greater for fluoxetine than nefazodone (*P*<0.05)	Fair
Beasley et al., 1991[103]	126	6 weeks	Fluoxetine 20-60 Trazodone 100-400	Improvement in sleep scores greater for trazodone than fluoxetine (*P*=0.001)	Fair
Cunningham et al., 1994[123]	227	6 weeks	Trazodone 150-400 Venlafaxine 75-200	Improvement in sleep scores greater for trazodone than venlafaxine (*P*<0.05)	Fair
Other second-generation antidepressants vs. placebo: Jefferson et. al., 2006[210] *	274	8 weeks	Bupropion XL 150-450 Placebo	Improvement in insomnia greater for bupropion than placebo (IDS-IVR-30 score: bupropion XL -2.1 vs. placebo -1.5, *P*=0.023)	Fair
SSRI vs. SSRI plus concomitant medication: McCall, et al., 2010[211] *	60	8 weeks	Fluoxetine 20-40 Fluoxetine 20-40 PLUS Eszopiclone 3	Improvement in depression scores similar for both groups (excluding insomnia scales; *P*=0.11) Improvement in sleep scores greater for fluoxetine plus eszopiclone than for fluoxetine alone (*P*<0.05)	Fair
Fava, 2006[212]	545	8 weeks	Fluoxetine 20-40 Fluoxetine PLUS Eszoplicone 3	Improvement in depression scores greater for fluoxetine plus eszoplicone than fluoxetine alone (*P*=0.009) Improvement in sleep latency, wake time after sleep onset and total sleep time better for combination of fluoxetine plus eszoplicone versus fluoxetine alone (*P<0.0005)*	Fair

HAM-D = Hamilton Rating Scale for Depression; IDS-IVR-30 = 30-item Inventory of Depressive Symptomatology - (Interactive Voice Response) Self Report; NR = not reported; SSRI = selective serotonin reuptake inhibitor; vs. = versus; XL = extended release

*Study added during update.

Insomnia: Detailed Analysis

Head-to-Head Evidence

Six head-to-head trials addressed this issue.

Escitalopram Versus Fluoxetine

One trial compared low-dose escitalopram (10 mg/day) and low-dose fluoxetine (20 mg/day) over 8 weeks in 240 Chinese patients with MDD.[43] The investigators did not require insomnia for inclusion, nor did they present trial results for a subgroup of patients with insomnia. Response rates for the three HAM-D items for initial-, middle-, and delayed-insomnia (items 4, 5, and 6) showed no statistically significant difference between escitalopram and fluoxetine (initial, 77 percent vs. 73 percent; middle, 61 percent vs. 64 percent; delayed, 70 percent vs. 69 percent, respectively).

Fluoxetine Versus Nefazodone

One trial compared low-to-medium doses of fluoxetine (20–40 mg/day) with low-medium doses of nefazodone (200–500 mg/day) in an 8-week trial of 44 MDD patients with insomnia.[102] The authors assessed sleep disturbance and improvement using polysomnographic recordings and the sleep items of the HAM-D. Overall nefazodone resulted in significantly less worsening of sleep parameters than fluoxetine (e.g., sleep efficiency and number of awakenings, $P<0.05$) and more improvement in the combined HAM-D sleep items "sleep disturbance factor" (mean ±SE: fluoxetine 1.5 ±0.4; nefazodone 2.5 ±0.3, $P<0.05$). Improvement in HAM-D score was similar for the two groups (mean improvement from baseline and 95% CI for fluoxetine 10.3 ±1.35 and for nefazodone 11.5 ±1.41).

Fluoxetine Versus Paroxetine Versus Sertraline

One trial compared low-to-high doses of fluoxetine (20–60 mg/day), paroxetine (20–60 mg/day), and sertraline (50–200 mg/day) in a trial of MDD patients with at least a moderate degree of depression that lasted between 10 and 16 weeks.[55] A secondary analysis evaluated depression outcomes in patients with insomnia, defined as a score of at least 4 points on the HAM-D sleep disturbance subscale (a 0 to 6 scale consisting of a summed score of three HAM-D_{17} sleep items [assessing initial, middle, and terminal insomnia], where higher scores indicated worse insomnia). For the 125 patients in this subgroup, the three SSRIs did not differ significantly on the HAM-D score (overall $P=0.853$).

This trial also assessed the effect of medications on insomnia. Again, treatment groups did not differ. Insomnia (measured as above on the 6-point scale) improved to a similar degree for all three groups (fluoxetine, -3.1; paroxetine, -2.9; sertraline, -3.1; overall $P=0.852$).

Fluoxetine Versus Trazodone

One trial compared low-dose fluoxetine (95 percent of participants took 20 mg/day) with low-to-medium dose trazodone (50–400 mg/day, median 250 mg) over 6 weeks in patients with major depression.[103] Investigators did not require insomnia symptoms for inclusion and did not analyze an insomnia subgroup. Overall HAM-D sleep disturbance scores improved more in the trazodone group than in the fluoxetine group (-2.7 vs. -1.6; $P=0.001$).

Fluoxetine Versus Mirtazapine

One trial compared low-to-medium doses of fluoxetine (20–40 mg/day) with low-to-high doses of mirtazapine in an 8-week trial of patients with severe MDD.[76] The investigators did not categorize subgroups of patients by the presence or absence of insomnia. They compared outcomes on the Leeds Sleep Evaluation Questionnaire for all trial participants. Total scores

were not reported; efficacy on individual items did not differ in any substantial or consistent way between treatment groups.

Venlafaxine Versus Trazodone Versus Placebo

One trial compared low-to-medium doses of venlafaxine (75–200 mg/day) and trazodone (150–400 mg/day) over 6 weeks in patients with major depression.[123] Investigators did not require insomnia symptoms for inclusion and did not analyze an insomnia subgroup. HAM-D sleep disturbance scores were better (lower) at endpoint in patients receiving trazodone than in those receiving either venlafaxine or placebo (score 1.42 for trazodone, 2.22 for venlafaxine, 1.95 for placebo; $P<0.05$). HAM-D sleep disturbance factor scores at endpoint did not differ between venlafaxine and placebo (P=NR).

Fluoxetine Versus Fluoxetine Plus Eszopiclone

Two trials compared fluoxetine (20–40 mg/day) with fluoxetine (20–40 mg/day) and concomitant eszopiclone (3 mg/day) over 8 weeks in depressed patients with insomnia.[211, 212] In one trial, the investigators measured an improvement in insomnia using prospective sleep diaries (completed by patients) and the Insomnia Severity Index (ISI) score.[211] The other trial used an interactive voice recording system to monitor sleep functions and depression symptoms.[212] The adjusted odds ratio for an improvement of 6 points on the ISI for patients receiving fluoxetine plus eszopcilone compared with fluoxetine alone was 7.21 (95% CI, 1.51 to 34.4).[211] In the second trial, the patients reported statistically significant improvements in total sleep time and sleep latency.[212] Results regarding depressive symptoms were conflicting: there was no statistically significant difference between the two groups in improvement on the HAM-D when sleep items were excluded from the analysis in one trial,[211] and in the other trial, the improvement in depression based on the HAM-D remained statistically significant even when insomnia items were removed from the subanalysis.[212]

Placebo-Controlled Evidence

One placebo-controlled trial randomized 274 patients with depression and reduced energy, pleasure, and interest to 8 weeks of 150 mg/day to 450 mg/day of bupropion XL or placebo.[210] Investigators measured insomnia using the insomnia subset of the 30-item IDS-IVR-30. After 8 weeks, participants in the bupropion XL group demonstrated a significantly greater improvement in insomnia score (bupropion XL -2.1; placebo -1.5, P=0.023).

Low Energy: Key Points

One placebo-controlled RCT focused on patients with reduced energy, pleasure and interest (the authors combine low energy and anhedonia items in their analysis) (Table 32).[210]

Table 32. Trials of adults with major depressive disorder and accompanying low energy

Study	N	Duration	Interventions	Results	Quality Rating
Other second generation vs. placebo: Jefferson et. al., 2006[210] *	274	8 weeks	Bupropion XL 150-450 Placebo	Improvement in depression scores for bupropion XL superior to placebo (P=0.018) Improvement in reduced energy, pleasure and interest subset score for bupropion XL superior to placebo (P=0.007)	Fair

XL = extended release

*New study added during update.

The strength of evidence that bupropion XL is superior to placebo for treating depression in patients with low energy or for treating the accompanying low energy is insufficient. The strength of evidence for the comparative efficacy of other antidepressants for treating low energy in depressed patients is insufficient.

Low Energy: Detailed Analysis

One 8-week, placebo-controlled RCT of bupropion XL involved 274 patients with reduced energy and pleasure as determined by their subset score on the self-rated IDS-IVR-30 scale.[210] Patients who received 150–450mg of bupropion XL showed a statistically significant greater mean improvement in their total IDS-IVR-30 score after 8 weeks than those who received placebo (bupropion XL -21.3 vs. placebo -17.6, P=0.018). Similarly, the bupropion XL group demonstrated a significantly greater improvement in the energy, pleasure, and interest subset of the IDS-IVR-30 scale after 8 weeks than those receiving placebo (bupropion XL -6.7; placebo -5.3, P=0.007).

Melancholia: Key Points

Two head-to-head studies examined whether, for patients with melancholia, medications differed in their effect on depressive symptoms (Table 33).[85, 202] We rated the strength of evidence for the comparative efficacy and effectiveness of second-generation antidepressants (fluoxetine, sertraline, and venlafaxine) for treating depression in patients with melancholia as insufficient.

Table 33. Trials of adults with major depressive disorders and accompanying melancholia

Study	N	Duration	Interventions	Results	Quality Rating
SSRIs vs. SSRIs: Flament et al., 1999[202]	286 overall; 197 with melancholia	6 weeks	Fluoxetine 20-40 Sertraline 50-100	Depression response rates for sertraline superior to fluoxetine (P<0.05); improvement in depression scores similar for both groups (P=NR)	Fair
SSRIs vs. SNRIs: Tzanakaki et al., 2000[85]	109 (all with melancholia)	6 weeks	Fluoxetine 60 Venlafaxine 225	Depression response and remission rates similar for both groups (P=NR)	Fair

NR = not reported; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

We found no evidence addressing the comparative efficacy and effectiveness of second-generation antidepressants for the treatment of accompanying melancholic symptoms; thus, the strength of evidence is insufficient.

Depressive Episode in Patients With Melancholia

Two head-to-head trial compared fluoxetine with sertraline[202] or venlafaxine.[85] One found a greater response rate in patients receiving sertraline than fluoxetine.[202] The other reported no difference between the fluoxetine and venlafaxine groups in response and remission rates.[85]

Melancholia in Depressed Patients

We identified no trial addressing treatment of melancholic symptoms.

Melancholia: Detailed Analysis

Head-to-Head Evidence

We identified two 6-week, fair-quality, head-to-head studies.[85, 202]

Fluoxetine Versus Sertraline

One trial enrolled patients who were at least moderately depressed (either MDD or the depressed phase of bipolar disorder); patients were randomized to low-to-medium dose fluoxetine (20–40 mg/day) or sertraline (50–100 mg/day) for 6 weeks.[202] In the subgroup with melancholia by DSM-III-R criteria, depression response rates (≥50 percent decrease in HAM-D) were significantly better for sertraline than for fluoxetine (59 percent vs. 44 percent, $P<0.05$).

Fluoxetine Versus Venlafaxine

One trial involved severely depressed hospitalized patients or outpatients with MDD and melancholia per DSM-IV criteria; patients were randomized to 6 weeks of either 60 mg/day of fluoxetine or 225 mg/day of venlafaxine.[85] Authors reported no statistically significant difference in response rates (≥50 percent decrease in HAM-D_{21} or MADRS and CGI improvement score of 1 or 2) between groups (58 percent for fluoxetine, 65 percent for venlafaxine). Similarly, remission rates (final HAM-D score<7) did not differ significantly (fluoxetine, 35.8 percent; venlafaxine, 40.7 percent).

Pain: Key Points

We included one systematic review,[218] one head-to-head trial[87] and five placebo-controlled trials[204-208] that assessed the efficacy of antidepressants for treatment of depression and accompanying pain symptoms (Table 34). The systematic review included studies that reported any pain-specific outcome.[218] Two placebo-controlled trials required baseline pain for inclusion;[204, 207] these studies provided data addressing both parts of this Key Question (depression outcomes in patients with accompanying pain; pain outcomes in MDD patients). The other four trials did not require pain for inclusion but rather assessed pain symptoms for all subjects; these trials provided information only for pain outcomes.[87, 205, 206, 208]

We rated all studies fair quality. The strength of evidence for the comparative efficacy of paroxetine and duloxetine for accompanying pain is moderate. The strength of evidence is insufficient for the superiority of duloxetine over placebo for treating the depressive episode, it is moderate for treating accompanying pain.

Depressive Episode in Patients With Pain

Two trials reported conflicting results regarding differences in efficacy between duloxetine and placebo for treatment of depression in patients with mild to moderate pain.[204, 207] One RCT of 282 patients suggested similar efficacy for duloxetine and placebo;[204] one RCT of 327 patients showed duloxetine to be superior to placebo in treating the depressive episode.[207]

Pain in Depressed Patients

Pooled results of four head-to-head studies in the systematic review and meta-analysis showed that improvement in pain scores was similar for paroxetine and duloxetine.[218] Six studies provided mixed evidence for efficacy of active drugs compared with placebo for treatment of accompanying pain. Six trials compared duloxetine with placebo;[87, 204-208] three of these reported

statistically greater pain improvement in at least one duloxetine treatment arm.[205-207] One study compared paroxetine with placebo;[87] and found a statistically greater improvement for paroxetine compared with placebo. Overall, mean differences in pain scores between groups were small and may not be clinically meaningful.

Table 34. Trials or other studies of adults with major depressive disorders and accompanying pain

Study	N	Duration	Interventions	Results	Quality Rating
SSRIs vs. SNRIs: Detke et al., 2004[87]	367	8 weeks	Duloxetine 80, 120 Paroxetine 20 Placebo	Improvement in pain for paroxetine superior to placebo (*P*=0.035) Improvement in pain scores similar for duloxetine 80 mg and placebo (*P*=0.063) and duloxetine 120 mg and placebo (*P*=0.086)	Fair
Krebs et al., 2008[218] *	NA	NA	Duloxetine Paroxetine Placebo	Improvement in VAS was similar for duloxetine and paroxetine (pooled WMD -0.8mm; 95% CI, -3.8mm to 2.3mm)	Fair
SNRIs vs. Placebo: Detke et al., 2002[205]	245	9 weeks	Duloxetine 60 Placebo	Pain score improvement slightly greater for duloxetine than placebo (*P*=0.019)	Fair
Detke et al., 2002[206]	267	9 weeks	Duloxetine 60 Placebo	Pain score improvement slightly greater for duloxetine than placebo (*P*=0.037)	Fair
Brannan et al., 2005[204] *	282	7 weeks	Duloxetine 60 Placebo	Improvement similar for duloxetine and placebo in depression scores (*P*=0.544), depression response rates (*P*=0.901), and remission rates (*P*=0.887) Improvement in pain scores was similar (*P*=0.066)	Fair
Brecht et. al., 2007[207] *	327	8 weeks	Duloxetine 60 Placebo	Greater improvement in depression severity for duloxetine than placebo (MADRS: duloxetine -- 16.69 vs. placebo -11.31, *P*≤0.0001) Greater improvement in pain for duloxetine than placebo (BPI-SF scale: duloxetine -2.57 vs. placebo -1.64, *P*=0.0008)	Fair
Raskin et. al., 2007[208, 219] *	311	8 weeks	Duloxetine 60 Placebo	Numerically greater improvement in pain for duloxetine than placebo; result not statistically significant (data NR).	Fair

BPI-SF = Brief Pain Inventory- Short Form; CI = confidence interval; MADRS = Montgomery-Asberg Depression Rating Scale; mg = milligram; mm = millimeter; NR = not reported; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; VAS = visual analogue scale; vs. = versus
*New study added during update.

For outcome measures, studies used a visual analog scale (VAS) for overall pain (0 mm to 100 mm scale, where higher scores indicate worse pain) or the Brief Pain Inventory (BPI) severity scale (0 to 10 scale, where higher scores indicate worse pain). No study reported percentages of patients with clinically important improvement in pain. All studies were funded by the maker of duloxetine.

Pain: Detailed Analysis

Head-to-Head Evidence

Paroxetine Versus Duloxetine Versus Placebo

Two multicenter trials compared the efficacy of duloxetine, paroxetine, and placebo. Neither trial required pain symptoms for inclusion; baseline pain severity was mild in both trials.

One systematic review of studies that included at least one pain-related outcome pooled the results of four head-to-head studies of paroxetine and duloxetine.[218] The results indicated that the

efficacy of duloxetine and paroxetine does not differ meaningfully for treating accompanying pain; the reviewers calculated a pooled weighted mean difference on the VAS of -0.8 mm, slightly favoring paroxetine over duloxetine (95% CI, -3.8 mm to 2.3 mm).

In addition, one trial compared two high doses of duloxetine (80 mg/day and 120 mg/day) to low-dose paroxetine (20 mg/day) and placebo.[87] Improvement in overall pain (decrease in 100 mm VAS) was similar for both duloxetine formulations and paroxetine (duloxetine 80 mg/day, -11.2 mm; duloxetine 120 mg/day, -12.2 mm; paroxetine, -16.0 mm; P=0.77 for duloxetine 80 mg vs. paroxetine; P=0.66 for duloxetine 120 mg vs. paroxetine). Mean pain improvement was statistically significantly superior to placebo for paroxetine (P=0.035) but not for either duloxetine formulation (P=0.063 for duloxetine 80 mg vs. placebo; P=0.086 for duloxetine 120 mg vs. placebo).

Placebo-Controlled Evidence

Duloxetine Versus Placebo

Overall, five trials provide evidence on duloxetine versus placebo.[204-208] Two trials randomized only patients with pain to high-dose duloxetine (60mg/day) for 7,[204] or 8 weeks.[207] In the 7-week, multicenter trial, participants were 282 outpatients who met DSM-IV criteria for major depression and reported accompanying pain, with a BPI average pain score of 2 or more at baseline. Patients who had "a primary pain complaint with a diagnosis such as arthritis, fibromyalgia, migraine headache, or acute injury" were excluded. Mean baseline pain severity was moderate (BPI average: 4.85 for duloxetine, 4.62 for placebo). The authors found no statistically significant difference between duloxetine and placebo on either depression or pain outcomes. Mean HAM-D_{17} improvement was similar for the groups (duloxetine, -10.9; placebo, -10.3; P=0.544). Depression response and remission rates did not differ between duloxetine and placebo (response 42 percent vs. 40 percent, P=0.901; remission 23 percent vs. 24 percent, P=0.887). Mean reduction in BPI average pain was similar for duloxetine and placebo (-2.32 vs. -1.80; P=0.066). Mean changes in BPI worst pain, least pain, and current pain intensity did not differ between treatment groups (P>0.10 for all comparisons). Mean changes in VAS overall pain did not differ between treatment groups (values NR, P=NR). In contrast, depressed patients with at least moderate pain (based on a BPI-SF score of 3 or more) receiving duloxetine in the 8-week RCT demonstrated a significantly better response to treatment than those receiving placebo for depression (MADRS total score: duloxetine -16.69; placebo -11.31, $P\leq$0.001) and pain (BPI-SF average pain: duloxetine -2.57 vs. placebo -1.64, P=0.0008).[207]

Three trials compared the efficacy of high-dose duloxetine (60 mg/day) to placebo over 8 to 9 weeks for treatment of pain in patients with depression who met DSM-IV criteria for MDD but were not required to have pain.[205, 206, 208] Mean baseline pain severity was mild (VAS for overall pain: 29.0, 25.4, and 30.1 for duloxetine, 28.2, 26.2, and 33.35 for placebo). All three studies reported differences in VAS overall pain improvement favoring duloxetine over placebo; in two cases this result reached statistical significance: -8.5 mm vs. -1.3 mm (P=0.019)[205] and -11.0 mm vs. -6.4 mm (P=0.037).[206]

Psychomotor Change: Key Points

One head-to-head trial examined depression response in subgroups with psychomotor change (including psychomotor retardation or psychomotor agitation) (Table 35).[202] We graded the strength of evidence for the comparative efficacy of fluoxetine and sertraline for treating the

depressive episode in patients with accompanying psychomotor change as insufficient. We found no evidence for the comparative efficacy and effectiveness of second-generation antidepressants for the treatment of accompanying psychomotor symptoms; strength of evidence is insufficient.

Table 35. Studies of adults with major depressive disorders and accompanying psychomotor change

Study	N	Duration	Interventions	Results	Quality Rating
SSRIs vs. SSRIs: Flament et al., 1999[202]	286 overall 47 with psychomotor retardation 78 with psychomotor agitation	6 weeks	Fluoxetine 20-40 Sertraline 50-100	In patients with psychomotor retardation, depression scores and response rates similar for both groups (*P*=NR) In patients with psychomotor agitation, depression scores (*P*=0.02) and response rates (*P*=0.04) were superior for sertraline	Fair

NR = not reported; SSRI = selective serotonin reuptake inhibitor

Depressive Episode in Patients With Psychomotor Changes

One trial provided evidence that fluoxetine and sertraline have similar efficacy for treatment of depression in patients with psychomotor retardation. It also reported that sertraline was more efficacious than fluoxetine for treating depression in patients with psychomotor agitation.[202]

Psychomotor Changes in Depressed Patients

We identified no efficacy trials addressing treatment of psychomotor change symptoms.

Psychomotor Change: Detailed Analysis

Head-to-Head Evidence

Fluoxetine Versus Sertraline

One 6-week trial compared low-to-medium doses of fluoxetine and sertraline for treating depression in subgroups of patients with MDD or the depressed phase of bipolar disorder and psychomotor retardation or psychomotor agitation.[202] The subgroup with psychomotor retardation comprised 47 patients with a score of 2 or more on HAM-D item 8 (retardation) and 1 or less on item 9 (agitation). In this subgroup, mean HAM-D scores improved similarly for fluoxetine- and sertraline-treated patients (-10.7 vs. -9.1 points, *P*=NR). Response rates (≥50 percent improvement on HAM-D-17 total score) were also similar for fluoxetine and sertraline (46 percent vs. 48 percent, *P*=NR). The same study evaluated depression response in a subgroup of 78 patients with psychomotor agitation, defined as a score of 1 or less on HAM-D item 8 and 2 or more on item 9. Among patients with psychomotor agitation, improvement in HAM-D total score was greater in patients receiving sertraline than in those receiving fluoxetine (-12.4 vs. -8.7 points, *P*=0.02). Response rates were also significantly better for sertraline than for fluoxetine (62 percent vs. 39 percent, *P*=0.04).

Somatization: Key Points

We identified one randomized, head-to-head trial and one open-label, head-to-head effectiveness trial that compared effects of medications on accompanying somatization in

depressed primary-care patients (Table 36).[43, 128] The strength of evidence that antidepressants demonstrate similar efficacy and effectiveness for the treatment of accompanying somatization is insufficient. We identified no trials that dealt with treating depression among patients with somatization; thus, the strength of evidence for this issue is insufficient.

Table 36. Studies of adults with major depressive disorders and accompanying somatization

Study	N	Duration	Interventions	Results	Quality Rating
SSRIs vs. SSRIs: Mao et. al., 2008[43] *	240	8 weeks	Escitalopram 10 Fluoxetine 20	Improvement in somatization items of HAM-D similar for escitalopram and fluoxetine	Fair

HAM-D = Hamilton Rating Scale for Depression; SSRI = selective serotonin reuptake inhibitor
*New study added during update.

Somatization in Depressed Patients

One RCT of escitalopram and fluoxetine found no difference in response rates on the somatization items of the HAM-D (items 12 and 13).[43] One open-label effectiveness study found no difference in effectiveness among paroxetine, fluoxetine, and sertraline on a somatization severity scale measure.[128]

Somatization: Detailed Analysis

Head-to-Head Evidence

Escitalopram Versus Fluoxetine

One trial compared low-dose escitalopram (10 mg/day) with low-dose fluoxetine (20 mg/day) over 8 weeks in 240 Chinese patients with MDD.[43] The investigators provided response rates for the two HAM-D items for gastrointestinal and general somatization (items 12 and 13). Escitalopram and fluoxetine did not differ significantly in efficacy detected.

Fluoxetine Versus Paroxetine Versus Sertraline

One open-label, head-to head trial compared the effectiveness of low-dose fluoxetine, paroxetine, and sertraline for the treatment of depression in primary care over 9 months.[128] Somatization severity was measured using the Patient Health Questionnaire Somatization Severity scale (0–28 scale, where higher scores indicate worse severity). The report did not present analyses stratified by levels of somatization severity. The authors reported no statistically significant differences in somatization severity scores among treatment groups (-3.1 for fluoxetine, -3.2 for paroxetine, and -4.1 for sertraline, *P*=NR).

Key Question 4: Safety, Adverse Events, Adherence

This section has two parts: the first relates to comparisons among second-generation antidepressants in general (e.g., as in KQ 1), and the second relates to comparisons between immediate- and extended-release compounds. The basic issues are whether the medications differ in safety, adverse events, or adherence and persistence. Of interest, as before, are the following: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline); SSNRIs and SNRIs (desvenlafaxine, duloxetine, mirtazapine, and venlafaxine); and all other second-generation agents (bupropion, nefazodone, and trazodone).

As described in more detail in the Methods section, we included data from head-to-head trials, placebo-controlled trials, and observational studies for the assessment of the comparative harms of second-generation antidepressants. We included observational studies when the sample size was larger than 1,000 and the study duration at least 3 months.

The two main parts dealing with these issues are generally presented in the same way as the earlier sections: an overview of the articles included a summary of the key points and a detailed analysis of studies. Because specific harms or categories of adverse events are of particular significance, we generally focus on those in subsections. Tables in the subsections on detailed analysis present information as in the tables for KQ 1, with information about comparisons (SSRIs, then SSNRIs and SNRIs, then other antidepressants) from head-to-head trials first, then placebo-controlled trials, then other types of studies. For this purpose, we regard systematic reviews and meta-analyses as observational studies.

Key Question 4a: Comparative Harms and Adherence for Second-Generation Antidepressants

We structured this section in four parts: a general overview, a synthesis of the evidence on adverse events and discontinuation rates, a section on serious adverse events, and a section on adherence. We have distinguished adverse events from serious adverse events based on a Food and Drug Administration (FDA) classification. FDA defines adverse events as any medical occurrence associated with the use of a drug, whether or not considered drug related.[220] A serious adverse event is any medical occurrence that results in death, is life threatening, requires hospitalization, results in persistent or significant disability or incapacity, or is a congenital birth defect.[220]

Adverse Events and Discontinuation Rates: Overview

Most of the studies that examined the efficacy of one drug relative to another also determined differences in harms. Methods of adverse events assessment differed greatly. Few studies used objective scales such as the UKU-SES (Utvalg for Kliniske Undersogelser Side Effect Scale) or the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Determining whether assessment methods were unbiased and adequate was often difficult. Rarely did authors report whether adverse events were prespecified and defined. Short study durations and small sample sizes also limited the validity of adverse events assessment in many trials.

Few randomized controlled trials (RCTs) were designed to assess adverse events as primary outcomes. Most published studies were post hoc analyses or retrospective reviews of databases.

Detailed information on included studies can be found in the evidence tables in Appendix C; information on systematic reviews and meta-analyses on this topic appears in the evidence tables. Most studies were rated fair quality; those rated otherwise are noted in text.

Adverse Events and Discontinuation Rates: Key Points

We analyzed adverse events data of 92 head-to-head efficacy studies of 22,586 patients and 51 additional studies of both experimental and observational design.

In efficacy trials, on average, 63 percent of patients experienced at least one adverse event during treatment. Diarrhea, dizziness, dry mouth, fatigue, headache, nausea, sexual dysfunction,

sweating, tremor, and weight gain were commonly reported adverse events. Overall, second-generation antidepressants led to similar adverse events; the frequencies of specific adverse events, however, differed among some second-generation antidepressants. These findings are generally consistent with results from observational studies. Specifically:

- Venlafaxine was associated with an approximately 49 percent (95% CI, 22 to 82) higher incidence of nausea and vomiting than with SSRIs as a class. The strength of evidence is high.
- Mirtazapine led to higher weight gains than comparator drugs.[75-77, 90, 92, 118] Mean weight gains relative to pretreatment weights ranged from 0.8 kg to 3.0 kg after 6 weeks to 8 weeks of treatment. The strength of evidence for higher risks of weight gain with mirtazapine than with other antidepressants is high.
- Sertraline led to higher rates of diarrhea than comparator drugs (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine) in most studies.[41, 56, 58-60, 64, 66, 96, 97, 112-114, 132, 133, 201, 221] The incidence was 8 percent (95% CI, 3 to 11) higher than with comparator drugs. Whether this finding can be extrapolated to comparisons of sertraline with the remaining second-generation antidepressants remains unclear. The strength of evidence that sertraline has a higher risk of diarrhea than other antidepressants is moderate.
- Trazodone was associated with an approximately 16 percent (3 percent less to 36 percent higher) higher incidence of somnolence than comparator drugs (bupropion, fluoxetine, mirtazapine, paroxetine, venlafaxine).[103, 104, 109, 119, 123, 124] Whether this finding can be extrapolated to comparisons of trazodone with the remaining second-generation antidepressants remains unclear. The strength of evidence that trazodone leads to higher rates of somnolence than comparator drugs is moderate.
- Overall discontinuation rates were similar between SSRIs as a class and other second-generation antidepressants. The strength of evidence is high.
- Discontinuation rates because of adverse events were also similar between SSRIs as a class and bupropion, mirtazapine, nefazodone, and trazodone. The strength of evidence is high. Duloxetine had a 67 percent (95% CI, 17 to 139) and venlafaxine an approximately 40 percent (95% CI, 16 to 73) higher risk for discontinuation because of adverse events than SSRIs as a class. The strength of evidence is high.
- Discontinuation rates because of lack of efficacy were similar between SSRIs as a class and bupropion, duloxetine, mirtazapine, nefazodone, and trazodone. Venlafaxine had a 34 percent (95% CI, 47 to 93) lower risk of discontinuation because of lack of efficacy than SSRIs as a class. The strength of evidence is high.

Adverse Events and Discontinuation Rates: Detailed Analysis

Tables 37–39 present data on the design, interventions, results, and quality ratings of studies we included to examine issues relating to key adverse events and discontinuation. We focused on general tolerability and discontinuation (including nausea and vomiting and selected gastrointestinal problems) (Table 37), weight change (Table 38), and discontinuation syndrome (Table 39). We rated the strength of evidence on general adverse events as high or moderate (depending on the specific measure) and on discontinuation rates as high.

Table 37. Studies assessing general tolerability and discontinuation

Study	Design Interventions	N	Results	Quality Rating
Rapaport et al., 1996[47]	RCT Fluoxetine vs. fluvoxamine	100	Significantly more nausea with fluoxetine	Fair
Brambilla et al., 2005[222]	Systematic review Fluoxetine vs. other SSRIs	15,920	No difference in discontinuation rates because of adverse events	Good
Mackay et al., 1999[223] Mackay, Dunn, and Mann,1999[224]	Prescription event monitoring Fluoxetine, fluvoxamine, sertraline, nefazodone, paroxetine, venlafaxine	>74,626	Similar side effects profiles;the most overall adverse events with fluvoxamine	Fair
Haffmans, Timmerman, and Hoogduin, 1996[40]	RCT Fluvoxamine vs. paroxetine	217	Significantly more diarrhea and nausea with fluvoxamine	Fair
Cipriani et al., 2010[221] *	Meta-analysis Sertraline vs. other second-generation antidepressants	NR	No differences in overall adverse events rates Significantly higher rates of diarrhea for sertraline than bupropion and mirtazapine	Good
Meijer et al., 2002[225]	Retrospective cohort study Sertraline vs. SSRIs	1,251	Significantly more diarrhea with sertraline	Fair
Greist et al., 2004[226]	Pooled analysis Duloxetine vs. fluoxetine and paroxetine	2,345	No differences in nausea between duloxetine and paroxetine or duloxetine and fluoxetine	Fair

NR = not reported; RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitors
*New study added during update.

Table 38. Studies assessing changes in weight

Study	Design Interventions	N	Results	Quality Rating
Kasper et al., 2009[227] *	Pooled analysis of 2 RCTs Escitalopram vs. paroxetine	777	No differences in weight gain between escitalopram and paroxetine	Fair
Fava et al., 2000;[127] Fava et al., 2002[55]	RCT Fluoxetine vs. paroxetine vs. sertraline	284	Highest weight gain with paroxetine Weight gain >7 percent more often with paroxetine	Fair
Hong et al., 2003[75]	RCT Fluoxetine vs. mirtazapine	133	Higher weight gain with mirtazapine	Fair
Versiani et al., 2005[76]	RCT Fluoxetine vs. mirtazapine	299	Higher weight gain with mirtazapine	Fair
Wheatley et al., 1998[77]	RCT Fluoxetine vs. mirtazapine	133	Significantly higher weight gain with mirtazapine	Fair
Wise et al., 2006[228] *	Pooled analysis Fluoxetine vs. paroxetine vs. duloxetine	5,194	Similar weight changes among duloxetine, fluoxetine, and paroxetine	Fair
Benkert, Szegedi, and Kohnen, 2000[90]	RCT Paroxetine vs. mirtazapine	275	Higher weight gain with mirtazapine	Fair

Table 38. Studies assessing changes in weight (continued)

Study	Design Interventions	N	Results	Quality Rating
Schatzberg et al., 2002[92]	RCT Paroxetine vs. mirtazapine	255	Higher weight gain with mirtazapine	Fair
Guelfi et al., 2001[118]	RCT Venlafax ine vs. mirtazapine	157	Higher weight increase with mirtazapine	Fair
Halikas, 1995[119]	RCT Trazodone vs. mirtazapine	150	Increased appetite reported with mirtazapine	Fair
Goldstein et al.,1997[229]	RCT Fluoxetine vs. placebo	671	Higher weight loss with fluoxetine in older patients	Fair
Michelson et al., 1999[190] Reimherr et al., 1998[155]	RCT Fluoxetine vs. placebo	395	Fluoxetine and placebo showed a weight gain	Fair
Croft et al., 2002[230]	RCT Bupropion vs. placebo	423	Small weight loss with bupropion over 44 weeks	Fair

NA = not applicable; NR = not reported; RCT = randomized controlled trial
*New study added during update.

Table 39. Studies assessing discontinuation syndrome

Study	Design Interventions	N	Results	Quality Rating
Judge et al., 2002[231]	Open-label trial Fluoxetine vs. paroxetine	150	Significantly fewer symptoms in the fluoxetine group than the paroxetine group	Fair
Montgomery and Andersen, 2006[232] *	Pooled analysis Escitalopram vs. venlafaxine XR	487	Significantly more discontinuation symptoms in the venlafaxine XR than in the escitalopram group	Fair
CSM Expert Working Group, 2004[233]	Systematic review and meta-analysis Second-generation antidepressants	NR	No differences in risk of discontinuation syndrome among second-generation antidepressants	Good
Zajecka et al., 1998[234]	RCT Fluoxetine vs. placebo	395	Dizziness significantly less frequent in fluoxetine patients at 4 and 6 weeks	Fair
Perahia et al., 2005[235]	Pooled analysis Duloxetine vs. placebo	3,624	Significantly higher rate of discontinuation syndrome with duloxetine than with placebo (44% vs. 23%)	Fair

RCT = randomized controlled trial; vs. = versus; XR = extended release
*New study added during update.

Table 40 summarizes, by specific drug, the mean incidence and 95 percent confidence interval for six specific adverse events commonly reported in head-to-head trials. We calculated descriptive statistics based on data from efficacy studies. Comparisons across different drugs, however, should be made with caution given differences in assessment and reporting of adverse events across trials.

Table 40. Incidence of specific adverse events across head-to-head trials (mean percentage) (95 percent confidence interval)[a]

Drug	Diarrhea	Dizziness	Headache	Insomnia	Nausea	Somnolence
Bupropion	8.9 (3.3-14.4)	9.3 (1.6-17.3)	27.6 (22.0-33.2)	14.6 (9.6-19.7)	14.3 (9.8-18.8)	5.4 (0.1 -10.7)
Citalopram	9.1 (5.5-12.6)	7.6 (3.4-11.9)	15.6 (8.2-23.0)	10.3 (5.0-15.5)	12.7 (8.5-16.9)	12.3 (5.2-19.4)
Desvenlafaxine	NR	NR	NR	12.5 (-6.5-31.6)	22.5 (16.2-28.9)	NR
Duloxetine	17.4 (8.6-26.2)	16.4 (11.7-21.2)	18.5 (8.8-28.1)	12.6 (9.5-15.7)	29.0 (19.7-38.2)	11.4 (6.5-16.3)
Escitalopram	12.0 (6.1-17.8)	8.8 (4.6-13.1)	18.1 (10.7-25.5)	8.9 (5.9-11.9)	15.8 (11.9-19.7)	5.5 (1.4-9.6)
Fluoxetine	10.9 (8.3-13.4)	3.9 (2.8-4.9)	8.9 (6.1-11.6)	13.2 (10.7-15.7)	11.6 (9.8-13.3)	9.0 (6.8-11.3)
Fluvoxamine	18.9 (-13.4-51.1)	9.6 (7.9-11.4	10.4 (7.3-13.6)	31.0 (18.2-43.8)	42.5 (39.5-45.5)	13.3 (-11.5-38.2)
Mirtazapine	6.4 (0-12.8)	9.8 (6.2-13.5)	13.0 (10.9-15.1)	6.5 (1.3-11.8)	8.4 (5.6-11.2)	18.7 (10.3-27.1)
Nefazadone	12 (6.8-17.1)	20.4 (14.3-26.6)	38.3 (28.2-48.4)	14.0 (17.9-20.2)	22.6 (13.3-32.0)	24.1 (11.1-37.1)
Paroxetine	12.0 (9.5-14.5)	4.9 (3.3-6.6)	6.8 (4.1-9.4)	11.8 (9.2-14.3)	14.4 (12.7-16.1)	16.0 (11.4-20.7)
Sertraline	16.5 (13.4-19.7)	4.5 (2.8-6.2)	9.3 (6.5-12.1)	16.7 (6.3-27.2)	11.6 (9.4-13.8)	10.9 (8.0-13.8)
Trazodone	4.1 (-0.4-8.6)	22.8 (14.4-31.2)	14.1 (3.3-24.9)	4.7 (3.6-5.7)	13.1 (6.4-19.8	42.4 (19.5-65.2)
Venlafaxine	10.5 (6.2-14.7)	17.3 (12.2-22.4)	20.3 (16.4-24.2)	14.6 (10.8-18.5)	29.3 (25.0-33.7)	14.1 (9.7-18.5)

[a] Weighted mean incidence calculated from randomized controlled trials. Method and extent of adverse event assessment differed across studies. Comparisons across drugs must be made cautiously.

General Tolerability and Discontinuation

In efficacy trials, on average, 63 percent of patients experienced at least one adverse event during the course of a given study. Diarrhea, dizziness, dry mouth, headache, insomnia, nausea, vomiting, and weight gain were commonly reported adverse events. Several observational studies examined the comparative rates of adverse events among second-generation antidepressants[223, 225, 236] Overall, no substantial differences among examined drugs were apparent. However, these studies did not investigate all currently approved antidepressants (Table 37).

The most extensive attempt came from a British study pooling data from prescription-event monitoring of general practitioners 6 months to 1 year after they had issued prescriptions.[223, 236] Included drugs were fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, and nefazodone. The final cohort exceeded 10,000 patients for each drug. Demographics and indications were similar among study groups. Overall, the mean incidence of any adverse events per 1,000 patient-months for SSRIs was highest for fluvoxamine (fluvoxamine, 17.6; fluoxetine, 7.0; paroxetine, 7.6; sertraline, 6.2). Physicians, not patients, reported adverse events; the nonresponse rate was 40 percent. Therefore, measurement bias, selection bias, and potential confounding may compromise these results.

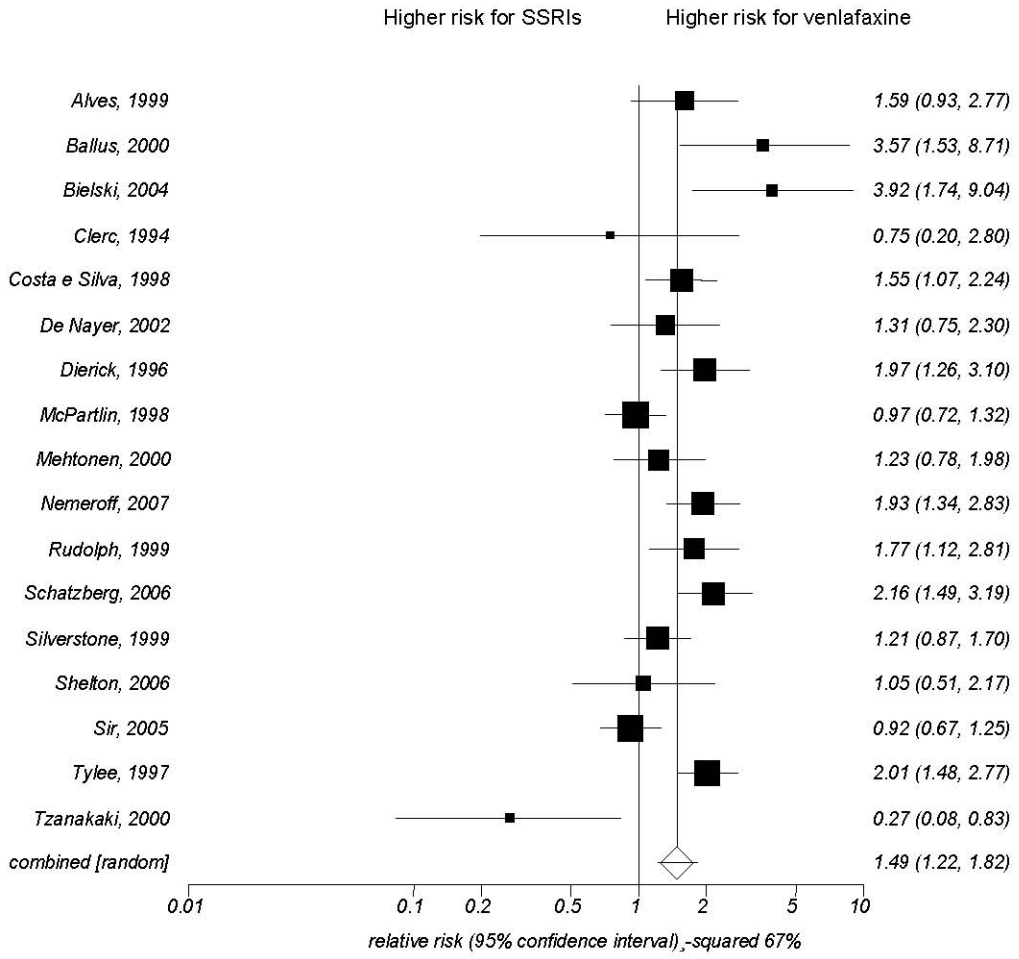
Nausea and Vomiting

In efficacy trials, venlafaxine had a consistently higher rate of nausea and vomiting than comparator SSRIs. In six studies, the difference reached statistical significance.[72, 73, 81, 83, 86, 93] The rate of patients reporting nausea or vomiting ranged from 6 percent to 48 percent.

These findings are consistent with a British prescription-event monitoring study described earlier.[223, 236] Nausea and vomiting were the two most frequent clinical reasons for withdrawal in the first month of treatment for all drugs.

Using data from efficacy trials, we compared the pooled relative risk (RR) of nausea and vomiting for venlafaxine with that for comparator SSRIs as a class (Figure 16). The RR was 1.49 (95% CI, 1.22 to 1.82). The corresponding number needed to harm (NNH) was nine (95% CI, 6 to 23).

Figure 16. Relative risk of nausea and vomiting with venlafaxine compared with SSRIs



In head-to-head trials, fluvoxamine also consistently exhibited higher rates of nausea than other SSRIs.

A pooled analysis of published and unpublished trials of duloxetine did not find significant differences in nausea between duloxetine (40–120 mg/day) and paroxetine (20 mg/day) or between duloxetine (120 mg/day) and fluoxetine (20 mg/day).[226]

Gastrointestinal Adverse Events

Two RCTs were designed primarily to detect differences in harms between fluvoxamine and citalopram[40] and fluvoxamine and fluoxetine.[47] A Dutch multicenter trial assessed gastrointestinal side effects from citalopram (20–40 mg/day) and fluvoxamine (100–200 mg/day).[40] A total of 217 patients were enrolled for 6 weeks. Overall, 57 percent of patients reported adverse events. Significantly more patients in the fluvoxamine group than in the citalopram group had diarrhea (+13 percent; *P*=0.026) or nausea (+16 percent; *P*=0.017). However, the authors did not provide a baseline comparison of gastrointestinal illnesses between groups, so differences at baseline could bias results.

Another trial assessed differences in adverse events between fluvoxamine (100–150 mg/day) and fluoxetine (20–80 mg/day) in 100 patients over 7 weeks.[47] No significant difference could be detected, except that patients on fluoxetine suffered nausea significantly more often than those on fluvoxamine (42.5 percent vs. NR; *P*=0.03).

In a Dutch prospective observational study (*n*=1,251), diarrhea occurred more frequently in the sertraline group than in patients on fluoxetine, fluvoxamine, and paroxetine *(P*<0.05).[225] This finding is consistent with results from head-to-head efficacy studies. In most studies, sertraline led to higher rates of diarrhea than did comparator drugs (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine).[41, 56, 58-60, 64, 66, 96, 97, 112-114, 132, 133, 201] Based on our own calculations from data of efficacy studies, the mean incidence was 8 percentage points (95% CI, 3 to 11) higher than with comparator drugs. Results from a Cochrane review confirm these findings; the pooled risk of diarrhea was significantly greater for patients on sertraline than patients treated with bupropion (OR, 3.88; 95% CI, 1.50 to 10.07) or mirtazapine (OR, 2.74; 95% CI, 1.52 to 4.97).[221] Whether these findings can be extrapolated to comparisons of sertraline with other second-generation antidepressants remains unclear.

Changes in Weight

Consistently, studies comparing mirtazapine with other second-generation antidepressants reported higher weight gains for mirtazapine than for the comparator groups.[75-77, 90, 92, 118, 119] In two RCTs, these differences reached statistical significance.[90, 92] Mean weight gains ranged from 0.8 kg to 3.0 kg after 6 to 8 weeks of treatment. Standard deviations of these changes, however, were large, suggesting that some patients had substantially higher weight increases (Table 38).

Two placebo-controlled RCTs specifically assessed weight changes with fluoxetine treatment.[155, 190, 229] Findings were mixed. One study, conducted in 671 patients older than 60 years,[229] recorded a statistically significant weight loss for fluoxetine compared with placebo.[229] The other study reported a weight gain.[155, 190]

A 32-week acute- and continuation-phase trial assessed differences in weight changes among patients treated with fluoxetine, paroxetine, and sertraline.[55, 127] Paroxetine patients showed a significantly greater mean weight change (+3.6 percent) than those taking fluoxetine (-0.2 percent; *P*=0.015) and sertraline (+1.0 percent; *P*<0.001). With respect to weight gain of more than 7 percent, significantly more patients in the paroxetine group (25.5 percent) than in the fluoxetine group (6.8 percent; *P*=0.016) and the sertraline group (4.2 percent; *P*=0.003) had weight gains of this magnitude.

A pooled analysis of two RCTs comparing escitalopram and paroxetine reported a similar gain in body weight for both patient groups.[227] After 27 weeks of followup, patients on escitalopram gained 1.68 kg and patients on paroxetine gained 1.64 kg.

A double-blinded, placebo-controlled, 52-week acute- and continuation-phase trial assessed weight changes during bupropion treatment.[230] Patients receiving bupropion showed a modest but nevertheless significant decrease in body weight from baseline (-1.15 kg; $P<0.001$). The magnitude of weight change was closely related to the patient's body mass index (BMI). Patients with a higher BMI experienced greater weight loss.

A pooled analysis of 10 trials assessed the effects of duloxetine on body weight in patients with MDD.[228] Both acute (8 to 9 weeks) and long-term (26, 34, and 52 weeks) studies were analyzed. In acute placebo-controlled studies, duloxetine-treated patients (doses ranging from 20 to 60 mg/day) lost significantly more weight from baseline to endpoint than did patients in the placebo group (-0.5 kg vs. +0.2 kg; $P<0.001$). The incidences of potentially clinically significant weight loss (≥7 percent) from baseline to endpoint or any time were significantly greater for patients receiving duloxetine compared with those on placebo treatment *(*$P=0.035$ and $P=0.010$, respectively). In acute studies that compared duloxetine with fluoxetine or paroxetine, respectively, no significant differences in weight changes was observed. During long-term treatment, weight changes in patients treated with duloxetine 120 mg (+0.9 kg) and paroxetine 20 mg (+1.0 kg) were similar but significantly greater than in placebo-treated patients (0.1 kg; $P\leq0.05$ for each). A long-term (52 weeks) uncontrolled analysis of a dataset reported a mean weight change from baseline to endpoint of +1.1 kg for duloxetine-treated (80-120 mg) patients *(*$P<0.001$).

Discontinuation Syndrome

Withdrawal syndromes (e.g., headache, dizziness, lightheadedness, nausea, anxiety) commonly occur following the abrupt discontinuation of second-generation antidepressants. A systematic review with good reporting conducted by an Expert Working Group of the U.K. Committee on Safety in Medicines (CSM) assessed the frequency of discontinuation syndromes in second-generation antidepressants.[233] Based on observational studies, spontaneous reporting data, and clinical trials data, discontinuation syndromes occurred in 0 percent to 86 percent of patients. Because of study durations, dosages, and different assessment methods, incidence rates could not be compared directly. Nevertheless, discontinuation syndromes occurred most commonly with paroxetine and venlafaxine and least commonly with fluoxetine (Table 39).

Four studies not included in the U.K. systematic review provide consistent results with the CSM report.[231, 232, 234, 235] One head-to-head trial compared fluoxetine with paroxetine.[231] Treatment interruption led to significantly fewer symptoms in the fluoxetine group than the paroxetine group ($P=0.001$) using the Discontinuation-Emergent Signs and Symptoms checklist (DESS). A placebo-controlled trial of fluoxetine did not find any differences in discontinuation syndromes between fluoxetine and placebo.[234] A pooled analysis of six trials investigated the effects of abrupt discontinuation of duloxetine and placebo.[235] Significantly more patients receiving duloxetine than receiving placebo reported discontinuation syndromes (44.3 percent vs. 22.9 percent; $P<0.05$). Finally, a pooled analysis of two RCTs reported more discontinuation-emergent signs and symptoms for patients who were treated with venlafaxine XR than escitalopram (DESS checklist: 5.0 points vs. 2.4 points; $P<0.001$).[232]

Discontinuation Rates

In efficacy trials, discontinuation rates because of adverse events were not substantially different.

Table 41 summarizes average discontinuation rates.

Table 41. Average rates of overall discontinuation, discontinuation because of adverse events, and discontinuation because of lack of efficacy

Drug or Drug Class	Overall Loss to Followup (%)	Discontinuation Because of Adverse Events (%)	Discontinuation Because of Lack of Efficacy (%)
SSRIs	20.9	7.2	3.6
Bupropion	14.9	6.0	3.1
Desvenlafaxine	22.1	12.1	NR
Duloxetine	23.3	8.2	2.4
Mirtazapine	23.4	10.2	2.9
Nefazodone	23.6	15.0	2.0
Trazodone	15.4	6.4	1.6
Venlafaxine	24.6	11.7	3.7

Using data from efficacy studies, we conducted meta-analyses to assess differences in the overall loss to followup, discontinuation rates because of adverse events, and discontinuation rates because of lack of efficacy of SSRIs as a class compared with other second-generation antidepressants (bupropion, duloxetine, mirtazapine, nefazodone, trazodone, and venlafaxine) in adult patients with MDD. Figures 17 through 19 depict relative risks of discontinuation rates comparing these agents with SSRIs as a class. The available data on desvenlafaxine were insufficient for such comparisons. According to our pooled analyses of relative risk, overall discontinuation rates did not differ significantly between SSRIs and bupropion, duloxetine, mirtazapine, nefazodone, trazodone, or venlafaxine (Figure 17). Duloxetine (RR, 1.67; 95% CI, 1.17 to 2.39) and venlafaxine (RR, 1.42; 95% CI, 1.14 to 1.77) had statistically significantly higher discontinuation rates because of adverse events than SSRIs as a class. (Figure 18). For venlafaxine, this finding was balanced by lower discontinuation rates because of lack of efficacy (RR, 0.66; 95% CI, 0.47 to 0.93) (Figure 19). A meta-analyses comparing discontinuation rates of fluoxetine with other SSRIs reported similar results as our analyses.[222]

Figure 17. Relative risks of overall discontinuation

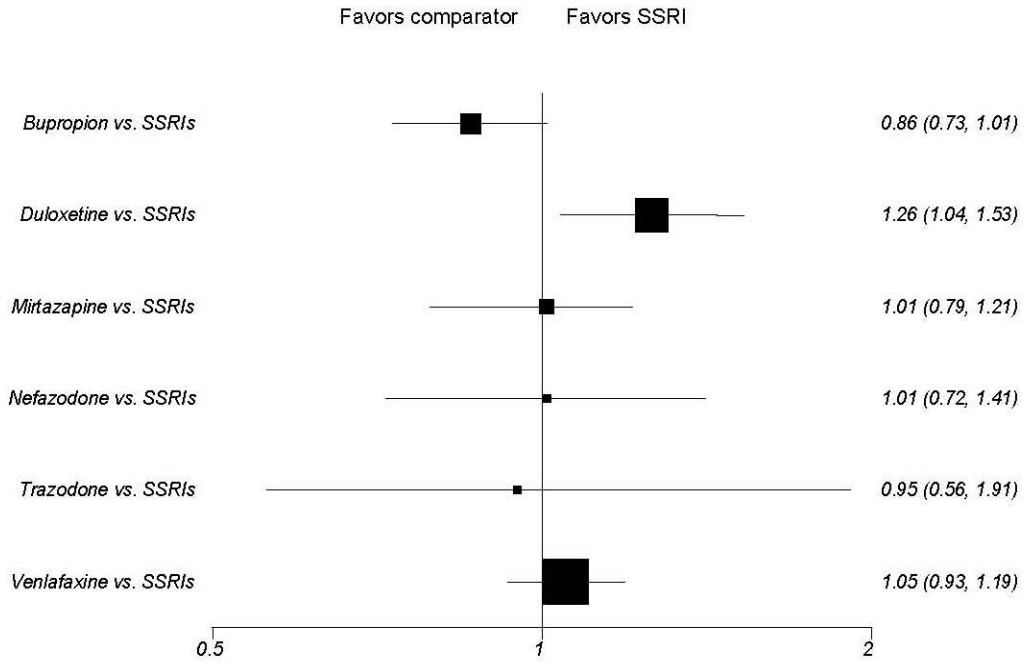


Figure 18. Relative risk of discontinuation because of adverse events

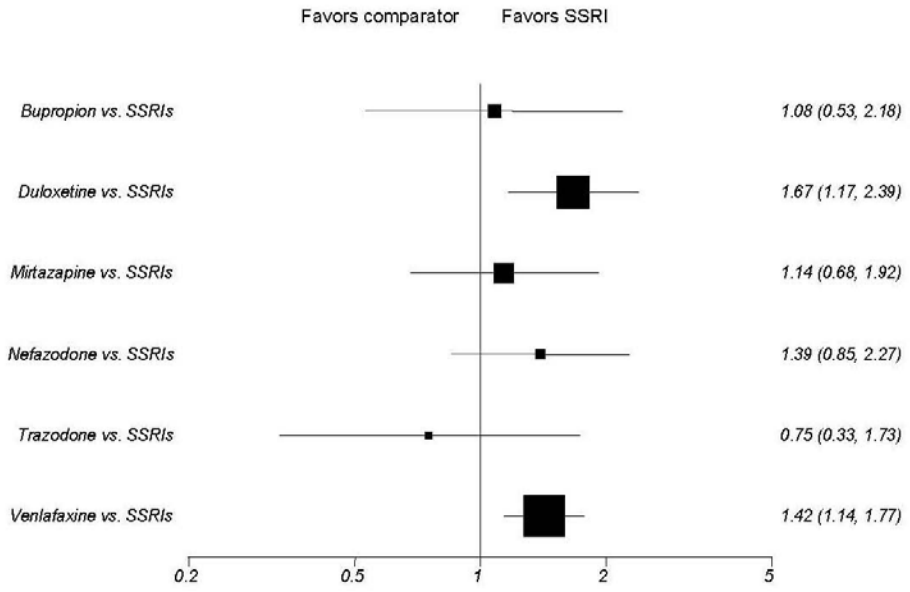
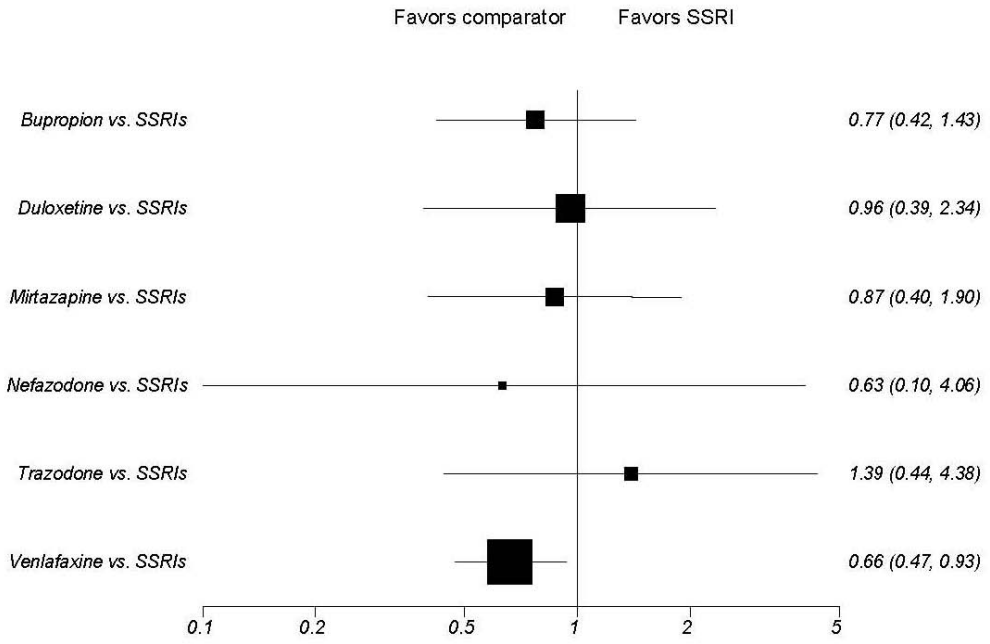


Figure 19. Relative risk of discontinuation because of lack of efficacy



Serious Adverse Events: Key Points

In general, trials and observational studies were too small and study durations too short to assess the comparative risks of rare but serious adverse events such as suicidality, seizures, cardiovascular adverse events, serotonin syndrome, hyponatremia, or hepatotoxicity. The strength of the evidence on the comparative risks of second-generation antidepressants on most serious adverse events is insufficient to draw firm conclusions. Long-term observational evidence is often lacking or prone to bias. Tables 42 to 46 summarize studies included for the assessment of serious adverse events: suicidality (suicidal thoughts and behavior) (Table 42), sexual dysfunction (Table 43), seizures (Table 44), cardiovascular events (Table 45), and other adverse events (Table 46).

An exception, however, is sexual dysfunction. Eight trials and a pooled analysis of two identical RCTs provide evidence that bupropion causes lower rates of sexual dysfunction than escitalopram,[237] sertraline,[110-112] and fluoxetine[100, 101, 105] (Table 43). The NNT to yield one additional person with a high overall satisfaction of sexual functioning is seven. This treatment effect was consistent across all studies. The strength of evidence that bupropion has lower rates of sexual dysfunction than comparator drugs is high.

Compared with other second-generation antidepressants (fluoxetine, fluvoxamine, nefazodone, and sertraline), paroxetine frequently led to higher rates of sexual dysfunction (16 percent vs. 6 percent).[55, 62, 108] The strength of evidence is moderate.

The strength of evidence about the comparative risk of second-generation antidepressants with respect to suicidality is insufficient.

Serious Adverse Events: Detailed Analysis

Suicidality

We found 15 studies that assessed the risk of suicidality (suicidal thinking or behavior) in patients treated with second-generation antidepressants.[233, 238-251] Data on the comparative risk of suicidality among second-generation antidepressants are sparse. Results from existing studies do not indicate that any particular drug of interest has an excess risk compared with that of other second-generation antidepressants.[239-242, 246, 249, 251] All these studies, however, were underpowered to detect a statistically significant difference between two drugs. Because suicides are a relatively rare event (about 1 in 8,000 psychiatric patients treated with second-generation antidepressants), to detect 20 percent increase in suicide risk, with 80 percent power and a 5 percent level of significance, a trial would need to have a sample size of 1.9 million participants.[240] However, 1 in 166 patients reported suicidal feelings while being treated with a second-generation antidepressants.[252]

In addition, several large attempts were undertaken to determine whether second-generation antidepressants lead to a general increase in the risk of suicidality.[239, 240, 249]

A recent meta-analysis of observational studies in a combined population of more than 200,000 patients resulted in different findings.[249] Results indicated that with the use of SSRIs the risk of attempted or completed suicide was decreased among adults (OR, 0.57, 95% CI, 0.47 to 0.70) and among people ages 65 or older, exposure to SSRIs had a protective effect (OR, 0.46, 95% CI, 0.27 to 0.79).[252] These findings were consistent with an FDA data analysis on more than 99,000 participants in 372 trials. FDA pointed out that the risk of suicidality is increased in children and patients 18 to 24 years of age but not in other adult patients.

Table 42. Studies assessing suicidality

Study	Design, Interventions	N	Results	Quality Rating
Didham et al., 2005[241]	Retrospective cohort study and nested case-control Citalopram, fluoxetine, paroxetine	57,000	Significant association between nonfatal suicide attempts and SSRIs	Fair
Gunnell, Saperia, and Ashby, 2005[240]	Meta-analysis Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, all vs. placebo	40,000	Increased risk of nonfatal suicide attempts compared with placebo	Good
Martinez et al., 2005[239]	Case-control study Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, TCAs	146,095	The use of SSRIs as a group or separately does not increase the risk of suicide	Good
Rahme et al., 2008[251] *	Retrospective cohort study Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	128,229	Similar risk among SSRIs	Fair
Jick, Kaye, and Jick, 2004[242]	Case-control study Fluoxetine, paroxetine	159,810	No significant association between specific AD and risk of suicide	Fair
Jick, Dean, and Jick, 1995[243]	Retrospective cohort study and nested case-control study Fluoxetine, trazodone, second-generation ADs	172,598	The risk of suicide was not determined by the antidepressant prescribed	Fair
Barbui et al., 2009[249] *	Systematic review of observational studies Second-generation antidepressants	>200,000	No association between individual antidepressants and suicide	Good

Table 42. Studies assessing suicidality (continued)

Study	Design, Interventions	N	Results	Quality Rating
CSM Expert Working Group, 2004[233]	Systematic review and meta-analysis Second-generation antidepressants	NR	Insufficient evidence to determine difference	Good
Olfson and Marcus, 2008[248] *	Case-control study Antidepressants vs. no antidepressants	1,078	Antidepressants not significantly related to risk of suicide	Fair
Schneeweiss et al., 2010[250]	Retrospective cohort study Antidepressants	287,543	Similar event rates among antidepressants	Good
Jick, Ulcickas, and Dean, 1992[244] *	Retrospective cohort study Fluoxetine, trazadone, first-generation antidepressants	8,730	Indicates that fluoxetine does not directly cause more suicidality than trazadone.	Fair
Pedersen, 2005[253]	Retrospective cohort study Escitalopram vs. placebo	4,091	Higher rate of nonfatal suicide attempts for escitalopram than for placebo	Fair
Aursnes et al., 2005[245]	Meta-analysis of unpublished data Paroxetine vs. placebo	1,466	Higher rate of suicides for paroxetine than for placebo	Fair
Khan et al., 2003[246]	Retrospective cohort study SSRIs vs. other antidepressants and placebo	48,277	Similar rates of suicide among groups	Fair
Lopez-Ibor, 1993[247]	Retrospective cohort study Paroxetine, first-generation antidepressants and placebo	4,686	Paroxetine is not associated with suicidality	Fair
Fergusson et al., 2005[238]	Meta-analysis SSRIs vs. placebo	87,650	Higher risk of suicide attempts for SSRI-treated patients than placebo	Good

AD = antidepressants; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; vs. = versus
*New study added during update.

Table 43. Studies assessing sexual dysfunction

Study	Design, Interventions	N	Results	Quality Rating
Montejo et al., 2001[254]	Prospective cohort study Citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine	1,022	Highest incidence of sexual dysfunction for citalopram, paroxetine, and venlafaxine; lowest for mirtazapine and nefazodone	Fair
Fava et al., 1998[51]	Pooled analysis Fluoxetine vs. paroxetine	128	No difference between fluoxetine and paroxetine	Fair
Philip et al., 2000[255]	Prospective cohort study Fluoxetine, fluvoxamine, paroxetine, sertraline, moclobemide	268	No difference among SSRIs	Fair
Nemeroff et al., 1995[64]	RCT Fluvoxamine vs. sertraline	95	Higher rate of sexual adverse events with sertraline	Fair
Aberg-Wistedt et al., 2000[66]	RCT Paroxetine vs. sertraline	353	Significantly more libido decreases in patients taking sertraline	Fair
Kennedy et al., 2000[256]	Prospective cohort study Paroxetine, sertraline, venlafaxine	174	No difference	Fair
Behnke et al., 2003[96]	RCT Sertraline vs. mirtazapine	346	Significantly more sexual adverse events with sertraline	Fair
Feiger et al., 1996[114]	RCT Sertraline vs. nefazodone	160	Sertraline had significant adverse effects on sexual function; nefazodone had none	Fair
Ferguson et al., 2001[257]	RCT Sertraline vs. nefazodone	75	Higher reemergence rate of sexual dysfunction for sertraline	Fair

Table 43. Studies assessing sexual dysfunction (continued)

Study	Design, Interventions	N	Results	Quality Rating
Clayton et al., 2007*[258]	RCT Duloxetine vs. escitalopram	684	Higher incidence of treatment-emergent sexual dysfunction with escitalopram	Fair
Delgado et al., 2005[259]	Pooled analysis Duloxetine vs. paroxetine vs. placebo	1,466	Higher rate of sexual dysfunction for paroxetine	Fair
Coleman et al., 2001[100]	RCT Bupropion SR vs. fluoxetine	456	Significantly more sexual adverse events with fluoxetine	Fair
Feighner et al., 1991[101]	RCT Bupropion vs. fluoxetine	123	Higher rate of sexual dysfunction for fluoxetine	Fair
Kennedy et al., 2006*[105]	RCT Buproprion SR vs. paroxetine	141	Statistically significant decrease in sexual functioning with paroxetine, for males only	Fair
Coleman et al., 1999[110]	RCT Bupropion SR vs. sertraline	364	Significantly more sexual adverse events with sertraline	Fair
Croft et al., 1999[111]	RCT Bupropion SR vs. sertraline	360	Significantly more sexual adverse events with sertraline	Fair
Kavoussi et al., 1997;[112] Rush et al., 2001[113]	RCT Bupropion vs. sertraline	248	Higher rate of sexual adverse events with sertraline	Fair
Segraves et al., 2000[260]	RCT Bupropion vs. sertraline	248	Significantly more sexual adverse events with sertraline	Fair
Clayton et al., 2006[237] *	Pooled analysis of 2 identical RCTs Bupropion XL vs. escitalopram	830	Higher incidence of orgasm dysfunction and worsened sexual dysfunction with escitalopram; worse sexual functioning with escitalopram	Fair
Nieuwstraten and Dolovich, 2001[261]	Meta-analysis Bupropion vs. SSRIs	1,332	Significantly higher rate of sexual satisfaction in bupropion group	Good
Clayton et al., 2002[262]	Cross-sectional survey Bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine	6,297	Highest risk for paroxetine, lowest risk for bupropion	Fair

RCT = randomized controlled trials; SR = sustained release; SSRIs = selective serotonin reuptake inhibitors; vs. = versus; XL = extended release

*New study added during update.

Table 44. Studies assessing seizures

Study	Design, Interventions	N	Results	Quality Rating
Whyte et al., 2003[263]	Prospective observational study SSRIs, TCAs, venlafaxine	538	Seizures more common in venlafaxine overdose than in SSRI or TCA overdose	Good
Dunner et al., 1998[264]	Uncontrolled, open-label trial Bupropion	3,100	Rate of seizures for bupropion within reported range of other antidepressants	Fair
Johnston et al., 1991[265]	Uncontrolled, open-label trial Bupropion	3,341	Rate of seizures for bupropion within range of other antidepressants	Fair

SSRI = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants

Table 45. Studies assessing cardiovascular events

Study	Design, Interventions	N	Results	Quality Rating
Martinez et al., 2010[266] *	Nested case-control study Citalopram, fluoxetine, venlafaxine	15,380	No differences in sudden cardiac arrest or near death	Good
Montgomery and Andersen, 2006[232] *	Pooled analysis Escitalopram, venlafaxine XR	487	Greater increase of systolic blood pressure for venlafaxine XR than escitalopram	Fair

XR = extended release
*New study added during update.

Table 46. Studies assessing other adverse events

Study	Design, Interventions	N	Results	Quality Rating
Vestergaard et al., 2008[267] *	Case-control study Citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine	498,617	Increased risk of fracture for citalopram, fluoxetine, sertraline	Good
Buckley and McManus, 2002[268]	Retrospective cohort study Citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine	47,329	Highest rate of fatal toxicity for venlafaxine	Fair
Thapa et al., 1998[269]	Retrospective cohort study Fluoxetine, paroxetine, sertraline, trazodone	2,428	No difference in the risk of falls	Fair
Andersohn et al., 2009[270] *	Nested case-control study Bupropion, citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine	11,206	Long-term use of antidepressants in moderate or high daily doses was associated with an increased risk of diabetes	Fair
Mackay et al., 1997[236]	Prescription event monitoring Fluoxetine, nefazodone, paroxetine, sertraline, venlafaxine	>60,000	Incidence rates of serotonin syndrome 0.5 to 1.0 per 1,000 patient months	Fair

*New study added during update.

In 2004 the CSM working group investigated ongoing safety concerns about suicidal behavior with some second-generation antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, venlafaxine) in patients with MDD.[233] They used data from 477 published and unpublished RCTs on more than 40,000 individuals as well as spontaneous reporting data. These data, however, were limited to studies funded by the pharmaceutical industry.

A meta-analysis limited the CSM data to placebo-controlled trials of SSRIs in about 40,000 adults. Results did not yield any evidence that SSRIs either increase or protect against the risk of suicide (OR, 0.85; 95% CI, 0.20 to 3.40).[240] The risk of suicide-related events was similar between second-generation antidepressants and active comparators, although some evidence of an increased risk of suicide attempts was detected (OR, 1.57; 95% CI, 0.99 to 2.55).

Another meta-analysis of published data on more than 87,000 patients in SSRI trials for various conditions reported a significantly higher risk of suicide attempts for SSRI patients than for placebo-treated patients (OR, 2.28; 95% CI, 1.14 to 4.55).[238] Furthermore, an increase in the odds ratio of suicide attempts was observed for SSRIs compared with interventions other than tricyclic antidepressants (TCAs) (OR, 1.94; 95% CI, 1.06 to 3.57). No significant difference existed in the pooled analysis of SSRIs compared with TCAs (OR, 0.88; 95% CI, 0.54 to 1.42).

The overall rate of suicide attempts was 3.9 (95% CI, 3.3 to 4.6) per 1,000 patients treated with SSRIs, for an incidence of 18.2 suicide attempts per 1,000 patient years.

In addition, the CSM group commissioned an observational study (a nested case-control study) using the General Practice Research Database (GPRD) to investigate the association between antidepressants and suicide attempts. This study used data on more than 146,000 patients with a first prescription of an antidepressant for depression.[239] It did not find any evidence that the risk of either suicide (OR, 0.57; 95% CI, 0.26 to 1.25) or suicide attempts (OR, 0.99; 95% CI, 0.86 to 1.14) was greater in patients on second-generation antidepressants than in patients on TCAs.

Findings of other large observational studies and meta-analyses are similar.[241-248, 253, 271] Most detected a correlation of SSRI use in suicide attempts and suicides compared with placebo. In general, no significant differences in risks regarding suicidality could be detected between second-generation antidepressants and TCAs.

Sexual Dysfunction

Multiple studies assessed the comparative risk of sexual dysfunction among second-generation antidepressants (Table 43).[100, 105, 110, 111, 237, 254, 260] The largest study was a Spanish open-label, prospective observational study using the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) in 1,022 outpatients treated with various antidepressants.[254] All patients had normal sexual functioning at study onset. Overall, 59 percent of patients experienced some type of sexual dysfunction. Among second-generation antidepressants, citalopram, paroxetine, and venlafaxine had the highest incidence of sexual dysfunction (73 percent, 71 percent, and 67 percent, respectively); mirtazapine and nefazodone had the lowest (24 percent and 8 percent, respectively). A cross-sectional survey of patients on second-generation antidepressants presented similar results.[262] Paroxetine had the highest rate of sexual dysfunction; nefazodone and bupropion had the lowest.

Sexual dysfunction was also a commonly reported adverse event for SSRIs and SNRIs in efficacy trials. Most of these studies did not report the use of targeted questions for sexual dysfunction. Therefore, patient-reported numbers might not reflect the true incidence. Patients receiving paroxetine and sertraline frequently reported significantly higher rates of sexual dysfunction[51, 64, 66, 96, 112, 114] than did patients in the active control groups. In one trial, significantly more patients on sertraline than on bupropion SR withdrew because of sexual dysfunction (13.5 percent vs. 3.3 percent; P=0.004).[112] A pooled analysis of four efficacy trials comparing paroxetine and duloxetine reported significantly higher rates of sexual dysfunction for patients on paroxetine.[259]

Ten RCTs assessed the comparative risk of sexual dysfunction between two or more second-generation antidepressants as primary outcome measures.[100, 105, 110, 111, 237, 257, 258, 260, 272] Table 47 summarizes results of RCTs about sexual dysfunction of patients treated with bupropion or SSRIs.

Citalopram Versus Sertraline

A subgroup analysis of a Swedish RCT examined the incidence of sexual dysfunction from citalopram (20–60 mg/day) and from sertraline (50–150 mg/day) in 308 study completers with MDD.[272] Outcome assessment was conducted at baseline and at week 24. Citalopram and sertraline did not differ significantly in the magnitude and frequency of sexual dysfunction. Only one patient was lost to followup attributable to sexual dysfunction in this study.

Bupropion Versus SSRIs

A good meta-analysis including data on 1,332 patients with MDD compared sexual adverse events of bupropion and three SSRIs (fluoxetine, paroxetine, sertraline) as a class.[261] We do not describe studies included in this meta-analysis individually.[101, 110, 111, 260] The rate of sexual satisfaction was significantly higher in patients receiving bupropion than in those receiving SSRIs (RR, 1.28; 95% CI, 1.16 to 1.41). Table 47 summarizes studies comparing bupropion with SSRIs on sexual dysfunction.

Table 47. Characteristics of trials comparing bupropion with SSRIs on sexual dysfunction

Study	Sample Size	Comparison	Effect Size	*P*-value	Comments
Clayton et al., 2006[237]	830	Escitalopram	Higher rates of worsened sexual functioning with escitalopram than bupropion XL (30% vs. 15%)	*P*<0.001	Sexual functioning assessed with CSFQ
Feighner et al., 1991[101]	61	Fluoxetine	Higher rates of impotence (4.7% vs. 0%), anorgasmia (1.7% vs. 0%), libido decrease (1.7% vs. 0%) for fluoxetine	NR	Self-reporting of sexual adverse events
Coleman et al., 2001[100]	456	Fluoxetine, placebo	Significantly more bupropion SR patients were satisfied with overall sexual functioning (analysis only for patients satisfied at baseline; no data reported)	*P*<0.05	DSM-IV criteria for sexual dysfunction disorders No statistically significant differences in efficacy outcome measures at endpoint (week 8)
Kennedy et al., 2006[105]	141	Paroxetine	Men treated with paroxetine experienced a significantly greater deterioration of sexual function than men on bupropion SR (Sex FX: -2.43 vs. +0.54)	*P<0.01*	Sexual function assessed in investigator-conducted questionnaire (Sex FX) No statistically significant differences in efficacy outcome measures at endpoint (week 8)
Coleman et al., 1999[110]	364	Sertraline	Beginning at day 21, significantly more patients on bupropion SR were satisfied with their sexual functioning (endpoint: 85% vs. 62%) Endpoint: RRR, 0.59 RD: 0.22 NNT: 5	*P*<0.05	DSM-IV criteria for sexual dysfunction disorders No statistically significant differences in efficacy outcome measures at endpoint (week 8)
Croft et al., 1999[111]	360	Sertraline, placebo	Beginning at day 7 through day 42, significantly more bupropion SR patients were satisfied with overall sexual functioning; difference was not statistically significant at endpoint (75% vs. 65%) endpoint: RRR, 0.29 RD: 0.10 NNT: 10	*P*<0.05	Sexual function assessed in investigator-conducted structured interview No statistically significant differences in efficacy outcome measures at endpoint (week 8)

Table 47. Characteristics of trials comparing bupropion with SSRIs on sexual dysfunction (continued)

Study	Sample Size	Comparison	Effect Size	*P*-value	Comments
Kavoussi et al.,1997 ; Segraves et al., 2000[112, 260]	248	Sertraline	Significantly more patients on sertraline experienced orgasm delays and/or failure Women: 41% vs. 7% RRR, 0.85 RD: 0.38 NNT: 3 Men: 61% vs. 10% RRR, 0.84 RD: 0.51 NNT: 2 Higher overall satisfaction with sexual functioning with bupropion SR at endpoint (79% vs. 58%) RRR, 0.50 RD: 0.21 NNT: 5	*P*<0.01 *P*<0.001	Sexual function assessed in investigator-conducted structured interview No statistically significant differences in efficacy outcome measures at endpoint (week 16)

CSFQ = Changes in Sexual Functioning Questionnaire; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; NNT = number needed to treat; NR = not reported; RD = risk difference; RRR = relative risk reduction; Sex FX = Sexual Effects Scale; SR = sustained release; vs. = versus; XL = extended release

Three additional trials were published since the meta-analysis described above had been conducted.[100, 105, 237] An 8-week RCT compared efficacy and sexual dysfunction of bupropion SR (150–400 mg/day), fluoxetine (20–60 mg/day), and placebo in 456 outpatients with MDD.[100] Findings were consistent with those from the earlier meta-analysis. Throughout the study, patients on bupropion SR experienced significantly less sexual dysfunction than those on fluoxetine. Moreover, beginning at week 1 until endpoint, significantly fewer patients on bupropion than on fluoxetine were dissatisfied with their overall sexual function *(P*<0.05). The NNT to gain one more patient with high satisfaction with sexual functioning is 6 (95% CI, 4 to 9).

Two identically designed 8-week RCTs compared efficacy and sexual functioning of bupropion XL (150–400 mg/day), escitalopram (10–20 mg/day), and placebo in 830 outpatients (pooled data) with MDD.[237] In both of the individual studies and the pooled dataset, the incidence of orgasm dysfunction as well as the incidence of worsened sexual dysfunction at the end of the treatment period was lower with bupropion XL than with escitalopram. In the pooled dataset the incidence rates of orgasm dysfunction at endpoint were 15 percent for bupropion XL and 30 percent for escitalopram *(P*<0.01); the incidence rates of worsened sexual dysfunction were 20 percent for bupropion XL and 36 percent for escitalopram *(P*<0.01). Furthermore, at endpoint, escitalopram was associated with statistically significantly worse sexual functioning than bupropion XL in both individual studies and the pooled dataset.

An 8-week RCT evaluated sexual functioning in men and women with MDD receiving either bupropion SR (150–300 mg/day) or paroxetine (20–40 mg/day).[105] Sexual functioning decreased significantly in male paroxetine patients, whereas no change in sexual functioning was observed in men receiving bupropion SR. No significant drug differences of sexual functioning were observed for women.

Duloxetine Versus Escitalopram

An 8-month RCT (8 weeks fixed-dose acute-treatment phase followed by a 24-week flexible-dose extension-treatment phase) compared efficacy and sexual functioning of duloxetine (60 mg/day), escitalopram (10 mg/day), and placebo in 684 outpatients with MDD.[258] The incidence of treatment-emergent global sexual dysfunction was significantly higher for patients with escitalopram treatment compared with those receiving duloxetine. At the 8-week point, more male patients treated with escitalopram reported worsening in global sexual functioning compared with duloxetine-treated male patients (59.2 percent vs. 36.7 percent; P=0.019), whereas no differences in categorical assessment of changes in global sexual functioning were observed for females.

Sertraline Versus Nefazodone

In one RCT, the emergence of sexual adverse events in patients who experienced sexual dysfunction with sertraline treatment was significantly greater for those receiving sertraline than for those receiving nefazodone.[257]

Seizures

Evidence from controlled trials and observational studies was insufficient to conclude for or against an increased risk of seizures in patients taking any of the reviewed drugs, including bupropion (Table 44). Two open-label trials examined the rate of seizures during bupropion treatment.[264, 265] Both trials reported that the rate of seizures was within the range of other marketed antidepressants, but we rate the strength of this uncontrolled, open-label evidence as low.

A recent review of medical charts on 538 patients with deliberate self-poisoning with antidepressants reported that seizures were more common in patients with venlafaxine overdose than in patients with TCA or SSRI overdose.[263]

Cardiovascular Events

A nested case-control study examined the risk of sudden cardiac death or near death in patients treated with citalopram, fluoxetine, or venlafaxine (Table 45).[266] The study was based on the United Kingdom General Practice Research Database, which included data on more than 207,000 patients who initiated treatment with citalopram, fluoxetine, or venlafaxine for MDD or anxiety. The followup time was an average of 3.3 years. Within the cohort 568 cases of sudden cardiac arrest or near death occurred. These cases were matched with more than 14,000 controls. Results showed that no significant differences in risks for sudden cardiac death or near death were obvious among the examined medications. The adjusted odds ratio associated with venlafaxine relative to fluoxetine was 0.66 (95% CI, 0.38 to 1.14), of venlafaxine relative to citalopram was 0.89 (95% CI, 0.50 to 1.60).

Two case-control studies, not included in this review, indicated an increased risk of ischaemic stroke for SSRIs as a class.[273, 274] Neither of these studies provide data on the comparative risks among second-generation antidepressants.

Likewise, a case-control study found no excess risk of idiopathic venous thromboembolism in SSRIs as a class.[275] We did not include the study in this report because it does not provide any evidence on the comparative risks among antidepressants.

Other Adverse Events

Diabetes Mellitus

In a cohort of 165,958 patients with depression included in the U.K. General Practice Research Database, a total of 2,243 cases of incident diabetes mellitus and 8,963 matched comparison subjects were identified.[270] This nested case-control study showed that recent long-term use (>24 months) of antidepressants in moderate to high daily doses was associated with an increased risk of diabetes (incidence rate ratio (IRR), 1.84; 95% CI, 1.35 to 2.52). The study investigated tricyclic and tetracyclic antidepressants, SSRIs, monoamine oxidase inhibitors, and other antidepressants. For users of SSRIs as a group, increased risk was observed only for recent long-term use of moderate to high daily doses (IRR, 2.06; 95% CI, 1.20 to 3.52). When individual antidepressants were analyzed, increased risk estimates only in long-term users were observed for recent use of fluvoxamine, paroxetine, and venlafaxine. Antidepressant treatment for shorter periods or with lower daily doses was not associated with an increased risk.

Fractures

A large, well-conducted case-control study, including 498,617 subjects (124,655 cases and 373,962 controls) from a Danish national prescription database, reported a significant dose-response relationship for citalopram, fluoxetine, and sertraline with respect to an increase of the risk of fracture (Table 46).[267] Among SSRIs, high-dose citalopram, fluoxetine, paroxetine, and sertraline were associated with the highest risk for hip fracture (OR, 1.98, 95% CI, 1.82 to 2.16) and other fractures except fractures of the forearm and spine (OR, 1.38, 95% CI, 1.33 to 1.44). Evidence regarding the impact of the duration of use on the risk of fractures was mixed for second-generation antidepressants.

A Dutch case-control study that did not meet eligibility criteria reported an increase for nonvertebral fractures for SSRIs as a class.[276]

Increased Risk of Bleeding

Evidence from three case-control studies indicated an increased risk of upper gastrointestinal tract bleeding during SSRI treatment (Table 46).[277-279] These studies did not meet eligibility criteria because they provided no information on the comparative risks among individual SSRIs.

Hepatotoxicity

Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of liver toxicity during nefazodone treatment (Table 46). Nevertheless, numerous case reports or prescription event monitoring studies not included in this report contain low quality but potentially important evidence citing an increased risk of liver toxicity during nefazodone treatment.[280, 281]

Hyponatremia

A retrospective cohort study that did not meet our eligibility criteria reported that hyponatremia in elderly inpatients (mean age 74 years) was significantly more common in patients treated with SSRIs or venlafaxine than in controls not on these drugs (OR, 3.5; 95% CI, 1.4 to 8.9) (Table 46).[282] Otherwise, evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of hyponatremia in patients treated with SSRIs.

Our methods for this comparative effectiveness review did not permit inclusion of case reports and case series. The published literature includes numerous case reports of hyponatremia and inappropriate secretion of an antidiuretic hormone as rare side effects.[283] Even if this evidence is considered weak, such findings might be important in the absence of studies with the methodological strength to account for rare adverse events.

Serotonin Syndrome

Serotonin hyperstimulation syndrome is characterized by symptoms that include mental status changes, agitation, myoclonus, hyperreflexia, sweating, shivering, tremor, diarrhea, lack of coordination, and fever; it can lead to death (Table 46).[224] Evidence from controlled trials and observational studies is insufficient to draw conclusions about differences in risk among second-generation antidepressants. The published literature has numerous case reports of serotonin syndrome.[284]

A postmarketing survey identified cases of the serotonin syndrome in British general practice among patients who received nefazadone.[224] In a cohort of 11,834 patients, 19 cases met criteria for the syndrome (incidence=1 case per 1,000 patient-months of treatment with nefazodone). Similar rates of the syndrome were reported for fluoxetine, sertraline, paroxetine, and venlafaxine.

Toxicity

A database analysis in the United Kingdom on fatal toxicity of second-generation antidepressants found venlafaxine to have the highest fatal toxicity rate (13.2 per 1,000,000 prescriptions) among second-generation antidepressants (Table 46).[268] A retrospective review of the charts of 2,428 nursing home residents did not detect differences in the risk of falls among residents treated with fluoxetine, paroxetine, and sertraline.[269]

Adherence and Persistence: Key Points

Adherence rates in efficacy trials range between 90 and 100 percent. Results from efficacy RCTs did not indicate any differences in adherence among second-generation antidepressants. The evidence, however, is limited to few comparisons for which the strength of the evidence is moderate. For the majority of possible comparisons among second-generation antidepressants, the strength of the evidence is insufficient to draw conclusions about the comparative adherence. Findings from highly controlled efficacy studies may have limited applicability to "real-world" practice especially because of the overall short duration of these trials. The evidence is insufficient to conclude on adherence and persistence in effectiveness studies.

Adherence and Persistence: Detailed Analysis

The published literature frequently uses the terms "compliance" and "adherence" interchangeably. Compliance has traditionally been used to describe a patient's ability to take medications as prescribed. Some authors argue, however, that adherence better represents the more complex relationship among patients, providers, and medications; it is meant to reflect the fact that following a medication regimen is not necessarily a simple choice.[285] Given the lack of a clear definition, we use the term adherence.

Few efficacy studies reported rates of adherence. Lack of adherence, however, was often used as a reason to exclude patients from the study. Table 48 summarizes included head-to-head trials on adherence. The majority of RCTs that reported on the comparative adherence stated

rates between 90 percent and 100 percent. We found 8 head-to-head trials that reported comparative data on adherence.[41, 100, 106, 110-112, 124, 260] Overall, adherence rates in RCTs were similar. Most studies, however, provided little or no information on the methods of assessment. For example, a fair study reported that both treatment arms exhibited 100 percent adherence, but the investigators did not describe their method of determining adherence.[76]

None of the three effectiveness studies reported on adherence. To what extent results from highly controlled efficacy trials can be extrapolated to effectiveness settings remains unclear.

Persistence refers to the act of continuing the treatment for the prescribed duration.[285] We did not find any studies on persistence.

Only 10 of 18 RCTs reported adherence rates for different treatment arms;[41, 50, 100, 103, 109, 110, 136, 147, 286] of these, 8 were head-to-head comparisons (Table 48).[41, 100, 106, 110-112, 124, 260] None of these studies noted a significant difference in adherence.

Table 48. Head-to-head trials reporting adherence to second-generation antidepressants

Study	Drugs and Dose Duration	N	Rate of Adherence	Quality Rating
Ekselius, von Knorring, and Eberhard, 1997[41]	Citalopram 20-60 mg/day Sertraline 50-100 mg/day 24 weeks	400	Citalopram 95% Sertraline 90%	Good
Coleman et al., 2001[100]	Bupropion SR 150-400 mg/day Fluoxetine 20-60 mg/day Placebo 8 weeks	456	97% to 99% in all groups	Fair
Weihs et al., 2000[106]	Bupropion SR 100-300 mg/day Paroxetine 10-40 mg/day 6 weeks	100	Bupropion SR 95% Paroxetine 98%	Good
Coleman et al., 1999[110]	Bupropion SR 150-400 mg/day Sertraline 50-200 mg/day Placebo 8 weeks	364	Tablet: Bupropion SR 96% Sertraline 97% Placebo 96% Capsule: Bupropion SR 98% Sertraline 98% Placebo 98%	Fair
Croft et al., 1999[111]	Bupropion SR 150-400 mg/day Sertraline 50-200 mg/day Placebo 8 weeks	360	Bupropion SR 98% Sertraline 97% Placebo 98%	Fair
Kavoussi et al., 1997[112]	Bupropion SR 100-300 mg/day Sertraline 50-200 mg/day 16 weeks	248	Bupropion SR 98% Sertraline 99%	Fair
Segraves et al., 2000[260]	Bupropion SR 100-300 mg/day Sertraline 50-200 mg/day 16 weeks	248	Bupropion 98% Sertraline 99%	Fair
Weisler et al., 1994[124]	Bupropion 225-450 mg/day Trazodone 150-400 mg/day 6 weeks	124	Bupropion 95% Trazodone 90%	Fair

mg/day = milligram per day; SR = sustained release

None of the three effectiveness studies reported on adherence. To what extent results from highly controlled efficacy trials can be extrapolated to effectiveness settings remains unclear.

We did not find any studies on persistence.

Key Question 4b: Comparative Harms, Adherence, and Persistence for Immediate- and Extended-Release Second-Generation Antidepressants

This part presents information on studies that examined differences in, first, harms or adverse events and, then, adherence and persistence. The medications of interest are bupropion, fluoxetine, fluvoxamine, mirtazapine, paroxetine, and venlafaxine, which can be administered in daily or weekly dosing regimens or have a variety of formulations, including immediate-release (IR), extended-release (XR), and controlled release (CR). (Some medications may use slightly different terminology or acronyms for long-acting formulations, such as XL for extended release or SR for sustained release).

Harms of Immediate- Versus Extended-Release Formulations: Overview

Of the five head-to-head studies that investigated the comparative efficacy (KQ 1c, above) of daily versus weekly dosing or IR versus ER formulations of various types, four also reported on differences in harms (Table 49).[140-143]

One study compared fluoxetine daily with fluoxetine weekly.[139, 140] Two trials assessed paroxetine IR versus paroxetine CR;[141, 142] and one study compared venlafaxine IR with venlafaxine XR.[143] No studies of either fluvoxamine or bupropion (the remaining agents with these formulations) reported on harms.

Table 49. Interventions, numbers of patients, results, and quality ratings of studies comparing harms of daily versus weekly and immediate- versus extended-release formulations

Study	Design, Interventions	N	Results	Quality Rating
Schmidt et al., 2000[140]	RCT Fluoxetine 20 mg daily Fluoxetine 90 mg weekly Placebo	501	Similar adverse events rates between daily and weekly fluoxetine maintenance treatment	Fair
Rapaport et al., 2003[142]	RCT Paroxetine IR 40 mg Paroxetine CR 50 mg Placebo	319	Similar adverse events rates for paroxetine IR and CR	Fair
Golden et al., 2002[141]	Pooled analysis of 2 identical RCTs Paroxetine IR 20-50 mg Paroxetine CR 25-62.5 mg Placebo	640	Higher rates of nausea with paroxetine IR than CR; no differences in other adverse events rates	Fair
Cunningham, 1997[143]	RCT Venlafaxine IR 37.5-150 mg Venlafaxine XR 75-150 mg Placebo	278	Similar adverse events rates between venlafaxine IR and XR	Fair

CR = controlled release; IR = immediate release; mg = milligram; mg/day = milligram per day; RCT = randomized controlled trial; XR = extended-release

Harms of Immediate- Versus Extended-Release Formulations: Key Points

One trial compared the harms of daily versus weekly dosing of fluoxetine.[140] Overall, adverse events rates were similar between fluoxetine daily and fluoxetine weekly dosing regimens. The strength of evidence is moderate that no differences in adverse events exist between daily and weekly formulations of fluoxetine.

Three studies investigated differences in harms for IR versus ER formulations of two other second-generation antidepressants.[141-143] Adverse event rates were similar between paroxetine IR and paroxetine CR, except for higher rates of nausea in patients treated with paroxetine IR than paroxetine CR. In addition, venlafaxine IR and venlafaxine XR had similar adverse event rates. The strength of evidence is low that paroxetine IR leads to higher rates of nausea than paroxetine CR.

We could not find any studies on IR and ER formulations of either fluvoxamine or buproprion that reported on harms.

Harms of Immediate- Versus Extended-Release Formulations: Detailed Analysis

Fluoxetine Daily Versus Fluoxetine Weekly

As described in KQ 1, no extended-release formulation of fluoxetine exists. Because of the long elimination half-lives of fluoxetine and its active metabolite norfluoxetine, investigators have explored different dosing regimens for fluoxetine during continuation-phase treatment. A weekly formulation of fluoxetine is administered as an enteric-coated medication.

One RCT determined the comparative harms between daily and weekly fluoxetine regimens.[140] In it, the acute treatment period was open label and lasted 7 weeks. Patients who achieved response were randomized to double-blinded continuation treatment with fluoxetine once daily 20 mg, or fluoxetine once weekly 90 mg. During 25 weeks of followup, rates for most adverse event were similar for patients on daily or weekly treatments.

Paroxetine IR Versus Paroxetine CR

One double-blinded RCT[142] and a pooled analysis of two identical RCTs[141] compared the harms of paroxetine IR with those of paroxetine CR. These studies contained data on 639 patients. Overall, adverse events rates were similar for the treatment groups. One exception, however, was nausea, which occurred significantly more often in patients treated with paroxetine IR than CR during the first weeks of treatment (23 percent vs. 14 percent; $P<0.05$).[141]

Venlafaxine IR Versus Venlafaxine XR

One flexible-dose, placebo-controlled RCT compared the efficacy and safety of twice-daily venlafaxine IR (115–125 mg/day) with once-daily venlafaxine XR (124–140 mg/day) in 293 patients with acute-phase MDD.[143] During 12 weeks of treatment, the groups did not differ significantly in adverse event rates.

Comparative Adherence and Persistence of Immediate- versus Extended-Release Formulations: Overview

Three studies assessed the comparative adherence of different formulations (Table 50).[142, 287, 288] One compared fluoxetine daily with fluoxetine weekly; the other two evaluated paroxetine IR with paroxetine CR and bupropion SR with bupropion XL. We could not find any studies on fluvoxamine and venlafaxine.

We did not find any studies that directly investigated persistence.

Table 50. Interventions, numbers of patients, results, and quality ratings of studies comparing adherence of immediate versus extended release formulations

Study	Design, Interventions	N	Results	Quality Rating
Claxton et al., 2000[287]	Open-label RCT Fluoxetine 20 mg daily Fluoxetine 90 mg weekly	109	Higher adherence during maintenance treatment for fluoxetine weekly than fluoxetine daily	Fair
Rapaport et al., 2003[142]	RCT Paroxetine IR 40 mg Paroxetine CR 50 mg Placebo	319	Similar adherence rates between paroxetine IR and paroxetine CR	Fair
Stang, Young, and Hogue, 2007[288] *	Retrospective cohort study Bupropion XL Bupropion SR	269,517	Higher refill persistence with bupropion XL than bupropion SR	Fair

CR = controlled release; IR = immediate release; mg = milligram; RCT = randomized controlled trial; SR = sustained release; XL = extended-release

*New study added during update.

Comparative Adherence and Persistence of Immediate- versus Extended-Release Formulations: Key Points

Three studies assessed the comparative adherence of immediate- and extended-release formulations.[142, 287, 288] Based on one open-label RCT, adherence to fluoxetine weekly was higher than to fluoxetine daily.[287] The strength of evidence is low.

The only double-blinded RCT available reported no significant differences in adherence between patients treated with paroxetine IR and those receiving paroxetine CR (93 percent vs. 96 percent) over a 25-week followup period.[142] The strength of evidence is moderate.

A retrospective cohort study, based on U.S. prescription data, showed higher refill persistence for prescriptions of bupropion XL than for those of bupropion SR.[288] The strength of evidence is low.

Comparative Adherence and Persistence of Immediate- versus Extended-Release Formulations: Detailed Analysis

Fluoxetine Daily Versus Fluoxetine Weekly

An open-label RCT randomized 109 patients who had responded to fluoxetine 20 mg during acute-phase treatment to fluoxetine 20 mg daily or fluoxetine 90 mg weekly for continuation treatment.[287] During a follow-up period of 3 months, adherence to fluoxetine 20 mg daily was significantly lower than to fluoxetine 90 mg weekly (79.4 percent vs. 85.9 percent; $P<0.01$).

Paroxetine IR Versus Paroxetine CR

A double-blinded RCT of 319 patients compared their adherence to paroxetine IR, paroxetine CR, and placebo.[142] Details of the study are described above. During the 12-week study period, adherence rates were similar for the paroxetine IR and paroxetine CR treatment groups (93.2 percent vs. 96.3 percent; *P*=NR).

Bupropion SR Versus Bupropion XL

A retrospective cohort study, based on a U.S. prescription database, compared refill rates as a proxy for persistence for twice-daily (bupropion SR) versus once-daily (bupropion XL) bupropion treatment for various indications.[288] The database collated prescription data on more than 12,000 pharmacy retail chain outlets covering about one-third of all U.S. prescriptions. Over 1 year, data were available on more than 12,000 patients on bupropion SR and more than 257,000 patients treated with bupropion XL. The percentage of patients with more than one refill over a 1-year period was 51.3 percent for bupropion SR and 60.1 percent for bupropion XL *(P*<0.001). The percentage of patients with more than 6 refills over 1 year was 9.5 percent for bupropion SR and 25.3 percent for bupropion XL *(P*=NR). Whether prescription refills can be extrapolated to adherence to the dosing schedules remains unclear.

Key Question 5: Efficacy, Effectiveness, and Harms for Selected Populations

Overview: All Subgroups

For this Key Question, we focus on the comparative benefits and harms of second-generation antidepressants for treating a depressive disorder (major depressive disorder [MDD], dysthymia, or subsyndromal depressive disorder) in subpopulations. We focused on the following subgroups: older adults (55 years of age or older); demographic groups defined by sex or race/ethnicity; patients with medical comorbidities (Alzheimer's disease, arthritis, cancer, diabetes, multiple sclerosis, stroke, or cardiovascular disease); patients with psychiatric or behavioral comorbidities (alcohol/substance abuse, generalized anxiety disorder); and patients taking other medications.

We found no studies directly comparing the efficacy, effectiveness, or harms of second-generation antidepressants for any subgroup and the general population. However, a large number of studies conducted subgroup analyses or used subgroups as the study population. Currently, this is the strongest available evidence with which to address this Key Question.

Overall, we included 40 trials (44 articles)[42, 48, 53, 58, 59, 65, 66, 68, 92, 105, 106, 119, 134-136, 142, 163, 174, 181, 286, 289-312] and one systematic review[313] addressing a subgroup of interest.

We found 11 head-to-head trials that addressed efficacy in older adult populations with MDD; the evidence on older adults with dysthymia or subsyndromal depression was limited to placebo-controlled trials. We did not find any studies that met our eligibility criteria and assessed the comparative efficacy, effectiveness, or harms of second-generation antidepressants in different racial or ethnic groups. Only one randomized controlled trial addressed the general efficacy of sertraline in Latinos and blacks with MDD (and diabetes). For comorbid illnesses, evidence was limited primarily to placebo-controlled trials with the exception of one head-to-head trial that conducted a subgroup analysis in patients with co-occurring generalized anxiety disorder and one systematic review in patients with depression or depressive symptoms after

myocardial infarction (MI). Detailed information on these studies appears in Appendix C in the evidence tables.

Because of the lack of evidence from included trials, in some cases we briefly summarize results of studies that did not meet our eligibility criteria but address this Key Question.

Age: Key Points

No studies directly compared the efficacy of second-generation antidepressants in older adults (55 years of age or older) and the general population. Fifteen trials (19 articles) provide mixed evidence on differences in efficacy, effectiveness, and harms in older adult patients treated with second-generation antidepressants.[42, 48, 53, 58, 59, 65, 68, 92, 106, 119, 134-136, 142, 163, 174, 289-291] Table 51 (head-to-head) and Table 52 (placebo-controlled) present selected information on these studies.

Age: MDD

Head-to-head trials provided mixed results on differences in benefits and harms in older adults with MDD. The majority of the trials found no differences in efficacy but suggested some differences in adverse events. Two trials comparing fluoxetine, paroxetine, and placebo reported conflicting results. One trial comparing escitalopram with fluoxetine found a significant difference favoring escitalopram over fluoxetine for efficacy; however, this trial also found neither to be significantly better than placebo. Strength of evidence is moderate for comparative efficacy; strength of evidence is low for harms.

Age: Dysthymia

Two placebo-controlled trials examined the general efficacy of second-generation antidepressants in older adults with dysthymia. One found no difference in response rates between fluoxetine and placebo; the other found significantly greater improvement with paroxetine. Strength of evidence for comparative efficacy and harms is insufficient.

Table 51. Head-to-head studies on efficacy and harms in older adults

Study	N	Duration	Comparison and Dose (mg/day)	Results	Quality Rating
SSRIs vs SSRIs: Kasper et al., 2005[42]	518	8 weeks	Escitalopram 10 Fluoxetine 20	Significantly greater improvement in MADRS score with escitalopram (P<0.01); no differences in AEs	Fair
Cassano et al., 2002[48]	242	52 weeks	Fluoxetine 20-60 Paroxetine 20-40	No significant differences in efficacy; significantly more severe AEs with fluoxetine	Fair
Schone and Ludwig, 1993[53] Geretsegger et al., 1994[290]	106	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	Significantly greater response rate for paroxetine; no significant differences in overall AEs	Fair
Newhouse et al., 2000[58] Finkel et al., 1999[59]	236	12 weeks	Fluoxetine 20-40 Sertraline 50-100	No significant differences in efficacy; subgroup analysis of patients≥70 years of age showed significantly greater HAM-D response rate with sertraline	Fair
Rossini et al., 2005[65]	93	7 weeks	Fluvoxamine 200 Sertraline 150	No significant difference in response rates; no data reported on AEs	Fair
Rapaport et al., 2003[142]	323	12 weeks	Paroxetine CR 50 Paroxetine IR 40 Placebo	No significant differences in efficacy or harms between CR and IR formulations	Good
Allard et al., 2004[68]	151	22 weeks	Citalopram 10-30 Venlafaxine XR 75-150	No significant differences in efficacy; more spontaneously reported AEs with citalopram	Fair
Schatzberg and Roose, 2006[291] *	300	8 weeks	Fluoxetine 20-60 Venlafaxine IR 37.5-225	No significant differences in efficacy measures; significantly more nausea, dry mouth, and constipation with venlafaxine; significantly more anxiety with fluoxetine	Fair
Schatzberg et al., 2002[92]	255	8 weeks	Paroxetine 20-40 Mirtazapine 15-45	No significant difference in response rates at endpoint; significantly faster time to response with mirtazapine; significantly higher rate of nausea and tremor with paroxetine; significantly more weight gain and dry mouth with mirtazapine	Fair
SSRIs vs. other second generation antidepressants: Weihs et al., 2000[106, 289]	100	6 weeks	Paroxetine 100-300 Bupropion SR 10-40	No significant differences in efficacy or harms	Fair
SNRIs vs. other second generation antidepressants: Halikas et al., 1995[119]	150	6 weeks	Mirtazapine 5-35 Trazodone 40-280 Placebo	No significant difference in efficacy	Fair

AEs = adverse events; CR = controlled release; HAM-D = Hamilton Depression Rating Scale; IR = immediate release; MADRS = Montgomery-Asberg Depression Rating Scale; SR = sustained release; XR = extended release

*New study added during update.

Table 52. Placebo-controlled studies on efficacy and harms in older adults

Study	N	Duration	Comparison and Dose (mg/day)	Results	Quality Rating
SSRIs: Gorwood et al., 2007[163] *	305	24 weeks	Escitalopram 10-20 Placebo	Significantly higher proportion of placebo-treated patients relapsed	Fair
Devanand et al., 2005[136]	90	12 weeks	Fluoxetine 20-60 Placebo	No significant difference in response rates and quality of life in dysthymia patients	Good
Barrett et al., 2001[135] Williams et al., 2000[134]	656	11 weeks	Paroxetine 10-40 Placebo Behavioral therapy	In patients older than 60 years with dysthymia or subsyndromal depression, significantly greater improvement in symptom scores for paroxetine than for placebo; in patients younger than 60 years, no difference	Fair
Wilson et al., 2003[174]	113	100 weeks	Sertraline 50-100 Placebo	No difference in prevention of depression; sertraline associated with longer time to recurrence	Fair

SSRI = selective serotonin reuptake inhibitor
*New study added during update.

Age: Subsyndromal Depression

We found no head-to-head evidence of differences in elderly populations with subsyndromal depression. One placebo-controlled trial of paroxetine assessed efficacy and harms in a mixed population (dysthymia or subsyndromal depression). Strength of evidence for comparative efficacy, effectiveness, and harms is insufficient.

Age: Detailed Analysis

MDD: Head-to-Head Evidence

Escitalopram Versus Fluoxetine

One 8-week study compared escitalopram (10 mg/day), fluoxetine (20 mg/day), and placebo in 518 participants older than 65 years of age (mean age in each treatment group, 75 years).[42] Outcome measures included the MADRS and the Clinical Global Impressions Severity Scale (CGI-S). Patients on escitalopram experienced greater improvement in MADRS total score at week 8 compared with those on fluoxetine ($P<0.01$). MADRS response rates showed that more escitalopram- than fluoxetine-treated patients achieved response (46 percent vs. 37 percent, P=not reported). Similar results were seen for MADRS remission rates and mean change in CGI-S scores. These efficacy results must be interpreted with caution because neither active treatment was significantly superior to placebo. For some efficacy measures, improvement in the placebo group was significantly greater than in the fluoxetine group. Adverse events were similar for both active treatment groups.

Fluoxetine Versus Paroxetine

Two trials (three articles) compared fluoxetine with paroxetine in patients older than 60 years old.[48, 53, 290] One 6-week trial compared fluoxetine (20–60 mg/day) and paroxetine (20–40 mg/day) in 106 depressed patients ages 61 to 85 years (mean age 74 years).[53, 290] Paroxetine-

treated patients achieved significantly higher HAM-D response rates than fluoxetine-treated patients (P=0.03). Groups did not differ significantly in overall adverse events.

A 1-year Italian study enrolled 242 patients to compare the effects of fluoxetine (20–60 mg/day) and paroxetine (20–40 mg/day) on depressive symptoms, mood, and cognitive function in nondemented patients 65 years of age or older.[48] In this long-term study, treatment groups did not differ significantly at study endpoint on HAM-D or CGI-S scores or on most cognitive scales (Blessed Information and Memory Test [BIMT], Mini-Mental State Examination [MMSE], Clifton Assessment Schedule [CLAS]). Severe adverse events were significantly more common in the fluoxetine group than in the paroxetine group (22 events vs. 9 events; P<0.002).

Fluoxetine Versus Sertraline

A 12-week study compared fluoxetine (20–40 mg/day) with sertraline (50–100 mg/day) in 236 participants ages 60 years and older.[58] Outcome measures included MADRS, HAM-D, quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire), and cognitive assessments (Shopping List Task [SLT], MMSE, and Digital Symbol Substitution Test [DSST]). Fluoxetine- and sertraline-treated patients demonstrated no significant differences on primary outcome measures (MADRS, HAM-D); HAM-D response rates (71 percent vs. 73 percent) and remission rates (46 percent vs. 45 percent) were similar. Quality of life and other patient-rated measures showed no differences between groups at endpoint. Sertraline-treated patients showed greater cognitive improvement than patients on fluoxetine on the DSST at endpoint (P=0.037). Adverse event rates were similar in the two treatment groups.

A subgroup analysis of this trial focused on 75 patients who were 70 years of age and older. Results demonstrated a greater HAM-D response rate for sertraline than for fluoxetine (58.5 percent vs. 42.4 percent, P=0.027).[59] Tolerability was similar between groups with two exceptions. Reports of the adverse event "shaking" differed significantly between the fluoxetine and sertraline groups (0 percent vs. 14.3 percent, P=0.03). Fluoxetine-treated patients showed greater weight loss from baseline to endpoint than sertraline-treated patients (2.8 pounds vs. 0.6 pounds, P<0.05).

Fluvoxamine Versus Sertraline

A 7-week trial compared fluvoxamine (200 mg/day) and sertraline (250 mg/day) in 93 patients 59 years of age and older (mean age for both treatment groups, 68 years).[65] HAM-D response rates favored fluvoxamine over sertraline but did not reach statistical significance (71.8 percent vs. 55.6 percent, P=0.12).

Paroxetine IR Versus Paroxetine CR

One 12-week trial compared the efficacy and tolerability of two formulations of paroxetine (paroxetine IR and paroxetine CR) and placebo in an elderly population (60 years of age or older).[142] This trial enrolled 323 elderly patients with acute MDD, randomizing them to paroxetine IR (up to 40 mg/day), paroxetine CR (up to 50 mg/day), or placebo. The primary outcome measure was the change of HAM-D scores after 12 weeks of treatment. Patients in both active treatment arms showed similar changes in HAM-D scores (paroxetine IR, -12.3, paroxetine CR, -12.1). Likewise, response rates (65 percent vs. 72 percent) and remission rates (44 percent vs. 43 percent) were similar for the IR and CR groups.

Citalopram Versus Venlafaxine XR

A European 22-week study compared citalopram (10–30 mg/day) with venlafaxine XR (75–150 mg/day) for the treatment of depression in 151 elderly outpatients (mean age, 73 years).[68] The investigators found no statistically significant differences at study endpoint in any efficacy outcome measures (MADRS, CGI-S, CGI-I). MADRS remission rates were 23 percent for citalopram and 19 percent for venlafaxine (*P*=not reported). Both treatment groups reached a 93 percent response rate at week 22 (response defined as a reduction of at least 50 percent in MADRS score). More spontaneously reported adverse events were reported by venlafaxine XR-treated patients than citalopram-treated patients (62 percent vs. 43 percent, respectively); tremor was more common in the citalopram group than the venlafaxine XR group, and nausea or vomiting was more common in the venlafaxine XR group than the citalopram group.

Fluoxetine Versus Venlafaxine

One study compared venlafaxine IR (37.5-225 mg/day) with fluoxetine (20–60 mg/day) and placebo in 300 elderly patients (mean age 71 years old).[291] Both treatment groups experienced a significant reduction in HAM-D total scores at 8 weeks; however, the active treatment groups did not differ significantly in HAM-D, MADRS, or CGI scores at endpoint. Remission rates at 8 weeks were 27 percent for venlafaxine and 20 percent for fluoxetine. Venlafaxine-treated patients experienced significantly higher rates of nausea (45 percent vs. 23 percent, $P<0.01$), dry mouth (23 percent vs. 6 percent, $P<0.01$), and constipation (22 percent vs.10 percent, $P<0.05$) but significantly less anxiety (2 percent vs. 10 percent, $P<0.005$) than patients on fluoxetine

Paroxetine Versus Mirtazapine

One study compared paroxetine (20–40 mg/day) with mirtazapine (15–45 mg/day) in 255 elderly patients 65 years old and older; the trial included an acute phase (8 weeks) and a continuation phase (16 weeks).[92] Although the two groups showed similar reductions in HAM-D scores at endpoint, mirtazapine led to a faster response. A Kaplan-Meier analysis showed a significantly faster time to response for mirtazapine than for paroxetine (mean 26 days vs. 40 days; $P=0.016$). The number needed to treat to yield one additional patient responding with mirtazapine at weeks 1 or 2 was 7. At study endpoint, the number of CGI responders was similar in the mirtazapine and paroxetine treatment groups (64 percent and 56.7 percent, respectively; $P=0.267$). Significantly more mirtazapine-treated patients reported dry mouth and weight gain ($P<0.05$). Paroxetine-treated patients reported a significantly higher rate of nausea, tremor, and flatulence ($P<0.05$).

Sertraline Versus Venlafaxine IR

One poor-quality 10-week trial compared sertraline (up to 100 mg/day) with venlafaxine IR (up to 150 mg/day) among 52 nursing home residents (61 to 99 years of age).[314] We graded the quality of this study as poor because of high loss to followup (44 percent), but we note it here because it is the only study comparing these two agents. Venlafaxine-treated patients had a significantly higher rate of withdrawal because of severe adverse events ($P=0.022$) and withdrawal because of severe adverse events or side effects ($P=0.005$) than did the sertraline-treated patients.

Paroxetine Versus Bupropion SR

One trial examined the efficacy of paroxetine (10–40 mg/day) and bupropion SR (100–300 mg/day) over 6 weeks in 100 outpatients of ages 60 years and older (range 60 to 88 years).[106, 289] This study found no significant differences in efficacy according to all outcome measures between treatment groups. Response rates (≥50 percent reduction in HAM-D scores) were similar in the paroxetine and bupropion SR groups (77 percent vs. 71 percent). Quality-of-life scales (Quality of Life in Depression Scale [QLDS], Medical Outcomes Study Health Survey-Short Form 36 [SF-36]) showed statistically significant improvements in both groups ($P<0.0001$), but they did not differ significantly between the groups.[289] In addition, overall adverse events were similar in the two treatment groups.

SSRIs Versus Venlafaxine

In one study, investigators pooled data from eight randomized trials of venlafaxine IR (75–375 mg/day) or venlafaxine XR (75–225 mg/day), one of several SSRIs (fluoxetine, 20–80 mg/day; fluvoxamine, 100-200 mg/day; paroxetine, 20-40 mg/day), or placebo in the treatment of depression.[315, 316] This study failed to meet our eligibility criteria for study design for this Key Question; however, we describe it because of the limited available evidence. The trials included in the analysis varied in length (6 weeks [three studies], 8 weeks [four studies], or 12 weeks [one study]) and included either outpatients (seven studies) or inpatients (one study). Four of the outpatient trials had a placebo arm. For venlafaxine-treated patients, neither age (<50 or≥50 years of age) nor sex affected remission rates.[315] Among patients treated with SSRIs, however, a significant interaction was observed between treatment and sex ($P=0.004$): older women had a poorer SSRI response rate (28 percent) than younger women (36 percent) and both older (35 percent) and younger men (36 percent). Remission rates for older women treated with venlafaxine were higher than remission rates for older women treated with SSRIs (48 percent vs. 28 percent, $P=0.0004$). Hormone replacement therapy appeared to eliminate these differences. Additional analyses of age subgroups (≤40, 41–54, 55–64, and≥65 years old) and sex subgroups revealed that no significant age-by-treatment, sex-by-treatment, or age-by-sex-by-treatment interactions occurred; men and women of different ages within each treatment group had similar rates of remission, response, and absence of depressed mood.[316] Among patients over 40 years old, the rates of adverse events were similar between the treatment groups, although venlafaxine-treated patients 55 to 64 years old reported significantly more nausea than placebo ($P\leq0.003$), and placebo patients 41 to 54 years old reported significantly more headache than venlafaxine ($P\leq0.01$).

Mirtazapine Versus Trazodone

One 6-week study compared mirtazapine with trazodone in patients with MDD older than 55 years old.[119] Efficacy outcome measures in this trial favored mirtazapine, but differences did not reach statistical significance. More mirtazapine-treated patients discontinued treatment than did those on either trazodone or placebo. Both treatments were associated with more somnolence and dry mouth than placebo ($P\leq0.05$); trazodone treatment was associated with significantly more dizziness and blurred vision compared with placebo ($P\leq0.05$).

MDD: Placebo-Controlled Evidence

We did not include any placebo-controlled trials assessing response or remission in older adults with MDD because we found ample head-to-head evidence. However, we included placebo-controlled trials reporting maintenance of remission or prevention of relapse.

Escitalopram Versus Placebo

One trial assessed prevention of relapse in MDD patients 65 years of age and older.[163] After 12 weeks of open-label treatment with escitalopram, patients who achieved MADRS remission were eligible for randomization to escitalopram (10 or 20 mg/day) or placebo for 24 weeks of double-blind treatment. Of the 405 patients who entered the open-label period, 305 were randomized to double-blind treatment. Over 24 weeks, a significantly higher proportion of placebo- than escitalopram- treated patients relapsed (33 percent vs. 9 percent, $P<0.001$). The estimated hazard ratio for time to relapse (based on Cox proportional hazard model) was 4.44 (95% CI, 2.41 to 8.17); $P<0.001$.

Sertraline Versus Placebo

A 100-week maintenance trial assessed the efficacy of sertraline (50–100 mg/day) compared with placebo in preventing depression recurrence in 113 elderly (65 years old and older) community residents.[174] The trial found no statistically significant difference in the proportion of depression recurrence (HAM-D≥13 and met DSM-III-R criteria for MDD) between sertraline and placebo (45 percent vs. 54 percent, $P=0.21$). However, patients on sertraline experienced a longer time to recurrence than did patients on placebo (92 weeks and 48 weeks, respectively).

Dysthymia: Head-to-Head Evidence

We found no head-to-head trials satisfying our eligibility criteria that addressed efficacy or harms in older adults with dysthymia.

Dysthymia: Placebo-Controlled Evidence

Fluoxetine Versus Placebo

One randomized controlled trial of good quality examined the efficacy and harms of fluoxetine (20–60 mg/day) in dysthymia patients 60 years old and older over 12 weeks.[136] Intention-to-treat results indicated that fluoxetine had limited efficacy. Response rates on the HAM-D favored fluoxetine over placebo, but the two groups did not differ significantly (27.3 percent vs. 19.6 percent; $P<0.4$).

Paroxetine Versus Placebo

A large, primary-care-based effectiveness study (two articles) randomized 656 patients with dysthymia or minor depression to 11 weeks of paroxetine, placebo, or behavioral therapy.[134, 135] Participants were stratified into patients 60 years and older (n=415) and patients younger than 60 years (n=241) for ITT analysis. In the 60 or older subgroup, paroxetine-treated patients showed a greater change in HSCL-D-20 scores than placebo-treated patients ($P=0.004$).[134] Effects were similar for patients with dysthymia and minor depression. For older dysthymia patients with high or intermediate baseline functioning scores, paroxetine significantly improved mental health functioning compared with placebo. Overall, however, improvements of mental health functioning were not statistically significantly different between dysthymia patients receiving paroxetine and those receiving placebo.

Among the younger patients, treatment groups did not differ significantly on the HSCL-D-20 scale.[135] For dysthymia only, the remission rate of patients with at least 4 weeks of treatment was significantly higher in the paroxetine group than in the placebo group (80 percent vs. 44 percent; *P*=0.008). Paroxetine was not more efficacious than placebo in patients with minor depression.

Subsyndromal Depression: Head-To-Head Evidence

We found no head-to-head trials satisfying our eligibility criteria.

Citalopram Versus Sertraline

One nonrandomized trial evaluated citalopram (20 mg/day) and sertraline (50 mg/day) in the treatment of 138 nondemented elderly patients with minor depressive disorder and subsyndromal depression.[137] Although this trial does not meet eligibility criteria because of the study design (because of flawed randomization, it is essentially a nonrandomized trial), we describe it here because it is the only comparative evidence in this population. Both treatments improved depressive symptoms (as measured by the HAM-D); HAM-D remission rates did not differ significantly at endpoint (53 percent vs. 42 percent, *P*=0.25).

Subsyndromal Depression: Placebo-Controlled Evidence

We found one trial (described above) providing evidence on elderly patients with dysthymia or subsyndromal depression.[135]

Race or Ethnicity: Key Points

No studies directly compared the efficacy, effectiveness, or harms of second-generation antidepressants among different races or ethnicities. One study compared sertraline with placebo in low-income minorities with comorbid diabetes to assess quality of life (Table 53).[292] Strength of evidence is insufficient for comparative efficacy, effectiveness, and harms.

Table 53. Studies of efficacy, effectiveness, and harms for race or ethnicity subgroups

Study	N	Duration	Comparison and Dose (mg/day)	Results	Quality Rating
SSRIs: Echeverry et al., 2009[292] *	89	24 weeks	Sertraline 50-100 Placebo	No significant difference	Fair

*New study added during update.

Race or Ethnicity: Detailed Analysis

Head-to-Head Evidence

No head-to-head trials on the efficacy, effectiveness, or harms of second-generation antidepressants compared different racial or ethnic groups.

Placebo-Controlled Evidence

Fluoxetine

One poor trial evaluated the efficacy of fluoxetine compared with placebo in the treatment of patients with comorbid HIV/AIDS.[317] Owing to the scarcity of evidence examining race or ethnicity, we describe it here. A total of 118 patients were randomized to 8 weeks of treatment

with either fluoxetine or placebo. Of all participants, 67 percent were white, 19 percent black, and 14 percent Latino; only 1.7 percent (n=2) were female. Loss to followup was significantly greater among Latinos (53 percent) than blacks (14 percent) and whites (28 percent) ($P<0.05$). Ethnicity was not associated with the total number of treatment side effects or dosage. Response rates among subjects who completed the study were higher in the fluoxetine group (white, 84 percent; black, 50 percent; Latino, 67 percent) than the placebo group (white, 43 percent; black, 36 percent; Latino, 80 percent). The differences were not significant; however, this may be because of the small sample size, particularly in the Latino group.

Sertraline

One trial randomized 89 low-income Latinos and blacks with diabetes to sertraline (50–100 mg/day) or placebo for 6 months.[292] HAM-D scores decreased significantly in both groups but there was no difference between sertraline- and placebo-treated patients. Similar results were seen for quality of life subscales and scores—no differences between treatment groups.

Duloxetine

Two pooled analyses of seven placebo-controlled duloxetine trials assessed the efficacy and tolerability of duloxetine in Latino[318] and black patients[319] compared with white patients. We excluded both studies because they did not meet our study design eligibility requirements, but we describe them here because of the very limited available evidence on race or ethnicity. The first analysis included 1,342 white and 120 Latino patients and found no difference in efficacy outcomes.[318] These two groups did not differ significantly in discontinuation rates due to adverse events or in the types or occurrence of specific adverse events. The second analysis of 1,300 white and 123 black patients also found no evidence for a differential effect of duloxetine in these subgroups for either efficacy or safety outcomes.[319]

Sex: Key Points

Two head-to-head studies provided limited evidence on differences in men and women (Table 54). Strength of evidence for comparative efficacy and effectiveness is insufficient. Strength of evidence for harms is low.

Table 54. Studies of efficacy, effectiveness, and harms for sex subgroups

Study	N	Duration	Comparison and Dose (mg/day)	Results	Quality Rating
SSRIs: Aberg-Wistedt et al., 2000[66]	353	24 weeks	Paroxetine 20-40 Sertraline 50-150	Significantly greater rate of decreased libido in paroxetine-treated women than sertraline-treated women	Fair
Kennedy et al., 2006[105] *	141	8 weeks	Paroxetine 20-40 Bupropion SR150-300	No difference for sexual dysfunction in women; significant worsening of sexual function in paroxetine-treated men	Fair

SR = sustained release

*New study added during update.

Sex: Detailed Analysis

Head-to-Head Evidence

Paroxetine Versus Sertraline

A Swedish randomized controlled trial compared paroxetine (20-40 mg/day) with sertraline (50–150 mg/day) in a 24-week study involving 353 patients.[66] Paroxetine-treated women had significantly greater rates of decreased libido than sertraline-treated women (8.8 percent vs. 1.8 percent; $P<0.05$). Conversely, paroxetine-treated men had lower rates of decreased libido than sertraline-treated men; however, the differences were not statistically significant (12.7 percent vs. 3.8 percent; P=ns).

Paroxetine Versus Bupropion

One study randomized patients to paroxetine (20–40 mg) or bupropion (150–300 mg).[105] Subgroup analysis found a significant difference in antidepressant-related sexual dysfunction in men but not in women. Women treated with paroxetine or bupropion did not differ significantly in sexual function. However, paroxetine-treated men reported a worsening of sexual function whereas bupropion-treated men had no significant change in sexual function (Sex FX total, $P<0.002$).

One 14-week retrospective cohort study of paroxetine (mean dose 30.7 mg/day), sertraline (99.0 mg/day), venlafaxine (151.6 mg/day), and moclobemide (a monoamine oxidase inhibitors drug; 485 mg/day) evaluated disturbances in sexual drive/desire and arousal/orgasm in depressed patients who completed 8 weeks of the study.[256] This study did not meet our inclusion criteria; however, we describe it here because of the paucity of evidence on this topic. In this study, men reported greater impairment in drive/desire than did women ($P<0.05$). Men and women did not differ significantly on the arousal/orgasm scale ($P=0.21$). Rates of dysfunction in all treatment groups were similar for men; among women, sertraline and paroxetine appeared to be associated with greater dysfunction. All drugs appeared to be equally effective in reducing depressive symptoms (main effect for time, $P<0.001$); a favorable drug response was associated with less sexual dysfunction.

Placebo-Controlled Evidence

Duloxetine Versus Placebo

We briefly describe a study that did not meet our eligibility criteria. A pooled data analysis of seven placebo-controlled duloxetine trials assessed safety and tolerability of duloxetine for the treatment of MDD in 560 men and 1,062 women.[320] No clinically meaningful differences were observed between men and women in safety and tolerability with duloxetine treatment. This analysis showed no significant differential sex effects for pulse rate, blood pressure, or weight. Withdrawals attributed to adverse events were similar for men and women. The only significant difference was in the occurrence of nausea; the nausea rate among placebo-treated patients was significantly greater in females than in males (10.7 percent vs. 3.7 percent, $P<0.008$).

Comorbidities: Key Points

We found no studies directly comparing the efficacy, effectiveness, and harms of second-generation antidepressants between depressed patients with comorbidities and the general

population. However, numerous studies conducted subgroup analyses or used subgroups as the study population (Table 55). Strength of evidence is insufficient for comparative efficacy, effectiveness, and harms.

We present our findings differently in this section because we found just a handful of studies for each of the various subgroups with different comorbid illnesses. We note in the text whether the study addresses patients with MDD, dysthymia, or subsyndromal depression. In addition, the evidence is overwhelmingly placebo-controlled; therefore, we do not present the evidence under subheadings of head-to-head evidence and placebo-controlled evidence for each comorbid illness.

Table 55. Studies of efficacy, effectiveness, and harms for subgroups by comorbidity

Study	N	Duration	Comparison and Dose (mg/day)	Results	Quality Rating
Alcohol/ substance abuse: Petrakis et al., 1998[286]	44	12 weeks	Fluoxetine 20-60 Placebo	No significant difference in depressed opioid addicts	Fair
Gual et al., 2003[295]	83	24 weeks	Sertraline 50-150 Placebo	No significant differences in alcoholics with depressive symptoms	Fair
Kranzler et al., 2006[304] *	345	10 weeks	Sertraline 50-200 Placebo	In MDD with co-occurring alcohol dependence, no significant differences in efficacy; significantly more withdrawals due to adverse events with sertraline	Fair
Moak et al., 2003[297]	82	12 weeks	Sertraline 50-200 Placebo	In depressed alcoholics, greater depression improvement in females treated with sertraline	Fair
Hernandez-Avila et al., 2004[296]	41	10 weeks	Nefazodone 200-600 Placebo	No significant differences in efficacy in MDD with co-occurring alcohol dependence	Fair
Alzheimer's disease/ dementia: Lyketsos et al., 2003[298]	44	12 weeks	Sertraline 25-150 Placebo	Sertraline associated with greater response	Fair
Rosenberg et al., 2010[310] *	131	12 weeks	Sertraline 50-100 Placebo	No significant difference in efficacy; sertraline associated with more adverse events	Fair
Arthritis: Wohlreich et al., 2009[305] *	172	8 weeks	Duloxetine 60 Placebo	No significant differences in efficacy outcomes	Fair
Cancer: Fisch et al., 2003[312] *	163	12 weeks	Fluoxetine 20 Placebo	Significantly greater improvements in depressive symptoms with fluoxetine	Fair
Coronary artery disease: Lesperance et al., 2007[308] *	284	12 weeks	Citalopram 20-40 Placebo	Significantly greater improvements in depressive symptoms with citalopram	Fair
Diabetes: Echeverry et al., 2009[292] *	89	24 weeks	Sertraline 50-100 Placebo	No significant differences	Fair
Lustman et al., 2006[181] *	152	52 weeks	Sertraline 25-200 Placebo	Significantly greater maintenance of response with sertraline	Fair

Table 55. Studies of efficacy, effectiveness, and harms for subgroups by comorbidity (continued)

Study	N	Duration	Comparison and Dose (mg/day)	Results	Quality Rating
Generalized anxiety disorder: Silverstone et al., 2001[306] *	92	12 weeks	Fluoxetine 20-60 Venlafaxine XR 75-225 Placebo	Greater improvement with venlafaxine XR	Fair
Heart Failure: O'Connor et al., 2010[311] *	469	12 weeks	Sertraline 50-200 Placebo	No significant difference in efficacy; significantly more withdrawals due to adverse events with sertraline	Fair
HIV/AIDs: Rabkin et al., 1999[294]	120	12 weeks	Fluoxetine 20-60 Placebo	No difference in depressed HIV/AIDS patients	Fair
Rabkin et al., 2004[293]	123	12 weeks	Fluoxetine 20-60 Testosterone Placebo	No difference in depressed HIV/AIDS patients	Fair
Multiple sclerosis: Ehde et al., 2008[307] *	42	12 weeks	Paroxetine 10-40 Placebo	No significant differences	Fair
Myocardial infarction: Bush et al., 2005[313]	NR	Varied	Systematic review of SSRIs	SSRIs improved depression in post-MI patients	Fair
Strik et al., 2000[300]	54	25 weeks	Fluoxetine 20-60 Placebo	Significantly greater response with fluoxetine	Good
Glassman et al., 2002[299]	369	24 weeks	Sertraline 50-200 Placebo	Significantly greater response with sertraline	Fair
Honig et al., 2007[309] *	91	8 weeks	Mirtazapine 30-45 Placebo	Significantly greater CGI improvement with mirtazapine; no significant difference between groups in HAM-D and BDI scores in post-MI patients	Fair
Stroke: Andersen et al., 1994[301]	285	6 weeks	Citalopram 10-40 Placebo	Significantly greater improvement in depression scores with citalopram (P<0.05)	Fair
Li et al., 2008[303] *	150	8 weeks	Fluoxetine 20-40 Placebo FEWP (Herbal)	Significantly greater response with fluoxetine	Fair
Murray et al., 2005[302]	123	26 weeks	Sertraline 50-100 Placebo	No difference in response; greater improvements in quality of life with sertraline	Fair

CGI = Clinical Global Impressions; CR = controlled release; HRT = hormone replacement therapy; IR = immediate release; MI = myocardial infarction; NA = not applicable; SR = slow release; XR = extended release
*New study added during update.

Comorbidities: Detailed Analysis

Alcohol/Substance Abuse

Fluoxetine Versus Placebo

One randomized 12-week trial evaluated fluoxetine and placebo in the treatment of depression in methadone-maintained opioid addicts.[286] Among the entire sample (n=44), BDI (mean decrease for fluoxetine vs. placebo -8.0 vs. -4.7, respectively) and HDRS scores (mean decrease for fluoxetine vs. placebo: -6.0 vs. -7.7, respectively) decreased in both groups, but the treatment groups did not differ significantly. Among those subjects with major depression (n=31), the rate of change of depressive symptoms did not differ significantly by treatment group

(fluoxetine vs. placebo) over time (BDI, -7.8 vs. -3.4; respectively; HDRS, -5.1 vs. -6.9, respectively).

Sertraline Versus Placebo

Three trials comparing sertraline and placebo in the treatment of patients with depression and co-occurring alcoholism had consistent findings.[295, 297, 304] A 24-week study compared sertraline (50–150 mg/day) with placebo in recently detoxified alcohol-dependent patients with current depressive symptoms.[295] Response (>50 percent decrease in MADRS score) was slightly higher in sertraline- than placebo-treated patients (44 percent vs. 39 percent). Both groups experienced significant improvements in HAM-D and MADRS scores during the study, but the two groups did not differ significantly. Relapse rates were higher in sertraline- than placebo-treated patients (31.8 percent vs. 23.1 percent), but the difference did not reach statistical significance (P=0.37). Adverse event rates were similar for the treatment groups.

A 12-week trial showed similar results.[297] In this study, 82 currently depressed, actively drinking alcohol-dependent subjects were randomized to sertraline (50–200 mg/day) or placebo. The groups did not differ significantly in depression symptoms. However, in women, treatment with sertraline was associated with less depression at the end of treatment than placebo based on HAM-D scores (P=0.04) and BDI scores (P=0.005). There was no treatment group difference for men.

The third study was structured differently but produced similar results.[304] This study randomized 345 patients with co-occurring MDD and alcohol dependence to sertraline (50–200 mg/day) or placebo for 10 weeks. After the run-in period, two groups of patients were randomized separately based on HAM-D scores: Group A scores were≥17; Group B scores were≤16. Mean reduction in HAM-D scores did not differ significantly between all sertraline-treated (-10.8) and placebo-treated (-9.6) patients (P=0.14). HAM-D response rates did differ significantly: in Group A, sertraline led to a significantly higher response rate than placebo (64 percent vs. 47 percent, P=0.022) whereas in Group B, sertraline patients had a significantly lower response rate than placebo patients (58 percent vs. 77 percent, P=0.018). Overall, the incidence of adverse events was similar for the two groups; however, significantly more sertraline-treated patients discontinued because of adverse events than did placebo-treated patients (P<0.05).

Nefazodone Versus Placebo

One randomized trial compared nefazodone and placebo in the treatment of depressed patients with comorbid alcohol dependence over a period of 10 weeks.[296] Nefazodone was similar to placebo, as measured by improvement in depression on the HAM-D from intake to study endpoint (mean change in HAM-D score for nefazodone vs. placebo: -12.25 vs. -12.55, P=0.51).

Alzheimer's Disease or Dementia

Sertraline Versus Placebo

Two 12-week trials comparing sertraline and placebo in depressed patients with comorbid Alzheimer's disease provided mixed results.[298, 310] One trial randomized 44 patients to sertraline (25–150 mg/day) or placebo and showed statistically significant improvement in efficacy in sertraline-treated patients compared with placebo, as measured by both the Cornell Score for

Depression in Dementia (CSDD) (P=0.002) and the HDRS (P=0.01).[298] More patients treated with sertraline than with placebo responded (38 percent vs. 20 percent). The groups did not differ in frequency of adverse events.

The other trial randomized 133 patients to sertraline (50–100 mg/day) or placebo and found no significant difference between groups in CSDD scores (P=0.97) or remission rates (OR, 2.06; 95% CI, 0.84 to 5.04).[310] Also in contrast to the other trial, sertraline treatment was associated with more adverse events, but the groups did not differ significantly in occurrence of serious adverse events (P=0.23).

Arthritis

Duloxetine Versus Placebo

One trial evaluated the efficacy of antidepressants in depressed patients with comorbid arthritis.[305] This study is a subgroup analysis of a larger placebo-controlled trial in elderly patients randomized to duloxetine (60 mg/day) or placebo.[219] The subgroup analysis included 233 subjects with MDD and co-occurring arthritis, diabetes, and/or vascular disease. No statistically significant treatment-by-comorbidity interactions occurred for any comorbidity (P=0.266) in HAM-D, GDS, or SF-36 scores or in response or remission rates.

Cancer

Fluoxetine Versus Placebo

One study compared fluoxetine and placebo in cancer patients with accompanying depressive symptoms (subsyndromal or minor depression).[312] Eligibility criteria stated that to qualify for this study, patients had to have at least some depressive symptoms. The aim of the study was to assess adherence to cancer treatment regimen and changes in quality of life by treating patients with fluoxetine before a determination of clinical depression. The study randomized 163 patients to fluoxetine (20 mg/day) or placebo for 12 weeks. Fluoxetine-treated patients showed significant improvements compared with patients on placebo.

Coronary Artery Disease

Citalopram Versus Placebo

One 12-week Canadian study assessed the efficacy and tolerability of citalopram (20–40 mg/day) and placebo in reducing depressive symptoms in patients with co-occurring coronary artery disease (CAD).[308] Improvements in depressive symptoms were greater for citalopram than placebo. Mean HAM-D scores at endpoint showed significantly greater improvement in citalopram- than in placebo-treated patients (14.9 vs. 11.6, P=0.005); the between-group difference was 3.33 (95% CI, 0.80 to 5.85). Citalopram-treated patients also demonstrated significantly greater decrease in mean BDI-II scores at endpoint (P<0.05); between-group difference was 3.61 (95% CI, 0.58 to 6.64). The citalopram group had a lower overall withdrawal rate (13 percent vs. 30 percent, P=NR); however, withdrawals attributed to adverse events were similar between treatment groups.

Diabetes

Sertraline Versus Placebo

One study (described above in race/ethnicity) randomized 89 low-income Latino and black patients with diabetes to sertraline (50–100 mg/day) or placebo for 6 months.[292] HAM-D scores decreased significantly in both groups: sertraline- and placebo-treated patients did not differ at the end of the study. Similar results were seen for quality of life subscales and scores—no differences between treatment groups.

Only one study assessed prevention of recurrence of major depression in patients with diabetes.[181] In the induction phase, 351 patients with moderately severe and recurrent major depression and co-occurring type 2 diabetes were treated with sertraline for 16 weeks. Those who recovered (per DSM-IV criteria) were randomized to double-blind treatment with sertraline or placebo for 52 weeks or until recurrence of depression. Maintenance of response was significantly greater with sertraline (hazard ratio 0.51, 95% CI, 0.31 to 0.85; *P*=0.02).

Generalized Anxiety Disorder

Fluoxetine Versus Venlafaxine

A subgroup analysis of a trial described in KQ 1[84] assessed the efficacy of fluoxetine (20–60 mg/day), venlafaxine XR (75–225 mg/day), or placebo in 92 MDD patients with comorbid generalized anxiety disorder.[306] Treatment with venlafaxine XR resulted in greater HAM-D response than treatment with fluoxetine or placebo.

Heart Failure

Sertraline Versus Venlafaxine

The Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) trial randomized 469 patients with MDD and comorbid heart failure (left ventricular ejection fraction≤45 percent) to sertraline (50–200 mg/day) or placebo for 12 weeks.[311] Both groups showed reduction in HDRS score, but the between-group reduction was not significant (*P*=0.89). Significantly more sertraline-treated patients withdrew because of adverse events believed to be study-drug-related than did placebo-treated patients (11.5 percent vs. 6 percent, *P*=0.03). The groups did not differ significantly in serious adverse events.

HIV/AIDS

Fluoxetine Versus Venlafaxine

Two placebo-controlled studies evaluated the efficacy of fluoxetine versus placebo in the treatment of patients with depression and comorbid HIV/AIDS.[293, 294] The first study, a 12-week randomized trial, compared fluoxetine and placebo;[294] the second, a 12-week, randomized trial, compared fluoxetine, testosterone, and placebo.[293] In both studies, fluoxetine and placebo response rates (57 percent vs. 41 percent[294] and 54 percent versus 44 percent[293]) did not differ significantly. However, these studies may not have been powered to detect a statistically significant difference.

Multiple Sclerosis

Paroxetine Versus Venlafaxine

We identified only one study assessing the efficacy and tolerability of antidepressants for depression with comorbid multiple sclerosis (MS).[307] Forty-two MS patients diagnosed with MDD and/or dysthymia were randomized to paroxetine (10–40 mg/day) or placebo for 12 weeks. Although more paroxetine-treated patients achieved at least a 50 percent reduction in HAM-D scores (57 percent) compared with placebo-treated patients (40 percent), the difference was not statistically significant (P=0.354). Paroxetine- and placebo-treated patients showed improvement in secondary measures (CES-D, MFIS [Modified Fatigue Impact Scale], SF-36), but the treatment groups did not differ significantly on any of them. Paroxetine patients reported higher rates of nausea, headache, dry mouth, and sexual dysfunction.

Myocardial Infarction

One systematic review[313] and three placebo-controlled trials[299, 300, 309] addressed depression and comorbid myocardial infarction. Two of the trials were included in the systematic review.

SSRIs

AHRQ sponsored a systematic review of postmyocardial infarction (post-MI) depression; the authors concluded that SSRIs improved depression in post-MI patients.[313] A good-quality 25-week trial randomized 54 patients to fluoxetine (20–60 mg/day) or placebo for the treatment of depression after a first MI.[300] Another trial randomized patients to sertraline (50–200 mg/day) or placebo for 24 weeks for treating depression in patients with acute MI or unstable angina.[299] In both trials, active treatment was associated with a significantly greater response rate than placebo (sertraline, 67 percent; placebo, 53 percent; P=0.01;[299] fluoxetine, 48 percent; placebo, 26 percent; P=0.05[300]).

Mirtazapine Versus Venlafaxine

A study randomized 91 patients to mirtazapine (30–45 mg/day) or placebo for 8 weeks of acute treatment (and a 16-week continuation phase).[309] After 8 weeks of treatment, mirtazapine was superior to placebo based on BDI and CGI scales but not HAM-D. The difference between treatment groups in mean decrease in HAM-D score was not significant at 8 weeks (standardized effect size [SES] 1.30 vs. 0.96). Based on change in HAM-D score at 8 weeks, more mirtazapine-treated patients were responders (57 percent vs. 40 percent), but the difference was not significant (P=0.18). Mirtazapine-treated patients showed a significantly greater decrease in BDI score at 8 weeks (-4.6 vs. -1.72, P=0.02). Decrease in CGI score was greater in mirtazapine-treated patients but the difference was not statistically significant (P=0.06). The differences between groups in decrease in HAM-D scores and BDI scores over 24 weeks was not statistically significant (P=0.36 and P=0.07). The difference in CGI scores over 24 weeks favored mirtazapine; the difference was significant (P=0.05). Mirtazapine patients experienced significantly more fatigue (P=0.02) and changes in appetite (P=0.02) over 24 weeks.

Stroke

Three placebo-controlled studies evaluated the efficacy of citalopram, fluoxetine, or sertraline in the treatment of patients with poststroke depression.[301-303]

Citalopram Versus Venlafaxine

A 6-week randomized trial evaluated the efficacy of citalopram (10–40 mg/day) and placebo in poststroke depression.[301] Citalopram was associated with significantly greater improvements in depression than placebo on the HAM-D; mean improvements for citalopram compared with placebo were 8.0 vs. 7.2, respectively.

Fluoxetine Versus Venlafaxine

One 8-week trial compared fluoxetine (20–40 mg/day), an herbal supplement, and placebo in moderately to severely depressed patients after a stroke.[303] Fluoxetine-treated patients showed a significantly greater HAM-D response rate than placebo-treated patients (65.5 percent vs. 21.4 percent, $P<0.01$). No serious side effects were reported in either group, and no patients withdrew because of adverse events.

Sertraline Versus Venlafaxine

A 26-week trial evaluated the efficacy of sertraline and placebo in the treatment of minor depression and less severe depression in stroke patients.[302] Sertraline and placebo did not differ significantly in either response rates (week 6: 56 percent vs. 46 percent, respectively; week 26: 76 percent vs. 78 percent, respectively) or remission rates (week 6: 59 percent vs. 51 percent, respectively; week 26: 81 percent vs. 87 percent, respectively). However, at week 26, sertraline was associated with greater improvements in quality of life than placebo (effect size not reported, $P<0.05$).

Discussion

Organization of This Chapter

We first draw general conclusions about the findings of this comparative effectiveness review and present the strength of the evidence supporting these conclusions. We then discuss findings of each Key Question in more detail and, if relevant, put results into context with other studies. Finally, we outline topics for future research based on areas for which we have identified gaps in the current evidence.

General Conclusions

We provide a comprehensive summary of the comparative efficacy, effectiveness, and harms of 13 second-generation antidepressants for the treatment of major depressive disorder (MDD), dysthymia, and subsyndromal depression. They include bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine in three classes: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs and SSNRIs), and other second-generation antidepressants.

Therefore, our findings indicate that the existing evidence does not warrant the choice of one second-generation antidepressant over another based on either greater efficacy or greater effectiveness. Tables 56 through Table 65 briefly summarize our findings from evidence for five Key Questions and their subquestions and notes the strength of evidence in each case (high, moderate, low, or insufficient). For outcomes for which we had no studies whatsoever, we specify "no evidence" for strength of evidence.

Principal Findings for Treatment of MDD

Overall, the new evidence (78 new studies, 87 articles) we found during the update of our 2007 report[12] did not lead to changes in our main conclusion from that review—namely, that no substantial differences in efficacy exist among second-generation antidepressants for the treatment of MDD. Some results are now supported by better evidence than in 2007, which is reflected in a higher grade for the strength of the evidence for some outcomes. In addition, the more advanced statistical analysis that we were able to do for indirect comparisons of second-generation antidepressants when no or only insufficient head-to-head evidence was available also confirmed that conclusion.

Therefore, our findings indicate that the existing evidence does not warrant the choice of one second-generation antidepressant over another based on either greater efficacy or greater effectiveness. Some of the comparisons rendered statistically significant results, the magnitudes of the differences, however, are small and likely not clinically significant. Furthermore, because we had 78 pairwise comparisons, some are expected to be statistically significant by chance alone.

Table 56. Summary of findings with strength of evidence, Key Question 1a: Comparative efficacy and effectiveness of second-generation antidepressants

Disorder, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Major depressive disorder Comparative efficacy	Moderate	Results from direct and indirect comparisons based on 61 head-to head trials and 31 placebo-controlled trials indicate that no substantial differences in efficacy exist among second-generation antidepressants.
Comparative effectiveness	Moderate	Direct evidence from three effectiveness trials (one good) and indirect evidence from efficacy trials indicate that no substantial differences in effectiveness exist among second-generation antidepressants.
Quality of life	Moderate	Consistent results from 18 trials indicate that the efficacy of second-generation antidepressants with respect to quality of life does not differ among drugs.
Onset of action	Moderate	Consistent results from seven trials suggest that mirtazapine has a significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline. Whether this difference can be extrapolated to other second-generation antidepressants is unclear. Most other trials do not indicate a faster onset of action of one second-generation antidepressant compared with another.
Dysthymia Comparative efficacy	Insufficient	No head-to-head evidence exists. Results from five placebo-controlled trials were insufficient to draw conclusions about comparative efficacy.
Comparative effectiveness	Insufficient	No head-to-head evidence exists. One effectiveness trial provides mixed evidence about paroxetine versus placebo; patients older than 60 showed greater improvement on paroxetine; those younger than 50 did not show any difference.
Quality of life	Insufficient	No evidence
Onset of action	Insufficient	No evidence
Subsyndromal depression Comparative efficacy	Low	One nonrandomized, open-label trial did not detect any difference between citalopram and sertraline. Results from two placebo-controlled trials were insufficient to draw conclusions.
Comparative effectiveness	Insufficient	No evidence
Quality of life	Insufficient	No evidence
Onset of action	Insufficient	No evidence

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.
[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table 57. Summary of findings with strength of evidence, Key Question 1b: Greater efficacy and effectiveness with previously effective medications

Disorder, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Major depressive disorder	Insufficient	No evidence
Dysthymia	Insufficient	No evidence
Subsyndromal depression	Insufficient	No evidence

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.
[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table 58. Summary of findings with strength of evidence, Key Question 1c: Differences in efficacy and effectiveness between immediate- and extended-release formulations

Disorder, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Major depressive disorder	Moderate Low	Results from two trials indicate that no differences in response to treatment exist between paroxetine IR and paroxetine CR. Two trials did not detect significant differences in maintenance of response and remission between fluoxetine daily and fluoxetine weekly. One trial reported higher response rates for venlafaxine XR than venlafaxine IR.
Dysthymia	Insufficient	No evidence
Subsyndromal depression	Insufficient	No evidence

CR = controlled release; IR = immediate release; XR = extended release

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table 59. Summary of findings with strength of evidence, Key Question 2a: Efficacy and effectiveness of second-generation antidepressants for maintaining response or remission (i.e., preventing relapse or recurrence)

Outcome of Interest	Strength of Evidence[a]	Findings[b]
Continuing initial medications Comparative efficacy	Moderate	Based on results from six efficacy trials and one naturalistic study, no significant differences exist between escitalopram and desvenlafaxine, escitalopram and paroxetine, fluoxetine and sertraline, fluoxetine and venlafaxine, fluvoxamine and sertraline, and trazodone and venlafaxine for preventing relapse or recurrence.
Comparative effectiveness	Insufficient	No evidence
Switching medications Comparative efficacy	Insufficient	No evidence
Comparative effectiveness	Insufficient	No evidence

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table 60. Summary of findings with strength of evidence, Key Question 2b: Efficacy and effectiveness of second-generation antidepressants in managing treatment-resistant depression syndrome or treating recurrent depression

Outcome of Interest	Strength of Evidence[a]	Findings[b]
Comparative efficacy	Low	Results from four trials suggest no differences, or only modest differences, between SSRIs and venlafaxine. Numerical trends favored venlafaxine over comparator drugs in three of these trials, but differences were statistically significant in only one trial, which compared venlafaxine with paroxetine.
Comparative effectiveness	Low	Results from two effectiveness studies are conflicting. Based on one trial rated good, no significant differences in effectiveness exist among bupropion SR, sertraline, and venlafaxine XR. One effectiveness trial found venlafaxine to be modestly superior to citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline.

SR = slow release; SSRI = selective serotonin reuptake inhibitor; XR = extended release

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table 61. Summary of findings with strength of evidence, Key Question 3: Comparative efficacy and effectiveness of second-generation antidepressants for treatment of depression in patients with accompanying symptom clusters

Accompanying Symptoms, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Anxiety Comparative efficacy for depression	Moderate	Results from five head-to-head trials suggest that efficacy does not differ substantially for treatment of depression in patients with accompanying anxiety.
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for anxiety	Moderate	Results from eight head-to-head trials and three placebo-controlled trials suggest that no substantial differences in efficacy exist among second-generation antidepressants for treatment of accompanying anxiety symptoms
Comparative effectiveness for anxiety	Insufficient	No evidence
Insomnia Comparative efficacy for depression	Insufficient	Results from one head-to-head study are insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting insomnia.
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for insomnia	Low	Results from five head-to-head trials suggest that no substantial differences in efficacy exist among second-generation antidepressants for treatment of accompanying insomnia. Results are limited by study design; differences in outcomes are of unknown clinical significance.
Comparative effectiveness for insomnia	Insufficient	No evidence
Low energy Comparative efficacy for depression	Insufficient	Results from one placebo-controlled trial of bupropion XL are insufficient to draw conclusions about treating depression in patients with coexisting low energy. Results from head-to-head trials are not available.
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for low energy	Insufficient	Results from one placebo-controlled trial of bupropion XL are insufficient to draw conclusions about treating low energy in depressed patients. Results from head-to-head trials are not available.
Comparative effectiveness for low energy	Insufficient	No evidence
Melancholia Comparative efficacy for depression	Insufficient	Results from two head-to-head trials are insufficient to draw conclusions about treating depression in patients with coexisting melancholia. Results are inconsistent across studies.
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for melancholia	Insufficient	No evidence
Comparative effectiveness for melancholia	Insufficient	No evidence
Pain Comparative efficacy for depression	Insufficient	Results from two placebo-controlled trials are conflicting regarding the superiority of duloxetine over placebo. Results from head-to-head trials are not available.

Table 61. Summary of findings with strength of evidence, Key Question 3: Comparative efficacy and effectiveness of second-generation antidepressants for treatment of depression in patients with accompanying symptom clusters (continued)

Accompanying Symptoms, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for pain	Moderate	Evidence from one systematic review, two head-to-head trials (one poor) and five placebo-controlled trials indicate no difference in efficacy between paroxetine and duloxetine.
Comparative effectiveness for pain	Insufficient	No evidence
Psychomotor change Comparative efficacy for depression	Insufficient	Results from one head-to-head trial are insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting psychomotor change.
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for psychomotor change	Insufficient	No evidence
Comparative effectiveness for psychomotor change	Insufficient	No evidence
Somatization Comparative efficacy for depression	Insufficient	No evidence
Comparative effectiveness for depression	Insufficient	No evidence
Comparative efficacy for somatization	Insufficient	Results from one head-to-head trial are insufficient to draw conclusions about the comparative efficacy for treating somatization in depressed patients. Results indicate similar improvement in somatization.
Comparative effectiveness for somatization	Insufficient	Evidence from one open-label head-to-head trial is insufficient to draw conclusions about the comparative efficacy for treating coexisting somatization in depressed patients. Results indicate no difference in effectiveness.

CR = controlled release; IR = immediate release; RCT = randomized controlled trials; SR = slow release; XR = extended release
[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.
[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table 62. Summary of findings with strength of evidence, Key Question 4a: Comparative risk of harms (safety, adverse events), adherence, and persistence

Outcome of Interest	Strength of Evidence[a]	Findings[b]
General tolerability Adverse events profiles	High	Adverse events profiles, based on 92 efficacy trials and 48 studies of experimental or observational design, are similar among second-generation antidepressants. The incidence of specific adverse events differs across antidepressants
Comparative risk of nausea and vomiting	High	Meta-analysis of 15 studies indicates that venlafaxine has a higher rate of nausea and vomiting than SSRIs as a class.
Comparative risk of weight change	High	Results from seven trials indicate that mirtazapine leads to higher weight gains than citalopram, fluoxetine, paroxetine, and sertraline.
Comparative risk of gastrointestinal adverse events	Moderate	Results from 15 studies indicate that sertraline has a higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine. Results from one systematic review confirm some of these findings.
Comparative risk of somnolence	Moderate	Results from six trials indicate that trazodone has a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine.
Comparative risk of discontinuation syndrome	Moderate	A good systematic review indicates that paroxetine and venlafaxine have the highest rates of discontinuation syndrome; fluoxetine has the lowest.
Comparative risk of discontinuation of treatment	High	Meta-analyses of numerous efficacy trials indicate that overall discontinuation rates are similar. Duloxetine and venlafaxine have a higher rate of discontinuations because of adverse events than SSRIs as a class. Venlafaxine has a lower rate of discontinuations because of lack of efficacy than SSRIs as a class.
Severe adverse events Comparative risk of suicidality (suicidal thoughts and behavior)	Insufficient	Results from 11 observational studies (two good quality), five meta-analyses or systematic reviews (four good), and one systematic review yield conflicting information about the comparative risk of suicidality.
Comparative risk of sexual dysfunction	High	Results from six trials indicate that bupropion causes significantly less sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline.
	Low	Among SSRIs, paroxetine has the highest rates of sexual dysfunction.
Comparative risk of seizures	Insufficient	Results from three studies (one good observational design) yield conflicting information about the comparative risk of seizures.
Cardiovascular events	Insufficient	Results from one good observational study and one pooled analysis yield noncomparative or conflicting information about the comparative risk of cardiovascular events.
Comparative risk of hyponatremia	Insufficient	No trials or observational studies assessing hyponatremia met criteria for inclusion in this review. One cohort study not meeting inclusion criteria suggested that hyponatremia was more common in elderly patients treated with various antidepressants than in placebo-treated patients.
Comparative risk of hepatotoxicity	Insufficient	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of hepatotoxicity. Weak evidence indicates that nefazodone might have an increased risk of hepatotoxicity.
Comparative risk of serotonin syndrome	Insufficient	No trials or observational studies assessing serotonin syndrome were included in this review. Numerous case reports of this syndrome exist but were not included in this review.

Table 62. Summary of findings with strength of evidence, Key Question 4a: Comparative risk of harms (safety, adverse events), adherence, and persistence (continued)

Outcome of Interest	Strength of Evidence[a]	Findings[b]
Adherence Comparative adherence in efficacy studies	Moderate	Efficacy studies indicate no differences in adherence.
Comparative adherence in effectiveness studies	Insufficient	Evidence from existing studies is insufficient to draw conclusions about adherence in real-world settings.
Comparative persistence	Insufficient	No evidence

SSRI = selective serotonin reuptake inhibitor

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table 63. Summary of findings with strength of evidence, Key Question 4b: Differences in harms, adherence, and persistence between immediate- and extended-release formulations

Disorder, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Major depressive disorder Comparative risk of harms	Moderate	Findings from one trial each indicate that no differences in harms exist between fluoxetine daily and fluoxetine weekly or between venlafaxine IR and venlafaxine XR.
	Low	One trial provides evidence that paroxetine IR leads to higher rates of nausea than paroxetine CR.
Comparative adherence	Low	One trial provides evidence that fluoxetine weekly has better adherence rates than fluoxetine daily.
Comparative persistence	Low	Evidence from one observational study indicates that prescription refills are more common with the extended-release than the immediate-release formulation of bupropion.
Dysthymia	Insufficient	No evidence
Subsyndromal depression	Insufficient	No evidence

IR = immediate release; XR = extended release

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Table 64. Summary of findings with strength of evidence, Key Question 5: Subgroups

Subgroup, and Outcome of Interest	Strength of Evidence[a]	Findings[b]
Age Comparative efficacy	Moderate	Evidence from 11 trials indicates that efficacy does not differ substantially among second-generation antidepressants for treating MDD in patients age 60 years or older.
	Insufficient	No head-to-head evidence found for dysthymia or subsyndromal depression. Results from one good placebo-controlled trial showed no difference between fluoxetine and placebo.
Comparative effectiveness	Insufficient	No evidence in older patients with MDD.
	Insufficient	One effectiveness study showed greater improvement with paroxetine versus placebo in dysthymia patients older than 60 years; insufficient evidence to draw conclusions on comparative effectiveness.
Comparative harms	Low	Results from six studies indicate that adverse events may differ somewhat across second-generation antidepressants in older adults.
	Insufficient	No head-to-head studies were found for dysthymia or subsyndromal depression.
Sex Comparative efficacy	Insufficient	No evidence
Comparative effectiveness	Insufficient	No evidence
Comparative harms	Low	Two trials suggest differences between men and women in sexual side effects.
Comorbidities Comparative efficacy	Low	Results from a subgroup analysis of one trial indicate significantly greater response with venlafaxine XR than fluoxetine in patients with MDD and comorbid generalized anxiety disorder.
	Insufficient	Placebo-controlled trials assessed efficacy in patients with the following comorbidities: alcohol/substance abuse, Alzheimer's disease/dementia, arthritis, diabetes, HIV/AIDS, multiple sclerosis, stroke, and vascular disease. No head-to-head evidence exists on comparative efficacy.
Comparative effectiveness	Insufficient	No evidence
Comparative harms	Insufficient	No evidence

MDD = major depressive disorder; RCT = randomized controlled trials; vs. = versus; XR = extended release

[a]Strength of evidence grades (high, moderate, low, or insufficient) are based on methods guidance for the EPC program; outcomes for which we have no studies are designated no evidence.

[b]Good, fair, or poor designations relate to quality grades given to each study; see Methods chapter. We provide the designations only for good (or poor) studies; the remaining studies are all of fair quality.

Although second-generation antidepressants are similar in efficacy, they cannot be considered identical drugs. Evidence of high and moderate strength supports some differences among individual drugs with respect to onset of action, adverse events, and some measures of health-related quality of life; these differences are of modest magnitude but statistically significant. Specifically, consistent evidence from multiple trials demonstrates that mirtazapine has a faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline[76, 77, 90, 92, 96] and that bupropion has fewer sexual side effects than escitalopram, fluoxetine, paroxetine, and sertraline.[100, 101, 110-112, 237] It remains unclear whether the faster response of mirtazapine on depression rating scales might simply be caused by a better sleep profile of mirtazapine.

Some of these differences are small and might be offset by adverse events. For example, a faster onset of mirtazapine must be weighed against possible decreased adherence because of long-term weight gain. Nonetheless, some of these differences may be clinically significant and influence the choice of a medication for specific patients. For example, patients who have a history of nausea or who dread sexual dysfunction might be more adherent to a choice of treatment that takes these factors into consideration. Past treatment experiences may also frame

decisions regarding medications to either select or avoid, but no evidence exists to verify these inferences.

Principal Findings for Less Severe Depression, Symptom Clusters, and Subpopulations

For many other Key Questions, particularly those about dysthymia and minor depression, the underlying evidence remains insufficient to draw inferences about the comparative efficacy, effectiveness, and harms of second-generation antidepressants.

Evidence was completely unavailable (or at best insufficient) for several other topics. These included questions about switching medications and about medications to which a patient had previously responded for treating a new depressive episode.

Clinically, numerous physical and psychological symptoms accompany depressive disorders. Clinicians sometimes recommend using individual second-generation antidepressants for these problems, assuming differences in efficacy to treat these accompanying symptom clusters. The current evidence does not support the selection of one second-generation antidepressant over another for specific accompanying symptoms. The best comparative evidence suggests no difference in efficacy for anxiety and pain. For other symptom clusters such as melancholia, psychomotor change, pain, and somatization, the evidence is limited to few comparisons. For other common symptoms, such as appetite change, evidence is completely absent.

For important population subgroups, the evidence is sparse at best. No differences in comparative efficacy are apparent in elderly subgroups with MDD. The paucity of head-to-head trials addressing differences in other demographic subgroups or groups with co-occurring illnesses means that evidence is insufficient to draw conclusions about the comparative efficacy and effectiveness of second-generation antidepressants in such patients.

Specific Results for Efficacy and Effectiveness in Major Depressive Disorder

For MDD, direct evidence from head-to-head trials and indirect comparisons using head-to-head and placebo-controlled trials indicate that, overall, the efficacy and effectiveness of second-generation antidepressants do not differ substantially for the treatment of adults. We graded the strength of this evidence as moderate.

In some of our meta-analyses, results of pooled response rates indicate statistically significant differences in efficacy between some drugs. Specifically, for response, escitalopram is more efficacious than citalopram, sertraline more than fluoxetine, and venlafaxine more than fluoxetine. The magnitudes of these statistically significant differences, however, are small and likely not clinically relevant. In addition, accompanying meta-analyses of effect sizes and mixed treatment comparisons suggest that the actual differences in the mean treatment effects are most likely also not clinically significant.

For example, an odds ratio (OR) meta-analysis of response rates indicates that significantly more patients receiving escitalopram than receiving citalopram achieved treatment response (OR, 1.47; 95% CI, 1.07 to 2.01). An effect-size meta-analysis yielded a mean difference of 1.5 points on the Montgomery-Asberg Depression Rating Scale (MADRS), which represents about one-fifth to one-quarter of a standard deviation. Therefore, this difference most likely does not represent a minimal clinically significant difference. A recent methods study concluded that a change of about one-half of a standard deviation reflects a minimal important difference for a

patient.[321] Furthermore, mixed treatment comparisons taking relative treatment effects of citalopram and escitalopram compared with other second-generation antidepressants into consideration, do not indicate a statistically significant difference in treatment effects between the two drugs (OR, 0.5; 95% credible interval [CrI], 0.13 to 4.14). These findings might indicate underlying publication bias within the body of evidence of head-to-head trials comparing citalopram with escitalopram. Both drugs are produced by the same manufacturer. Citalopram is already available as a generic drug, while escitalopram is still patent protected.

Similarly, sertraline and venlafaxine had statistically significantly greater response rates than fluoxetine. Effect size meta-analyses, however, yielded no clinically significant mean differences on Hamilton Depression Rating Scale (HAM-D) scales.

Findings from mixed treatment comparisons also yielded some statistically significant differences in response rates for some comparisons. Again, the magnitudes of each of these differences were small and indicate no clinically relevant differences in efficacy among second-generation antidepressants.

Although response and remission rates are similar among second-generation antidepressants, 53 percent of patients in these trials did not achieve remission and 37 percent did not respond. Many of these patients will require a second-line treatment. Results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial—and effectiveness study that randomized patients to bupropion SR (sustained release), sertraline, or venlafaxine XR (extended release) after they had failed treatment with citalopram[194]—indicate that, even with second-line treatments, a substantial proportion of patients do not achieve remission.

Effectiveness trials have greater applicability of findings than efficacy studies; for acute-phase MDD we found only three such trials. Two of these effectiveness trials were conducted in French primary care settings and one was performed in the United States. Findings were generally consistent with efficacy trials—they did not detect any substantial differences in effectiveness. However, differences between French and U.S. health systems may limit the applicability of results from French effectiveness trials to U.S. patients.

No evidence exists on adherence in effectiveness studies. Although adherence was similar in efficacy trials, the applicability of such findings may be limited. Most likely, dosing regimens, adverse events, and costs substantially influence adherence of patients in everyday practice. Given similar efficacy and effectiveness, such factors need to be considered when choosing a medication.

Our findings are consistent with results of most other systematic reviews assessing the comparative efficacy and safety of second-generation antidepressants.[322-328] Our conclusions, however, contradict findings of a comparative effectiveness review conducted by the MANGA (Meta-analysis of New Generation Antidepressants) study group.[329] This 2009 review assessed all second-generation antidepressants included in our report except trazodone. Researchers employed Bayesian-based mixed treatment comparisons to determine the relative efficacy and acceptability of all possible comparisons. Results of the MANGA group indicate that escitalopram and sertraline have the best efficacy–acceptability ratio compared with that for other second-generation antidepressants.

The MANGA group's study has been criticized for methodological shortcomings.[330-334] Specifically, several letters to the editor criticized the following points: that the authors included studies with high risk of bias; they assumed that a response on the HAM-D scale equals a response on MADRS or CGI (Clinical Global Inventory); and they overstated the importance of statistically significant findings without considering the clinical relevance. In particular, the

assumption that responses on HAM-D, MADRS, and CGI are identical is not grounded in evidence;[335] thus, making such an assumption might introduce substantial bias in a mixed treatment comparisons model.

For our current update, we employed the same statistical methods as the MANGA authors. We retained, however, our more rigid systematic review methods; these specifically included omitting studies with high risk of bias or open-label designs and limiting pooled outcome measures to relative risks of a response on a single diagnostic scale (HAM-D or MADRS). Furthermore, whenever possible, we used meta-analyses of head-to-head trials as a method of determining the relative efficacy. We employed indirect comparisons as an additional analytic tool only when no sufficient head-to-head evidence was available.

Specific Results for Maintaining Response or Remission

The majority of studies included in our update involved treating patients with major depression in its acute phase; for this phase, the goal is reducing signs and symptoms of depression to achieve remission. Patients who achieve remission with acute-phase treatment should be followed to maintain that response and remission. That is, they should be managed in a continuation phase to prevent relapse and, if necessary, in a longer-term maintenance phase to prevent recurrence. (See Figure 1 in Introduction for clarification of these treatment cycles.)

Although evidence was sparse on the comparative efficacy and effectiveness for maintaining response or remission, treating recurrent depression, or treating depression that does not respond to first-line treatment, our findings are consistent with results from acute-phase trials. Overall, no substantial differences among second-generation antidepressants were apparent, but comparisons are limited to a few drugs.

Moderate strength evidence from six efficacy trials[44, 61, 123, 146-149] suggests that no substantial differences in efficacy exist between escitalopram and desvenlafaxine, escitalopram and paroxetine, fluoxetine and sertraline, fluoxetine and venlafaxine, fluvoxamine and sertraline, and trazodone and venlafaxine for these longer-term treatment goals. One naturalistic study also provides fair-quality evidence that rehospitalization rates do not differ between patients continuing fluoxetine versus venlafaxine.[150] Although results are consistent across these studies, evidence for other drug comparisons is not available; hence, these results are not generalizable to other second-generation antidepressants.

Additionally, trials differed in their design and conduct, further limiting the applicability (generalizability) of this evidence. For example, criteria used to define relapse and recurrence differed considerably across trials. As cases in point with respect to relapse: In the six head-to-head studies, one study defined relapse as an increase in the lowest HAM-D or MADRS score of at least 50 percent for 2 weeks, a HAM-D greater than 18 for 2 weeks, and a Clinical Global Impressions – Severity (CGI-S) score greater than 4;[61] a second study defined relapse as a HAM-D score greater than 15 with functional impairment;[146, 147] a third study defined relapse as a HAM-D score of 12 or greater for 2 consecutive visits;[149] two trials did not define relapse but rather examined continued response (≥50 percent improvement in MADRS or HAM-D_{17} from baseline) or remission (MADRS≤12 or HAM-D_{17}≤7);[44, 148] and a fifth simply assessed discontinuation rates.[123] Eligibility for continuation- or maintenance-phase treatment also varied considerably.

No evidence addressed how second-generation antidepressants compare when a patient responds to one agent and then is required to switch to a different agent (e.g., because of changes

in insurance benefit). Because these circumstances may be relevant for many patients, future studies should consider this question.

We advise that, in future studies, investigators try to build on past and current work by employing definitions of relapse that are similar to those commonly found in the published literature to date. In our view, convergence on standard, accepted definitions of recurrence would be useful as well.

A related question may be how long to continue treatment intended to prevent relapse and recurrence. Although we did not set out to answer this question, we believe that some evidence suggests that the risk of relapse decreases over time. For example, one placebo-controlled study compared 14 weeks, 38 weeks, and 50 weeks of continuation treatment with fluoxetine or placebo.[155] Relapse rates were significantly lower for patients on fluoxetine than for those on placebo at 14 and 38 weeks, but not at 50 weeks. This finding implies some degree of diminishing returns for longer treatment, although more work is needed to address this question.

Specific Results for Managing Treatment-Resistant or Recurrent Depression

Overall, approximately 40 percent of patients do not achieve clinical response with initial treatment. Moreover, approximately 10 percent to 15 percent of patients discontinue treatment because of adverse events. Five studies addressed the comparative efficacy or effectiveness among second-generation antidepressants in patients with treatment-resistant depression. These studies came to inconsistent conclusions, although some of these inconsistencies may be partially explained by variations in the quality and applicability (i.e., internal and external validity) of these investigations. We rated the strength of evidence as low.

The best evidence comes from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.[194, 198] Among patients who did not have a remission or could not tolerate citalopram, the investigators reported that bupropion SR, sertraline, and venlafaxine XR had similar effectiveness and tolerability as second-line treatment. Although the ARGOS study, another effectiveness study, found venlafaxine to be superior to citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline as a second-step treatment,[191] differences were relatively small. Further, we could not determine whether raters were blinded to treatment allocation, potentially limiting the ARGOS conclusions. In four other efficacy studies, venlafaxine was numerically favored over SSRIs in three studies, although only the comparison with paroxetine was statistically significant. Additional research is needed to determine whether trends favoring venlafaxine are meaningful, and whether differences might exist among drugs not included in these studies.

No study specifically compared one antidepressant with another in patients experiencing a depressive relapse (i.e., loss of response during continuation-phase treatment) or recurrence (i.e., loss of response during maintenance-phase treatment). Although STAR*D included patients with a history of recurrent depressive episodes at study entry, the analyses involved patients whose acute-phase treatment of the current episode had been unsuccessful; the analyses did not involve patients who initially responded and then lost response.

Specific Results for Treating Patients With Depression and Accompanying Symptoms

The range of physical and psychological symptoms that accompany depressive disorders is wide. Research involving depressed populations that may be more generalizable suggests that common presenting symptom clusters in both primary care and psychiatric clinics are anxiety, insomnia, and pain and other somatic symptoms.[199]

We found limited information for many accompanying symptom clusters; however, various symptoms may not have the same importance for clinical care. Our analyses concerned the efficacy and effectiveness of second-generation antidepressants for treating the depressive episode in patients with such symptoms and treating the accompanying symptoms in patients with depression.

In general, antidepressants were equally effective in treating the depressive episodes and the accompanying symptoms. The strength of evidence, however, was moderate only for few comparisons of second-generation antidepressants in patients with accompanying anxiety or pain. For all other symptom clusters, the strength of evidence was either low or insufficient or we found no evidence at all.

Seven head-to-head trials indicated that compared antidepressants have similar antidepressive efficacy in patients with accompanying anxiety symptoms.[80, 84, 99, 113, 201-203] Likewise, results from eleven head-to-head trials suggested that antidepressant medications do not differ in efficacy for treating anxiety associated with MDD.[43, 49, 52, 67, 84, 99, 107, 113, 201, 203] These studies involved comparisons of some SSRIs (fluoxetine, paroxetine, and sertraline), bupropion, and venlafaxine.

Patients with depression commonly experience physical symptoms; the majority are pain symptoms. In addition, depression is prevalent among patients with chronic pain disorders.[336] A well conducted meta-analysis of three fair head-to-head trials[87, 88, 218] and one poor trial[216] found no substantial difference between duloxetine and paroxetine in the relief of accompanying pain.

For all other symptom clusters or drug-to-drug comparisons, either the strength of evidence was low, insufficient, or no evidence was found. We identified no evidence at all addressing treatment of melancholic symptoms, psychomotor change, or low energy and anhedonia.

Specific Results for Harms (Adverse Events) and Adherence

Common Adverse Events

On average, 63 percent of patients experienced at least one adverse event during the course of the studies we reviewed. Nausea, headache, diarrhea, fatigue, dizziness, sweating, tremor, dry mouth, and weight gain were commonly reported adverse events.

Although the spectrum of adverse events is similar among second-generation antidepressants, the frequencies of specific adverse events differ among individual drugs. For example, venlafaxine had a higher rate of nausea and vomiting than the SSRIs as a class. Also, compared with other second-generation antidepressants, paroxetine frequently led to higher sexual side effects, mirtazapine and paroxetine to higher weight gains, and sertraline to a higher rate of diarrhea. Such differences did not lead to substantial differences in discontinuation rates.

For some patients, these differences might well be clinically important. For example, the choice of an agent with a low rate of sexual side effects might increase adherence in patients who consider sexual dysfunction an intolerable adverse event.

Severe Adverse Events

The evidence on the comparative risk for rare but severe adverse events such as suicidality, hyponatremia, seizures, or serotonin syndrome was insufficient to draw firm conclusions. The risk of such harms should be kept in mind during any course of treatment with a second-generation antidepressant.

Adherence and Persistence

Efficacy studies did not indicate any differences in adherence across agents. Observational studies indicated that extended-release formulations might have a better a persistence rate than immediate-release medications. This finding, however, could not be confirmed in the only double-blinded RCT that compared paroxetine IR (immediate release) with paroxetine CR (controlled release). An open-label RCT found better adherence in patients treated with fluoxetine weekly than fluoxetine daily during the maintenance phase of depression treatment. The evidence is insufficient to draw any conclusions about differences in adherence in effectiveness studies.

Specific Results for Population Subgroups

In efficacy studies, treatment effects were similar between different age groups. Despite the importance of the harms of second-generation antidepressants, especially in the elderly, little evidence is available on this topic. Evidence suggests that adverse events may differ across second-generation antidepressants in the elderly. We found little or no head-to-head evidence assessing potential differences in efficacy in different racial groups or in patients with common comorbidities. Specifically for different racial groups and for patients with common comorbidities, the evidence is sparse and limited mainly to placebo-controlled trials assessing the general efficacy of second-generation antidepressants in such subgroups. Some of these studies indicated that the general efficacy of second-generation antidepressants in patients with serious comorbidities (e.g., cancer, substance abuse) is limited.

Many of these studies had serious methodological flaws or were too small to detect clinically meaningful differences, although they may not have been powered to detect statistically significant differences. Differences in study populations, cutoff points on scales, and drug dosages do not allow analysts to compare initial treatment effects across individual placebo-controlled trials to assess differences in subgroups other than those defined by age and sex.

Specific Results for Dysthymia and Subsyndromal Depression

The evidence is sparse (strength of evidence for comparative efficacy is insufficient for dysthymia and subsyndromal depression). No conclusions can be drawn about comparative efficacy or effectiveness.

For dysthymia, the evidence on general efficacy is limited to fluoxetine, paroxetine, and sertraline; for subsyndromal depression, the evidence covers only citalopram, fluoxetine, and paroxetine. Results are mixed. For dysthymia, the two largest placebo-controlled studies did not detect any differences between fluoxetine or paroxetine and placebo for treating patients younger than 60 years.[135, 136] Similarly, the evidence on the general efficacy in subsyndromal depression is limited to few studies with mixed results.

Applicability of Results

A considerable limitation of our conclusions is that they have been derived primarily from efficacy trials. For example, for acute-phase MDD we found only 3 effectiveness studies out of 92 head-to-head RCTs. Two of these effectiveness studies were conducted in Europe, and the applicability to the U.S. health care system might be limited. Although findings from effectiveness studies are generally consistent with those from efficacy trials, the evidence is limited to a few comparisons. Whether, for acute-phase MDD, such findings can be further extrapolated to other second-generation antidepressants remains unclear.

Similar lack of applicability of findings pertains to treatment-resistant depression. For example, the STAR*D trial and the ARGOS study, which were both large effectiveness studies, provide evidence for only 8 of 13 antidepressants examined in this review.

Finally, the pharmaceutical industry funded a large percentage of the efficacy studies. Selective reporting is conceivable. Despite considerable effort to detect unpublished studies, we had no way to account for missing information.

Limitations of Report

Several limitations of our review should be considered. As mentioned above, a large majority of studies were efficacy trials conducted in highly selected populations. The applicability of results to the average patient suffering from acute MDD might be limited. Furthermore, most studies were not powered to detect superiority of one treatment over another. Because of the small sample sizes, many studies led to indeterminate findings with confidence intervals encompassing clinically relevant differences. Meta-analyses can help to overcome such limitations and establish equivalence or superiority among treatments. For most subquestions, however, meta-analyses were not feasible. Claims of equivalence, therefore, must be viewed cautiously, and the 95 percent confidence intervals of potential differences need to be taken into consideration.

Indirect comparisons have methodological limitations, most prominently the assumption that prognostic factors for a specific outcome (e.g., response to treatment) are similar across study populations in the network meta-analyses. Nevertheless, they are a valuable additional analytic tool when available head-to-head evidence is insufficient.

Publication bias is a concern for all systematic reviews and has been empirically proven for placebo-controlled trials of second-generation antidepressants. Selective availability of studies with positive results can seriously bias conclusions, particularly when a pharmaceutical company compares two of its own drugs (as in the case of citalopram and escitalopram). The validity of statistical methods to explore publication bias, such as funnel plots, is limited because of the small number of studies for individual comparisons.

Future Research

We identified multiple areas that require additional research to enable clinicians and researchers to draw firm conclusions about the comparative efficacy, effectiveness, and harms of second-generation antidepressants.

Efficacy and Effectiveness

Future research has to establish reliably the general efficacy of second-generation antidepressants for the treatment of dysthymia and subsyndromal depression. Ideally, multiple-

arm, head-to-head trials, including placebo groups, should evaluate the general and comparative efficacy of second-generation antidepressants in patients with these conditions. Effectiveness trials with less stringent eligibility criteria, health outcomes, long study durations, and a primary care population would be valuable to determine whether existing differences of second-generation antidepressants are clinically meaningful in "real world" settings. These trials should be powered to be able to assess minimal clinically significant differences. Furthermore, they could provide valuable information on differences in adherence among second-generation antidepressants.

Future research should also focus on differences in efficacy and effectiveness in subgroups such as the very elderly or patients with various common comorbidities.

Prevention of Relapse and Recurrence

More evidence is needed regarding the most appropriate duration of antidepressant treatment for maintaining remission. Such studies should also evaluate whether different formulations (i.e., controlled release vs. immediate release) lead to differences in adherence and subsequently to differences in relapse or recurrence.

Additionally, although most trials maintained the dose used in acute-phase treatment throughout continuation and maintenance treatment, little is known about the effect of drug dose on the risk of relapse or recurrence. The effect of switching to a new drug after successful completion of acute or continuation phase treatment is poorly understood.

Management of Treatment-Resistant or Recurrent Depression

Given the fact that approximately 40 percent of patients do not respond to initial treatment, additional head-to-head evidence is needed to resolve whether one second-generation antidepressant is better than another in patients who either did not respond or could not tolerate a first-line treatment. These studies also should assess how combinations of antidepressants compare with monotherapy in treatment resistant depression.

Likewise, evidence is lacking to determine whether one antidepressant is better than another in patients who cannot maintain remission during continuation- or maintenance-phase therapy. The role of other depression treatments, such as electroconvulsive therapy, psychotherapy, vagal nerve stimulation, repetitive transcranial magnetic stimulation, and others are used for treatment-resistant patients who do not respond to pharmacological treatment have to be explored.[337]

Accompanying Symptoms

More research is needed to evaluate whether outcomes of second-generation antidepressants differ in populations with accompanying symptoms such as anxiety, insomnia, pain, and fatigue. Given that outcomes for depression treatment do not differ substantially between specific antidepressants, a higher priority for research might be to generate information about treatment of accompanying symptoms with antidepressants. Such evidence is key for clinicians who must select among many antidepressant drugs for patients with widely varying co-existing symptoms.

Study questions must be based on a clinically meaningful metric that gives preference to symptoms of high frequency or those that cause a high level of distress. Each subgroup must be clearly and consistently defined. For example, different investigator teams should identify their own patient groups using a consistent definition accepted in the field. Furthermore, they should then conduct their analyses in such subgroups using similarly defined, widely accepted

outcomes. In this way, results can be compared across studies and across subgroups. Investigators should report the proportions of patients who reach a predefined threshold for clinically meaningful improvement.

The absence of any trials conducted in a population with change in appetite presents a clinically important void in the literature. In addition, future studies of depression with accompanying pain and other somatic symptoms should identify clinically relevant subgroups of patients with moderate to severe pain or other symptoms.

Adverse Events

Large, well-conducted observational studies are needed to assess reliably the comparative risks of second-generation antidepressants with respect to rare but serious adverse events such as suicidality, hyponatremia, hepatotoxicity, seizures, cardiovascular adverse events, and serotonin syndrome. Furthermore, these studies need to evaluate whether very elderly patients such as patients older than 85 years old have an excess risk of severe adverse events with any second-generation antidepressant.

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Appendix A. Search Strategy

PubMed Search as Reported in 2007 Report:

#16 Search "Antidepressive Agents, Second-Generation"[MeSH] OR "Fluoxetine"[MeSH] OR "Sertraline"[MeSH] OR "Paroxetine"[MeSH] OR "Citalopram"[MeSH] OR "Fluvoxamine"[MeSH] OR "Bupropion"[MeSH] OR "nefazodone"[Substance Name] OR "mirtazapine"[Substance Name] OR "venlafaxine"[Substance Name] OR "escitalopram" [tw] OR "duloxetine"[Substance Name] OR "Trazodone"[MeSH] =13604

#22 Search ("Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH]) OR "depression, involutional" [tw] OR "Dysthymic Disorder"[MeSH]OR "subsyndronal depressive disorder" [tw] 47030

#23 Search #16 AND #22 = 4043

#24 Search #16 AND #22 Field: All Fields, Limits: All Adult: 19+ years, English, Humans = 2783

#29 Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials"[MeSH]) OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] = 292497

#30 Search #24 AND #29 = 1056

#35 Search #24 NOT #30 Field: All Fields = 1727

#38 Search "Quality of Life"[MeSH] OR "Hospitalization"[MeSH] = 137196

#39 Search #35 AND #38 = 43

Adverse Events

#42 Search "adverse events" [tw] OR "drug hypersensitivity" [mh] OR "drug toxicity" [mh] OR hyponatremia [mh] OR seizures [mh] OR suicide [mh] OR "weight gain" [mh] OR "gastroesophogeal reflux" [mh] OR libido [mh] OR hepatoxicity [tw] = 124762

Longitudinal Studies

#44 Search longitudinal studies [mh] OR cohort studies [mh] OR case-control studies [mh] OR comparative study [mh] OR "observational studies" [tw] = 1819544

#45 Search #35 AND #42 = 226

#46 Search #35 AND #44 = 371

Drug Interactions

#47 Search drug interactions [mh] = 103115

#48 Search #35 AND #47 = 144

#51 Search "Recurrence"[MeSH] OR remission [tw] OR relapse [tw] = 193920

#52 Search #35 AND #51 = 173
Similar Search Strategy in EMBASE = 133

Total Database = 1922

PubMed Search (September 4, 2010)

Search	Most Recent Queries	Result
#1	Search "Antidepressive Agents, Second-Generation"[MeSH] OR "Fluoxetine"[MeSH] OR "Sertraline"[MeSH] OR "Paroxetine"[MeSH] OR "Citalopram"[MeSH] OR "Fluvoxamine"[MeSH] OR "Bupropion"[MeSH] OR "nefazodone"[Substance Name] OR "mirtazapine"[Substance Name] OR "venlafaxine"[Substance Name] OR "escitalopram" [tw] OR "duloxetine"[Substance Name] OR "Trazodone"[MeSH]	18899
#13	Search "Antidepressive Agents, Second-Generation"[MeSH] OR "Fluoxetine"[MeSH] OR "Sertraline"[MeSH] OR "Paroxetine"[MeSH] OR "Citalopram"[MeSH] OR "Fluvoxamine"[MeSH] OR "Bupropion"[MeSH] OR "nefazodone"[Substance Name] OR "mirtazapine"[Substance Name] OR "venlafaxine"[Substance Name] OR "escitalopram" [tw] OR "duloxetine"[Substance Name] OR "Trazodone"[MeSH] Limits: Entrez Date from 2005/01/01, Humans, English, All Adult: 19+ years	2640
#14	Search "O-desmethylvenlafaxine "[Substance Name] OR desvenlafaxine	96
#15	Search "O-desmethylvenlafaxine "[Substance Name] OR desvenlafaxine Limits: Humans, English, All Adult: 19+ years	37
#16	Search #15 OR #13	2666
#17	Search ("Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH]) OR "depression, involutional" [tw] OR "Dysthymic Disorder"[MeSH]OR "subsyndronal depressive disorder" [tw]	61592
#18	Search #16 AND #17	1028
#19	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials"[MeSH]) OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	345509
#20	Search #19 AND #18	404
#21	Search "Quality of Life"[MeSH] OR "Hospitalization"[MeSH]	191076
#22	Search #21 AND #18	52
#23	Search "adverse events"[tw] OR "drug hypersensitivity"[MeSH] OR "drug toxicity"[MeSH] OR “hyponatremia”[MeSH] OR “seizures”[MeSH] OR “suicide”[MeSH] OR "weight gain"[MeSH] OR "gastroesophogeal reflux"[MeSH] OR “libido”[MeSH] OR “hepatoxicity”[tw]	176101
#24	Search #18 AND #23	222
#25	Search “longitudinal studies”[MeSH] OR “cohort studies”[MeSH] OR “case-control studies”[MeSH] OR “comparative study”[MeSH] OR "observational studies" [tw]	1055406
#26	Search “Comparative Study"[Publication Type]	1433347
#27	Search #26 OR #25	2290232
#28	Search #18 AND #27	398
#29	Search “drug interactions”[MeSH]	120577
#30	Search #18 AND #29	46
#31	Search "Recurrence"[MeSH] OR “remission”[tw] OR “relapse”[tw]	241942

#32	Search #31 AND #18	274
#33	Search #32 OR #30 OR #28 OR #24 OR #22 OR #20	747

Analogous terms were used to search the Cochrane Library, EMBASE, International Pharmaceutical Abstracts (IPA), and PscyINFO.

PubMed Immediate-release and Extended-release Search (March 17, 2010)

Search	Most Recent Queries	Result
#13	Search "Antidepressive Agents, Second-Generation"[MeSH] OR "Fluoxetine"[MeSH] OR "Sertraline"[MeSH] OR "Paroxetine"[MeSH] OR "Citalopram"[MeSH] OR "Fluvoxamine"[MeSH] OR "Bupropion"[MeSH] OR "nefazodone"[Substance Name] OR "mirtazapine"[Substance Name] OR "venlafaxine"[Substance Name] OR "escitalopram" [tw] OR "duloxetine"[Substance Name] OR "Trazodone"[MeSH] OR "O-desmethylvenlafaxine "[Substance Name] OR desvenlafaxine	19556
#14	Search ("Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH]) OR "involutional depression" OR "Dysthymic Disorder"[MeSH] OR "subsyndromal depression" OR Depressive Disorder, Major/drug therapy*	63657
#15	Search #13 AND #14	5681
#16	Search orally disintegrating	208
#17	Search controlled release	25169
#18	Search extended release	5473
#19	Search sustained release	15592
#20	Search immediate release	6982
#21	Search #16 OR #17 OR #18 OR #19 OR #20	46338
#22	Search SR OR XL OR XR OR CR	73038
#23	Search #21 OR #22	117320
#24	Search #23 AND #15	269
#25	Search "Metabolic Clearance Rate"[Mesh]	19468
#26	Search "Half-Life"[Mesh]	32669
#27	Search #25 OR #26	49118
#28	Search #15 AND #27	79
#29	Search #24 OR #28	342
#30	Search #29 Limits: Humans, English	324
#44	Select 4 document(s)	4
#47	Search #30 Limits: All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	64
#48	Search #30 NOT #47	260
#49	Search #48 Limits: Editorial, Letter, Case Reports	27
#50	Search #48 NOT #49 Sort by: PublicationDate	233

PubMed Search (January 13, 2011)

Search	Most Recent Queries	Result
#1	Search "Antidepressive Agents, Second-Generation"[MeSH] OR "Fluoxetine"[MeSH] OR "Sertraline"[MeSH] OR "Paroxetine"[MeSH] OR "Citalopram"[MeSH] OR "Fluvoxamine"[MeSH] OR "Bupropion"[MeSH] OR "nefazodone"[Substance Name] OR "mirtazapine"[Substance Name] OR "venlafaxine"[Substance Name] OR "escitalopram"[tw] OR "duloxetine"[Substance Name] OR "Trazodone"[MeSH] OR "O-desmethylvenlafaxine"[Substance Name] OR desvenlafaxine	20568
#2	Search "Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR "Dysthymic Disorder"[MeSH] OR ("depression"[tiab] AND "involutional"[tiab]) OR ("subsyndromal"[tiab] AND "depressive disorder"[tiab])	66867
#3	Search #1 AND #2	5936
#4	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH]) OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR "Randomized Controlled Trial"[tiab]	439856
#5	Search #3 AND #4	2024
#6	Search "longitudinal studies"[MeSH] OR "cohort studies"[MeSH] OR "case-control studies"[MeSH] OR "Comparative Study"[Publication Type] OR observational stud*	2447452
#7	Search #3 AND #6	1955
#8	Search ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR ("review"[Publication Type] AND "systematic"[tiab]) OR ("systematic review"[All Fields])	37806
#9	Search #3 AND #8	46
#10	Search "Quality of Life"[MeSH] OR "Hospitalization"[MeSH]	210665
#11	Search #3 AND #10	245
#12	Search adverse event* OR "drug hypersensitivity"[MeSH] OR "drug toxicity"[MeSH] OR "hyponatremia"[MeSH] OR "seizures"[MeSH] OR "suicide"[MeSH] OR "weight gain"[MeSH] OR "Gastroesophageal Reflux"[Mesh] OR "libido"[MeSH] OR "hepatoxicity"[tw]	215756
#13	Search #3 AND #12	1040
#14	Search "drug interactions"[MeSH]	125761
#15	Search #3 AND #14	348
#16	Search "Recurrence"[MeSH] OR "remission"[tiab] OR "relapse"[tiab]	237282
#17	Search #3 AND #16	987
#18	Search #5 OR #7 OR #9 OR #11 OR #13 OR #15 OR #17	3845
#19	Search #18 Limits: Humans, All Adult: 19+ years	2917
#20	Search #19 Limits: Editorial, Letter, Case Reports	503
#21	Search #19 NOT #20	2414

Cochrane Search (January 12, 2011)

ID	Search	Hits
#1	"Antidepressive Agents, Second-Generation"[MeSH] OR "Fluoxetine"[MeSH] OR "Sertraline"[MeSH] OR "Paroxetine"[MeSH] OR "Citalopram"[MeSH] OR "Fluvoxamine"[MeSH] OR "Bupropion"[MeSH] OR "nefazodone" OR "mirtazapine" OR "venlafaxine" OR "escitalopram" OR "du	8196
#2	"Depressive Disorder"[MeSH]	7012
#3	"Depressive Disorder, Major"[MeSH]	1717
#4	"Dysthymic Disorder"[MeSH]	251
#5	(depression AND involutional)	35
#6	(subsyndromal AND depressive disorder)	49
#7	(#2 OR #3 OR #4 OR #5 OR #6)	7132
#8	(#1 AND #7)	2360
#9	"Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH]	315860
#10	"Single-Blind Method"[MeSH]	10659
#11	"Double-Blind Method"[MeSH]	93996
#12	"Random Allocation"[MeSH]	24861
#13	(Randomized Controlled Trial*)	373183
#14	(#9 OR #10 OR #11 OR #12 OR #13)	387219
#15	(#8 AND #14)	2008
#16	"Quality of Life"[MeSH] OR "Hospitalization"[MeSH]	34854
#17	(#8 AND #16)	296
#18	(adverse event*)	32596
#19	"drug hypersensitivity"[MeSH] OR "drug toxicity"[MeSH]	1762
#20	"hyponatremia"[MeSH]	249
#21	"seizures"[MeSH] OR "suicide"[MeSH] OR "weight gain"[MeSH] OR "Gastroesophageal Reflux"[Mesh] OR "libido"[MeSH] OR "hepatoxicity"[tw]	9716
#22	(#18 OR #19 OR #20 OR #21)	42004
#23	(#8 AND #22)	584
#24	"longitudinal studies"[MeSH] OR "cohort studies"[MeSH] OR "case-control studies"[MeSH] OR "Comparative Study"[Publication Type] OR (observational studies[All Fields] OR observational study[All Fields])	147846
#25	(#8 AND #24)	939
#26	"drug interactions"[MeSH]	4758

#27	(#8 AND #26)	33
#28	"Recurrence"[MeSH] OR "remission"[tiab] OR "relapse"[tiab]	32620
#29	(#8 AND #28)	629
#30	(#15 OR #17 OR #23 OR #25 OR #27 OR #29)	2155
#31	"adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields]	271482
#32	"humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields]	466240
#33	(#30 AND #31 AND #32)	1470
#34	("review literature as topic"[MeSH] AND "systematic"[tiab]) OR ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields]	25330
#35	(#8 AND #34)	199
#36	(#30 OR #35)	2161
#37	(#36 AND #31 AND #32)	1472
#38	(#37), from 2005 to 2011	542

IPA & PsycINFO Search (January 12, 2011)

ID#	SEARCH TERMS	RESULTS
1	DE "Antidepressant Drugs" OR DE "Bupropion" OR DE "Citalopram" OR DE "Fluoxetine" OR DE "Fluvoxamine" OR DE "Nefazodone" OR DE "Paroxetine" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Sertraline" OR DE "Trazodone" OR DE "Tricyclic Antidepressant Drugs" OR DE "Venlafaxine"	19759
2	mirtazapine OR escitalopram OR duloxetine OR O-desmethylvenlafaxine OR desvenlafaxine	2507
3	S1 or S2	21203
4	MM "Major Depression" OR DE "Dysthymic Disorder" OR DE "Depression (Emotion)"	77335
5	depression AND involutional	243
6	subsyndromal AND depressive disorder	101
7	"Depressive Disorder"	11625
8	S4 or S5 or S6 or S7	81059
9	S3 and S8	9093
10	DE "Experimental Design" OR DE "Between Groups Design" OR DE "Clinical Trials" OR DE "Cohort Analysis" OR DE "Followup Studies" OR DE "Longitudinal Studies" OR DE "Prospective Studies" OR DE "Repeated Measures" OR DE "Quantitative Methods" OR DE "Quasi Experimental Methods" OR DE "Sampling (Experimental)" OR DE "Biased Sampling" OR DE "Random Sampling" OR DE "Statistical Analysis" OR DE "Central Tendency Measures" OR DE "Cluster Analysis" OR DE "Confidence Limits (Statistics)" OR DE "Consistency (Measurement)" OR DE "Effect Size (Statistical)" OR DE "Error of Measurement" OR DE "Frequency Distribution" OR DE "Fuzzy Set Theory" OR DE "Goodness of Fit" OR DE "Interaction Analysis (Statistics)" OR DE "Meta Analysis" OR DE "Multivariate Analysis" OR DE "Predictability (Measurement)" OR DE "Statistical Correlation" OR DE "Statistical Data" OR DE "Statistical Estimation" OR DE "Statistical	88726

	Norms" OR DE "Statistical Probability" OR DE "Statistical Regression" OR DE "Statistical Reliability" OR DE "Statistical Significance" OR DE "Statistical Tests" OR DE "Statistical Validity" OR DE "Statistical Weighting" OR DE "Time Series" OR DE "Variability Measurement"	
11	"randomized controlled trial"	6358
12	S10 or S11	94457
13	S9 and S12	468
14	DE "Quality of Life" OR DE "Quality of Work Life" OR DE "Hospitalization" OR DE "Commitment (Psychiatric)" OR DE "Hospital Admission" OR DE "Hospital Discharge" OR DE "Psychiatric Hospitalization" OR DE "Side Effects (Treatment)" OR DE "Side Effects (Drug)" OR DE "Hyponatremia" OR DE "Seizures" OR DE "Audiogenic Seizures" OR DE "Epileptic Seizures" OR DE "Grand Mal Seizures" OR DE "Petit Mal Seizures" OR DE "Status Epilepticus" OR DE "Suicide" OR DE "Weight Gain" OR "Gastroesophageal Reflux" OR DE "Libido" OR "hepatoxicity"	76245
15	S9 and S14	1721
16	DE "Evidence Based Practice"	6625
17	S9 and S16	29
18	DE "Drug Interactions" OR DE "Recurrent Depression" OR DE "Relapse (Disorders)"	10578
19	S9 and S18	452
20	S13 or S15 or S17 or S19	2507
21	S20 Limiters - Published Date from: 20050101-20110131; Language: English; Articles about Human Studies; Publication Year from: 2005-2011; Publication Type: All Journals; English; Language: English; Age Groups: Adulthood (18 yrs & older); Population Group: Human; Document Type: Journal Article; Exclude Dissertations	328

After search results across years were combined and duplicates were removed, the EndNote X4 database contained 3,722 references.

Appendix B. Excluded Studies

Foreign Languages (6):

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Appendix C. Evidence Tables

INDEX FOR THE EVIDENCE TABLES

In this Appendix, we present two Evidence Tables:

1) Evidence Table 1: Evidence from Randomized Controlled Trials and Observational Studies
2) Evidence Table 2: Evidence from Systematic Reviews and Meta-analyses

Within each of the Evidence Tables, the studies are presented in alphabetical order by first author. When more than one article is cited, the main article is cited first, followed by the subsequent published articles or subgroup analyses.

Below we provide an index for each study included as evidence for each Key Question, including a note of when a particular citation is located under the main article for that particular study in the Evidence Table. A glossary for the Evidence Tables follows.

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GLOSSARY

A/S	Aktieselskap (Company type in Denmark)
AD	antidepressant
AE	adverse event
AG	(Pharma AG)
AGECAT	computerised diagnostic system for use with the Geriatric Mental State
AIDS	acquired immune deficiency syndrome
AMT	awake and moving time
ARV	antiretroviral
ASEX	acute phase treatment-emergent dysfunction
ATVI	aortic time velocity interval
BDI	Beck Depression Inventory
BMI	body mass index
BP	blood pressure
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
bpm	beats per minute
BQOL	Battelle Quality of Life Measure
BSI	Brief Symptom Inventory of Depression
BUP SR	bupropion sustained release
BUP	bupropion
CAD	coronary artery disease
CBT	cognitive-behavioral therapy
CDC	Centers for Disease Control and Prevention
CDIS	Computerized Diagnostic Interview Survey
CES-D	Center for Epidemiologic Studies-Depression
CGI	Clinical Global Impressions
CGI–I	Clinical Global Impressions Improvement Scale
CGI–S	Clinical Global Impressions Severity Scale
CI	confidence interval
CIHR	Canadian Institutes of Health Research
CIT	citalopram
cm	centimeter
CR	controlled release
CSDD	Cornell Scale for Depression in Dementia
CSFQ	Changes in Sexual Functioning Questionnaire
CYP450	**cytochrome P450**
D	drug
DBP	diastolic blood pressure
DEAE(s)	discontinuation-emergent adverse events
DES	desvenlafaxine
DESS	Discontinuation-Emergent Signs and Symptoms checklist
df	degrees of freedom
diff	difference(s)
DLRF	Daily Living and Role Functioning (health related quality of life measure on Q-LES-Q)
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, version III
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, version III revised
DSM–IV	Diagnostic and Statistical Manual of Mental Disorders, version IV
DSP	deliberate self-poisoning
DUL	duloxetine
ECG	electrocardiogram
ECT	electroconvulsive therapy
EEG	electroencephalogram
ER	extended release

ESC	escitalopram
ESZ	eszopiclone
FDA	Food and Drug Administration
FEWP	Free and Easy Wanderer Plus
FLUOX	fluoxetine
FLUV	fluvoxamine
FOT	final on-therapy
FSQ	Functional Status Questionnaire
FX	Function
GAD	Generalized Anxiety Disorder
GAF	Global Assessment of Functioning
GBS	Gottfrey-Brane-Steen scale
GDS	Geriatric Depression Scale
GHC	group health cooperative
GLF	general life functioning
GmBH	company with limited liability in Germany
GP	general physician
GPRD	General Practice Research Database
GSI	General Symptomatic Index
HAD	Hospital Anxiety and Depression Scale
HAM–A	Hamilton Rating Scale for Anxiety
HAM–D	Hamilton Rating Scale for Depression
HAM-D-17	Hamilton Rating Scale for Depression (17 item)
HAM-D-21	Hamilton Rating Scale for Depression (21 item)
HAM-D24	Hamilton Rating Scale for Depression (24 item)
HCAb	hepatitis C surface antibody
HF	heart failure
HgA1C	glycosylated hemoglobin
HIV	Human immunodeficiency virus
HR	Hazard Ratio
HSCL-D	Hopkins Depression Scale
HTN	hypertension
ICD10	International Classification of Diseases – 10th revision
ICD-9 CM	International Classification for Diseases – 9th revision Clinical Modification
IDS	Inventory for Depressive Symptomatology
IDS-C	Inventory for Depressive Symptomatology - Clinician Rated
IDS-IVR	Inventory of Depressive Symptomatology - Self Report
IDS-SR	Inventory for Depressive Symptomatology - Self Report
IMI	imipramine
Inc	Incorporated
IPT	Interpersonal psychotherapy
IR SD-F	Investigator Rated Sexual Desire and Functioning Scale
IR	immediate release
ITT	intent to treat
kg	kilogram
KQ	key question
LOCF	last-observation-carried-forward
LTF	loss to follow-up
mADCS-CGIC	modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change
MADRS	Montgomery Asberg Depression Rating Scale
MAF	Multidimensional
MAOI	monoamine oxidase inhibitor
m-CPP	meta-chlorophenylpiperazine
MD	medical doctor
MDD	major depressive disorder
MDE	major depressive episode

MEI	Motivation and Energy Inventory
MFIS	Modified Fatigue Impact Scale
mg	milligram
mg/d	milligram per day
MHRA	Medicine and Healthcare Regulatory Agency
MI	myocardial infarction
mil	milnacipran
MINI	Mini International Neuropsychiatric Interview
MIR	mirtazapine
mmHG	millimeters of mercury
MMRM	mixed-effect model repeated measures
MMSE	Mini Mental State Examination
mo(s)	month(s)
MRI	Magnetic Resonance Imaging
MS	multiple sclerosis
N	number
N/A	not applicable
NEF	nefazodone
NIH	National Institute of Health
NIHM	Health Diagnostic Interview Schedule
NIMH	National Institute of Mental Health
NNH	number needed to harm
NNT	number needed to treat
NoVASC	no other comorbid vascular illness
NR	not reported
NS	not sig
NSAIDs	non-steroidal anti-inflammatory drug(s)
NV	(NV Organon)
NV	Naamloze Vennootschap (dutch company type)
NYHA	New York Heart Association
OB/GYN	Obstetrics/Gynecology
OCD	obsessive compulsive disorder
ODT	oral disintegrating tablets
OR	odds ratio
P	statistical test: probability (P-value)
PAR	paroxetine
PBO	placebo
PCP	primary care physician
PDQ	Perceived Deficits Questionnaire
PGI	Patient Global Impression
PGIS	Patient Global Improvement Scale
Phys-SFR	Physicians Sexual Functioning Rating
PSD	poststroke depression
PTSD	post traumatic stress disorder
px	prescription
QD	every day
QIDS-C-16	Quick Inventory of Depressive Symptomatology – clinician rated
QLDS	Quality of Life in Depression Scale
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QOL	quality of life
QRS	time of ventricular contraction
QTcF	Fridericia-corrected time of ventricular contraction
RCT	randomized controlled trial
RD	Risk difference
RNZCGP	Royal New Zealand College of General Practitioners
RR	relative risk

RRR	relative risk ratio
Rx	prescription
SADHART-CHF	Sertraline Against Depression and Heart Disease in Chronic Heart Failure
SAE	serious adverse event
SCAG	Sandoz Clinical Assessment Geriatric scale
SCID	Structured Clinical Interview for DSM-III Revised
SCL-20	Symptom Check List
SD	standard deviation
SDS	Self rating Depression Scale
SDS	Sheehan Disability Scale
SE	standard error
SER	Sertraline
SES	standard error of skewness
SEM	standard error of measurement
SF-36	Medical Outcomes Study Health Survey - Short Form 36
sig	significant/significantly
SIP	Sickness Impact Profile
SNRI	serotonin norepinephrine reuptake inhibitor
SR	sustained release
SSI	Somatic Symptom Inventory
SSRI	selective serotonin reuptake inhibitor
TCA(s)	tricyclic antidepressant(s)
TMT-A	Trail Making Test – Part A
TMT-B	Trail Making Test – Part B
TRA	trazodone
TRD	Treatment Refractory Depression
TST	total sleep time
txt	treatment
UK	United Kingdom
UKU	Utvalg for Kliniske Undersogelse (Side Effect Scale)
US	United States
USA	United States of America
UT	Utah
VA	Veterans' Administration
VAMP	previous name of the General Practitioners Research Database
VAS	visual analog scale
VASC	patients with a history of cardiovascular illness (excluding hypertension)
VAS-PI	Visual Analog Scale – Pain Intensity
VEN ER	venlafaxine extended release
VEN XR	venlafaxine extended release
VEN	venlafaxine
VF	verbal fluency test
VHA	Veteran Health Administration
vs.	versus
w/o	without
WHO	World Health Organization
WHO-S	World Health Organization – Item Well-Being Index
wk(s)	week(s)
WMS	Wechsler Memory Scale
x	times
XL	extended release
yr(s)	year(s)
z	statistical test: z test
ZDS	Zung self rating depression scale

Evidence Table 1. Randomized controlled trials and observational studies

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Aberg-Wistedt et al., 2000[l] **Country and setting:** Sweden Multicenter **Funding:** Pfizer, Inc	**Research objective:** SER vs. PAR clinical outcomes after 6 mos of continuous therapy **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 353 **Intervention:** D1: SER 50-150 mg/d D2: PAR 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • MDD diagnosis according to DSM-III or -IV **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** Overall: 43 **Sex (% female):** Overall: 67.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Response 8 wks- SER: 63% PAR: 63% LOCF at 24 wks: SER: 72% PAR: 69% Response-Observed Cases at 24 wks: SER: 89% PAR: 89% Remission No sig diff at endpoint or at any other study point measures 8 wks: SER: 51.6% PAR: 57.3% No sig diff in CGI severity change score or improvement score Relapse during wks 9 to 24: PAR 8.6% SER 1.9% (*P* -value NR) No sig diffs on BQOL	**Constipation:** D1: 5.7 D2: 16.4 **Diarrhea:** D1: 35.2 D2: 15.2 **Libido decrease (men):** D1: 12.7 D2: 3.8 **Libido decrease (women):** D1: 1.8 D2: 8.8 $P \leq 0.05$	**Overall attrition rate:** 35.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Allard et al., 2004[2] **Country and setting:** Sweden and Denmark Multicenter (12 sites) **Funding:** Wyeth	**Research objective:** Compare efficacy and tolerability of VEN ER 75-150 mg/d with of CIT 10-20 mg/d in elderly patients with major depression according to DSM-IV criteria **Duration of study:** 22 wks **Study design:** RCT **Overall study N:** 150 **Intervention:** D1: VEN 37.5-150 mg/d D2: CIT 10-30 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Uncontrolled hypertension • Sig cardiovascular or cerebrovascular disorders	**Mean age (yrs):** D1: 73.6 D2: 72.5 **Sex (% female):** D1: 73.6 D2: 72.7 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	No statistically sig diffs between treatments in any outcome measures (MADRS, CGI-S, CGI-I) Response rates were 93% in both groups at wk 22 MADRS remission rate was 19% for VEN and 23% for CIT (*P* = NR) Side effects were common during both treatments but differed in tremor being more common during CIT and nausea/vomiting during VEN treatment	**Overall adverse events:** D1: 62 D2: 43 **Constipation:** D1: 6.6 D2: 2.7 **Dizziness:** D1: 34 D2: 30 **Headache:** D1: 26 D2: 31 **Nausea:** D1: 30 D2: 16 **Sweating (increase):** D1: 2.6 D2: 2.7	**Overall attrition rate:** 22.2% **ITT analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Alves et al., 1999[3] **Country and setting:** Portugal Multicenter (3 sites) **Funding:** Wyeth-Ayerst International	**Research objective:** Efficacy and tolerability of VEN and FLUOX in MDD **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 87 **Intervention:** D1: VEN 75-150 mg/d D2: FLUOX 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 45.4 D2: 42.3 **Sex (% female):** D1: 92.5 D2: 91.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diffs between study groups in any outcome measures at endpoint. HAM-D responders: VEN: 87%, FLUOX: 74% (*P* = NR); HAM-D Remitters: VEN: 51%, FLUOX: 41% (*P* = NR) VEN showed faster onset with sig diffs in various outcome measures during wks 1 to 4: mean decreases of HAM-D and MADRS scores were sig greater with VEN (*P* < 0.05) during wks 1-4 Suicide ideation scores at wk 6 were sig lower for VEN on MADRS and HAM-D scales Remission (HAM-D < 8) at wk 3 was found in 30% of VEN treated patients and 11% of FLUOX treated patients (*P* = 0.03)	**Overall adverse events:** D1: 56.4 D2: 51.1 **Constipation:** D1: 7.7 D2: 2.1 **Dizziness:** D1: 10.3 D2: 2.1 **Insomnia:** D1: 5.1 D2: 10.6 **Nausea:** D1: 33.3 D2: 27.7	**Overall attrition rate:** 21.8% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Andersen et al., 1994[228] **Country and setting:** Denmark 2 hospitals and an outpatient clinic **Funding:** Lundbeck Foundation	**Research objective:** To investigate efficacy and safety of CIT in treatment of post-stroke depression in post-stroke patients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 66 **Intervention:** D1: CIT: 10-40 mg/d D2: PBO	**Inclusion criteria:** • Adults 25 to 80 • Minimum HAM-D score of 13 • Concomitant condition: post-stroke • Diagnosed with PSD according to DSM-III **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Subarachnoid or Binswanger's disease or other degenerative diseases • Patients with decreased consciousness, dementia, or aphasia to such a degree that they could not explain themselves or gave conflicting verbal and nonverbal signals	**Mean age (yrs):** D1: 68.2 D2: 65.8 **Sex (% female):** D1: 64 D2: 58 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 19.4 (3.1) D2: 18.9 (2.8)	Sig improvement was seen in patients treated with CIT compared to PBO ($P < 0.05$)	NR	**Overall attrition rate:** 13.6% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Andersohn et al., 2009[173] **Country and Setting** United Kingdom, multicenters (general practices) **Funding** Bayer Schering Pharma AG. **Quality rating:** Fair	**Research objective** To investigate whether use of antidepressants in despressive disorders is associated with an increase risk of diabetes mellitus in patients at least 30 years of age and whether risk is influenced by treatment duration or daily dose. **Drugs, Doses, and Range** • BUP (100-450 mg 3 x daily): cutoff value: 300 mg/day; low-medium • CIT (20-60 mg 1 x daily): cutoff value: 20 mg/day; low • ESC (10-20 mg 1 x daily): cutoff value: 10 mg/day; low • FLUOX (10-80 mg 1-2 x daily): cutoff value: 20 mg/day; low • FLUV (25, 50, 100 mg 1-2 x daily): NR • MIR (15-45 mg 1 x daily): cutoff value: 30 mg/day; low-medium • NEF (200-600 mg 2 x daily): cutoff value: 200 mg/day; low • PAR (10-60 mg 1 x daily): cutoff value: 20 mg/day; low-medium • SER (25-200 mg 1 x daily): cutoff value: 50 mg/day; low-high • TRA (150-400 mg 3 x daily): cutoff value: 100 mg/day • VEN (75-375 mg 2-3 x daily): cutoff value: 75	**Inclusion criteria:** • Adults (age range): ≥ 30 years of age (more likely type 2 diabetes) at time of cohort entry • No diagnosis of diabetes or impaired glucose tolerace and no treatment with oral antidiabetics or insulin before cohort entry • Diagnosis of depression within 180 days before or 90 days after cohort entry • No treatment with antidepressants in year prior to their first prescription of an antidepressant (cohort entry) • At lease one database entry of BMI before cohort entry • Registered with a practice with ensured GPRD quality standards of recorded data for at least 1 year prior to cohort entry. To be included as a case subject (potential cases of diabetes), a patient had to have at least one prescription of an antidiabetic drug, or two diagnoses of diabetes on different calendar days, or a diagnosis of diabetes and a diabetes-specific test (i.e., glycosylated hemoglobin) on	**Groups similar at baseline** Yes **n =** D1: 2243 D2: 8963 **Mean age, years** D1: 56.0 D2: 56.0 **Sex, % female** D1: 60.1 D2: 60.1 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** The population characteristics information was presented as case subjects vs. comparison subjects, not based on types of medications used by patients. Additional characteristics were presented, including comorbidity (hyperlipidemia and hypertension), body mass index, smoking history, and recent use of other	**HAM-D** NR **MADRS** NR **CGI-S** NR **CGI-I** NR **CGII** No Number of patients achieving a score 12345 **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** **Additional Results:** • Recent long-term use of antidepressants in moderate or high daily doses was associated with an increased risk of diabetes (incidence rate ratio: 1.84; 95% CI, 1.35-2.52). Recent use of shorter duration, use in lower daily doses, former use, and past use were not associated with an increased risk of diabetes. For users of	**Attrition** **Overall attrition, %:** NR **Attrition rate, %:** NR **Withdrawals due to adverse events, %** NR **Withdrawals due to lack of efficacy, %** NR **Comments** Attrition was not reported in observational study.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
	mg/day; low • Other (augmentation): other prescriptions identified during follow-up: Amitriptyline (cutoff value: 38 mg/day), Amoxapine (NR), Clominpramine (cutoff value: 20 mg/day) Dothiepine (cutoff value: 62.5 mg/day), Doxepin (cutoff value: 30 mg/day), Lofepramine (cutoff value: 140 mg/day), Imipramine (cutoff value: 50 mg/day), Iprindole (NR), Nortriptyline (cutoff value: 30 mg/day), Protriptyline (cut off value: 5 mg/day), Trimipramine (cutoff value: 50 mg/day), Maprotiline (NR), Mianserin (cutoff value: 25 mg/day), Isocarboxazid (NR), Moclobemide (NR), Phenelzine (15 mg/day), Tranylcypromine (NR), Reboxetine (8 mg/day) **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** Observational **Duration** 15.5 years **Type of depression** • Article states that patients had to have a diagnosis of	different calendar days. [cohort entry was defined as date of first description of an antidepressant] **Exclusion criteria:** • Excluded from case group: patients who had a suspected diagnosis of diabetes that was not confirmed later on (internal validation) **Outcome measures** NR	drugs.	tricyclic antidepressants and SSRIs as groups, increased risk was observed only for recent long-term use of moderate or high daily doses (incidence rate ratio: 1.77, 95% CI, 1.21-2.59, and incidence rate ratio: 2.06; 95% CI, 1.20-3.52, respectively). analysis for other antidepressants as a group was limited by small number of exposed case and comparison subjects and revealed no increased risk with long-term use of moderate or high daily doses (incidence rate ratio: 1.64; 95% CI, 0.34-7.81). incidence rate ratios associated with long-term use were 2.49 (95% CI, 1.52-4.08) for amitriptylin, 9.05 (95% CI, 1.08-75.58) for FLUV, 1.75 (95% CI, 1.13-2.72) for PAR, and 3.01 (95% CI, 1.01-9.02) for VEN. • Incidence rate rations associated with recent use of individual antidepressants (Selective serotonin reuptake inhibitors): CIT 1.13 (95% CI, 0.85–1.51), ESC (95% CI, 1.27 0.57–2.86), FLUOX 1.06 (95% CI,	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
	depression (prescription of an antidepressant), but does not specify what type of depression. **Intervention** Case Subjects Comparison Subjects			0.84–1.34), FLUV 4.91 (95% CI, 1.05–23.03), PAR 1.33 (95% CI, 1.02–1.73), SER 1.25 (95% CI, 0.89–1.78); (other antidepressants): MIR 1.14 (95% CI, 0.39–3.30), NEF 0.79 (95% CI, 0.06–8.27), Reboxetine 1.63 (95% CI, 0.10–25.86), TRA 2.16 (95% CI, 0.89–5.25), VEN 2.03 (95% CI, 1.18–3.48)	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Baldomero et al., 2005[106] **Country and setting:** Spain Psychiatric outpatient centers **Funding:** Wyeth Pharma, S.A	**Research objective:** To compare efficacy of VEN to conventional treatments in patients that failed to tolerate or respond to initial treatment **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 3502 **Intervention:** D1: VEN: 75-225 mg/d D2: Conventional txt: CIT: 20-40 mg/d FLUOX: 20-40 mg/d MIR: 30-45 mg/d PAR: 20-40 mg/d SER: 50-150 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Adults 18 and over • Minimum HAM-D score > 16 **Exclusion criteria:** • Concomitant psychotherapeutic or psychotropic medications • ECT within 30 days • MAOI or St. Johns Wort in last 14 days	**Mean age (yrs):** D1: 46.6 D2: 46.0 Sex (% female): D1: 72.8 D2: 68.9 Race (% white): NR Baseline HAM-A: D1: 22.8 D2: 22.2 Baseline HAM-D: D1: 23.9 (4.9) D2: NR	Conventional therapy (pooled): Response 1034(71%) Remission 754(52%) CIT 20-40: Response 209 (71%) Remission 153 (52%) FLUOX 20-40: Response 174 (70%) Remission 128 (52%) MIR 30-45: Response 75 (65%) Remission 52 (45%) PAR 20-40: Response 226 (73%) Remission 161 (52%) SER 50-150: Response 197 (71%) Remission 147 (53%) VEN 75-225: Response 1262 (78%) Remission 963 (59%) VEN sig better than conventional therapy on response and remission ($P < 0.001$)	Overall adverse events: D1: 26.4 D2: 28.2 Cardiovascular adverse events: D1: 3.3 D2: 1.1 Sexual dysfunctional: D1: 8.7 D2: 13.6	**Overall attrition rate:** 21.3% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Baldwin et al., 1996[4] **Country and setting:** UK, Ireland, Multicenter (20 psychiatric outpatient clinics) **Funding:** Bristol Myers Squibb	**Research objective:** To compare efficacy, safety, and tolerance of NEF and PAR in treatment of depressed outpatients **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 206 **Intervention:** D1: NEF 200-600 mg/d D2: PAR 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Rated at least moderately ill on CGI-S **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 6 mos • Suicidal tendencies • Failed to respond to at least 2 adequate courses of anti-depressant treatment • History of allergy or hypersensitivity to TRA, etoperidone, m-CPP, or PAR	**Mean age (yrs):** D1: 38.3 D2: 37.9 **Sex (% female):** D1: 60 D2: 50 **Race (% white):** NR **Baseline (HAM-A):** D1: 19 D2: 18.3 **Mean HAM-D score at baseline:** D1: 24.6 D2: 24.8	Both groups showed sig improvements from baseline HAM-D, HAM-A and MADRS scores Proportion of CGI responders similar between treatment groups (NEF: 58% vs. PAR: 60%, *P* = NR) No sig diffs between treatment groups	**Overall adverse events:** D1: 84 D2: 78 **Dizziness:** D1: 17 D2: 9 **Headache:** D1: 35 D2: 25 **Nausea:** D1: 27 D2: 30 **Somnolence (fatigue):** D1: 16 D2: 24	**Overall attrition rate:** 27.2% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Baldwin, 2006[5] **Country and Setting** multinational, multicenter **Funding** H. Lundbeck A/S **Quality rating:** Fair	**Research objective** To evaluate short- and long-term antidepressant tolerability and efficacy of ESC and PAR. **Drugs, Doses, and Range** D1: ESC (10-20 mg 1 x daily): low-high; 10-20 mg D2: PAR (10-60 mg 1 x daily): medium; 20-40 mg **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** Yes **Study design** RCT **Duration** 8 weeks (includes both acute and maintainence periods) **Type of depression** MDD **Intervention** D1: PAR D2: ESC	**Inclusion criteria:** • Adults (age range): 18 years old and over • Diagnosed with MDD according to DSM-III or -IV: Current epidsode of MDD • MADRS: 22 or greater and 40 or less **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications: includes tryptophan, benzodiazepines, antipsychotics, psychoactive herbal remedies, MAOIs, prophylactic treatment dopamine antagonists • Schizophrenia, psychotic disorders, mania or hypomania, eating disorders, obsessive-compulsive disorder, bipolar disorder • Investigational drug use within last 3 months • MADRS item 10 score of 5 or greater • Another Axis I disorder within previous 6 months • Learning disability • Cognitive disorder • Nonresponse or hypersensitivity to CIT and/or PAR	**Groups similar at baseline** Yes **n =** D1: 159 D2: 166 Overall: 325 **Mean age, years** D1: 45.1 D2: 44.9 Overall: 45 **Sex, % female** D1: 74.7 D2: 72.7 Overall: 75.0 **Race, % white** D1: 99.4 D2: 98.8 Overall: NR **Baseline HAM-A** NR Overall: NR **Insomnia, %** NR Overall: NR **Concomitant anergia, %** NR Overall: NR **Experienced prior depressive episodes, %** NR Overall: NR	**HAM-D** NR **MADRS** D1: PAR D2: ESC n at baseline: D1: 159 D2: 166 No. of remitters: Week 8 D1: 95 D2: 93 Mean score at endpoint (SD): Week 8 D1: 11.31 (NR) D2: 12.44 (NR) Mean score change among severely depressed patients at week 8 (PAR vs. ESC, respectively): -20.2; -23.6 **CGI-S** NR **CGI-I** NR **CGII** No **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or**	**Overall adverse events, %:** D1: 82.9 D2: 81.8 **Constipation, %:** D1: 8.2 D2: 3.6 **Diarrhea, %:** D1: 6.3 D2: 10.3 **Dizziness, %:** D1: 6.3 D2: 6.1 **Headache, %:** D1: 13.3 D2: 20.0 **Insomnia, %:** D1: 4.4 D2: 6.7 **Nausea, %:** D1: 13.9 D2: 11.5 **Sexual dysfunction, %:** D1: 57.7 D2: 57.0 **Attrition** **Overall attrition, %:** 28 **Attrition rate, %:** D1: 34 D2: 21 **Withdrawals due to adverse events, %** D1: 11 D2: 9

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		• History of severe allergy or hypersensitivity • History of lactose intolerance • Antidepressants within 2 weeks before screening • Triptans, oral anticoagulants • Sildenafil citrate • Cimetidine • Type 1c anti-arrhythmics • Cardiac glycosides • Narcotic analgesics • Receiving formal psychotherapy **Outcome measures** • MADRS • Quality of life scales: ASEX scale	**compliance** NR **Additional Results:** NR	**Withdrawals due to lack of efficacy, %** D1: 10.1 D2: 3.6 **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Ballus et al., 2000[6] **Country and setting:** Spain Multicenter **Funding:** NR	**Research objective:** To compare efficacy and tolerability of VEN and PAR in patients MDD and dsythmia **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 84 **Intervention:** D1: VEN 75-150 mg/d D2: PAR 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Minimum HAM-D score of 17 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 44 D2: 45.1 **Sex (% female):** D1: 88 D2: 88 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.4 (4.1) D2: 24.3 (4.7)	No sig diffs between groups on HAM-D, MADRS, or CGI scales at 24 wks or endpoint At wk 12, percent of patients with HAM-D score < 8 was sig greater in VEN group than PAR group (57% vs. 33%; *P* = 0.011) More patients exhibited a drug response (> 50% decrease in HAM-D) on VEN than PAR at wk 6 (*P* = 0.03) Response rates at wk 24: NR	**Overall adverse events:** D1: 68 D2: 79 **Constipation:** D1: 12.5 D2: 16.3 **Diarrhea:** D1: 0 D2: 9.3 **Headache:** D1: 17.5 D2: 39.5 **Insomnia:** D1: 7.5 D2: 9.3 **Nausea:** D1: 27.5 D2: 9.3 **Sweating (increase):** D1: 2.5 D2: 7.0	**Overall attrition rate:** 32% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Barrett et al., 2001[7] **Country and setting:** United States Multicenter, primary care clinics **Funding:** Hartford and MacArthur Foundation	**Research objective:** To compare PAR vs. PBO vs. behavioral treatment for dysthymia and minor depression in primary care patients **Duration of study:** 11 wks **Study design:** RCT **Overall study N:** 241 **Intervention:** D1: PAR 10-40 mg/d, individually titrated D2: PBO	**Inclusion criteria:** • Adults 18 to 59 • Minimum HAM-D score of 10 • Dysthymia **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies • Current depression treatment	**Mean age (yrs):** D1: 45.2 D2: 42.6 **Sex (% female):** D1: 57.5 D2: 66.7 **Race (% white):** D1: 90 D2: 89 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	ITT analysis: mean decrease in HSCL-D-20; PAR: 0.88 (0.08), PBO: 0.85 (0.09); behavior therapy: 0.79 (0.09), no sig diffs between arms Remission by HAM-D-17 score < 6: PAR: 80%, PBO: 44.4%; behavior therapy: 56.8% (*P* = 0.008 for diff among all 3 arms) Minor depression: PAR 60.7%, PBO 65.6%; behavior therapy 65.5% (*P* = 0.906 for diff among all 3 arms)	NR	**Overall attrition rate:** 20.7% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Beasley et al., 1991[8] **Country and setting:** Country NR (appears to be United States) Multicenter **Funding:** Eli Lilly and Company	**Research objective:** To evaluate comparative safety and efficacy of FLUOX and TRA in major depression and to evaluate incidence and temporal patterns of activation and sedation **Duration of study:** Up to 6 wks (after a single-blind PBO run-in approximately 1 wk in duration) **Study design:** RCT **Overall study N:** 126 randomized 120 included in analysis **Intervention:** D1: FLUOX: 20-60 mg/d D2: TRA: 100-400 mg/d	**Inclusion criteria:** • Adults 18 or older • Outpatients • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • DSM depression but 4 wks in duration **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • PBO response during lead-in	**Mean age (yrs):** D1: 40.0 D2: 40.0 **Sex (% female):** D1: 64.6 D2: 68.8 **Race (% white):** Overall NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.4 (2.7) D2: 24.3 (3.6) **Baseline HAM-D Sleep Factor:** D1: 3.8 (1.7) D2: 3.8 (1.8)	Response rates (≥50% HAM-D at endpoint), n (%) D1: 40.5 (62.3) D2: 42.0 (68.9) Remission rates (HAM-D ≤ 7 at endpoint), n (%) D1: 33.1 (50.9) D2: 25.7 (42.2) PGIS, mean change at endpoint SD) D1: 2.4 (1.2) D2: 2.3 (1.2) *P* = NR **Sleep outcomes** Improvement in HAM-D Sleep Disturbance Factor: D1: 1.6 D2: 2.7 *P* = 0.001	**Diarrhea:** D1: 7.7 D2: 3.3 **Dizziness:** D1: 6.2 D2: 21.3 **Headache:** D1: 21.5 D2: 27.9 **Insomnia:** D1: 9.2 D2: 3.3 **Nausea:** D1: 27.7 D2: 24.6 **Somnolence (fatigue):** D1: 20.0 D2: 45.9 **Sweating (increase):** D1: 4.6 D2: 0	**Overall attrition rate:** 34.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Behnke et al., 2003[9] **Country and setting:** Multinational Multicenter **Funding:** NV Organon	**Research objective:** To compare onset of antidepressant efficacy of MIR and SER **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 346 **Intervention:** D1: MIR: 30-45 mg/d D2: SER: 50-150 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Epilepsy • History of seizure disorder or anti-convulsant treatment • Current eating disorders diagnosis • Previous postpartum depression or anxiety disorder diagnosis	**Mean age (yrs):** D1: 42 D2: 41 **Sex (% female):** D1: 55.7 D2: 61.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Onset of action faster in MIR group At all assessments during first 2 wks mean change of HAM-D from baseline sig greater in MIR group than in SER group ($P < 0.05$) After wk 2 diff remained greater with MIR but lacked statistical significance HAM-D response rate showed similar findings HAM-D remission rate higher with MIR than SER at all assessments; diff reached statistical significance at day 14 Reduction in sleep disturbance was sig greater in MIR group at all assessments ($P \leq 0.01$) CGI scores not sig diff	**Overall adverse events:** D1: 64 D2: 68 **Diarrhea:** D1: 4 D2: 9.5 **Dizziness:** D1: 6.8 D2: 10.1 **Headache:** D1: 14.2 D2: 18.3 **Insomnia:** D1: 5.1 D2: 8.9 **Nausea:** D1: 7.4 D2: 22.5 **Somnolence (fatigue):** D1: 19.9 D2: 7.7 **Sweating (increase):** D1: 1.1 D2: 5.3 **Libido decrease:** D1: 1.1 D2: 5.9 $P = 0.02$	**Overall attrition rate:** 20.8% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Benkert et al., 2000[10] **Country and setting:** Germany Multicenter (50) **Funding:** Organon, GmBH, Munich, Germany	**Research objective:** Safety and efficacy of MIR and PAR in treatment of major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 275 **Intervention:** D1: MIR: 15-45 mg/d (32.7) D2: PAR: 20-40 mg/d (22.9)	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Suicidal tendencies	**Mean age (yrs):** D1: 47.2 D2: 47.3 **Sex (% female):** D1: 63 D2: 65 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 22.4 (3.3) D2: 22.4 (3.2)	No significant difference between MIR and PAR in HAM-D response rates at endpoint (58.3% vs. 53.7%) No significant difference between MIR and PAR in HAM0D remission rates (score ≤ 7) at endpoint (40.9% vs. 34.1%) Faster onset of action with MIR: significantly more responders (23.2% vs. 8.9%, *P*=0.002) and remitters (8.8% vs. 2.4%, *P*=0.03) at day 7 with MIR	**Overall adverse events:** D1: 68.1 D2: 63.4 **Changes in weight (increase):** D1: 14.8 D2: 3.7 **Constipation:** D1: 7.4 D2: 6.7 **Dizziness:** D1: 8.9 D2: 8.2 **Headache:** D1: 9.6 D2: 10.4 **Nausea:** D1: 4.4 D2: 11.2 **Somnolence (fatigue):** D1: 11.1 (8.9) D2: 7.5 (8.2) **Sweating (increase):** D1: 2.2 D2: 7.5	**Overall attrition rate:** 23% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Benkert, 2006[11] **Country and Setting** Germany; multicenter **Funding** NV Organon, Netherlands **Quality rating:** Fair	**Research objective** To compare time of onset of antidepressant action between mitrazapine ODT and VEN XR in outpatients with major depression **Drugs, Doses, and Range** D1: MIR (15-45 mg 1 x daily): low; 30 mg; high;45 mg D2: VEN XR (75-225 mg 1 x daily): • low; 75 mg • medium; 150 mg • high; 225 mg **Fixed dose** No **Flexible dose** No **Dosages equivalent** Yes **Study design** RCT **Duration** 6 weeks **Type of depression** MDD **Intervention** D1: MIR D2: VEN XR	**Inclusion criteria:** • Adults (age range): 18-70 years old • Diagnosed with MDD according to DSM-III or -IV: major depressive episode for single (296.2) or recurrent (296.3) episodes • HAM-D: 21 or greater **Exclusion criteria:** **Outcome measures** • HAM-D • CGI-S or CGI-I	**Groups similar at baseline** Yes **n =** D1: 127 D2: 115 Overall: 242 **Mean age, years** NR Overall: NR **Sex, % female** NR Overall: NR **Race, % white** NR Overall: NR **Baseline HAM-A** NR Overall: NR **Insomnia, %** NR Overall: NR **Concomitant anergia, %** NR Overall: NR **Experienced prior depressive episodes, %** NR Overall: NR **Comments:** NR **Outpatients/Inpatients** Outpatients **Baseline mean HAM-A > 25?** NR	**HAM-D** D1: MIR D2: VEN n at baseline: D1: 127 D2: 115 No. of responders: Day 8: D1: 25 D2: 7 Day 11: D1: 40 D2: 18 Day 22: D1: 60 D2: 38 No. of remitters: D1: day 15: 21 D2: day 15: 8 Mean score at baseline (SD): D1: 24.6 (2.8) D2: 24.9 (2.9) Mean score change (SD): D1: NR, in figure only D2: NR, in figure only Mean score of change (MIR and VEN, respectively) for HAM-D 14 item (subtacts sleep items): -10.0; -9.8; Retardation Factor: -3.8; -3.8; Sleep Disturbance Factor: -2.5; -1.8; Anxiety/Somatization Factor: -4.0; -3.5; Bech 6 Factor: -6.1; -6.0; percent of responders and remitters only reported on	**Headache, %:** D1: 14.6 D2: 14.8 **Insomnia, %:** D1: NR D2: 14.8 **Nausea, %:** D1: NR D2: 23.4 **Attrition** **Overall attrition, %:** 35.5 **Attrition rate, %:** D1: 30.7 D2: 40.9 **Withdrawals due to adverse events, %** D1: 17.3 D2: 25.2 **Withdrawals due to lack of efficacy, %** D1: 0.79 D2: 1.7 **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
			Mean age at baseline Less than 65 years **Mean HAM-D at baseline** NR	days where results were significant **MADRS** NR No. of responders: Day 8 D1: 25 D2: 7 Day 11 D1: 40 D2: 18 Day 22 D1: 60 D2: 38 Mean score at baseline (SD): D1: 24.6 (2.8) D2: 24.9 (2.9) **CGI-S** NR Mean score change (SD): Day 8: D1: -0.6 (*P:* 0.014) D2: -0.3 Day 11: D1: -0.8 (*P:* 0.033) D2: -0.5 **CGI-I** n at baseline: D1: 127 D2: 115 **CGII** No **QOL scale** NR **Another QOL scale** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				Is adherence reported? Adherence **Rate of adherence or compliance** 85% compliance; comparable between groups **Additional Results:** • Median times to response for combined treatment and PBO groups were 2 and 8 weeks, respectively. • Time to response was significantly shorter for combined treatment group compared with PBO group (log-rank test x1(squared): 5.03; *P:* 0.0248). • Among responders alone, combination treatment also showed shorter median times to response (2 weeks) than monotherapy (6 weeks) with significance (log-rank test x1(squared): 9.73; *P:* 0.0018), which showed rapid onset of efficacy of combination.	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Bennie et al., 1995[12] **Country and setting:** UK Multicenter (20 centers) **Funding:** Pfizer, Inc	**Research objective:** To compare SER and FLUOX in outpatients with depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 286 **Intervention:** D1: SER: 50-100 mg/d D2: FLUOX: 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 49.9 D2: 49.9 **Sex (% female):** D1: 57.7 D2: 64.6 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.2 D2: 23.4	No sig diffs between treatment groups in any outcome measures at any point in time (changes in HAM-D, HAM-A, CGI, Raskin, Covi scales) Response rate (≥ 50% improvement on HAM-D): SER: 59%, FLUOX: 51%	**Overall adverse events:** D1: 56 D2: 60 **Diarrhea:** D1: 4.9 D2: 3.5 **Dizziness:** D1: 1.4 D2: 5.6 **Headache:** D1: 14.1 D2: 14.6 **Nausea:** D1: 21.1 D2: 25.0 **Somnolence (fatigue):** D1: 4.2 D2: 4.2	**Overall attrition rate:** 13.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Bielski et al., 2004[13] **Country and setting:** United States Outpatient centers **Funding:** Forrest Laboratories, Inc	**Research objective:** To compare ESC and VEN XR in depressed outpatients at highest recommended doses in United States **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 198 **Intervention:** D1: ESC: 20mg D2: VEN: XR 225mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • HAM-D24 > 20 • Normal physical exam, labs, and ECG (or any abnormality insignficant) • Using contraceptive **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Previous treatment with VEN or ESC • Failure to respond to adequate trials of 2+ antidepressants	**Mean age (yrs):** D1: 37.3 D2: 37.5 **Sex (% female):** D1: 69.4 D2: 47.0 **Race (% white):** D1: 77.6 D2: 73.0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 28.6 (4.1) D2: 27.4 (4.5)	Response (≥ 50% dec in MADRS): ESC: 58.8% VEN :48% Response (≥ 50% decrease in HAM-D): ESC: 61% VEN: 48% Response (CGI-I ≤ 2): ESC: 65% VEN: 57% Remission (MADRS < 12): ESC: 50.5 VEN: 41.8 Remission (MADRS ≤ 10): ESC: 41.2 VEN: 36.7 Remission (HAM-D17 ≤ 7): ESC: 36.1 VEN: 31.6 LOCF results, mean change from baseline (SD): ESC: CES-D -15.1 (11.9) Q-LES-Q 12.8 (11.4) VEN: CES-D -12.8 (12.7) Q-LES-Q 9.9 (11.1)	**Overall adverse events:** D1: 68 D2: 85 **Headache:** D1: 15.3 D2: 14.0 **Nausea:** D1: 6.1 D2: 24.0 **Sexual dysfunction :** D1: 6.7 D2: 22.6 **Somnolence (fatigue):** D1: 9.2 D2: 17.0 **Sweating (increase):** D1: 5.1 D2: 11.0	**Overall attrition rate:** 30% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Blier et al., 2009[14] **Country and Setting** Canada, university clinic **Funding** Organon Pharmaceuticals **Quality rating:** Fair	**Research objective** Compare antidepressant efficacy of monotherapy (MIR or PAR) and initial combination (MIR + PAR) **Drugs, Doses, and Range** D1: MIR (15-45 mg 1 x daily): monotherapy: max 45 mg D2: PAR (10-60 mg 1 x daily): monotherapy: max 30 mg D3: Other (augmentation): MIR (30mg) + PAR (20mg) - no dose changes **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** Yes **Study design** **Duration** 6 wks (actually goes to 52 but results for last two weeks are confounded - see comments under attrition) **Type of depression** MDD	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • HAM-D: 17 item score: 18+ **Exclusion criteria:** • Bipolar • Clinically significant medical disease: abnormal lab results, seizure disorder **Outcome measures** • HAM-D • MADRS • CGI-S or CGI-I	**Groups similar at baseline** No- unequal distribution of gender, # of recurrent epidsode, and failed 1+ txt, BUT baseline depression scores were similar across groups **n =** D1: 21 D2: 19 D3: 21 **Mean age, years** D1: 46 D2: 40 D3: 43 **Sex, % female** D1: 23.8 D2: 52.6 D3: 61.9 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 28.6 D2: 36.8 D3: 47.6 **Comments:** NR	**HAM-D** D1: MIR D2: PAR D3: Combo n at baseline: D1: 21 D2: 19 D3: 21 Mean score at baseline (SD): D1: 23.5 (4.5) D2: 23.9 (3.0) D3: 24.2 (5.2) Mean score at endpoint (SD): D1: reported in graph only D2: NR D3: NR Mean score change (SD): D1: reported in graph only D2: NR D3: NR Sig greater improvement (all *P* >0.05) in combo compared to MIR at day 35, and combo compared to MIR or PAR on day 42. **MADRS** D1: MIR D2: PAR D3: Combo n at baseline: D1: 21 D2: 19 D3: 21 No. of remitters at week 6: D1: 4 (19%)	**Attrition** **Overall attrition, %:** 9.8***data reported for 56 days which is AFTER monotherapy nonresponders were given other drug, thus switching to combination treatment starting at day 42 thru 56. It is unclear whether or not any of dropouts were from Day 42 combo group (rather than 21 randomized to group at Day 1). **Attrition rate, %:** D1: 0 D2: 10.5 D3: 19.0 **Withdrawals due to adverse events, %** D1: 0 D2: 5.3 D3: 9.5 **Withdrawals due to lack of efficacy, %** D1: 0 D2: 5.3 D3: 4.8 **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				D2: 5 (26%) D3: 9 (43%) Mean score at baseline (SD): D1: 32.0 (6.4) D2: 32.3 (5.9) D3: 34.4 (7.2) **CGI-S** Sig greater improvement (all *P* >0.05) in combo compared to MIR or PAR on day 42. **CGI-I** NR **CGII** No **QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Boulenger et al., 2006[15] and Boulenger et al. 2010[159] **Country and Setting** Multinational; psychiatric and primary care settings **Funding** H. Lundbeck A/S **Quality rating:** Fair	**Research objective** To compare efficacy and tolerability of ESC (20 mg/day) and PAR (40 mg/day) in patients with severe MDD over a treatment period of 24 weeks and to investigate if treatment outcome for severely depressed patients depends on their baseline level of anxiety. **Drugs, Doses, and Range** D1: ESC (10-20 mg 1 x daily): 20 mg 1 x daily; high D2: PAR (10-60 mg 1 x daily): 40 mg 1 x daily; medium **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** No **Study design** RCT **Duration** 24 weeks **Type of depression** MDD **Intervention** D1: ESC 20 mg/day D2: PAR 40 mg/day	**Inclusion criteria:** • Adults (age range): 18 to 75 years • Diagnosed with MDD according to DSM-III or -IV • MADRS: score greater than or equal 30 at baseline • Duration of depressive episode had to be more than 2 wks, but less than 1 yr **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Bipolar disorder, psychotic disorder or features, obsessive-compulsive disorder, current eating disorders (anorexia nervosa, bulimia), mental retardation, any pervasive developmental disorder or cognitive disorder • Illicit drug and alcohol abuse: within 12 months • ECT within last: 6 months • Suicidal tendencies • History of lactose intolerance • History of hypersensitivity or non-	**Groups similar at baseline** Yes **n =** D1: 232 D2: 227 (For subgroup analysis of highly anxious patients: n=286) **Mean age, years** D1: 43.8 (12.5) D2: 44.7 (13.0) **Sex, % female** D1: 67 D2: 70 **Race, % white** D1: 97.8 D2: 99.6 **Baseline HAM-A** D1: 23.5 (7.5) D2: 23.5 (7.1) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** Mean baseline MADRS total score was approximately 35 in both treatment groups, indicating a severely to very severely depressed population.	**HAM-D** D1: ESC 20 mg/day D2: PAR 40 mg/day n at baseline: D1: 232 D2: 227 Mean score at baseline (SD): D1: 31.9 (6.0) D2: 31.5 (6.1) Mean score at endpoint (SD): D1: 9.4 D2: 11.5 Mean score change (SD): D1: -22.5 D2: -20.0 Statistically significant ($P < 0.01$) separation was evident from week 4 onwards. **MADRS** D1: ESC 20 mg/day D2: PAR 40 mg/day n at baseline: D1: 232 D2: 227 No. of remitters: D1: 171 D2: 149 Mean score at baseline (SD): D1: 31.9 (6.0) D2: 31.5 (6.1) Mean score at endpoint: D1: 10	**Overall adverse events, %:** D1: 7.8 D2: 15.4 **Constipation, %:** D1: 2.2 D2: 5.3 **Diarrhea, %:** D1: 6.5 D2: 10.1 **Dizziness, %:** D1: 9.1 D2: 8.8 **Headache, %:** D1: 24.1 D2: 20.3 **Insomnia, %:** D1: 7.3 D2: 7.9 **Nausea, %:** D1: 24.6 D2: 25.6 **Sexual dysfunction, %:** D1: 1.7, 0.9 D2: 1.8, 2.6 **Attrition** **Overall attrition, %:** 26.3 % attrition rate based on number of patients randomized, n= 459. **Attrition rate, %:** D1: 20,3 D2: 32,6 **Withdrawals due to adverse events, %** D1: 7.8

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		response to CIT, ESC or PAR. • Score ≥ 5 on item 10 of MADRS scale • Those who were receiving formal behaviour therapy or systematic psychotherapy **Outcome measures** • HAM-D • MADRS: total score mean change from baseline to week 24 • CGI-S or CGI-I • Quality of life scales • HAM-A		D2: 11.7 Mean score change (SD): D1: -2.8 D2: -2.6 There was statistically significant ($P < 0.05$) separation from week 8 onwards. **CGI-S** D1: ESC 20 mg/day D2: PAR 40 mg/day n at baseline: D1: 232 D2: 227 Mean score at baseline (SD): D1: 5.1 (0.7) D2: 5.1 (0.7) Mean score at endpoint (SD): D1: 2.3 D2: 2.5 The difference in mean change in CGI-S was significant from week 12 onwards ($P < 0.05$). **CGI-I** D1: ESC 20 mg/day D2: PAR 40 mg/day **CGII** Yes Intervention: D1: ESC 20 mg/day D2: PAR 40 mg/day n at baseline: D1: 232 D2: 227	D2: 15.4 **Withdrawals due to lack of efficacy, %** D1: 4.3 D2: 6.2 **Comments** The calculations were based on number of patients randomized (Overall n= 459; ESC 20 mg/day n= 232, PAR 40 mg/day n= 227). Significantly more patients ($P < 0.01$) withdrew from PAR group than from ESC group.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				Mean score at endpoint: D1: 2.0 D2: 2.2 **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results: at 24 weeks** Mean change from baseline; SE Baseline HAM-A 20 or less HAM-A • ESC: (n = 87) -10.2 (0.9) • PAR: (n=84) -9.1(0.9) • MADRS ESC: (n=87) -25.1(1.5) • PAR: (n=84) -23.8 (1.5) Baseline HAM-A > 20 HAM-A • ESC: (n=141) -17.6 (0.9)* • PAR: (n=139) -15.2 (0.9) • MADRS ESC: (n=141) -24.2(1.0)* • PAR: (n=139) -21.5(1.1) *$P < 0.05$ vs. PAR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Boyer et al., 1998[16] **Country and setting:** France Multicenter, primary care settings (57 general practitioners) **Funding:** NR	**Research objective:** To compare efficacy, tolerability, QOL outcomes, and costs of SER and FLUOX in treatment of depression **Duration of study:** 180 days **Study design:** RCT **Overall study N:** 242 **Intervention:** D1: FLUOX: 50-150 mg/d D2: SER: 20-60 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • History of serious allergy or AE reaction related to medicines	**Mean age (yrs):** D1: 43.7 D2: 43.0 **Sex (% female):** D1: 79.1 D2: 77.6 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diffs in changes in MADRS, FSQ, CGI-I, and CGI-S scores between treatment groups No sig diffs in response rates (improvement of MADRS ≥ 50%) between treatment groups Day 120: FLUOX: 54.3% SER: 49% Day 180: FLUOX: 42.6% SER: 47.4% Sig improvements observed in both treatment groups in all dimensions of FSQ	**Overall adverse events:** D1: 51.3 D2: 57.8	**Overall attrition rate:** NR **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Brannan et al., 2005[160] **Country and setting:** United States, multicenter (25 psychiatry clinics) **Funding:** Eli Lilly and Company	**Research objective:** To evaluate efficacy of DUL for treatment of pain and depression in patients with major depression and painful physical symptoms **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 282 randomized; 268 included in analysis **Intervention:** D1: DUL 60 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-IV • Minimum HAM-D-17 score of 15 • CGI-S of 4 or more • BPI average pain score of 2 or more **Exclusion criteria:** • Additional mental illness or organic mental disorder • Substance abuse or dependence • Clinically sig medical disease • Suicidal (serious risk) • Primary pain disorder with diagnosis such as arthritis, migraine, or fibromyalgia • Treatment resistant depression or lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** D1: 40.8 D2: 40.3 **Sex (% female):** D1: 68.1 D2: 62.4 **Race (% white):** D1: 81.6 D2: 79.4 **Baseline HAM-D-17:** D1: 23.4 (3.5) D2: 22.4 (3.4) **BPI average pain:** D1: 4.85 (1.69) D2: 4.62 (1.54) **Baseline 100mm VAS (overall pain):** D1: 49.8 (22.2) D2: 46.8 (19.7) **Baseline HAM-A:** NR	**Depression outcomes in patients with pain:** Mean HAM-D-17 improvement was similar for both groups (-10.9 for DUL vs. -10.3 for PBO, *P* = 0.544). Response rates were similar for DUL and PBO (42% vs. 40%, *P* = 0.901). Remission rates were also similar (23% vs. 24%, *P* = 0.887) **Pain outcomes:** Mean reduction in BPI average pain was 2.32 (0.21) for DUL-treated patients compared to 1.80 (0.20) for those receiving PBO (*P* = 0.066). Mean changes in BPI worst pain, least pain, and current pain did not differ between groups (*P* > 0.10 for all). Mean changes in VAS overall pain did not differ between groups (values NR and *P* = NR)	**Cardiovascular adverse events (high systolic BP):** D1: 4.1 D2: 4.1 **(High diastolic BP):** D1: 1.6 D2: 5.5 **Changes in weight (decrease):** D1: 7.1 D2: 0.7 **Constipation:** D1: 9.2 D2: 6.4 **Diarrhea:** D1: 17.7 D2: 10.6 **Dizziness:** D1: 9.9 D2: 5.7 **Headache:** D1: 14.2 D2: 13.5 **Insomnia:** D1: 10.6 D2: 6.4 **Nausea:** D1: 39.7 D2: 9.9 **Fatigue:** D1: 16.3 D2: 1.4	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Brecht, 2007[161] **Country and Setting** Multinational, outpatient setting **Funding** Boehringer Ingelheim GmbH and Eli Lilly and Company **Quality rating:** Fair .	**Research objective** To evaluate efficacy and safety of DUL in treatment of patients with moderate pain associated with depression. **Drugs, Doses, and Range** D1: DUL (40-60 mg 1-2 x daily): 60mg once daily (low) D2: PBO **Fixed dose** No **Flexible dose** No **Dosages equivalent** Yes **Study design** RCT **Duration** NR **Type of depression** MDD **Intervention** DUL PBO	**Inclusion criteria:** • Adults (age range): 18 years or older • Diagnosed with MDD according to DSM-III or -IV • MADRS: Total score of 20 or higher. • CGIS: Moderately ill as measured by a score of 4 or higher. • Other: Devoid of any diagnosed pain syndrome as per medical history and no further differential diagnostic work-up was performed. **Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): Current Axis I disorder (other than MDD); anxiety disorder as a primary diagnosis within past 6 months. Axis II disorder that could interfere with compliance with study protocol • Illicit drug and alcohol abuse: History of substance abuse or dependence within a year of study entry;positive urine drug screen for drug abuse • Clinically significant medical disease:	**Groups similar at baseline** Yes **n =** D1: 162 D2: 165 **Mean age, years** D1: 48.1 D2: 52.3 **Sex, % female** D1: 75.9 D2: 71.5 **Race, % white** D1: 99.4 D2: 98.2 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** NR **MADRS** D1: DUL D2: PBO n at baseline: D1: 162 D2: 165 No. of remitters: D1: 52.6% D2: 28.9% *P* < 0.001 Mean score at endpoint (SD): D1: 12.91 D2: 17.89 **CGI-S** D1: DUL D2: PBO n at baseline: D1: 162 D2: 165 Mean score change (SD): DUL: 46.1% rated as "normal" with a score of 1 or 2; 3.9% severely ill at week 8. PBO: 27.7% rated as "normal" with a score of 1 or 2; 6.9% severely ill at week 8/*P* > 0.001. **CGI-I** NR **CGII** No **QOL scale** BPI-SF Average Pain Subscale	**Overall adverse events, %:** D1: 55.6 D2: 45.5 **Constipation, %:** D1: 5.6 D2: 1.2 **Diarrhea, %:** D1: 4.3 D2: 1.8 **Dizziness, %:** D1: 5.6 D2: 3.6 **Headache, %:** D1: 7.4 D2: 9.1 **Insomnia, %:** D1: 3.7 D2: 1.8 **Nausea, %:** D1: 24.7 D2: 7.9 **Vomiting, %:** D1: 4.3 D2: 1.2 **Attrition** **Overall attrition, %:** 76 **Attrition rate, %:** D1: 74.7 D2: 77.6 **Withdrawals due to adverse events, %** D1: 10.5 D2: 5.5% **Withdrawals due to lack of efficacy, %**

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		Suicidal tendencies (acute or other): Basis of MADRS item 10 scoring • Other: Lack of response in current depressive episode to two or more adequate courses of antidepressant therapy.(in opinion of investigator)pain medication on a regular basis for last 6 monthsPer protocol patients were discontinued from study if their depression deteriorated during observation period (as judged by investigator) **Outcome measures** • MADRS: Remission MADRS total score ¡Ü 12. • CGI-S or CGI-I: Normal classification was a score of 1 or 2 on CGI-S. • Others: BPI-SF (24 hr average pain score (item 5).		Intervention: D1: DUL D2: PBO n at baseline: D1: 165 D2: NR Mean score change (SD): D1: General Activity Mean Change (SE): -1.18 (0.29)/ 95% CI, -1.76 to -0.60/ *P* >0.0001 D2: NR Pain interference on functioning, so may not be a direct outcome measure of depressive episode on QOL item and only reported for DUL. **Another QOL scale** GSI Intervention: D1: DUL D2: PBO n at baseline: D1: 162 D2: 165 Mean score at baseline (SD): NR Mean score at endpoint (SD): NR Mean score change (SD): D1: -0.65 (SE: 0.04) D2: -0.45 (SE: 0.05) Difference from PBO: Mean(SE)-0.21 (0.06)/ 95% CI, (-0.33 to -0.09)/	D1: NR D2: 9 **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				P: 0.008 **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Buckley and McManus, 2002[177] **Country and setting:** UK Database **Funding:** NR	**Research objective:** To establish relative frequency with which VEN and other new antidepressants result in fatal poisoning **Duration of study:** 1993-1999 data **Study design:** NR **Overall study N:** 121,927 **Intervention:** TCAs and related drugs Serotoninergic drugs	**Inclusion criteria:** • Deaths due to acute poisoning of a single drug **Exclusion criteria:** NR	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Among second generation antidepressants, VEN had highest fatal toxicity index (deaths/million prescriptions): VEN: 13.2 (9.2-18.5) FLUV: 3.0 (0.3-10.9) CIT: 1.9 (0.6-4.5) SER: 1.2 (0.5-2.4) FLUOX: 0.9 (0.5-1.4) PAR: 0.7 (0.4-1.3) NEF: 0 (0-6.4) Highest rate of fatal toxicity for VEN	NR	**Overall attrition rate:** N/A **ITT Analysis** NR **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Burke et al., 2002[17] **Country and setting:** United States Multicenter (35 centers) **Funding:** Forest Laboratories	**Research objective:** To evaluate efficacy and tolerability of ESC in treatment of MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 369 **Intervention:** D1: PBO D2: ESC 10 mg/d D3: ESC 20 mg/d D4: CIT 40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of at least 2 on item 1 (depressed mood) • Depressive episode ≥ 4 wks • MADRS ≥ 22 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies • Any DSM-IV Axis I disorder other than MDD • Score at least 5 on item 10 of MADRS	**Mean age (yrs):** D1: 40.1 D2: 40.7 D3: 39.6 D4: 40.0 **Sex (% female):** D1: 60 D2: 70 D3: 68 D4: 62 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25.8 (5.9) D2: 24.3 (6.2) D3: 25.8 (5.7) D4: 25.9 (5.9)	Responders (50 % improvement in MADRS from baseline): 50% vs. 51.2% vs. 45.6% for ESC 10 mg/d, ESC 20 mg/d and CIT 40 mg/d, PBO treatment (27.7%, $P < 0.01$) For QOL, diff in mean change from baseline for ESC vs. PBO treatment was 2.4 for 10 mg/d group ($P = 0.04$) and 4.8 for 20 mg/d group ($P < 0.01$) ESC 10 mg/d was equally effective as CIT 40 mg/d on majority of outcome measures (MADRS, HAM-D, CGI-I, CGI-S) All treatment groups were sig more efficacious than PBO group	**Overall adverse events:** D1: 70.5 D2: 79 D3: 85.6 D4: 86.4 **Diarrhea:** D1: 7 D2: 10 D3: 14 D4: 11 **Insomnia:** D1: 3 D2: 10 D3: 14 D4: 11 **Nausea:** D1: 6 D2: 21 D3: 14 D4: 22 **Sexual dysfunction :** D1: 0 D2: 9 D3: 12 D4: 4	**Overall attrition rate:** 24% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Cassano et al., 2002[18] **Country and setting:** Italy Multicenter (38 centers) **Funding:** SmithKline, Beecham	**Research objective:** To assess efffects of PAR and FLUOX on mood and cognitive function in depressed non-demented geriatric patients **Duration of study:** 1 yr **Study design:** RCT **Overall study N:** 242 **Intervention:** D1: PAR: 20-40 mg/d D2: FLUOX: 20-60 mg/d	**Inclusion criteria:** • Adults 18 or older • Minimum HAM-D score of 18 • ICD-10, mini mental state, Raskin, Covi Anxiety **Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** D1: 75.6 D2: 74.9 **Sex (% female):** D1: 61 D2: 50 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Both treatment groups showed sig improvements in cognitive performance on all test scales No sig diffs between treatment groups and cognitive performance except for Buschke test at wk 3 and 6 where PAR showed a sig greater improvement on a number of tests Both treatment groups sig improved HAM-D total scores but overall no diffs in HAM-D improvement between treatment groups A Kaplan Meier analysis evaluating percentage of responders (HAM-D < 10) over time showed a sig diff in favor of PAR ($P < 0.03$) No sig diffs on CGI scores	**Overall adverse events:** D1: 27.6 D2: 32.8 **Cardiovascular adverse events:** D1: 6.5 D2: 7.5	**Overall attrition rate:** 39.3% **ITT Analysis** No another type of analysis was used (define): Observed case **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Chouinard et al., 1999[19] **Country and setting:** Canada Multicenter (8) **Funding:** SmithKline, Beecham	**Research objective:** To evaluate antidepressant and anxiolytic efficacy of PAR and FLUOX in patients with major depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 203 **Intervention:** D1: PAR: 20-50 mg/d D2: FLUOX: 20-80 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 and score of 2 on HAM-D item 1 • Depression symptoms for at least 1 mo **Exclusion criteria:** • Pregnant or lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 2 mos • Suicidal tendencies	**Mean age (yrs):** D1: 40.6 D2: 41.2 **Sex (% female):** D1: 63.7 D2: 59.4 **Race (% white):** D1: 95.1 D2: 98.0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25.91 (0.46) D2: 25.45 (0.46)	No statistically sig diffs in response rates: (LOCF endpoint) PAR: 67.0% FLUOX: 68.4% No statistically sig diffs in remission rates: (LOCF endpoint) PAR: 58.0% FLUOX: 59.2% **Anxiety outcomes** Improvements in Covi Anxiety Scale, State-Trait Anxiety Inventory, and HAM-D Anxiety/Somatization Factor were similar in 2 treatment groups (scores NR; *P* = NR) Mean improvement from baseline in HAM-D Psychic Anxiety item was 1.17 for PAR and 1.21 for FLUOX (*P* = 0.823). Improvement from baseline in HAM-D Agitation item was 0.40 for PAR and 0.39 for FLUOX (*P* = 0.978)	**Changes in weight (decrease):** D1: 11.9 D2: 2.9 **(increase):** D1: 10.8 D2: 13.9 **Constipation:** D1: 17.7 D2: 4.0 **Diarrhea:** D1: 11.8 D2: 18.8 **Headache:** D1: 36.3 D2: 36.6 **Insomnia:** D1: 26.5 D2: 22.8 **Nausea:** D1: 37.3 D2: 31.7 **Somnolence (fatigue):** D1: 18.6 D2: 16.8 **Sexual dysfunction:** D1: 10.8 of males D2: 7.3 of males **Sweating (increase):** D1: 5.9 D2: 13.7	**Overall attrition rate:** 36% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Claghorn and Feighner, 1993[107] **Country and setting:** United States, outpatient **Funding:** SmithKline Beecham	**Research objective:** To compare effectiveness of PAR vs. IMI and PBO maintaining antidepressant response up to 1 yr after acute treatment response, and to compare tolerability and safety **Duration of study:** 1 yr **Study design:** 1-yr extension of a 6-wk PBO-controlled trial **Overall study N:** 219 of 717 patients randomized to acute phase continued in double-blind extension **Intervention:** D1: PAR: 10-50 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Successful completion of 6-wk trial • Raskin Depression rating of 7+; Raskin score > Covi Anxiety score **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease	**Mean age (yrs):** D1: 42.2 D2: 40.6 **Sex (% female):** D1: 60.6 D2: 28.3 **Race (% white):** D1: 87.2 D2: 89.1 **Baseline HAM-A:** NR **Baseline HAM-D (SD):** D1: 9.9 D2: 8.7	Response rates = 63.8%(PAR) vs. 69.6% (PBO). HAM-D: declined from 26.2 to 9.9 during short-term trial, then stabalized over 1 yr in PAR group; declined from 26.4 to 10.1 during short-term, then to 6.3 at 1 yr in PBO group. CGI-S: 4.2 baseline to 2.0 at 1 yr (PAR) vs. 4.3 baseline to 1.6 at 1 yr (PBO) Relapse rates in responders: PAR 15%, PBO 25%	**Constipation:** D1: 19 **Diarrhea:** D1: 17 **Dizziness:** D1: 15 **Headache:** D1: 21 **Insomnia:** D1: 20 **Nausea:** D1: 16 **Sexual dysfunctional (male ejaculation):** D1: 16 **Somnolence (fatigue):** D1: 20 **Sweating (increase):** D1: 14	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events	Analysis Quality Rating
Author: Clayton et al., 2002[180] **Country and setting:** US Multicenter 1101 primary care clinics) **Funding:** Glaxo Wellcome Inc.	**Research objective:** To estimate prevalence of sexual dysfunction among patients taking newer antidepressants **Duration of study:** N/A **Study design:** Cross-sectional survey **Overall study N:** 6,297 **Intervention:** BUP: IR: 255.0; SR: 273.7 CIT: 24.9 FLUOX: 25.5 MIR: 28.6 NEF: 293.2 PAR: 23.3 SER: 81.4 VEN: Regular: 124.9; XR: 114.9	**Inclusion criteria:** • Adults 18+ • Taking monotherapy for depression (no TRA in addition, e.g. with one of newer antidepressants earlier specified, sexually active within last 12 mos, willing to discuss his/her sexual functioning with physician **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Taking monotherapy antidepressants for reason other than treatment of depression	**Mean age (years):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:**	Overall population: BUP IR (22%) and SR (25%) and NEF (28%) were associated with lowest risk for sexual dysfunction Highest rates in PAR (43%) and MIR (41%) groups CSFQ scores averaged 24% for all antidepressants combined and ranged from 7% (BUP SR) to 30% (CIT and VEN XR) Patients aged 50-59 had sigly higher odds of having sexual dysfunction compared with reference age group of 20 to 29 yr. old patients. OR, 1.42 (95 CI, 1.14-179)	N/A	**Overall attrition rate:** NR **ITT Analysis** N/A **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Clayton et al., 2006[181] **Country and Setting** United States, multicenter **Funding** GlaxoSmithKline **Quality rating:** Fair	**Research objective** To compare effects on sexual functioning and antidepressant efficacy of once-daily BUP XL and ESC in adults with MDD. **Drugs, Doses, and Range** D1: BUP XL (150-450 mg 1 x daily): 150 mg 1x daily week 1 (low); 300 mg 1 x daily during weeks 2 to 4 (medium); on week 5, daily dose could be increased to 450 mg (high) if additional efficacy was desired D2: ESC (10-20 mg 1 x daily): 10 mg 1 x daily during weeks 1 to 4 (low); ESC dose could be increased to 20 mg 1 x daily (medium) for weeks 5 to 8 if additional efficacy was needed\ D3: PBO **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **Duration** 8 weeks **Type of depression** MDD	**Inclusion criteria:** • Adults (age range): ≥ 18 years • Diagnosed with MDD according to DSM-III or -IV • HAM-D: HAM-D-17 total score ≥ 19 at screening and on the day of randomization to treatment • Currently experiencing a MDE lasting ≥ 12 weeks and < 2 years, but were otherwise healthy • Normal orgasm function as assessed by investigator interview and were willing to discuss their sexual functioning with investigator and engaged in sexual activity leading to orgasm at least once every 2 weeks. Patients who had a sexual desire disorder were eligible for study if investigoator considered it to be secondary to MDE. **Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): A diagnosis of bipolar I or II disorder,	**Groups similar at baseline** Yes **n =** Pooled D1: 276 D2: 281 D3: 273 **Mean age, years** Pooled D1: 37 D2: 36 D3: 36 **Sex, % female** Pooled D1: 58 D2: 57 D3: 60 **Race, % white** Pooled D1: 70 D2: 68 D3: 70 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 100 D2: 100 D3: 100	NR	**Constipation, %:** D1: 9 D2: 3 D3: 6 **Insomnia, %:** D1: 14 D2: 10 D3: 8 **Sexual dysfunction, %:** Orgasm dysfunction: Pooled D1: 15 D2: 30 D3: 9 Worsening sexual function: Pooled D1: 20 D2: 36 D3: 15 **Withdrawals due to adverse events, %** Pooled: D1: 6 D2: 4 D3: 5 Study 1: D1: 3 D2: 5 D3: 5 Study 2: D1: 10 D2: 3 D3: 5 **Withdrawals due to lack of efficacy, %** D1: NR D2: NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
	Intervention BUP XL ESC PBO	schizophrenia, or other psychotic disorders • Suicidal tendencies (acute or other): history of attempted suicide within 6 months before screening. • Any sexual dysfunction at screening or at randomization except sexual desire disorder related to depression as determined by structured investigator interview • History or current diagnosis of anorexia nervosa, bulimia, seizure disorder, or brain injury • Diagnosis of panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, or acute stress disorder within 12 months before study entry **Outcome measures** • HAM-D: HAM-D-17 • CGI-S or CGI-I • CSFQ (secondary endpoint) • HAD			D3: NR **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Clayton et al., 2007[182] **Country and Setting** United States, multicenter (36 psychiatric clinical settings) **Funding** Eli Lilly and Company **Quality rating:** Good	**Research objective** Comparisons of changes in sexual functioning for DUL and ESC in which primary objective was to compare onset of antidepressant action for DUL 60 mg/day with that of ESC 10 mg/day. secondary objection was to compare differential drug effects on sexual functioning over acute and longer-term course of study. **Drugs, Doses, and Range** D1: DUL (40-60 mg 1-2 x daily): 60 mg/day (medium) for initial eight-week acute-treatment phase; DUL 60-120 mg/day (medium-high) during extension phase D2: ESC (10-20 mg 1 x daily): 10 mg/day (low) for initial 8-week acute-treatment phase; 10-20 mg/day (low-high) during extension phase D3: PBO **Fixed dose** Yes **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **Duration** 8 months- included initial 8-week, acute-treatment phase	**Inclusion criteria:** • Adults (age range): ≥ 18 years of age • Diagnosed with MDD according to DSM-III or -IV • MADRS: total score ≥ 22 • CGI-S: ≥ 4 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): Illicit drug and alcohol abuse: history of substance dependence within past 6 months • Clinically significant medical disease: Investigational drug use within last: A history of a lack of response, at any time, to an adequate trial of DUL (≥ 60 mg/day for ≥ 4 weeks), ESC (≥ 10 mg/day for ≥ 4 weeks), or CIT (≥ 20 mg/day for ≥ 4 weeks) • ECT or transcranial magnetic stimulation within past year • Suicidal tendencies (acute or other): serious suicidal risk • Any current primary Axis I disorder other than MDD • Any anxiety disorder as	**Groups similar at baseline** Yes **n =** D1: 273 D2: 274 D3: 137 **Mean age, years** D1: 41.1 D2: 43.3 D3: 42.5 **Sex, % female** D1: 63.4 D2: 67.9 D3: 63.5 **Race, % white** D1: 75.5 D2: 77.4 D3: 82.5 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** The mean age of patients in DUL treatment group was significantly lower than that in ESC (41.1 years vs. 43.3 years; *P:* 0.036). CGI-S means (SD) for treatment groups were reported at baseline. results are as follow: DUL	**HAM-D** NR. **MADRS** NR **CGI-S** NR **CGI-I** NR **CGII** No **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** At end point of acute-treatment phase (8 weeks or last observation), categorical assessment of changes in global sexual functioning in DUL-treated male patients showed that 54.4% reported improvement, 8.9% reported no change, and 36.7% reported worsening; whereas in ESC-treated male patients, 34.2% reported improvement, 6.6% reported no change, and 59.2% reported worsening (*P* = 0.019 DUL vs. ESC).	**Overall adverse events, %:** NR **Attrition** **Overall attrition, %:** Overall rate of attrition (8-months) = 65.8. rate of attrition for acute treatment phase (initial 8 weeks) = 28.5. **Attrition rate, %:** 8 weeks: D1: 31.9 D2: 24.5 D3: 29.9 8 months: D1: 63.7 D2: 55.8 D3: 89.8* **Withdrawals due to adverse events, %** Sexual side effects at 8 months: D1: 0.7 D2: 2.6 D3: NR **Withdrawals due to lack of efficacy, %** D1: NR D2: NR D3: NR **Comments** Over 8-month course of study, withdrawal rates for sexual side effects did not differ for DUL (2/273) compared with ESC (7/274) (*P* = 0.07). Due to attrition and PBO rescue, number of PBO-treated

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
	+ 24-week, double-blind, extension phase **Type of depression** MDD **Intervention** D1: DUL 60 mg QD D2: ESC 10 mg QD D3: PBO	a primary diagnosis within past 6 months • Treatment-resistant depression • Current and primary Axis II disorder that could interefere with compliance with study protocol • Initiating, stopping, or changing psychotherapy during study • Treatment with MAOI within 14 days prior to visit 2; treatment with FLUOX within 30 days prior to visit 2. **Outcome measures** • HAM-D-17 • CSFQ	60 mg QD: 4.2 (0.7); ESC 10 mg QD: 4.2 (0.7); and PBO: 4.2 (0.7).		patients significantly decreased after acute treatment.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Claxton et al. 2000[179] **Country and Setting** UK, , multicenter – primary care **Funding** Eli Lilly **Quality rating:** Fair	**Research objective –** To assess differences in adherence between daily and weekly dosing of Fluox **Drugs, Doses, and Range** D1: Fluox 90 mg weekly D2: Fluox 20 mg daily **Fixed dose** - yes **Flexible dose** - No **Dosages equivalent -** Yes **Study design –** RCT, open-label **Duration – 3 months** **Type of depression** • MDD	**Inclusion criteria:** • Adults; • Diagnosed with MDD and treated with 20 mg fluox daily successfully for 6-16 wweks **Exclusion criteria:** • NR	**Groups similar at baseline** **n =** D1: 56 D2: 53 **Mean age, years** Overall:46 **Sex, % female** Overall 83: **Race, % white** Overall 100: **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, % NR** **Comments:** NR	**HAM-D -** NR **MADRS** - NR **CGI-S -** NR **CGI-I** NR **QOL scale** NR **Is adherence reported?** Yes **Rate of adherence or compliance** D1: 87.5% D2: 79.4%	**Attrition** **Overall attrition, %:** 14.3 **Withdrawals due to adverse events, %** D1: 1.8 D2: 1.9 **Withdrawals due to lack of efficacy, %** D1: 10.7 D2: 3.8

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Coleman et al., 1999[20] **Country and setting:** United States Multicenter (9 centers) **Funding:** Glaxo Wellcome Inc	**Research objective:** To compare sexual functioning as well as safety and efficacy of BUP SR and SER **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 240 **Intervention:** D1: SER: 50-200 mg/d D2: BUP: 150-400 mg/d D3: PBO	**Inclusion criteria:** • Adults 18+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Be in a stable relationship, have normal sexual functioning, and sexual activity at least once every 2 wks • Currently experiencing recurrent major episode of depression **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 38.3 D2: 38.1 D3: 38.5 **Sex (% female):** D1: 54 D2: 56 D3: 59 **Race (% white):** D1: 92 D2: 87 D3: 88 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 34.5 D2: 34.8 D3: 34.0	Mean HAM-D scores in BUP SR but not SER group were statistically better than PBO (by day 28 $P < 0.05$) Sig fewer BUP SR patients had sexual desire disorder than SER patients ($P < 0.05$) Orgasm dysfunction occurred sig more in SER patients compared with PBO or BUP SR patients ($P < 0.05$) Diagnosed with at least one sexual dysfunction: SER: 39%, BUP SR: 13%, PBO: 17% Sig more BUP patients were satisfied with their sexual functioning (endpoint BUP 85% vs. SER 62%; $P< 0.05$) Mean Compliance: Tablet: PBO: 96.1%, BUP 96.4%, SER 97.1% Capsule: PBO: 98.4%, 97.9%, SER 98.3%	**Diarrhea:** D1: 12 D2: 18 **Headache:** D1: 34 D2: 27 **Insomnia:** D1: 20 D2: 17 **Nausea:** D1: 19 D2: 23 **Sexual dysfunction:** D1: 39 D2: 13	**Overall attrition rate:** 30% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Coleman et al., 2001[21] **Country and setting:** United States Multicenter (15 centers) **Funding:** Glaxo Wellcome	**Research objective:** Comparison of BUP, FLUOX and PBO on safety, efficacy and sexual functioning in patients with recurrent major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 456 **Intervention:** D1: FLUOX: 20-60 mg/d (26) D2: BUP: 150-400 mg/d (319) D3: PBO	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Have sexual activity at least once every 2 wks • Currently experiencing episode lasting 2 to 24 mos • Currently in a stable relationship **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 37.1 D2: 36.6 D3: 36.7 **Sex (% female):** D1: 66 D2: 63 D3: 61 **Race (% white):** D1: 82 D2: 83 D3: 82 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 24.6 D2: 24.5 D3: 24.4	More BUP SR remitters (47%) compared to PBO (32%) Orgasm dysfunction occurred sig more in FLUOX patients compared with PBO or BUP SR patients ($P < 0.001$) At endpoint, more FLUOX treated patients had sexual desire disorder than BUP SR treated patients ($P < 0.05$) Sig more buproion SR-treated patients were satisfied with sexual function (analysis only for patients satisfied at baseline; no data reported) $P < 0.05$ Compliance: 96.8% to 98.8% in all groups	**Diarrhea:** D1: 12 D2: 9 D3: 9 **Headache:** D1: 31 D2: 28 D3: 20 **Insomnia:** D1: 15 D2: 21 D3: 10 **Nausea:** D1: 12 D2: 21 D3: 16 **Somnolence (fatigue):** D1: 11 D2: 3 D3: 4	**Overall attrition rate:** 34% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Colonna, et al., 2005[22] **Country and setting:** Mulitnational Primary care centers **Funding:** H Lundbeck A/S, Denmark	**Research objective:** Compare efficacy and safety of ESC to CIT in patients with moderate to severe MDD **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 357 **Intervention:** D1: ESC: 10 mg/d D2: CIT: 20 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 22 and < 40 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications or ECT • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • History of severe drug allergy • Had lack of response to more than 1 antidepressant treatment	**Mean age (yrs):** D1: 46 D2: 46 **Sex (% female):** D1: 127 (73) D2: 138 (76) **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	MADRS responders: Wk 8: ESC: 63% vs. CIT 55% Wk 24: ESC 80%; CIT 78% MADRS remitters: Wk 8: ESC 55% vs. CIT 45% Wk 24: ESC 76%; CIT 71% CGI-S mean change: ESC -2.49 CIT -2.24	**Overall adverse events:** D1: 62.9 D2: 72 **Changes in weight (increase):** D1: 1.1 D2: 6.6 **Headache:** D1: 6.9 D2: 8.8 **Nausea:** D1: 16 D2: 9.9	**Overall attrition rate:** 17.7% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Corya et al., 2006[108] **Country and Setting** Multinational (90 sites in 16 countries) **Funding** Lilly Research Laboratories **Quality Rating** Fair for KQ2 Poor for KQ1	**Research objective** To compare efficacy of Olanzapine/FLUOX combination, Olanzapine, FLUOX, and VEN in a TRD population **Drugs, Doses, and Range** D1: FLUOX 25 or 50 mg/day, mean 37.5 mg/day (medium dose) D2: VEN XR 75-375 mg/day, mean 275.4 mg/day (medium dose) Other (augmentation): Benzodiazepine use, % of subjs; mean mg/day (SD)): FLUOX: 70%; 1.99 (1.31), **Study design** RCT **n** 483, of which 119 are of interest (VEN continuation and FLUOX monotherapy) **Duration** 12 weeks randomized to FLUOX or VEN, but VEN group had 7 weeks of open label lead-in plus 5-9 days of pseudo taper **Type of depression** Major depressive disorder	**Inclusion criteria** • Diagnosed with MDD according to DSM-III or -IV: single episode or recurrent w/out psychotic features • CGI ≥ 4; documented history or a failure to achieve a satisfactory response to a SSRI after 6 weeks • MADRS: subjects who displayed less than 30% improvement in MADRS total score during 7-wk lead-in phase **Exclusion criteria** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications: except benzodiazepines (permitted at doses up to an equivalent of 4 mg of lorazepam per day) • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) schizophrenia, schizoaffective disorder, other psychotic disorders, bipolar I disorder, bipolar II disorder, posttraumatic stress disorder • MDD w/seasonal pattern; dissociative disorders	**Groups similar at baseline** No, VEN group received drug 7-weeks longer (lead-in phase); larger female population (72.5%) **n =** D1: 60 D2: 59 Overall: 483 **Mean age, years** Overall: 45.7 **Sex, % female** Overall: 72.5 **Race, % white** Overall: 89.9 **Baseline HAM-A** Overall: 17.5 **Insomnia, %:** Overall: NR **Concomitant anergia, %** Overall: NR **Experienced prior depressive episodes, %** Overall: 51.4 (> 3 MDD episdoes over lifetime); 22.2 (> 2 MDD episodes over past 24 mos)	**HAM-D** **Responders, n:** D1: 19 D2: 29 **Remitters, n:** D1: 10 D2: 13 **Mean score at baseline (SD):** D1: 30 D2: 30 **Mean score at endpoint (SD):** D1: 18.3 D2: 16.27 **Mean score change (SE):** D1: -11.70 (1.14) D2: -13.73 (1.16) Mean score at baseline is for all study arms (n = 483). **CGI-S** NR **CGI-I** NR **CGI** NR **QOL scale** NR **Adherence** Rate of compliance, % D1: 98 D2: 97	**Overall rate of attrition, %** 22.7 **Attrition rate, %** D1: 20 D2: 25.4 **Withdrawals due to adverse events, %** D1: 5 D2: 1.7 **Attrition due to lack of efficacy, %** D1: 6.7 D2: 11.9 **Additional comments** Lost to follow up, % D1:1.7 D2: 3.4 Other FLUOX (6.7) Other VEN (8.5) **Overall adverse events, %:** D1: 5 D2: 1.7 **Weight gain, %:** D1: 13 D2: 5 **Dizziness, %:** D1: 10 D2: 5 **Headache, %:** D1: 17 D2: 17 **Somnolence (fatigue), %:** D1: 5 D2: 8

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Costa e Silvia, 1998[23] **Country and setting:** South America Multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** Safety and efficacy of VEN vs. FLUOX in patients with depression in Latin America and Brazil **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 382 **Intervention:** D1: VEN: 75-225 mg/d D2: FLUOX: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 60 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days • Suicidal tendencies	**Mean age (yrs):** D1: 40.5 D2: 39.8 **Sex (% female):** D1: 80.1 D2: 77.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	HAM-D and MADRS scores decreased sig in both treatment groups ($P < 0.05$) No sig diffs between treatment groups in primary efficacy measures (HAM-D, MADRS, CGI) Global response NR ($P = 0.15$) Remission was observed in 60.2% of patients in each group Patients who increased dose to VEN 150 mg and FLUOX 40 mg after 3 wks sig more achieved CGI score of 1 in VEN group ($P < 0.05$)	**Overall adverse events:** D1: 69.4 (whole study) D2: 65 (whole study) **Dizziness:** D1: 8.3 D2: 3.2 **Headache:** D1: 11.3 D2: 7 **Insomnia:** D1: 6.2 D2: 8.1 **Nausea:** D1: 28.9 D2: 18.9 **Somnolence (fatigue):** D1: 8.3 D2: 1.6	**Overall attrition rate:** 12.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Croft et al., 1999[24] **Country and setting:** United States Multicenter (8 centers) **Funding:** Glaxo Wellcome	**Research objective:** Comparison of efficacy and effects on sexual functioning of depressed patients using BUP, SER, or PBO **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 239 **Intervention:** D1: SER: 50-200 mg/d (mean = 121) D2: BUP: 150-400 mg/d (mean = 293) D3: PBO	**Inclusion criteria:** • Adults 18 and over • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • In stable relationship • Have normal sexual functioning and sexual activity at least once every 2 wks • Current depressive episode of 8 wks to 24 mos **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 36.0 D2: 35.9 D3: 37.4 **Sex (% female):** D1: 50 D2: 51 D3: 50 **Race (% white):** D1: 87 D2: 86 D3: 88 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Mean HAM-D scores in both BUP and SER group were statistically better than PBO ($P < 0.05$) At day 56, both BUP and SER had higher sexual arousal disorder ($P < 0.05$) than PBO Orgasmic dysfunction occurred sig more in SER patients compared with PBO or BUP patients ($P < 0.001$) Beginning at day 7 through day 42 sig more BUP patients were satisfied with their overall sexual functioning. At day 56 no sig diff between treatment groups (BUP 75% vs SER 65%; $P < 0.05$) Compliance: BUP 98% SER 97.2% PBO 97.9% Endpoint: RRR, 0.29 RD: 0.10 NNT: 10	**Diarrhea:** D1: 26 D2: 7 D3: 11 **Headache:** D1: 40 D2: 34 D3: 30 **Insomnia:** D1: 18 D2: 13 D3: 4 **Nausea:** D1: 31 D2: 18 D3: 10 **Somnolence (fatigue):** D1: 17 D2: 3 D3: 6	**Overall attrition rate:** 32% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Cunningham et al., 1994[26] **Country and setting:** 5 United States sites and 1 in Montreal, Canada Multicenter **Funding:** Wyeth-Ayerst Research	**Research objective:** To compare efficacy and safety of VEN, TRA, and PBO in outpatients with major depression **Duration of study:** Short-term study: 6 wks Long-term study: 1 yr **Study design:** RCT **Overall study N:** 225 **Intervention:** D1: VEN: 156-160 mg/d D2: TRA: 294-300 mg/d D3: PBO	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Must have major depression • Symptoms for at least 1 mo prior to initial visit **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 2 yrs • ECT within last 14 days • Suicidal tendencies • No formal psychotherapy allowed during study period	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25.02 D2: 24.66 D3: 24.41	Results for HAM-D, MADRS, CGI available (results below) At wk 6, CGI response rates based on score of 1 or 2 were 72% for VEN group and 60% for TRA group ($P \leq 0.05$)	**Overall adverse events:** D1: 18 D2: 23 D3: 4 **Constipation:** D1: 22 D2: 9 D3: 4 **Dizziness:** D1: 17 D2: 36 D3: 5 **Nausea:** D1: 44 D2: 19 D3: 5 **Somnolence (fatigue):** D1: 43 D2: 61 D3: 12 **Sweating (increase):** D1: 12 D2: 3 D3: 1	**Overall attrition rate:** 33.78% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Cunningham, 1997[25] **Country and Setting** USA. Multicenter **Funding** Wyeth-Ayerst Research **Quality rating:** Fair	**Research objective** Comparison of the efficacy and safety of once-daily Venlafaxine extended release (XR) and immediate release versus placebo **Drugs, Doses, and Range** D1: Venlafaxine XR 75-150 mg D2: Venlafaxine IR 75-150 mg D3: Placebo **Fixed dose** **Flexible dose - yes** **Dosages equivalent - yes** **Study design – RCT (m-ITT)** **Duration – 12 weeks** **Type of depression** • MDD	**Inclusion criteria:** • Outpatients aged 18 years or older • *DSM-III-R* criteria for a major depressive episode; • minimum baseline score of 20 on HAM-D 21 • not more than a 20% decrease in score between screening and baseline; and had symptoms of depression for at least one month **Exclusion criteria:** • lactating • or of childbearing potential with a positive • pregnancy test • history of clinically significant medical disease or clinically significant abnormalities • acute suicidal tendencies; • History of a seizure disorder; presence of an organic mental disorder; bipolar disorder; or a history of any psychotic disorder not associated with depression • Any investigational drug, antipsychotic drug, or ECT within 30 days, fluoxetine within 21 days, or monoamine oxidase inhibitor, • paroxetine, or sertraline	**Groups similar at baseline - yes** **n =** D1: 92 D2: 87 D3: 99 **Mean age, years** D1: 39.7 D2: 42.8 D3: 39.7 **Sex, % female** D1: 63 D2: 67 D3: 59 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** **Comments:** NR	**HAM-D** Mean score at baseline (SD): D1: 24.5 D2: 24.0 D3: 24.9 Mean score at endpoint (SD): D1: 9.4 D2: 12.3 D3: 15.8 P < 0.001 for both vs. placebo Mean score change (SD): D1: 15.1 D2: 11.7 D3: 9.1 (calculated by 1st reviewer) **MADRS** Mean score at baseline (SD): D1: 26.7 D2: 26.5 D3: 26.6 Mean score at endpoint (SD): D1: 10.6 D2: 13.3 D3: 18.3 P < 0.001 for both vs. placebo Mean score change (SD): D1: 16.1 D2: 13.2 D3: 8.3 (calculated by 1st reviewer) **CGI-S** Mean score at baseline	**Attrition** **Overall attrition, %: 37%** **Attrition rate, %:** D1: 29% D2: 40% D3: 41% **Withdrawals due to adverse events, %** D1: 11 D2: 13 D3:2 **Withdrawals due to lack of efficacy, %** D1: 2 D2: 4 D3:12 Anorexia (%) D1: 10 D2: 6 D3: 4 Constipation (%) D1: 16 D2: 15 D3: 4 Diarrhea (%) D1: 13 D2: 5 D3: 6 Dry mouth (%) D1: 16 D2: 22 D3: 8 Nausea (%) D1: 45 D2: 45 D3: 10 Abnormal dreams (%) D1: 12 D2: 7 D3: 0 Dizziness (%) D1: 29 D2: 35 D3: 6 Somnolence (%) D1: 21 D2: 24 D3: 9 Sweating (%) D1: 19 D2: 14 D3: 3 Abnormal ejaculation/orgasm (men) (%) D1: 27 (10/37) D2: 6 (2/31) D3: 0(0/41)

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		within 14 days, or use of any other antidepressant, anxiolytic, sedative-hypnotic drug, or psychotropic drug or substance within 7 days • any nonpsychotropic drug with psychotropic effects unless the dosage had been • stable for a minimum of one month		(SD): NR Mean score at endpoint (SD): D1: 2.08 D2: 2.67 D3: 3.18 **CGI-I** NR **QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Dalery and Honig 2003[27] **Country and setting:** Europe Multicenter **Funding:** Solvay Pharmaceuticals	**Research objective:** Comparison of efficacy and safety of FLUV and FLUOX **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 184 **Intervention:** D1: FLUOX: 20 mg/d D2: FLUV: 100 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of ≥ 17 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 42.0 D2: 42.1 **Sex (% female):** D1: 63.3 D2: 62.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 22.3 D2: 22.2	Both treatment groups resulted in sig improvements of symptoms No sig diffs between study groups in changes of HAM-D scores from baseline at any point in time. After 2 wks of treatment, percentage of patients who responded was sig higher in FLUV group (29% vs. 16%; $P \geq 0.05$), as was improvement of CGI-I scores ($P \geq 0.05$). Sig diff not evident after wk 2 Improvement in sleep disturbance sub scores (HAM-D) was sig greater in FLUV group at wk 4 and at endpoint ($P \geq 0.05$)	**Headache:** D1: 14 D2: 13 **Nausea:** D1: 20 D2: 24	**Overall attrition rate:** 20.9% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: De Nayer et al., 2002[28] **Country and setting:** Belgium Psychiatric practices (14) **Funding:** NR	**Research objective:** To compare efficacy and safety of VEN and FLUOX in patients with depression and anxiety **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 146 **Intervention:** D1: VEN: 75-150 mg/d D2: FLUOX: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 70 • HAM-D score of 18-25 • Covi Anxiety scale > 8 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 41.6 D2: 43.9 **Sex (% female):** D1: 71.2 D2: 65.8 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23 D2: 23.1	VEN group showed sig higher response rates in MADRS scores (75.0 vs. 49.3%, *P* = 0.001) and HAM-D scores (71.9% vs. 49.3%; *P* = 0.008) compared to FLUOX group VEN treated patients also showed sig greater improvements in Covi Anxiety scores (*P* = 0.0004) and CGI scores (*P* = 0.016) At final visit 59.4% of VEN patients were in remission vs. 40.3 % of FLUOX patients (*P* = 0.028) Fewer VEN patients required dose increase (37.1% vs. 52.9%)	**Overall adverse events:** D1: 55.7 D2: 67.1 **Headache:** D1: 8.6 D2: 11.4 **Nausea:** D1: 28.6 D2: 21.4	**Overall attrition rate:** 36.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: De Wilde et al., 1993[29] **Country and setting:** Belgium Multicenter **Funding:** SmithKline, Beecham	**Research objective:** To compare efficacy and tolerability of PAR and FLUOX **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** D1: PAR: 20-40 mg/d D2: FLUOX: 20-60 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score > 18 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Suicidal tendencies • MAOIs or oral neuroleptics in last 14 days • Depot neurolecptics in last 4 wks • Lithium use	**Mean age (yrs):** D1: 44.6 D2: 44.1 **Sex (% female):** D1: 57 D2: 66 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 27 (4.8) D2: 28.2 (5.3)	Responders at wk 6 (i.e., reduction > 50% from baseline HAM-D21): PAR: ~ 67% FLUOX: ~ 62% no sig diff HAM-A score reduction statistically sig diff for PAR vs. FLUOX at wk 3; no sig diff at wks 4 or 6 At wk 4, 53% of PAR patients and 23% of FLUOX patients showed CGI response of at least 2; diff is sig ($P < 0.01$) No sig diffs in CGI response noted at wks 1, 3, or 6	**Overall adverse events:** D1: 43 D2: 58 **Changes in weight (increase):** D1: 6 D2: 4 **Nausea:** D1: 20 D2: 20 **Sweating (increase):** D1: 2 D2: 14	**Overall attrition rate:** 21.2% **ITT analysis:** NR **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Delgado et al., 2005[184] **Country and setting:** Country not reported, pooled analysis of 4 studies - setting not described in article **Funding:** Eli Lilly	**Research objective:** To assess sexual functioning in patients receiving DUL or PAR **Duration of study:** 8 wk acute phase followed by a 26 wk extension phase (for 2 of 4 studies) **Study design:** Pooled analysis of 4 RCTs **Overall study N:** 1,466 **Intervention:** D1: DUL: 40, 80, or 120 mg/d D2: PAR: 20 mg/d D3: PBO	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** NR	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	ASEX in 475 patients who did not have sexual dysfunction at baseline, incidence of treat-emergent sexual dysfunction was sig higher for DUL vs. PBO DUL = 46.4% PBO = 28.8% t = 2.69, df = 1337, *P* = 0.007 PAR vs. PBO PAR = 61.4% PBO = 28.8% *P* < 0.001 DUL vs. PAR, *P* = 0.015 (incidence for DUL sig lower than incidence for PAR)	**Overall adverse events:** NR	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Detke et al., 2002[163] **Country and setting:** United States, multicenter (18 sites) **Funding:** Eli Lilly and Company	**Research objective:** To evaluate efficacy of DUL vs. PBO for treatment of MDD and associated painful symptoms **Duration of study:** 9 wks **Study design:** RCT **Overall study N:** 245 **Intervention:** D1: DUL 60 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Minimum HAM-D-17 score of 15 • Other: CGI-S of 4 or more Note: Painful symptoms not required for inclusion **Exclusion criteria:** • Additional mental illness or organic mental disorder • Psychotherapy within 6 wks • Substance abuse or dependence (within 1 yr) • Clinically sig medical disease • Treatment resistant depression or lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** D1: 42.44 D2: 42.34 **Sex (% female):** D1: 65.0 D2: 68.0 **Race (% white):** D1: 87.0 D2: 84.4 **Baseline HAM-D-17:** D1: 21.42 (4.11) D2: 21.14 (3.72) **Baseline 100mm VAS (overall pain):** D1: 29.02 (25.10) D2: 28.16 (23.21) **Baseline HAM-A:** NR	**Pain outcomes:** Mean reduction in 100mm VAS for overall pain was statistically sig greater for DUL (~8.5 mm) compared to PBO (~2.5 mm) (Mean change estimated from figure; *P* = 0.019)	**Cardiovascular adverse events (new hypertension):** D1: 0.8 D2: 0 **Constipation:** D1: 13 D2: 1.6 **Diarrhea:** D1: 18.7 D2: 6.6 **Dizziness:** D1: 20.3 D2: 8.2 **Insomnia:** D1: 15.4 D2: 5.7 **Nausea:** D1: 46.3 D2: 9.0 **Sexual dysfunction:** NR but 2.4% of DUL-treated patients dropped out due to abnormal ejaculation **Somnolence:** D1: 21.1 D2: 4.9	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Detke et al., 2002[162] **Country and setting:** United States, multicenter (21 psychiatric clinical sites) **Funding:** Not reported but authors worked for Eli Lilly and Company	**Research objective:** To evaluate efficacy of DUL compared to PBO for treatment of emotional and painful physical symptoms of MDD **Duration of study:** 9 wks **Study design:** RCT **Overall study N:** 267 **Intervention:** D1: DUL 60 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Minimum HAM-D-17 score of 15 • CGI-S of 4 or more Note: Painful symptoms not required for inclusion **Exclusion criteria:** • Additional mental illness or organic mental disorder • Psychotherapy within 6 wks • Substance abuse or dependence (within 1 yr) • Clinically sig medical disease • Treatment resistant depression or lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** D1: 41 D2: 41 **Sex (% female):** D1: 66 D2: 71 **Race (% white):** D1: 78.1 D2: 78.4 **Baseline HAM-D:** D1: 20.33 (3.39) D2: 20.46 (3.39) **Baseline 100mm VAS (overall pain):** D1: 25.40 (23.98) D2: 26.20 (23.10) **Baseline HAM-A:** NR	**Pain outcomes:** Mean reduction in VAS for overall pain was ~10 mm for DUL compared to ~6 mm for PBO at endpoint (change score estimated from figure; *P* = 0.037)	**Cardiovascular adverse events (new hypertension):** D1: 0.8 D2: 0 **Constipation:** D1: 14.1 D2: 5.0 **Diarrhea:** D1: 10.2 D2: 7.9 **Dizziness:** D1: 14.8 D2: 2.9 **Headache:** D1: 25.8 D2: 22.3 **Insomnia:** D1: 16.4 D2: 13.7 **Nausea:** D1: 29.7 D2: 11.5	**Overall attrition rate:** 36.3% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Detke et al., 2004[30] **Country and setting:** United States Multicenter, university clinics **Funding:** Eli Lilly	**Research objective:** To determine comparative efficacy and safety of DUL and PAR for treatment of MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 274 **Intervention:** D1: DUL 80 mg/d D2: DUL 120 mg/d D3: PAR: 20 mg/d D4: PBO	**Inclusion criteria:** • Adults 18 or older • Met DSM-IV and MINI criteria for MDD • CGI-S rating > 4 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 15 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** D1: 43.1 D2: 44.7 D3: 42.0 D4: 42.0 **Sex (% female):** D1: 70 D2: 70 D3: 58 D4: 58 **Race (% white):** D1: 95 D2: 92 D3: 86 D4: 86 **Baseline (HAM-A):** D1: 17.8 D2: 18.0 D3: 18.5 D4: 17.9 **Mean HAM-D score at baseline:** D1: 19.9 (3.6) D2: 20.2 (3.4) D3: 20.3 (4.1) D4: 19.9	Response and remission rates did not differ sig among DUL 120 mg (71%; 52%), DUL 80 mg (65%; 46%) and PAR (74%; 44%) (*P* = NR) (ns) PGI scores were sig superior in patients receiving PAR than patients receiving 80 mg/d DUL (*P* < 0.05)	**Headache:** D1: 5.3 D2: 5.4 D3: 4.7 **Nausea:** D1: 12.6 D2: 5.4 D3: 11.6 **Somnolence (fatigue):** D1: 2.1 D2: 7.5 D3: 5.8 **Sweating (increase):** D1: 4.2 D2: 8.6 D3: 5.8	**Overall attrition rate:** 13.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Devanand et al., 2005[31] **Country and setting:** United States Outpatient clinic **Funding:** NIMH	**Research objective:** FLUOX vs. PBO for treatment of dysthymia in patients over 60 **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 90 **Intervention:** D1: FLUOX: 20-60 mg (individually titrated by protocol according to response) D2: PBO	**Inclusion criteria:** • Minimum HAM-D score of 8, max score 25 • Dysthymia • Adults at least 60 yrs old • CGI-s score ≥ 3 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Active suicidal ideation or plan • MDD during current dysthymia episode • Lack of response of current episode to prior trial of any SSRI • Major neurologic disorder • MMSE <24	**Mean age (yrs):** D1: 69.0 D2: 70.8 **Sex (% female):** D1: 32.6 D2: 40.9 **Race (% white):** D1: 86.4 D2: 89.1 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 15.3 (5.1) D2: 14.4 (3)	No sig diffs in response rates between treatment groups Responders: FLUOX: 27.3% PBO: 19.6% (*P* = 0.4) No sig diffs in QOL measures on Q-LES-Q	NR	**Overall attrition rate:** 21% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Didham et al., 2005[185] **Country and setting:** New Zealand RNZCGP Research Unit Database **Funding:** New Zealand Government	**Research objective:** Identify incidence and risk of suicide and self-harm among patients prescribed ADs **Duration of study:** 120 days **Study design:** Observational **Overall study N:** 57,361 **Intervention:** D1: CIT D2: FLUOX D3: PAR	**Inclusion criteria:** • Patients that received a prescription for an anti-depressant from 1996 to 2001 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Less than 10 yrs old	**Mean age (yrs):** Median: 46 **Sex (% female):** Overall: 68.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	No sig increase in suicides for SSRIs as a class: OR, 1.28; 95% CI, 0.38-4.35 No sig diff in suicides between drugs D1: NR D2: 0.80 (0.22-2.89) D3: 2.25 (0.47-10.72) Self-harm SSRIs vs. TCAs incidence rate 2.57 95% CI, 2.03-3.28 Increased risk of self-harm for SSRIs as a class OR, 1.66 95% CI, 1.23-2.23 No sig diffs in self-harm between drugs FLUOX; 1.30 (0.96-1.75) PAR 1.21 (0.84-1.72)	NR	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Dierick et al., 1996[32] **Country and setting:** France NR **Funding:** Wyeth-Ayerst International	**Research objective:** Comparison of efficacy and safety of VEN and FLUOX in outpatients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 314 **Intervention:** D1: VEN: 75-150 mg/d (mean daily dose for VEN: 109-122 mg/d from day 15 forward) D2: FLUOX: 20 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 14 days • ECT within last 14 days • Suicidal tendencies	**Mean age (yrs):** D1: 43.7 D2: 43.2 **Sex (% female):** D1: 65 D2: 64 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 27.0 (4.2) D2: 26.6 (4.1)	Response rate on HAM-D scale was sig higher in VEN group at wk 6: D1: 72% D2: 60% (P = 0.023) In low dose comparison, no sig diffs between groups	**Overall adverse events:** D1: 63 D2: 56 **Headache:** D1: 10 D2: 12 **Insomnia:** D1: 6 D2: 4 **Nausea:** D1: 28 D2: 14 **Somnolence (fatigue):** Asthenia: D1: 5 D2: 2 **Sweating (increase):** D1: 6 D2: 4	**Overall attrition rate:** 25% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Doogan and Caillard, 1992[110] **Country and setting:** Multinational (France, Germany, Austria, Switzerland, Great Britain, Ireland), multicenter **Funding:** Pfizer Central Research	**Research objective:** To investigate whether SER could alter course of affective symptoms and episodes in patients who had satisfactory response to acute therapy **Duration of study:** 52 wks **Study design:** RCT **Overall study N:** 480 entered single-blind PBO period; 295 entered double-blind therapy **Intervention:** D1: SER: 50-200 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 17 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • History of peptic ulceration • Hypersensitivity or resistance to antidepressant drugs	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 9.4 (6.7) D2: 10.2 (6.8)	Statistically sig lower proportion of SER patients relapsed compared to PBO patients (13.0% vs. 45.7%; *P* < 0.001). Protective effect of SER was maintained throughout 44 wks of double-blind portion of study. SER prevents relapse of index episode of depression as well as recurrence of further episodes and has few side effects	**Overall adverse events:** D1: 36.8 D2: 29.1 **Cardiovascular adverse events:** D1: < 1 D2: < 1 **Constipation:** D1: < 1 D2: 1.8 **Diarrhea:** D1: 1.1 D2: 2.7 **Dizziness:** D1: 4.9 D2: 5.5 **Headache:** D1: 5.9 D2: 7.3 **Insomnia:** D1: 3.8 D2: 4.5 **Nausea:** D1: 3.8 D2: < 1 **Somnolence (fatigue):** D1: 3.2 D2: 1.85 **Suicidality:** D1: 1 D2: 0 **Sweating (increase):** D1: 0 D2: 0	**Overall attrition rate:** 51.2% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Dunner et al., 1998[186] **Country and setting:** United States Multicenter (105 sites) **Funding:** Glaxo Wellcome Inc	**Research objective:** Safety of BUP sustained-release in acute and continuation treatment, especially in regards to seizures **Duration of study:** Acute phase of 8 wks with continuation up to 1 yr **Study design:** Uncontrolled, open-label trial **Overall study N:** 3,100 **Intervention:** D1: BUP: 100-300 mg/d	**Inclusion criteria:** • Adults 18+ • Diagnosed with MDD according to DSM-III or -IV • Bipolar I or II depression • Depression not otherwise specified bipolar depression not otherwise specified **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease • Suicidal tendencies • Known predisposition for seizures or previous treatment with BUP • History or current diagnosis of bulimia and/or anorexia	**Mean age (yrs):** D1: 42 **Sex (% female):** D1: 62.4 **Race (% white):** D1: 89.5 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Observed seizure rate during 8-wk acute phase was 2 seizures in 3,094 evaluable patients, or 0.06% and for acute and continuation phases combined was 3 seizures in 3,094 patients, or 0.10% Survival analysis yielded cumulative seizure rate of 0.08% for acute phase and 0.15% for both phases combined Rate of seizures for BUP within range of other antidepressants	**Overall adverse events:** D1: 50 patients experienced 54 serious AEs	**Overall attrition rate:** 34% **ITT Analysis** No, Survival analysis **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Echeverry et al., 2009[231] **Country and Setting** US, diabetes clinic **Funding** UCLA/DREW Project EXPORT, National Center on Minority Health and Health Disparities and National Institutes of Health **Quality Rating** Fair	**Research objective** To determine whether use of an antidepressans in minority population with uncontrolled diabetes improved their A1C levels, QOL and depression compared with PBO **Intervention Drugs, Doses, and Range** D1: SER 50-100mg/d (low dose) D2: PBO **Study design** RCT **n** 89 **Duration** 6 months **Type of depression** Major depressive disorder	**Inclusion criteria** • HAM-D: Concomitant condition (e.g., alcoholism, anxiety, stroke) • Repeat A1C levels > 8% • Whooley's questionnaire postitive result for depression • CDIS **Exclusion criteria** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): history of severe depression (hospitalization or suicide attempts) • Clinically significant medical disease: dialysis, liver disease; blood pressure >160mmHg systolic or >95 mmHg diastolic • Suicidal tendencies (acute or other) • Repeat A1C levels <8%	**Groups similar at baseline** Yes **n =** D1: 45 D2: 44 **Mean age, years** D1: 52 D2: 53 **Sex, % female** D1: 33 D2: 32 **Race, % Hispanic** D1: 39 D2: 39 **Baseline HAM-D (SD)** D1: 19 (5) D2: 20 (6) **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** **Mean score at baseline (SD):** D1: 19 (5) D2: 20 (6) **Mean score at endpoint (SD):** D1: 11 (6) D2: 13 (8) **Mean score change (SD):** D1: 8; *P* = NS D2: 7; *P* = NS **MADRS** NR **CGI-S** NR **CGI-I** NR **QOL scale** Diabetes-39 Questionnaire **Mean score at baseline (SD):** D1: 3.5 (3) D2: 3.0 (2) **Mean score at endpoint (SD):** D1: 50 (3) D2: 4.0 (2) **Mean score change (SD):** D1: 46.5 D2: NR **Adherence** D1: 67% D2: NR	**Overall rate of attrition, %** 15.7 **Attrition rate, %** D1: 13.3 D2: 18.2 **Withdrawals due to adverse events, %** D1: 0 D2: 4.5 **Attrition due to lack of efficacy, %** D1: 0 D2: 4.5 **Overall adverse events, %:** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Ehde et al., 2008[232] **Country and Setting** US University Medical Center **Funding** National Institute of Disability and Rehabilitation Research, Department of Education, Multiple Sclerosis Rehabilitation Research and Training Center **Quality Rating** Fair	**Research objective** Evaluate efficacy of PAR in treating MDD in persons with MS **Intervention Drugs, Doses, and Range** D1: PAR 10-40 mg/d D2: PBO **Study design** RCT **n** 42 **Duration** 12 wks **Type of depression** MDD and/or dysthymia	**Inclusion criteria** • 18 or more • Diagnosed with MDD according to DSM-III or -IV: Dysthymia • Diagnosis of MS as confirmed by a neurologist or an MS-specialized psychiatris **Exclusion criteria** • Pregnant or not using an effective contraceptive method or Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse: based on SCID • Investigational drug use currently enrolled • Suicidal ideation necessitating immediate psychiatric intervention • Corticosteroids within 2 weeks prior to enrollment • Taking 5 mg or more of amitriptyline or equivalent for sleep or pain • Failed PAR in past • Bipolar disorder or evidence of psychosis based on SCID	**Groups similar at baseline** NR **n =** D1: 22 D2: 20 **Intervention** NR **Mean age, years** 45.0 **Sex, % female** 52.4 **Race, % white** 85.7 **Baseline HAM-A** D1: NR **Insomnia, %:** D1: NR **Concomitant anergia, %** D1: NR **Experienced prior depressive episodes, %** D1: NR	**HAM-D** **Responders, n (%):** D1: 13 (57.1) D2: 8 (40.0) *P* = 0.354 **Remitters, n (%):** D1: 10 (47.6) D2: 5 (25.0) *P* = 0.197 **Mean score at baseline (SD):** D1: 17.2 (4.3) D2: 19.0 (4.6) **Mean score at endpoint (SD):** D1: 9.4 (5.9) D2: 11.4 (5.9) *P* = 0.920 **Mean score change (SD):** NR **MADRS** NR **CGI-S** NR **CGI-I** NR **CGI** NR **QOL scale** SF36 Physical **Mean score at baseline (SD):** D1: 40.8 (13.2) D2: 36.0 (11.4) **Mean score at endpoint (SD):** D1: 37.0 (12.0)	**Overall rate of attrition, %** 9.5 **Attrition rate, %** D1: 18.2 D2: 0 **Withdrawals due to adverse events, %** D1: 9.1 D2: 0 **Attrition due to lack of efficacy, %** D1: NR D2: 0 **Headache, %:** D1: 47.6 D2: 10 *P* = NR **Nausea, %:** D1: 57.1 D2: 5 *P* = NR **Sexual dysfunction, %:** D1: 23.8 D2: 5 *P* = NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
				D2: 35.5 (13.3) *P* = 0.076 **Mean score change (SD):** D1: 3.8 D2: 0.5 **QOL scale** SF36 Mental **Mean score at baseline (SD):** D1: 32.3 (10.7) D2: 35.6 (8.9) **Mean score at endpoint (SD):** D1: 44.6 (12.9) D2: 42.5 (9.7) *P* = 0.076 **Mean score change (SD):** D1: -12.3 D2: -6.9 **Mean score at baseline (SD):** D1: 57.2 (14.1) D2: 56.7 (12.6) **Mean score at endpoint (SD):** D1: 53.4 (31.3) D2: 51.8 (17.8) *P* = 0.657 **Mean score change (SD):** NR **Adherence, %** D1: 50 D2: 53 Adherence only known for 29 participants (D1: 7, D2: 8); adherence= did not miss any drug doses	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
				Greater improvement in PAR group in CES-D; *P* = NS PAR patients showed greater improvement on psychosocial subscale of MFIS (*P* = 0.02), on attention and concentration subscale of PDQ (*P* = 0.04) and SCL-20 (*P* = 0.02), but not on overall scales or on any of other subscales	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Ekselius et al., 1997[33] and Ekselius et al., 2001[187] **Country and setting:** Sweden Multicenter (general physicians) **Funding:** Swedish Medical Research Council, Pfizer	**Research objective:** To compare efficacy and safety of SER with CIT in patients with major depression and examine occurrence and severity of sexual dysfunction symptoms beforea nd after 6 mos of treatment. **Duration of study:** 24 wks **Study design:** RCT (Completers analysis for sexual dysfunction) **Overall study N:** 400 **Intervention:** D1: SER: 50-100 mg/d D2: CIT: 20-60 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • MADRS at least 21 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Previous treatment with SER or CIT w/o sig effect	**Mean age (yrs):** D1: 47.0 D2: 47.2 **Sex (% female):** D1: 71 D2: 72.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Both treatment groups showed sig decreases in MADRS and CGI scores from baseline at all wks starting at wk 2 No sig diffs between treatment groups in any primary outcome variables at any time Response rates Wk 12: D1: 69.5% D2: 68.0% Wk 24: D1: 75.5% D2: 81.0% Compliance: D1: 90.3% D2: 94.5% No statistically sig diffs between SER and CIT in magnitude or frequency of adverse sexual side effects Female patients reporting no sexual dysfunction at baseline, 11.8% reported decreased sexual desire and 14.3% reported orgasmic dysfunction Male patients reporting no sexual dysfunction at baseline, 16.7%	**Overall adverse events:** D1: 90 D2: 85.5 **Cardiovascular adverse events:** D1: 3 D2: 4 **Changes in weight (decrease):** D1: 4.5 D2: 9.5 **Changes in weight (increase):** D1: 15 D2: 13 **Constipation:** D1: 3 D2: 2 **Diarrhea:** D1: 8.5 D2: 5.5 **Headache:** D1: 9 D2: 6.5 **Insomnia:** D1: 3.5 D2: 6 **Nausea:** D1: 6 D2: 2.5 **Sexual dysfunction :** D1: 4 D2: 6.5 **Somnolence (fatigue):** D1: 5 D2: 4.5	**Overall attrition rate:** 22% **ITT analysis:** Yes **Quality rating:** Good for KQ1 Fair for KQ4

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
				reported decreased sexual desire, 18.9% reported orgasmic dysfunction, 25% experienced ejaculatory dysfunction	**Sweating (increase):** D1: 13 D2: 17	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Fang et al. 2010[111] **Country and Setting** China **Funding** "10th Five-year Plan" of National Key Technologies R&D Program grants 2004BA720A21-02 and the "Climbing Mountain Action Plan" Program grants 064119533 and partly supported by National High-tech R&D Program (grants 2006AA02Z430) **Quality rating:** Fair	**Research objective** Efficacy and tolerability of antidepressants switch with extended-release venlafaxine (venlafaxine-XR), mirtazapine, and paroxetine in Chinese patients with MDD who had 2 consecutive unsuccessful antidepressant trials **Drugs, Doses, and Range** D1: Venlafaxine 225 mg/d D2: Mirtazapine 45 mg/d D3: Paroxetine 20 mg/d **Fixed dose** **Dosages equivalent - Yes** **Study design** RCT **Duration** 8 weeks **Type of depression** • MDD resistant to at least two previous treatments	**Inclusion criteria:** • 18 and 65 years with a diagnosis of MDD • inpatient and outpatient services of 8 psychiatric hospitals • stage 2 TRD criteria described by Thase and Rush **Exclusion criteria:** • Bipolar disorder, schizoaffective disorder, schizophrenia, or other psychotic disorders; • Risk for suicide; • medical contraindication to antidepressants or other psychotropic medication; • Unstable general medical condition or a condition that required the combination treatment of an antidepressant and any other psychotropic medication • Modified ECT within 1 month • Pregnant, planning to become pregnant, or breast-feeding	**Groups similar at baseline - yes** **n =** D1: 50 D2: 55 D3: 45 **Mean age, years** Overall: 40.5 **Sex, % female** Overall: 54 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** **Comments:** NR	**HAM-D** Remission Ham-D < 7 (SD): D1: 21 (42.0%) D2: 20 (36.4%) D3: 21 (46.7%) P=0.578 Response reduction HAM-D > 50%: D1: 32 (64.0%) D2: 32 (58.2%) D3: 60 (66.7%) P=0.780 SDS remission (< 50): D1: 23 (46.0%) D2: 19 (34.5%) D3: 18 (40.0%) P=0.489 **CGI-I = 1** D1: 24 (48.0%) D2: 16 (29.1%) D3:18.0 (40%) P = 0.136 **Change in SF 36 from baseline Mean (SD) Physical/Mental** D1: 13.89 (11.57)/22.42 (17.42) D2: 10.05 (14.22) / 16.84 (19.26) D3: 13.68 (11.43) / 19.98/ 17.18) **Is adherence reported?** NR	**Attrition** **Overall attrition, %: 18.0** **Attrition rate, %:** D1: 18.0 D2: 18.2 D3:17.8 **Withdrawals due to adverse events, %** D1: 0 D2: 0 D3: 1 (2%) **Withdrawals due to lack of efficacy, %** D1:2 % D2: 6% D3:6%

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 1998[34] **Country and setting:** United States Multicenter (5 sites) **Funding:** SmithKline, Beecham	**Research objective:** Efficacy and tolerability of PAR and FLUOX **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 128 **Intervention:** D1: PAR: 20-50 mg/d (initial dosage of 20 mg/d could be increased wkly by 10 mg/d up to 50 mg/d) D2: FLUOX: 20-80 mg/d (initial dosage of 20 mg/d could be increased wkly by 20 mg/d up to 80 mg/d) D3: PBO	**Inclusion criteria:** • Minimum HAM-D score of 18 • Raskin Depression score of > 8 (and larger in value than Covi anxiety scale) **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • ECT within last 3 mos • Suicidal tendencies	**Mean age (yrs):** D1: 41.3 D2: 41.3 D3: 41.3 **Sex (% female):** D1: 50 D2: 50 D3: 50 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.1 (3.4) D2: 23.9 (3.8) D3: 23.7 (12.2)	No sig diffs among 3 treatment groups in degree of depression and anxiety improvement **HAM-D** Responders, %: D1: (58) D2: (57) *P* = NR (ns) Remitters, n (%): D1: NR D2: NR	**Cardiovascular adverse events:** D1: 5 D2: 11 D3: 11 **Insomnia:** D1: 29 D2: 20 D3: 11 **Sexual dysfunction :** D1: 25 D2: 7 D3: 0	**Overall attrition rate:** 28% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 2000[188] Fava et al, 2000[188] **Country and setting:** United States Multicenter (15 sites) **Funding:** Eli Lilly Research	**Research objective:** To compare tolerability and efficacy of FLUOX, PAR and SER in treatment of anxious depression **Duration of study:** 10 to 16 wks (4 wks with additional wks determined by response on CGI) **Study design:** RCT **Overall study N:** 108 (drawn from larger sample of 284 MDD outpatients) **Intervention:** D1: FLUOX: 20-60 mg/d D2: SER: 50-200 mg/d D3: PAR: 20-60 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • HAM-D-Anxiety/ Somatization Factor score of at least 7 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Presence of seizure disorder with seizure in last yr • History of allergy to study drugs • Use of MAOIs within 2 wks of active therapy	**Mean age (yrs):** D1: 40.3 D2: 44.1 D3: 41.4 **Sex (% female):** D1: 65.7 D2: 62.8 D3: 66.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.6 (3.9) D2: 23.9 (3.4) D3: 25.0 (3.8)	No statistically sig diffs between FLUOX, SER and PAR in baseline-to-endpoint improvement in HAM-D total (overall $P = 0.323$) No sig diffs in efficacy and tolerability of FLUOX, SER, and PAR in treating anxious depression For all treatments, incidence of substantial emergence or any worsening was low with improvement at highest frequency for all HAM-D items	**Changes in weight (increase 7%):** D1: 1.6 D2: 9.0 D3: 2.9 Completers analysis of 26 to 32 weeks change from baseline **Diarrhea:** D2: 25.6 D3: 20.0 **Headache:** D1: 22.9 D2: 25.6 D3: 23.3 **Insomnia:** D1: 17.1 D2: 23.3 D3: 23.3 **Nausea:** D3: 26.7 **Somnolence (fatigue):** D1: 11.4 D2: 16.3 D3: 10.0 **Mean weight change:** D1: -0.2% D2: +1.0% D3: + 3.6% **Changes in weight (increase 7%):** D1: 6.8% D2: 4.2% D3: 25.5%	**Overall attrition rate:** NR **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 2002[35] MAIN STUDY **Country and setting:** United States Multicenter (15 academic centers) **Funding:** Eli Lilly Research	**Research objective:** To assess effects of SSRI treatment interruption after successful initial treatment (acute phase) of major depression. Acute treatment phase of study reported here **Duration of study:** 10 to 16 wks **Study design:** RCT **Overall study N:** 284 **Intervention:** D1: FLUOX: 20-60 mg/d D2: SER: 50-200 mg/d D3: PAR: 20-60 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • MDD for at least 1 mo **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Presence of seizure disorder with seizure occurring in last yr • History of allergy to study drugs • Use of MAOIs within 2 wks of active therapy	**Mean age (yrs):** D1: 42.1 D2: 44.0 D3: 42.5 **Sex (% female):** D1: 63.0 D2: 57.3 D3: 58.3 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.1/18.4 D2: 23.5/19.2 D3: 22.6/18.9	No statistically sig diffs between FLUOX, SER and PAR on all outcome measures of HAM-D No statistically sig diffs between FLUOX, SER and PAR in response rates (50% or greater reduction in total HAM-D score from baseine) or remission rates (HAM-D total score of 7 or less at endpoint); response rates: 64.8%, 72.9%, and 68.8% respectively, P = 0.49; remission rates: 54%, 59%, and 57.0% respectively, *P* = 0.80	**Diarrhea:** D2: 26.0 **Headache:** D1: 25 D2: 28.1 D3: 21.9 **Insomnia:** D2: 26 D3: 20.8 **Nausea:** D2: 20.8 D3: 25.0 **Sexual dysfunction :** D1: 11.8 D2: 4.9 D3: 20.0	**Overall attrition rate:** 27.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Fava et al., 2002[35] (Subgroup of MAIN PAPER on Sleep Disturbance) **Country and setting:** United States, multicenter (15 sites) **Funding:** Eli Lilly and Company	**Research objective:** To compare efficacy and tolerability of FLUOX vs. PAR and SER for treatment of depression associated with sleep disturbance **Duration of study:** 10 to 16 wks (depending on response to initial dose; all received 6 wks of therapy at effective dose) **Study design:** RCT **Overall study N:** 284 overall; 125 in sleep disturbance subgroup **Intervention:** D1: FLUOX: 20-60 mg/d D2: PAR: 20-60 mg/d D3: SER: 50-200 mg/d	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-IV • Minimum HAM-D-17 score of 16 • Note: Sleep disturbance defined as HAM-D Sleep Disturbance Factor score of at least 4 **Exclusion criteria:** • Additional mental illness or organic mental disorder • Concomitant psychotropic medications • Substance use or dependence (within 6 mos) • Pregnant, lactating, or child-bearing potential without contraception • Clinically sig medical disease • Suicide risk (serious) • Seizure within 1 yr • Response to PBO in lead-in phase	**Mean age (yrs) in sleep disturbance subgroup:** D1: 42.2 D2: 41.9 D3: 43.0 **Sex (% female) in sleep disturbance subgroup:** D1: 60.5 D2: 65.2 D3: 63.4 **Race (% white):** NR **Baseline HAM-D-17 in sleep disturbance subgroup:** D1: 23.4 (3.9) D2: 22.6 (4.2) D3: 23.5 (3.9) **Baseline HAM-D Sleep Disturbance factor in sleep disturbance subgroup:** D1: 5.1 (0.9) D2: 4.8 (0.8) D3: 5.1 (0.8) **Baseline HAM-A:** NR	**Depression outcomes in patients with sleep disturbance:** No statistically sig diffs between FLUOX, PAR and SER in HAM-D-17 total score improvement (overall $P = 0.853$) **Sleep outcomes:** Improvement in HAM-D Sleep Disturbance factor was similar for all 3 groups: D1: (-3.1), D2: (-2.9), D3: (-3.1) (overall $P = 0.852$)	**Diarrhea:** D1: NR D2: NR D3: 26.0 **Headache:** D1: 25.0 D2: 21.9 D3: 28.1 **Insomnia:** D1: NR D2: 20.8 D3: 26.0 **Nausea:** D1: NR D2: 25.0 D3: 20.8 **Sexual dysfunction (abnormal ejaculation):** D1: NR D2: 20.0 (of males) D3: NR	**Overall attrition rate:** 49% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Fava, 2006[252] **Country and Setting** U.S., multicenter **Funding** Sepracor **Quality rating:** Fair	**Research objective** Evaluate effect of adding ESZ to FLX in MDD patients with comorbid insomnia. **Drugs, Doses, and Range** D1: FLUOX (20-40): starting dose 20mg; dosage range 20-40mg/day; low-medium PLUS placebo D2: FLUOX (20-40 mg): starting dose 20mg; dosage range 20-40mg/day; low-medium plus augmentation with ESZ 3 mg/day **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **Duration** 8 wks **Type of depression** MDD Somnia **Intervention** PBO+FLX ESZ+ FLX	**Inclusion criteria:** • Adults (age range): 21-64 • Diagnosed with MDD according to DSM-IV; 2 wks to 6 mos • HAM-D: score of > or:14 (after subtracting three sleep related item scores) • Concomitant condition (e.g., alcoholism, anxiety, stroke): insomnia that did not predate symptoms of MDD by more than 10 wks • Patients had to record TST ≥6.5 hrs; sleep latency ≥30 min and wake time after sleep onset ≥45 min per night at least 3 times per month **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications: at least 14 days prior to randomization • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): psychiatric or personality disorder • Illicit drug and alcohol abuse: use within 6 months or positive skin test at screening	**Groups similar at baseline** Yes **n =** D1: 275 D2: 270 **Mean age, years** D1: 40.4 D2: 41.6 Overall: NR **Sex, % female** D1: 66.4 D2: 66.9 Overall: 67 **Race, % white** D1: 60.2 D2: 65.4 Overall: 63 **Baseline HAM-A** NR Overall: NR **Insomnia, %** D1: 100 D2: 100 Overall: NR **Concomitant anergia, %** NR Overall: NR **Experienced prior depressive episodes, %** NR Overall: 100 **Comments:** CGI-S: 4.3 (0.6) 4.3 (0.6) NR **Outpatients/Inpatients** Outpatients	**HAM-D: mean (SD)** D1: 22.1 (4.5) D2: 22.4 (4.5) n at baseline: D1: 275 (ITT 274) D2: 270 (ITT 269) No. of responders, n (%) At week 4 D1: *P:* 0.01 D2: *P:* 0.16 At week 8 D1: 132 (48) *P:* 0.002 D2: 159 (59) *P:* 0.04 No. of remitters: D1: (33%) 90 D2: (42%) 113 Mean score at baseline (SD): D1: 22.1 (4.5) D2: 22.4 (4.5) Mean score at endpoint (SD): NR Mean score change (SD): NR HAM-D 17 with all items change from baseline analyses with analysis of covariance: *P:* 0.01 Wk 4 and *P:* .002. Excluding insomnia items: *P:* 0.16 Wk 4 and *P:* 0.04 wk.8. Mean score change reported in figures 4,5,6. **MADRS** No. of responders:	**Overall adverse events, %:** D1: 71.5 D2: 76.2 **Dizziness, %:** D1: 3.3 D2: 8.6 **Headache, %:** D1: 14.6 D2: 16.7 **Insomnia, %:** D1: NA D2: NA **Sexual dysfunction, %:** D1: 2 D2: 1 **Attrition** **Overall attrition, %:** 31.6 **Attrition rate, %:** D1: 32.5 D2: 30.9 **Withdrawals due to adverse events, %** D1: 7.7 D2: 6.3 **Withdrawals due to lack of efficacy, %** Insomnia failure: D1: 0.7 D2: 0.7 **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		• Clinically significant medical disease: clinically unstable or uncontrolled serious medical conditions • Suicidal tendencies (acute or other): Other: sensitivity to SSRI, zopiclone, or ESZ, MDD refractory to treatment with an SSRI **Outcome measures** • HAM-D: Response ≥ 50% decrease from baseline remission ≤ 7 • CGI-S or CGI-I: time to antidepressant response: 1-very much improved/ 2-much improved/ negative change from baseline • QOLs: WASO, sleep latency, increased total sleep time	**Baseline mean HAM-A > 25?** NR or NA **Mean age at baseline** Less than 65 years **Mean HAM-D at baseline** Greater than 17 (moderate to severe)	D1: Wk 8: (48%) 132/ *P:* 0.01 Wk 4 and *P:* 0.002 Wk 8 D2: Wk 8: (59%) 159/ *P:* 0.16 Wk 4 and *P:* 0.04 Wk 8 Mean score at baseline (SD): D1: 22.1 (4.5) D2: 22.4 (4.5) **CGI-S** D1: PBO + FLX D2: ESZ + FLX n at baseline: D1: 275 D2: 270 Mean score at baseline (SD): D1: 4.3 (0.6) D2: 4.3 (0.6) CGI results were consistent with HAM-D-17, indicating that ESZ+FLX group had significantly better CGI-I scores (all *P* < .004; data not shown) and improvement in CGI-S scores (reported in Figure 7) scores after Week 1 relative to ESZ+PBO group (all *P* ¡Ü .01).Patients in ESZ+FLX group had significantly shorter times to antidepressant response on basis of CGI-I (*P*: .0002; Figure 9) and on CGI-S (*P*: .01; data not shown).	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				CGI-I D1: PBO + FLX D2: ESZ + FLX Mean score change (SD): Refer to SRS items 66. and 72. Refer to SRS items 66. and 72. **CGII** Yes Intervention: D1: PBO + FLX D2: ESZ + FLX n at baseline: D1: 275 D2: 270 CGI results were consistent with HAM-D-17, indicating that ESZ+FLX group had significantly better CGI-I scores (all *P* < .004; data not shown) and improvement in CGI-S scores (reported in Figure 7) scores after Week 1 relative to ESZ+PBO group (all *P* <.01). Patients in ESZ+FLX group had significantly shorter times to antidepressant response on basis of CGI-I (*P*: .0002; Figure 9) and on CGI-S (*P*: .01; data not shown). **QOL scale** Sleep Latency Intervention:	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				D1: PBO + FLX D2: ESZ + FLX n at baseline: D1: 275 (ITT 274) D2: 270 (ITT 268) Mean score at baseline (SD): D1: 129.8 (250.7) D2: 125.4 (234.5) Mean score at endpoint (SD): D1: 47.5 (89.0) D2: 30.0 (55.0) Mean score change (SD): NR *P:* 0.0001, scores are median (IR) **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: FDA Center for Drug Evaluation & Research (Unpublished study SCT-MD-02), 2001[36] **Country and setting:** US Multicenter (22) **Funding:** Forest Laboratories, Inc.	**Research objective:** To assess efficacy and safety of ESC vs. CIT and PBO **Duration of study:** 8 weeks **Study design:** RCT **Overall study N:** 248 **Intervention:** D1: Escitalopram: 20-40 mg/d D2: Citalopram: 10-20 mg/d D3: PBO	**Inclusion criteria:** • Adults 18 to 80 • MDD diagnosis according to DSM-III or -IV • MADRS ≥ 22 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (years):** D1: 41.4 D2: 42.0 D3: 42.3 **Sex (% female):** D1: 52 D2: 48 D3: 58 **Race (% white):** D1: 82 D2: 86 D3: 82 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 24.8 D2: 25.0 D3: 25.0 **Mean MADRS score at baseline:** D1: 28.7 D2: 28.3 D3: 28.8	Mean change from baseline (*P*-values vs. PBO) **HAM-D** D1: 10.4 (*P* = 0.506) D2: 11.4 (*P* = 0.068) D3: 9.6 **MADRS** D1: 12.9 (*P* = 0.251) D2: 13.0 (*P* = 0.151) D3: 11.2 MADRS response rate (≥ 50% decrease from baseline) (%): D1: 46 D2: 51 D3: 41 (*P* = NR)	**Diarrhea:** D1: 9.6 D2: 14.6 D3: 8.7 **Fatigue:** D1: 12.0 D2: 4.1 D3: 2.4 **Headache:** D1: 21.6 D2: 22.8 D3: 18.1 **Insomnia:** D1: 13.6 D2: 11.4 D3: 6.3 **Nausea:** D1: 16.0 D2: 14.6 D3: 12.6 **Somnolence:** D1: 10.4 D2: 7.3 D3: 4.7	**Overall attrition rate:** 20% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Feiger et al., 1996[37] **Country and setting:** Europe Multicenter (4) **Funding:** Bristol Myers Squibb	**Research objective:** To compare safety and efficacy of NEF with SER in outpatients with moderate to severe depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 160 **Intervention:** D1: NEF: 100-600 mg/d D2: SER: 50-200 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Illicit drug and alcohol abuse • Investigational drug use • Suicidal tendencies	**Mean age (yrs):** D1: 43 D2: 44.5 **Sex (% female):** D1: 48 D2: 55 **Race (% white):** D1: 90 D2: 79 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.5 D2: 23.5	No statistically sig diffs between treatment groups Response rates: D1: 59% D2: 57% Difficulty with ejaculation: D1: no sig AE on sexual function $P < 0.01$ D2: had sig AEs on sexual function	**Overall adverse events:** D1: 96 D2: 95 **Diarrhea:** D1: 9 D2: 20 **Dizziness:** D1: 32 D2: 7 **Headache:** D1: 55 D2: 55 **Insomnia:** D1: 21 D2: 23 **Nausea:** D1: 32 D2: 27 **Somnolence (fatigue):** Asthenia: D1: 18 D2: 24 Somnolence D1: 23 D2: 21 **Sweating (increase):** D1: 6 D2: 17	**Overall attrition rate:** 24.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Feiger et al., 1999[116] **Country and setting:** United States; outpatient **Funding:** Bristol Meyers Squibb	**Research objective:** To evaluate efficacy of NEF in prevention of relapse during continuation phase treatment of patients with MDD **Duration of study:** 36 wks **Study design:** RCT **Overall study N:** 131 **Intervention:** D1: NEF: 400-600 mg/d D2: PBO	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Must have responded to 16 wks of single-blind NEF treatment (≤ 10 HAMD-D for 2 consecutive visits) **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • ECT • MAOI use in past 4 wks	**Mean age (yrs):** D1: 40 D2: 42.6 **Sex (% female):** D1: 72 D2: 71 **Race (% white):** D1: 94 D2: 98 **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 24.4 (0.3) D2: 24.2 (0.3)	Kaplan-Meier survival curves show relapse rate sig lower (P = 0.0009) in NEF (1.8%) group vs. PBO (18.3%) group Discontinuation due to lack of efficacy 17.3% for NEF and 32.8% for PBO Relative risk of relapse (HAM-D) was sig lower for NEF than PBO overall (0.094; P = 0.003) and stratified by recurrent depression, melancholia, and sex (P < 0.005 for all) Relative risk of relapse based on discontinuation due to lack of efficacy also was sig lower for NEF than PBO (0.445; P = 0.04)	**Changes in weight (increase):** D1: +0.6kg D2: +0.9kg **Headache:** D1: 20 D2: 14 **Nausea:** D1: 12 D2: 8	**Overall attrition rate:** 45% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Feighner et al., 1991[38] **Country and setting:** United States Multicenter (2 sites) **Funding:** Burroughs Wellcome Co	**Research objective:** Efficacy and safety of BUP and FLUOX in depressed outpatients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** D1: BUP: 225-450 mg/d (382) D2: FLUOX: 20-80 mg/d (38)	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** D1: 40.9 D2: 42.9 **Sex (% female):** D1: 62 D2: 61 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25.3 D2: 26.1	No sig diffs in changes of HAM-D score between treatment groups No sig diffs in percentage of clinical responders (more than 50% HAM-D scale reduction) between treatment groups, D1: 62.7%, D2: 58.3% No sig diffs in changes of CGI-S, CGI-I, and HAM-A scores Higher rate of impotence (4.7% vs 0%), anorgasmia (1.7% vs 0%), and libido decrease (1.7% vs 0%) for FLUOX (*P* = NR)	NR	**Overall Attrition rate:** 7.3% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Ferguson et al., 2001[189] **Country and setting:** United States Multicenter (9 sites) **Funding:** Bristol Myers Squibb	**Research objective:** To compare effects of NEF and SER on reemergence rates of sexual dysfunction in depressed patients who'd had sexual dysfunction with previous SER treatment **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 75 **Intervention:** D1: NEF: 200-400 mg/d D2: SER: 50-100 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Receiving SER and experiencing attributable sexual dysfunction **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days	**Mean age (yrs):** D1: 43.2 D2: 44.8 **Sex (% female):** D1: 46 D2: 48 **Race (% white):** D1: 95 D2: 97 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 11.5 D2: 10.5	More SER treated patients had reemergence of sexual dysfunction than nefazadone-treated (76% vs. 26%; $P < 0.001$); similar response rate for both treatments (numerical data NR)	**Overall adverse events:** D1: 100 D2: 97 **Sexual dysfunctional (male ejaculation):** D1: 76 D2: 26	**Overall attrition rate:** 32% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Flament et al., 1999[165] **Country and setting:** UK, multicenter (20 psychiatric clinics) **Funding:** Not reported, but 2nd author employed by Pfizer Inc	**Research objective:** To compare response rates of FLUOX vs. SER for treatment of depression in subgroups of patients with depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 286 randomized 248 included in analysis 174 in melancholia subgroup (defined by DSM-III-R criteria) 131 in anxiety subgroup (7 or more on Covi Anxiety Scale) 47 in psychomotor retardation group (HAM-D item 8 ≥2 and item 9 ≤ 1) 78 in psychomotor agitation subgroup (HAM-D item 8 ≤ 1 and item 9 ≥2) **Intervention:** D1: FLUOX 20-40 mg/d (mean 25) D2: SER 50-100 mg/d (mean 62.5)	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD or bipolar, depressed by DSM-III-R criteria • Minimum HAM-D-17 score of 18 • Raskin Depression score higher than Covi Anxiety score **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant psychotherapeutic drugs • Concomitant ECT or psychotherapy • Substance use or dependence (within 6 mos) • Pregnant, lactating, or child-bearing potential without contraception • Clinically sig medical disease • Suicide risk • PBO response during washout • Previous use of study drugs	**Mean age (yrs):** D1: 49.9 D2: 49.9 **Sex (% female):** D1: 65 D2: 57 **Race (% white):** NR **Baseline HAM-D-17:** D1: 23.4 D2: 23.2 **Baseline HAM-A:** NR	**Depression results in patients with melancholia:** Mean HAM-D change did not differ between groups (-9.8 FLUOX vs. -11.0 SER). Response rates were higher for SER (59%) vs. FLUOX (44%) ($P < 0.05$) **Depression results in anxiety:** FLUOX and SER groups had similar HAM-D mean change (-10.6 vs. -9.7) and response rates (48% vs. 47%; P = NR) **Depression results in psychomotor change:** In retardation, HAM-D change and response were similar (Change/ response: -10.7/46% for FLUOX vs. -9.1/ 48% for SER; P = NR). In agitation, HAM-D improvement was 8.7 for FLUOX vs. 12.4 for SER ($P = 0.02$); response rate was 39% for FLUOX vs. 62% for SER ($P = 0.04$)	**Overall adverse events:** D1: 60 D2: 57	**Overall attrition rate:** 13.3% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Franchini et al., 1997[117] and Franchini et al., 2000[118] **Country and setting:** Italy Mood disorder clinic **Funding:** Not reported	**Research objective:** Efficacy and safety of fluvoxamine and sertraline in the long-term treatment of depression **Duration of study:** 24/48 months **Study design:** RCT **Overall study N:** 64 (4-year followup: enrolled 47) **Intervention:** Drug 1: Sertraline: 100-200 mg/d Drug 2: Fluvoxamine: 200-300 mg/d	**Inclusion criteria:** • Asymptomatic patients; unipolar patients with prior episodes; depressive episode within past 18 months; at least 4 months of remission confirmed by absence of symptoms according to DSM-IV; absence of other Axis I diagnosis **Exclusion criteria:** • Other Axis I diagnosis; low compliance with past treatments; mania or hypomania; prior long-term maintenance treatment; recurrence cycle not longer than 18 months	**Mean age (years):** Drug 1: 47.3 Drug 2: 49.0 **Sex (% female):** Drug 1: 78 Drug 2: 75 **Race (% white):** Drug 1: NR Drug 2: NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	2-years: 21.9% of sertraline-treated patients and 18.7% of fluvoxamine-treated patients had a single recurrence (z = 0.14; *P* = 0.88) 4-year follow-up: No significant difference in recurrences between the treatment groups; sertraline: 13.6%, fluvoxamine: 20%	**Headache:** Drug 1: NR Drug 2: 3.1 **Nausea:** Drug 1: 6.2 Drug 2: 9.4 **Sexual dysfunctional (male ejaculation):** Drug 1: 12.5 **Somnolence (fatigue):** Drug 2: 3.1	**Overall attrition rate:** NR **ITT Analysis** No, but not necessary since 100% completed trial with outcome assessments **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Gagiano, 1993[41] **Country and setting:** South Africa University hospital **Funding:** NR	**Research objective:** Safety and efficacy comparison of PAR and FLUOX in patients with MDD **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 90 **Intervention:** D1: FLUOX: 20-60 mg/d D2: PAR: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Suicidal tendencies	**Mean age (yrs):** D1: 39.6 D2: 37.8 **Sex (% female):** D1: 80 D2: 80 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diffs in mean total scores for HAM-D, CGI-I or CGI-S, HAM-A, and MADRS at endpoint or any other study point measures No sig diff in patients responding (at least 50% improvement of HAM-D) between treatment groups (PAR: 70%, FLUOX: 63%; no *P* value reported) No sig diffs in groups on HAM-D (item 3) measure for suicidal ideation, both groups showed reduction over 6-wk period	**Diarrhea:** D1: 13.0 D2: 13.0 **Headache:** D1: 47.0 D2: 53.0 **Insomnia:** D1: 20.0 D2: 11.0 **Nausea:** D1: 33.0 D2: 36.0	**Overall attrition rate:** 21% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Gelenberg et al., 2003[119] **Country and setting:** United States Multiclinic **Funding:** Bristol-Myers-Squibb	**Research objective:** Comparison of NEF and PBO in prevention of depression recurrence **Duration of study:** 52 wks **Study design:** RCT **Overall study N:** 165 for maintenance phase **Intervention:** D1: NEF: 300-600 mg/d (495.2) D2: PBO D3: Overall	**Inclusion criteria:** • Adults 18 to 75 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Suicidial tendencies	**Mean age (yrs):** D1: 44.4 D2: 44.1 D3: 44.0 **Sex (% female):** D1: 69.7 D2: 65.5 D3: 67.5 **Race (% white):** Overall: 96.5 **Baseline HAM-A:** NR **Baseline HAM-D:** NR	At end of 1 yr, conditional probability of recurrence was 30.3% for NEF-treated patients, compared with 47.5% for PBO-treated patients	**Changes in weight (decrease):** D1: 14.1 D2: 9.5 **Changes in weight (increase):** D1: 4.7 D2: 14.3 **Headache:** D1: 41.0 D2: 32.2 **Insomnia:** D1: 17.9 D2: 19.5 **Nausea:** D1: 10.3 D2: 6.9 **Sexual dysfunction (male ejaculation):** D1: 2.6 D2: 3.4 **Somnolence (fatigue):** D1: 15.4 D2: 4.6	**Overall attrition rate:** 50.6% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Gibbons et al., 2007[191] **Country and Setting** United States, multicenter (VHA health care centers) **Funding** NIMH **Quality rating:** Fair	**Research objective** To examine relationship between antidepressant treatment and suicide attempts in adult patients in Veterans Administration health care system. **Drugs, Doses, and Range** D1: MIR (15-45 mg 1 x daily) D2: NEF (200-600 mg 2 x daily) D3: VEN (75-375 mg 2-3 x daily) D4: Other (augmentation): SSRI monotherapy (not specified), non-SSRI monotherapy (BUP , MIR, NEF, and VEN), or tricyclic monotherapy **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** Observational **Duration** Article does not provide start and end dates, but does state that investigators were examining those that experienced depressive disorders or unipolar mood disorders in 2003 or 2004 **Type of depression** MDD Dysthmia	**Inclusion criteria:** • Adults (age range) was not provided; however, focus of article was on adult population. • Patients who experienced depressive disorders or unipolar mood disorders (ICD-9 CM codes 296.2, 296.3, 300.4, and 311) in 2003 or 2004, had at least 6 months of follow-up, had no history of these disorders or antidepressant treatment from 2000 to 2002. **Exclusion criteria:** **Outcome measures** • Analysis based on suicide attempts that were sufficiently serious to have led to contact with VA health care system (coded by ICD-9 code E950-E959).	**Groups similar at baseline** Yes **n =** D1: 59,432 D2: 82,828 D3: 27,548 D4: 4,099 **Mean age, years (SD)** D1: 57.6 (15.1) D2: 60.3 (15.0) D3: 55.6 (14.3) D4: 57.3 (14.1) **Sex, % female** D1: 8.4 D2: 7.8 D3: 7.7 D4: 8.0 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: *NR- see comments D2: *NR-see comments D3: *NR-see comments D4: *NR-see comments **Comments:** The article reports that 26.0 % of cohort (N: 226,866) was White. It should also be noted that race of 64.3% of cohort was unknown. Additional results:	**HAM-D** NR **MADRS** NR **CGI-S** NR **CGI-I** NR **CGII** No **QOL scale** NR **Another QOL scale** Activities Questionnaire Total Score n at baseline: 102 104 102 Mean score at endpoint (SD): 53.0 (11.5) 52.3 (9.7) 50.4 (11.3) **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:**	**Attrition** **Overall attrition, %:** NA **Attrition rate, %:** NR **Withdrawals due to adverse events, %** NR **Withdrawals due to lack of efficacy, %** NR **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
	Patients who experienced depressive disorders or unipolar mood disorders **Intervention** D1: No antidepressant D2: SSRI monotherapy D3: Non-SSRI Monotherapy D4: Tricyclic Monotherapy		Duration of follow-up (days and SD): • No Antidepressants: 450 (160) • SSRI Monotherapy: 464 (161) • Non-SSRI Montherapy: 462 (163) • Tricyclic Monotherapy: 484 (164) Diagnosis-major categories: • MDD, single episode- No Antidepressant: 2,734 • SSRI Monotherapy: 3,893 • Non-SSRI Montherapy: 1,763 • Tricyclic Monotherapy: 139 MDD, recurrent • No Antidepressants: 3,923 • SSRI Monotherapy: 4,307 • Non-SSRI Monotherapy: 2,617 • Tricyclic Monotherapy: 230 Dysthymic disorder • No Antidepressant: 7,022 • SSRI Monotherapy: 7,786 • Non-SSRI Monotherapy: 2,810 • Tricyclic Monotherapy: 406 • Depression not otherwise specified: 45,584 • SSRI Monotherapy: 66,510 • Non-SSRI Monotherapy: 20,165 • Tricyclic Monotherapy: 3,312; Method of suicide attempt: Poisoning • No Antidepressants: 22,108 • SSRI Monotherapy: 27,582 • Non-SSRI Monotherapy: 8,981 • Tricyclic Monotherapy: 1,119 Hanging or strangulation • No Antidepressant: 25,080 • SSRI Monotherapy: 36,610 • Non-SSRI Monotherapy: 12,066 • Tricyclic Monotherapy: 1,865 Cutting or piercing	NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
			• No Antidepressant: 4,755 • SSRI Monotherapy: 6,129 • Non-SSRI Monotherapy: 1,956 • Tricyclic Monotherapy: 373 Firearm • No Antidepressant: 892 • SSRI Monotherapy: 2,071 • Non-SSRI Monotherapy 248 • Tricyclic Monotherapy: 742 Other or unspecified • No Antidepressant: 6,597 • SSRI Monotherapy: 10,436 • Non-SSRI Monortherapy: 4,297 • Tricyclic Monotherapy: 0. The diagnostic codes and entrance criteria were select patients who were experiencing a new depressive episode. article did note that cohort had no history of depressive disorders(or unipolar disorder) or antidepressant treatment from 2000 to 2002. data that was abstracted was based on patients who were not treated with an antidepressant (n: 59,432), and those who were treated with one or more medications of a single antidepressant type (n: 114,475) - a total of 173,907 patients. **Outpatients/Inpatients** Both **Baseline mean HAM-A > 25?** NR **Mean age at baseline** Less than 65 years **Mean HAM-D at baseline** NR		

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Gilaberte et al., 2001[120] **Country and setting:** Spain; multicenter (10) **Funding:** Eli Lilly and Co	**Research objective:** To evaluate efficacy and safety of FLUOX compared to PBO in maintenance treatment of recurrent unipolar depression **Duration of study:** 1 yr for maintenance (2 yrs total) **Study design:** RCT **Overall study N:** 140 (double-blind maintenance phase) **Intervention:** D1: FLUOX: 20-40 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • At least one prior depressive episode in last 5 yrs • CGI-S score at least 4 in index episode **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidial tendencies • Previous resistance to pharmacologic treatment	**Mean age (yrs):** D1: 44.4 D2: 43.8 **Sex (% female):** D1: 78.6 D2: 78.6 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 2.8 (2.0) D2: 3.1 (2.7)	20% recurrence rate with FLUOX vs. 40% with PBO (P = 0.010); symptom-free period sig longer for FLUOX vs. PBO (295 days vs. 192 days, P = 0.002); mean end-point HAMD sig lower in FLUOX vs. PBO (6.5 ± 8.6 vs. 9.9 ± 9.4; P = 0.027)	**Overall adverse events:** D1: 62.9 D2: 68.6 **Changes in weight (decrease):** D1: 11.4 D2: 7.1 **Dizziness:** D1: 10.0 D2: 17.1 **Headache:** D1: 20 D2: 27.1 **Insomnia:** D1: 21.4 D2: 14.3 **Nausea:** D1: 12.9 D2: 12.9	**Overall attrition rate:** 44.3% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Gillin et al., 1997[42] **Country and Setting** United States; multicenter **Funding** Bristol-Myers-Squibb National Center for Research Resources; Mental Health Clinical Research Center, National Institutes of Health **Quality rating:** Fair	**Research objective** To compare effects of NEF and FLUOX on sleep architecture and subjective sleep complaints in depressed outpatients with insomnia. **Drugs, Doses, and Range** D1: NEF (200-600 mg 2 x daily): 200 mg/day for week 1; low; 400 mg/day for week 2-8; med D2: FLUOX (20 mg 1 x daily): 20 mg/day; low **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **Duration** 8 weeks **Type of depression** MDD **Intervention** D1: NEF D2: FLUOX	**Inclusion criteria:** • Adults (age range): 21-55 yo • Diagnosed according to DSM-III-R with non-psychotic, moderate to severe MDD • HAM-D-17: minimum score of 18 • Must meet subjective criteria of sleep disturbance **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse • History of psychoactive substance use disorder in last 12 months • Clinically significant medical disease: current general medical conditions • Shift workers • Primary sleep disorders independent of affective disturbance **Outcome measures** • HAM-D: total score, Depressed Mood Item, Sleep Disturbance Items • Sleep efficiency • Sleep architecture	**Groups similar at baseline** Yes **n =** D1: 24 D2: 20 Overall: 44 **Mean age, years** D1: 35.3 D2: 36.7 **Sex, % female** D1: 67 D2: 70 **Race, % white** D1: 63 D2: 75 **Baseline HAM-A** NR **Insomnia, %** D1: 100 D2: 100 **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Previous antidepressant use, %** D1: 42 D2: 50 **Baseline mean HAM-A > 25?** NR	**HAM-D mean change from baseline** D1: -11.5 (1.41) D2: -10.3 (1.35) *P*=NR (ns) **HAM-D depressed mood item mean change from baseline** D1: -1.4 (0.28) D2: -1.1 (0.18) *P*=NR (ns) **Sleep efficiency mean change from baseline** D1: 0.2 (1.73) D2: -4.8 (1.66) *P*=0.05	**Attrition** **Overall attrition, %:** 18.2 **Attrition rate, %:** D1: 20.8 D2: 15.0 **Withdrawals due to adverse events, %** D1: 17 D2: 15 **Withdrawals due to lack of efficacy, %** D1: 0 D2: 0

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Glassman et al., 2002[234] **Country and setting:** multinational, conduceted in 40 outpatient cardiology centers and psychiatry clinics **Funding:** Pfizer	**Research objective:** To evaluate safety and efficacy of SER treatment of MDD in patients hospitalized for acute MI or unstable angina free of other life-threatening medical conditions **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 369 **Intervention:** D1: SER: 50-200 mg/d D2: PBO	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • Acute MI or hospitalization for unstable angina in past 30 days **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Sig suicide risk • Women of childbearing potential not on adequate contraception • Current use of antiarrythmic medications	**Mean age (yrs):** D1: 56.8 D2: 57.6 **Sex (% female):** D1: 37 D2: 36 **Race (% white):** D1: 74 D2: 79 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 19.6 (5.3) D2: 19.6 (5.4)	HAM-D mean score (SD) and mean score change: All randomized patients: D1: 19.6 (5.3) and -8.4 (0.41) D2: 19.6 (5.4) and -7.6 (0.41) Any recurrent depression: D1: 20.6 (5.1) and -9.8 (0.59) D2: 20.8 (5.6) and -7.6 (0.61) Patients with 2 prior episodes, plus HAM-D score ≥ 18: D1: 22.9 (3.6) and -12.3 (0.88) D2: 24.5 (4.4) and -8.9 (0.98) # CGI responders total sample: D1: 125 (67%) D2: 97 (53%) (*P* = 0.01) Any recurrent MDD: D1: 69 (72%) D2: 46 (51%) (*P* = 0.003) Patients with more severe (2 prior episodes plus HAM-D score ≥ 18): D1: 39 (78%) D2: 18 (45%) (*P* = 0.001)	**Cardiovascular adverse events:** D1: 52.7 D2: 59.0 **Diarrhea:** D1: 18.8 D2: 7.7 **Dizziness:** D1: 15.6 D2: 12.0 **Headache:** D1: 20.4 D2: 16.4 **Insomnia:** D1: 18.8 D2: 18.8 **Nausea:** D1: 19.9 D2: 10.9 **Somnolence (fatigue):** D1: 14.5 D2: 13.7	**Overall attrition rate:** 26.8% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Golden et al., 2002[43] **Country and Setting** USA and Canada, multicenter **Funding** GlaxoSmithKline **Quality rating:** Fair high attrition, adverse events not with valid scale	**Research objective** To determine antidepressant efficacy and tolerability of PAR CR and PAR IR in adult patients with MDD. **Drugs, Doses, and Range** • PAR (10-60 mg 1 x daily): 20-50 mg/day (low to high) • PAR CR (12.5-75 mg 1 x daily): 25-62.5 mg/day (low to high) **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** Yes **Study design** RCT **Duration** 12 weeks **Type of depression** MDD **Intervention** D1: PAR CR D2: PAR IR D3: PBO	**Inclusion criteria:** • Adults (age range): 18-65 • Diagnosed with MDD according to DSM-III or -IV • HAM-D: 20 or more (and did not decrease by more than 25% between screening and baseline **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications: treatment with monoamine oxidase inhibitor, benzodiazepine, or other psychoactive agent (excluding chloral hydrate) • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse within 6 months of screening • ECT within last: 3 months • Suicidal tendencies (acute or other) • History of brief depressive episodes (≤8 weeks) • Homicidal risk • Currently taking PAR or history of PAR nonresponse or	**Groups similar at baseline** Yes **n =** D1: 212 D2: 217 D3: 211 **Mean age, years** D1: 40.7 D2: 39.9 D3: 39.7 **Sex, % female** D1: 63.2 D2: 69.1 D3: 63.0 **Race, % white** D1: 88.2 D2: 86.6 D3: 85.3 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** **Outpatients/Inpatients** **Baseline mean HAM-A > 25?** NR **Mean age at baseline** Less than 65 years **Mean HAM-D at baseline**	**HAM-D** D1: NEF D2: FLUOX n at baseline: D1: 22 D2: 21 Mean score at baseline (SD): D1: 23.5 D2: 23.6 Mean score at endpoint (SD): D1: 11.5 D2: 11.5 Mean score change (SD): D1: -12.0 D2: -12.1 **MADRS** NR Mean score at baseline (SD): D1: 23.5 D2: 23.6 **CGI-S** NR **CGI-I** NR Mean score change (SD): Not a QOL Scale- HAM-D Sleep Disturbance item Not a QOL Scale- HAM-D Sleep Disturbance item **CGII** NR **QOL scale** D1: NEF	**Weight gain, %:** D1: 3.8 D2: 4.2 D3: 1.4 **Weight loss, %:** D1: 4.3 D2: 2.3 D3: 1.4 **Constipation, %:** D1: 10.4 D2: 12.0 D3: 4.3 **Diarrhea, %:** D1: 18.4 D2: 13.4 D3: 7.1 **Dizziness, %:** D1: 19.3 D2: 16.6 D3: 4.7 **Nausea, %:** D1: 23.6 D2: 30.9 D3: 14.2 **Sexual dysfunction, %:** Abnormal ejaculation: D1: 26.9 D2: 23.9 D3: 1.3 Female genital disorders: D1: 10.4 D2: 5.3 D3: 0.8 **Attrition** **Overall attrition, %:** 30.7 **Attrition rate, %:** D1: 25.7

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		intolerability **Outcome measures** • HAM-D: 17-item total score, depressed mood (item 1), psychic anxiety (item 10)	Greater than 17 (moderate to severe)	D2: FLUOX Intervention: D1: 22 D2: 21 n at baseline: D1: 4.3 (1.24) D2: 4.0 (1.38) Mean score at baseline (SD): D1: 1.7 (1.35) D2: 2.5 (1.85) Mean score at endpoint (SD): D1: -2.6 (1.69) D2: -1.5 (1.96) Mean score change (SD): NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	D2: 31.3 D3: 26.3 **Withdrawals due to adverse events, %** D1: 10 D2: 16 D3: 6 **Withdrawals due to lack of efficacy, %** NR **Comments** Dropout rate of patients with PAR IR sign. higher compared to PBO (*P* = 0.0008)

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Goldstein et al., 1997[192] **Country and setting:** United States multicenter, outpatient trial **Funding:** Lilly	**Research objective:** To assess effect of FLUOX 20 mg/d on weight loss in older patients **Duration of study:** 6 wks (after a 1-wk PBO lead-in) **Study design:** RCT **Overall study N:** 671 **Intervention:** D1: FLUOX: 20 mg/d D2: PBO	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Adults 60+ **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Clinically sig medical disease • Suicidal tendencies • Score less than 25 on MMSE • History of allergic reaction to FLUOX • History of nonresponse to at least 2 antidepressants at usual doses	**Mean age (yrs):** D1: 68 D2: 68 **Sex (% female):** D1: 55 D2: 55 **Race (% white):** D1: 94 D2: 94 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Mean change (SD) in body weight: Low/normal BMI: D1: -0.88 (2.11) D2: 0.11 (1.96) (*P* < 0.001) High BMI: D1: -1.14 (1.99) D2: 0.04 (1.72) (*P* < 0.001) Pooled: D1: -1.01 (2.05) D2: 0.08 (1.85) (*P* < 0.001) % with weight loss of at least 5% low/normal BMI: D1: 2.4 D2: 1.1 (*P* = 0.225) High BMI: D1: 3.7 D2: 0 (*P* = 0.021) Pooled: D1: 3.1 D2: 0.6 (*P* = 0.017)	**Cardiovascular adverse events:** D1: 2.7 D2: 3.3 **Changes in weight (decrease):** D1: 3.3 D2: 1.2	**Overall attrition rate:** NR **ITT Analysis** No another type of analysis was used (define): included patients with complete data only **Quality rating:** Fair for AE reporting

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Goldstein et al., 2002[44] **Country and setting:** United States Multicenter (8 sites) **Funding:** Eli Lilly and company	**Research objective:** Evaluation of DUL for efficacy and safety vs. PBO and FLUOX in patients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 103 **Intervention:** D1: PBO D2: DUL: 40-120 mg/d D3: FLUOX: 20 mg/d	**Inclusion criteria:** • Adults 19 to 65 yrs • Minimum HAM-D score of 15 • Mini confirmation of MDD • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Illicit drug and alcohol abuse • Failed 2 or more courses of antidepressant therapy during current episode • Additional mental illnesses or organic mental disorder	Mean age (yrs): D1: 41.4 D2: 42.3 D3: 39.7 Sex (% female): D1: 68.6 D2: 62.9 D3: 57.6 Race (% white): D1: 81.4 D2: 88.6 D3: 72.7 Baseline (HAM-A): D1: 15.4 (4.8) D2: 14.2 (4.2) D3: 15.5 (5.8) Mean HAM-D score at baseline: D1: 19.2 (5.0) D2: 18.4 (4.0) D3: 17.9 (4.3)	No statistically sig diffs between DUL and FLUOX in response (49% vs. 45%) and remission (43% vs. 30%) Change from baseline on HAM-D subscale of anxiety was DUL (-2.92) which showed a statistically better result in comparison to PBO (-1.95) *P* = 0.027 and FLUOX (-1.82) (*P* = 0.041) Change from baseline on HAM-A subscale of anxiety was DUL (-6.87) in comparison to PBO (-5.05) *P* = 0.077 and FLUOX (-6.97) (*P* = NR)	**Constipation:** D1: 5.7 D2: 11.4 D3: 15.2 Diarrhea: D1: 10.0 D2: 14.3 D3: 30.3 Dizziness: D1: 7.1 D2: 15.7 D3: 6.1 Headache: D1: 31.4 D2: 20.0 D3: 33.3 Insomnia: D1: 7.1 D2: 20.0 D3: 9.1 Nausea: D1: 12.9 D2: 12.9 D3: 18.2 Somnolence (fatigue): D1: 10.0 D2: 18.6 D3: 21.2 Sweating (increase): D1: 8.6 D2: 18.6 D3: 9.1	**Overall Attrition Rate:** 35% **ITT analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Gorwood et al., 2007[121] **Country and Setting** Mulitnational; multicenter **Funding** H. Lundbeck A/S **Quality Rating** Fair	**Research objective** To investigate efficacy and tolerability of ESC in prevention of relapse of MDD in older patients **Intervention Drugs, Doses, and Range** D1: ESC 10-20 mg/day (low-high dose) D2: PBO **Study design** RCT **n** 305 **Duration** 12 week open-label; 24 week double blind phase; 36 weeks total **Type of depression** Major depressive disorder	**Inclusion criteria** • Adults (age range): 65 years old or greater • Diagnosed with MDD according to DSM-IV • MADRS: 22 or more • Current major depressive episode for at least 4 weeks • MMSE total score of greater than 24 at screening visit **Exclusion criteria** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse • Clinically significant medical disease • Investigational drug use within last week before screening (includes all antidepressants except FLUOX was disallowed 5 weeks before screening) • ECT within last: month before screening • Suicidal tendencies (acute or other) • Rating of 5 or greater on item 10 of MADRS • Any neurologic disorder, neurogenerative disorder	**Groups similar at baseline** Yes **n =** D1: 152 D2: 153 **Mean age, years** D1: 73 D2: 72 **Sex, % female** D1: 78 D2: 79 **Race, % white** D1: 99.7 D2: 100 **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** NR **MADRS** At week 36 Remission(MADRS score ≤ 12), % D1: 88.2 D2: 59.5 Relapse (MADRS score ≤ 12), rate D2: 4.44 times greater than D1 (95% CI, 2.41-8.17) **Mean score at baseline (SD):** D1: 5.1 (4.8) D2: 5.1 (4.8) **Mean score at endpoint (SD):** D1: 5.96 D2: 11.72 **Mean score change (SD):** D1: 0.86 (NR) D2: 6.62 (NR) Used LOCF analysis. **CGI-S** **Mean score at baseline (SD):** D1: 1.60 (0.97) D2: 1.68 (0.99) **Mean score at endpoint (SD):** D1: 1.66 (NR) D2: 2.50 (NR) **Mean score change (SD):** D1: 0.06 (NR) D2: 0.82 (NR)	**Overall rate of attrition, %** 28.2 (including withdrawals due to lack of efficacy; 7.5% excluding these) **Attrition rate, %** D1: 15.1 D2: 41.2 **Withdrawals due to adverse events, %** D1: 2.6 D2: 4.6 **Attrition due to lack of efficacy, %** D1: 8.6 D2: 32.7 Overall withdrawal rate of 6.6% for ESC and 8.5% for PBO. **Overall adverse events, %:** D1: 35.3 D2: 34.9 **Diarrhea, %:** D1: 3.3 D2: 2.6 **Dizziness, %:** D1: 4.6 D2: 3.3 **Headache, %:** D1: 2.6 D2: 3.3 **Nausea, %:** D1: 0 D2: 0

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		• Personality disorder • Benzodiazepines, anxiolytics, hypnotics, and serotonin agonists any use within last week of screening • Patients who began or continued psychotherapy • Treatment-resistant depression patients • Previous lack of response to CIT or ESC Study started as an acute open-label study with n = 405. Those patients who were remitted (n = 305) were randomized in a double-blind trial. Remission was defined as MADRS score of 12 or less.		At end of of week 36 Response rates (CGI score less than or equal to 2), n (%) D1: 152 (90.8) D2: 153 (62.1) **CGI-I** Baseline score (SD) D1: 1.26 (0.69) D2: 1.34 (0.70) Change at endpoint D1: 0.24 D2: 1.01 **QOL scale** NR **Adherence** Non-compliance, % D1: 1.97 D2: 1.31 According to clinical judgement of investigators, 19 patients relapsed with 18 in PBO group and 1 in ESC group. These patients had a mean MADRS score of 17.4 (SD = 3.1) at week 36	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Gual et al, 2003[235] **Country and setting:** Spain, single-center, hospital **Funding:** Pfizer	**Research objective:** To evaluate efficacy and safety of SER at achieving stable maintenance, at amerliorating depressive symptoms, and at improving QOL in patients with alcohol dependence and current depressive symptoms **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 83 **Intervention:** D1: PBO D2: SER: 50-150 mg/d	**Inclusion criteria:** • Adults 18 to no upper limit • Diagnosed with MDD according to DSM-III or -IV • Alcohol dependence (according to DSM-IV and ICD10) • Dysthymia • MDD according to DSM-IV and ICD-10 • Abstinent from alcohol for at least 2 wks following detoxification **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 6 mos • Suicidal tendencies • ECT within 3 mos	**Mean age (yrs):** D1: 47.3 D2: 46.1 **Sex (% female):** D1: 46.1 D2: 47.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 12.8 (4.0) D2: 13.9 (5.6)	Treatment response (≥ 50% improvement in MADRS score), % D1: 39 D2: 44 No sig diff in SF-36 physical component score, mean (SD) SER = 48.6 (9.6); change from baseline ~ 2.5 points PBO = 47.0 (11.0); change from baseline ~ 4 points	**Diarrhea:** D1: 7.7 D2: 9.1 **Dizziness:** D1: 12.8 D2: 11.4 **Headache:** D1: 28.2 D2: 27.3 **Nausea:** D1: 7.7 D2: 9.1	**Overall attrition rate:** 45% **ITT Analysis** Yes **Quality rating:** Fair:

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Guelfi et al., 2001[45] **Country and setting:** France, Denmark, Belgium, Netherlands Multicenter (33) **Funding:** N.V. Organon, Oss, Netherlands	**Research objective:** To compare antidepressant efficacy and tolerability of MIR and VEN in treatment of hospitalized patients with DSM-IV diagnosis of severe depressive episode with melancholic features **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 157 **Intervention:** D1: MIR: 49.5 mg D2: VEN: 255.0 mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 25 • DSM-IV melancholic features **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use • ECT within last 3 mos • Suicidal tendencies • Current episode > 12 mos • > 2 previous episodes of major depression that did not respond to AD therapy	**Mean age (yrs):** D1: 45.9 D2: 44.5 **Sex (% female):** D1: 62.8 D2: 68.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 29.5 (3.0) D2: 29.2 (2.9)	Although not statistically sig, at all assessment times higher percentages of patients treated with MIR were classified as responders (≥ 50% reduction) on HAM-D (at endpoint, 62% vs. 52%) and MADRS (at endpoint: 64% vs. 58%). Likewise were percentages of remitters (HAM-D score ≤ 7; MADRS score ≤ 12) also higher in MIR group Q-LES-Q- estimate of treatment diff (MIR minus VEN) = -3.0, 95% CI, -11.0, 4.9 (*P* = 0.46) QLDS- estimate of treatment diff (MIR minus VEN) = 2.6, 95% CI, -2.1, 7.3 (*P* = 0.289)	**Overall adverse events:** D1: 74.4 D2: 65.8 **Changes in weight (increase):** D1: 10.3 D2: 5.1 **Constipation:** D1: 3.8 D2: 15.2 **Headache:** D1: 7.7 D2: 11.4 **Nausea:** D1: 6.4 D2: 10.1 **Somnolence (fatigue):** D1: 7.7 D2: 5.1 **Sweating (increase):** D1: 0 D2: 19.0	**Overall attrition rate:** 29.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Haffmans et al., 1996[46] **Country and setting:** The Netherlands Multicenter **Funding:** Lundbeck	**Research objective:** To evaluate and compare efficacy and tolerability of CIT and FLUV; to determine diff in incidence of gastrointestinal side-effects based on UKU side effects scale **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 217 **Intervention:** D1: CIT: 20-40 mg/d D2: FLUV: 100-200 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Reasonable knowledge of Dutch language **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Clinically sig medical disease • Treated with MAOIs or FLUOX within last 3 wks	**Mean age (yrs):** D1: 44.2 D2: 40.2 **Sex (% female):** D1: 58 D2: 60 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 24.7 D2: 24.5	No diff in mean HAM-D-17 scores after 6 wks Complete Response (HAM-D17) < 7: D1: 14% D2: 8% no sig diff Mean % reduction in score at wk 6: D1: 33% D2: 26% Responders (reduction in score from baseline > 50%): D1: 30.5%, D2: 28.4%	**Diarrhea:** higher incidence for FLUV: +13% (P = 0.026) **Nausea:** higher incidence for FLUV: +16% (P = 0.017)	**Overall attrition rate:** 23% **ITT analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Halikas, 1995[47] **Country and setting:** United States University **Funding:** Organon, Inc	**Research objective:** To assess clinical efficacy and safety of "Org 3770" (MIR) and TRA in treatment of elderly outpatients with moderate to severe depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** D1: MIR: 5-35 mg D2: TRA: 40-280 mg D3: PBO	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Age 55+ • Able to complete Zung Self Rating Depression Scale • Chloral hydrate (500 mg) at bedtime was permitted **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos of baseline • Suicidal tendencies • Rapid PBO responders (reduction of 20%+ in total HAM-D score)	**Mean age (yrs):** D1: 63 D2: 61 D3: 62 **Sex (% female):** D1: 42.9 D2: 60.4 D3: 59.2 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 24.6 D2: 24.6 D3: 23.5	On 21-item HAM-D, diffs between MIR and PBO were statistically sig at 2, 3, 4, and 6 wks. Using MADRS, statistically sig diffs were found between both active compounds and PBO at wks 2 and 3. MIR and TRA were associated with sig higher frequencies of dizziness and blurred vision as compared to PBO At wk 6, 51% of MIR and 41% of TRA treated patients were HAM-D responders (not statistically sig) Mean weight gain in MIR group = 1.3 kg Mean weight gain in Trazodone and placebo group are not reported	**Cardiovascular adverse events:** D1: 2% Tachycardia; 4% Palpitations D2: 12% Tachycardia; 12% Palpitations D3: 2% Tachycardia; 2% Palpitations **Constipation:** D1: 18 D2: 24 D3: 16 **Dizziness:** D1: 22 D2: 27 D3: 8 **Headache:** D1: 14 D2: 20 D3: 20 **Nausea:** D1: 10 D2: 14 D3: 14 **Somnolence (fatigue):** D1: 54 D2: 55 D3: 22 **Increased appetite:** D1: 24% D2: 6% D3: 4%	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Hernandez-Avila et al., 2004[236] **Country and setting:** United States Outpatient **Funding:** Bristol-Meyers Squibb NIH Grants	**Research objective:** To compare NEF or PBO in a sample of alcohol dependant subjects with current major depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 41 **Intervention:** D1: NEF: 200-600 mg/d (412.9) D2: PBO	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 17 • Alcoholism • Age 21 to 65 • Spoke english **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Suicidal tendencies • Drug dependance other than alcohol • Major mental illness other than depression or anxiety	**Mean age (yrs):** D1: 43.1 D2: 42.7 **Sex (% female):** D1: 52.4 D2: 50.0 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 16.33 (2.31) D2: 17.35 (1.98)	NEF group showed greater reductions in depression, effects did not reach statistical significance (P = 0.82); however, NEF subjects showed sig greater reduction in heavy drinking days (P = 0.01)	NR	**Overall attrition rate:** 31.7 **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Hewett et al., 2009[48] **Country and Setting** Multinational, multicenter (49) **Funding** NR **Quality rating:** Fair	**Research objective** The efficacy, safety and tolerability of BUP XR and VEN XR was assessed and compared with PBO in adult outpatients with MDD **Drugs, Doses, and Range** D1: BUP XL (150-450 mg 1 x daily): 150-300 mg/day D2: VEN XR (75-225 mg 1 x daily): 75-150 mg/day D3: PBO **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **N** 374 **Duration** 8 weeks **Type of depression** MDD **Intervention** D1: PBO D2: BUP XR D3: VEN XR	**Inclusion criteria:** • Adults (age range): 18-64 • Diagnosed with MDD according to DSM-III or -IV • HAM-D: 18 or more • CGIS: 4 or more • Concomitant condition (e.g., alcoholism, anxiety, stroke): stable for 3 months • Other: HAM-A, MEI, SDS **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse • Suicidal tendencies (acute or other) or homicide • TRD **Outcome measures** • MADRS • CGI-S and CGI-I • QOL: Q-Les-Q • Others: HAM-A, MEI, SDS	**Groups similar at baseline** Yes **n =** D1: 197 D2: 187 D3: 187 **Mean age, years** D1: 41.8 D2: 41.8 D3: 42.7 **Sex, % female** D1: 72 D2: 74 D3: 68 **Race, % white** D1: 96 D2: 96 D3: 97 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 64 D2: 76 D3: 73 **Comments:** NR **Outpatients/Inpatients** Outpatients **Baseline mean HAM-A > 25?** No	**HAM-D** NR **MADRS** n at baseline: D1: 197 D2: 187 D3: 182 No. of remitters: D1: 63 D2: 88 D3: 93 Mean score at endpoint (SD): D1: 16.9 D2: 14.4 D3: 12.9 Mean score change (SD): D1: -1.5 (0.10) D2: -1.9 (0.10) *P:* 0.003 D3: -2.1 (0.10) *P* < 0.001 D4: LS mean (SE) *P* vs. PBO **CGI-S** n at baseline: D1: 197 D2: 187 D3: 182 **CGI-I** NR **CGII** Yes Intervention: n at baseline: D1: 197 D2: 187 D3: 182 Number of patients achieving a score	**Overall adverse events, %:** D1: 48 D2: 47 D3: 50 **Dizziness, %:** D1: 7 D2: 4 D3: 5 **Headache, %:** D1: 10 D2: 12 D3: 13 **Insomnia, %:** D1: 2 D2: 5 D3: 4 **Nausea, %:** D1: 11 D2: 6 D3: 19 **Attrition** **Overall attrition, %:** 15% **Attrition rate, %:** D1: 15 D2: 18 D3: 12 **Withdrawals due to adverse events, %** D1: 5 D2: 4 D3: 3 **Withdrawals due to lack of efficacy, %** NR **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
			Mean age at baseline Less than 65 years **Mean HAM-D at baseline** Greater than 17 (moderate to severe)	1: 104 2: 127 3: 118 **QOL scale** Q-Les-Q-SF general activities and life satisfaction and contentment scores n at baseline: D1: 197 D2: 187 D3: 182 Mean score change (SD): D1: 16.1 and 0.9 D2: 21.9 *P* > 0.001 and 1.3 *P* < 0.001 D3: 21.1 *P:* 0.004 and 1.2 *P* < 0.001 D4: LS mean changes *P* vs. PBO **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Hewett et al. 2010[49] **Country and Setting** Multinational and Multicenter **Funding** GlaxoSmithKline **Quality rating:** Fair	**Research objective** The efficacy, safety, and tolerability of BUP and VEN and PBO for major depressive disorder (MDD) **Drugs, Doses, and Range** D1: flexible-dose BUP (150-300 mg/d) D2: flexible-dose VEN (75-150 mg/d) D3: PBO **Flexible dose** **Dosages equivalent** Yes **Study design** 8 week RCT **Duration** 8 weeks **Type of depression** • MDD	**Inclusion criteria:** • Between 18-64 years of age with a • Primary diagnosis of MDD • HAM-D 18 or more **Exclusion criteria:** • History of manic episodes • Past or current psychotic disorder or a current Axis II diagnosis that suggested non-responsiveness or non-compliance • Homicidal at any time in their lives or suicidal within past 6 months • Anorexia nervosa or bulimia within past year • Myocardial infarction within past year • Seizure disorder or brain injury • Blood pressure >150/95 mmHg • Unstable medical disorder • BUP or VEN within past six months • Experienced significant adverse response to either TRD	**Groups similar at baseline** **n =** D1: 203 D2: 198 D3: 187 **Mean age, years** D1: 45.6 D2: 44.1 D3: 44.5 **Sex, % female** D1: 63 D2: 68 D3: 67 **Race, % white** D1: 97 D2: 94 D3: 96	**MADRS** Mean score at baseline (SE): D1: 30.6 (0.34) D2: 30.1 (0.37) D3: 30.6 (0.38 Mean score at endpoint: D1: 15.9 D2: 13.1 D3: 17.4 Mean score change (SE): D1: -14.7 (0.74) *P* < 0.001 D2: -17.0 (0.76) *P* < 0.001 D3: -13.2 (0.78 Response at 8 weeks D1: D2: D3: HAM-A Base line D1: 23.0 (0.46) D2: 22.5 (0.49) D3: 23.6 (0.50) Change at endpoint D1: -10.1 (0.63) *P*= 0.248 D2: -11.7 (0.66) *P* = 0.002 D3: -8.8 (0.66) QLES-Q Base line D1: 31.7 (0.86) D2: 32.0 (0.91) D3: 30.7 (0.86) Change at endpoint D1: 21.5 (1.44) *P* = 0.113 D2: 24.0 (1.51) *P* = 0.006 D3:18.3 (1.53) CGI-S Base line D1: 5.0 (0.05)	**Attrition** **Overall attrition, %:** 22 **Attrition rate, %:** D1: 22 D2: 23 D3: 22 **Withdrawals due to adverse events, %** D1: 5 D2: 8 D3: NR **Withdrawals due to lack of efficacy, %** D1: 5 D2: NR D3: 6 **Adverse Events n (%)** Any adverse event D1: 108 (53 D2: 133 (67) D3: 133 (67) Headache D1: 30 (15) D2: 28 (14) D3:31 (17) Diarrhea D1: 8(4) D2: 10 (5) D3: 9 (5) Constipation D1: 7 (3) D2: 12 (6) D3:3 (2)

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
				D2: 5.0 (0.04) D3: 4.9 (0.05) Change at endpoint D1: -1.9 (0.11) D2: -2.2 (0.11) D3:-1.7 (0.11) Sheehan Disability Scale Base line D1: 20.7 (0.36) D2: 20.8 (0.36) D3: 21.0 (0.36) Change at endpoint D1: -7.8 (0.60) *P* = 0.013 D2: -9.2 (0.62) *P* < 0.001 D3: -5.8 (0.62) CSFQ Base line D1: 36.5 (0.70) D2: 36.6 (0.74) D3: 35.1 (0.70) Change at endpoint D1: 4.2 (0.63) *P* = 0.758 D2: 3.6 (0.68) *P*= 0.765 D3: 3.9 (0.67)	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Hicks et al., 2002[50] **Country and setting:** UK Outpatient clinic **Funding:** Bristol Myers Squibb	**Research objective:** Compare NEF and PAR for treatment of depression and sleep in patients with mod-severe MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 40 **Intervention:** D1: NEF: 400-600 mg/d D2: PAR: 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use within last 30 days • Shift workers • Current sleep disorders	**Mean age (yrs):** D1: 42.75 D2: 42.95 **Sex (% female):** D1: 60 D2: 55 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 22 D2: 22.5	Total sleep time D1: 396 D2: 388 *P* = 0.05 NEF sig increased objective sleep efficiency and total sleep time. PAR decreased sleep efficiency in early treatment and some disruption remained at wk 8	**Constipation:** D1: 5 D2: 15 **Dizziness:** D1: 25 D2: 15 **Headache:** D1: 50 D2: 50 **Sexual dysfunction :** D1: 0 D2: 20 **Somnolence (fatigue):** D1: 40 D2: 55 **Suicidality:** D1: 0 D2: 5 **Sweating (increase):** D1: 0 D2: 35	**Overall attrition rate:** 20% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Hochstrasser et al., 2001[253] **Country and setting:** Multinational, multicenter **Funding:** H. Lundbeck A/S	**Research objective:** To compare prophylactic efficacy of CIT vs. PBO in unipolar, recurrent depression following response to treatment with CIT in previous study periods **Duration of study:** 48-77 wks **Study design:** RCT **Overall study N:** (For period III): 269 **Intervention:** D1: CIT: 20, 40, or 60 mg (3 groups + PBO) D2: PBO	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 22 • Two or more previous depressive episodes (one within last 5 yrs) **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 days to 8 wks • Suicidial tendencies • MADRS item 10 ≥ 5 • Current depressive episode longer than 6 mos • Family history of bipolar disorder	**Mean age (yrs):** D1: 43.8 (9.7) D2: 42.4 (11.5) **Sex (% female):** D1: 67.4 D2: 75 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Time to recurrence was longer in patients taking CIT than in patients taking PBO CIT 24/132 (18.2%); PBO 59/132 (44.7%) ($P < 0.001$). Prophylactic treatment well tolerated. Risk ratio related to recurrence of depression (CIT / PBO) estimated at 0.321 (95% CI, 0.199-0.516). Diff in time to recurrence between CIT and PBO groups statistically sig at all dose levels (log rank test: 20 mg, $P = 0.0043$; 40 mg, $P = 0.0008$; 60 mg, $P = 0.0157$). In Period III of study, AE profile of CIT was comparable to PBO group	**Cardiovascular adverse events:** D1: 5.3 D2: 2.9 **Diarrhea:** D1: 3.8 D2: 2.2 **Dizziness:** D1: 8.3 D2: 16.1 **Headache:** D1: 16.7 D2: 15.3 **Insomnia:** D1: 15.9 D2: 14.6 **Nausea:** D1: 6.1 D2: 10.2 **Somnolence (fatigue):** D1: 8.3 D2: 7.3 **Sweating (increase):** D1: 6.1 D2: 8.8	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Hong et al., 2003[51] **Country and setting:** Taiwan Multicenter **Funding:** NV Organon, Oss, Netherlands	**Research objective:** To compare efficacy and tolerability of MIR and FLUOX treatment in sample population of Chinese patients with moderate-to-severe depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 133 **Intervention:** D1: MIR: 15 mg-45 mg/d D2: FLUOX: 20 mg-40 mg/d	**Inclusion criteria:** • Adults 18 to 75 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 15 • Current episode between 1 wk and 1 yr **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • History of seizures • Epilepsy	**Mean age (yrs):** D1: 47.2 D2: 47.2 **Sex (% female):** D1: 62 D2: 64 **Race (% white):** D1: 0 D2: 0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 24.6 D2: 23.1	No sig diffs in HAM-D responders (MIR: 58% vs. FLUOX: 51%) At day 42, diff in HAM-D remitters (MIR: 35% vs. FLUOX: 27%, *P* = NR) MIR had more remitters and responders at all time points; however, no statistical significance in diffs was reached Based on LOCF approach, approximately 50% of subjects in both treatment groups were CGI responders by endpoint Weight increase ≥ 7% in 8 MIR patients Weight decrease ≥ 7% in 2 MIR patients and 2 FLUOX patients Mean body weight increase MIR + 1.84 kg FLUOX -0.54 kg *P* = 0.0001	**Overall adverse events:** D1: 71.2 D2: 57.6 **Changes in weight (decrease):** D2: 3 **Changes in weight (increase):** D1: 13.6 **Constipation:** D1: 15.2 D2: 9.1 **Dizziness:** D1: 19.7 D2: 13.6 **Nausea:** D2: 12.1 **Somnolence (fatigue):** D1: 12.1	**Overall attrition rate:** 39.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Honig et al., 2007[237] **Country and Setting** Netherlands, academic hospital and 7 general hospitals **Funding** Unrestricted grants from Organon (Netherlands) and Lundbeck (Denmark) Grant from Netherlands Heart Foundation **Quality Rating** Fair	**Research objective** To examine antidepressant efficacy of a dual-acting antidepressant (MIR) in patients with post-myocardial infarction (MI) depressive disorder **Intervention Drugs, Doses, and Range** D1: MIR 30-45 mg 1 x daily D2: PBO **Study design** RCT **n** 91 **Duration** 24 weeks (8 week acute phase; 16 week continuation) **Type of depression** Major depressive disorder	**Inclusion criteria** • Adults • Diagnosed with MDD according to DSM-III or -IV • Concomitant condition (e.g., alcoholism, anxiety, stroke) • 3-12 months post acute MI • Free of other life-threatening medical conditions **Exclusion criteria** • Clinically significant medical disease • Myocardial infarction less than 3 months ago or more than 1 year ago • Suicidal tendencies (acute or other) • Current antidepressant txt	**Groups similar at baseline** Yes **n =** D1: 47 D2: 44 **Intervention** D1: MIR D2: PBO **Mean age, years** D1: 56.6 D2: 57.9 **Sex, % female** D1: 12.8 D2: 18.2 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** **Responders, n (%):** D1: 23 (48.9) D2: 17 (38.6) *P* = 0.22 **Remitters, n (%):** D1: 20 (42.6) D2: 15 (34.1) *P* = 0.27 **Mean score at baseline (SD):** D1: 18.66 (5.2) D2: 16.81 (3.6) **Mean score at endpoint (SD):** D1: 10.66 D2: 11.25 **Mean score change (SES):** D1: 8.0 (1.21) D2: 5.56 (0.78) *P* = 0.36 **MADRS** NR **CGI-S** **Mean score at baseline (SD):** D1: 4.0 D2: 3.79 **Mean score at endpoint (SD):** D1: 2.50 D2: 2.91 **Mean score change (SES):**	**Overall rate of attrition, %** At 8 weeks (acute): 14 At 24 weeks: 45 **Attrition rate, %** At 8 weeks D1: 16.8 D2: 21.3 At 24 weeks D1: 59.1 D2: 53.2 **Withdrawals due to adverse events, %** NR **Attrition due to lack of efficacy, %** NR **Dizziness, %:** D1: 5 D2: 8 *P* = 0.31 **Headache, events:** D1: 7 D2: 2 *P* = 0.61 **Somnolence (fatigue), events:** Fatigue D1: 21 D2: 9 *P* = 0.02

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
				D1: 1.5 (1.80) D2: 0.88 (1.09) *P* = 0.05 **CGI-I** **Mean score change (SES):** D1: 1.03 (1.34) D2: 0.42 (0.47) *P* = 0.074 **BDI** **Mean score at baseline (SD):** D1: 14.61 D2: 13.44 **Mean score at endpoint (SD):** D1: 9.79 D2: 11.47 **Mean score change (SES):** D1: 4.82 (0.64) D2: 1.97 (0.36) *P* = 0.07 **QOL scale** NR **Adherence** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Jefferson et al., 2006[166] **Country and Setting** US, multicenter **Funding** GSK **Quality rating:** Fair	**Research objective** Assess efficacy of Buproprion XL in treatment of MDD with prominent symptoms of decreased energy, pleasure, and interest **Drugs, Doses, and Range** D1: BUP XL (150-450 mg 1 x daily): 300-450mg/day (med-high) D2: PBO **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **Duration** 8 weeks **Type of depression** MDD **Intervention** D1: BUP XL D2: PBO	**Inclusion criteria:** • Adults (age range): 19-69 • Diagnosed with MDD according to DSM-IV, psychiatric interview, MINI • Concomitant condition (e.g., alcoholism, anxiety, stroke): minimum score of 1 on 4 of 5-item subset of energy, pleasure and interest • Other: symptoms of depression:>12 wks and < 2 years; min score of 25 on IDS-IVR-30 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications: w/in 2 wks prior to screening (4 wks for FLUOX) • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): bipolar I or II, or schizo; panic disorders, OCD, PTSD, acute stress disorder w/in previous 12 mos. • Illicit drug and alcohol abuse: w/in past 12 mos. • Other: history of seizures or brain injury, eating disorders; IDS-	**Groups similar at baseline** Yes **n =** D1: 135 (ITT = 133) D2: 139 (ITT = 137) **Mean age, years** D1: 40.0 D2: 39.8 **Sex, % female** D1: 66 D2: 69 **Race, % white** D1: 77 D2: 78 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** NR **MADRS** NR **CGI-S** n at baseline: NR **CGI-I** D1: BUP D2: PBO **CGII** Yes n at baseline: D1: 135 (ITT = 133) D2: 139 (ITT = 137) Mean score at endpoint (SD): D1: graph only D2: graphy only Number of patients achieving a score NR • CGI-I responders (def as score of "much" or "very much" improved) at 8 wks. BUP: 53% (N: 70) v. PBO 38% (N: 52). • *P*'s for BUP vs. PBO comparison: Wk1, 2, 6, & 8: $P \leq 0.01$; Wk4: $P \leq 0.05$ **QOL scale** IDS-IVR-30 Intervention: D1: BUP D2: PBO	**Overall adverse events, %:** Patients reporting 1+ D1: 79 D2: 61 **Weight gain, %:** Gain ≥ 7% D1: 0 D2: 1.4 **Weight loss, %:** Loss ≥ 7% D1: 3.7 D2: 2.2 **Dizziness, %:** D1: 10 D2: 2 **Insomnia, %:** D1: 7 D2: 1 **Nausea, %:** D1: 10 D2: 5 **Attrition** **Overall attrition, %:** 22.3 **Attrition rate, %:** D1: 24 D2: 21 **Withdrawals due to adverse events, %** D1: 9 D2: 2 **Withdrawals due to lack of efficacy, %** D1: 1 D2: 4 **Comments**

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		IVR-30 score ± > 25% between screening and baseline measures **Outcome measures** • CGI-I • Quality of life scales: IDS-C-30, IDS-IVR-30		n at baseline: D1: 135 (ITT = 133) D2: 139 (ITT = 137) Mean score at baseline (SEM): D1: 45.9 (0.8) D2: 46.0 (0.8) Mean score at endpoint (SD): D1: 24.6 D2: 28.4 Mean score change (SEM): D1: -21.3 (1.4) (LOCF) D2: -17.6 (1.4) (LOCF) • *P* < .05, mean change from baseline for BUP XL • Improvement in depressive symptoms w/ BUP XL: energy, pleasure, interest: *P:* .007; insomnia: *P:* .023 **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** • It is important to note mean daily doses of treatment drugs in two studies. In study 1, mean daily dose of BUP XL was 323 mg (SD: 59.4), and that of	NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				ESC was 13 mg (SD: 2.6). For study 2, mean daily dose of BUP XL was 309 mg (SD: 58.3) and 13 mg (SD: 3.2) for ESC. The HAD scale, mean change (SE) results were also reported and were as follows: • BUP XL: Pooled: -10.5 (0.5), Study 1: -11.0 (0.7), Study 2: -9.9 (0.8); • ESC: Pooled: -11.1 (0.5), Study 1: -11.5 (0.7), Study 2: -10.8 (0.8); • PBO Pooled: -8.1 (0.5), Study 1: -8.6 (0.7), Study 2: -7.5 (0.8). The p-values were also reported for HAD scale and were as follows: • BUP XL vs. PBO: Pooled, *P:* .001, Study 1, *P:* .015, and Study 2, *P:* .026; • ESC vs. PBO: Pooled, *P* < .001, Study 1, *P:* .003, Study 2, *P:* .002; • BUP XL vs. ESC Pooled, *P:* .343, Study 1: .570, Study 2: .394. • Both BUP XL and ESC were more effective than PBO with respect to mean change from randomization in HAD	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				total score at week 8 in individual studies. Results of CSFQ: Total Scores are as follows: BUP XL: Score at Randomization, Mean (SE) • Study 1 (N: 133): 50.5 (0.7) • Study 2 (N: 129): 53.8 (0.6) Change at Week 8, Least Square Mean (SE) • Study 1: 2.7 (0.7) and • Study 2: 2.1 (0.7); ESC: Scores at Randomization, Mean (SE) • Study 1 (N: 130) = 52.1 (0.7) • Study 2 (N: 133): 53.4 (0.7) Change at Week 8, Least Square Mean (SE) • Study 1: 0.2 (0.7) and • Study 2: -1.1 (0.7); 3) PBO: Score at Randomization Mean (SE) • Study 1 (N: 127): 51.8 (0.7) • Study 2 (N: 125): 52.9 (0.6) Change at Week 8, Least Square Mean (SE) • Study 1: 2.4 (0.7) • Study 2: 1.3 (0.7). At treatment week 8, ESC was associated with statistically significantly	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				worse sexual functioning than BUP XL with respect to mean changes in total score and subscale scores for pleasure and orgasm in study 1; in total score and subscale scores for desire/frequency, desire/interest, arousal, and orgasm in study 2; and in total score and subscale scores for pleasure, desire/frequency, desire/interest, arousal and orgasm in pooled dataset. CSFQ subscales (pleasure, desire/frequency, desire/interest, arousal, and orgasm) were also reported.	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Jick et al., 1992[195] **Country and setting:** United Kingdom General practice **Funding:** Burroughs Wellcome	**Research objective:** Evaluate whether FLUOX causes important increased risk of suicidal behavior by reiviewing previously gathered data from practitioners **Duration of study:** Jan 1988 to April 1990 **Study design:** Database review **Overall study N:** 8,730 **Intervention:** Mianserin and Lofepramine D1: FLUOX D2: TRA	**Inclusion criteria:** • Age 15 to 74 • Patients who received a px for FLUOX, lofepramine, mianserin, or TRA. From this list, all who had diagnosis of aggressive, abusive, suicidal behavior **Exclusion criteria:** NR	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	FLUOX does not directly cause suicidal behavior at a substantially higher frequency than do lofepramine, mianserin, and TRA	N/A	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Jick et al., 1995[196] **Country and setting:** UK General practices in UK using VAMP database **Funding:** Various pharmaceutical companies (Berlex, Boots, Burroughs Wellcome, Ciba-Geigy, Hoeschst, Hoffman-LaRoche, RW Johnson, Pfizer, Proctor and Gamble, Sanofi Winthrop)	**Research objective:** To estimate rate and means of suicide among people taking 10 commonly prescribed antidepressants **Duration of study:** Patient records from Jan 1988 to Feb 1993 **Study design:** Cohort study with nested case-control analysis **Overall study N:** 172,598 **Intervention:** FLUOX TRA Dothiepin Amitriptyline Clomipramine Imipramine Flupenthixol Lofepramine Mianserin Doxepin	**Inclusion criteria:** • Received a prescription for 1 or more antidepressants in VAMP database (General Practice Research Database) • All patients who committed suicide identified in cohort evaluation were included as cases **Exclusion criteria:** NR	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	143 sucides within 6 mos of using antidepressants Rates of suicide higher in men than women (RR, 2.8, 95% CI, 1.9 - 4.0), people with history of feeling suicidal (RR, 19.2, 95% CI, 9.5 - 38.7), and people who had taken several different antidepressants (RR, 2.8, 95% CI, 1.8 - 4.3) From cohort analysis: overall rate of suicide for all antidepressant users: 8.5/10,000 person yrs (95% CI, 7.2 - 10.0); FLUOX: 19.0/10,000, adjusted RR, 2.1 (95% CI, 1.1-4.1); TRA: 14.8/10,000, adjusted RR, 1.7 (95% CI, 0.6 - 4.6), both relative to dothiepin Compared with dothiepin, only FLUOX and mianserin yielded RRs that were sig raised	N/A	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Jick et al., 2004[197] **Country and setting:** UK General practices using GPRD **Funding:** Boston Collaborative Drug Surveillance Program	**Research objective:** To estimate risk ratios of nonfatal suicidal behavior in patients starting treatment with 1 of 3 antidepressant drugs vs. patients starting treatment with dothiepin **Duration of study:** 1993-1999 **Study design:** Matched case-control **Overall study N:** 159,810 **Intervention:** D1: Case D2: Controls	**Inclusion criteria:** • Using anti-depressants **Exclusion criteria:** NR	**Mean age (yrs):** NR **Sex (% female):** D1: 65.4 D2: 66.8 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	**Suicidal behavior risk:** D1: RR, 1.16 (95% CI, 0.90-1.50) D2 vs D3: RR, 1.29 (95% CI, 0.97-1.70) Suicide risk increased in first mo after starting antidepressants, especially during first 9 days (RR, 4.07; 95% CI, 2.89-5.74)	NR	**Overall attrition rate:** N/A **ITT Analysis** NR **Quality rating:** N/A

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Johnston et al., 1991[198] **Country and setting:** United States Multicenter (102 sites) **Funding:** Burroughs Wellcome	**Research objective:** To determine incidence of seizures associated with use of BUP **Duration of study:** 8 wk treatment stage with unlimited humanitarian continuation phase **Study design:** Uncontrolled, open-label trail **Overall study N:** 3,341 **Intervention:** D1: BUP: 300-450 mg/d	**Inclusion criteria:** • Adults 18 and over • Diagnosis of depression for which antidepressant treatment was clinically appropiate **Exclusion criteria:** • Pregnant • Lactating • Investigational drug use within last 30 days • Previous diagnosis of bulimia or anorexia nervosa • Known predisposition of seizures	**Mean age (yrs):** Overall: 43.5 **Sex (% female):** Overall: 59.4 **Race (% white):** Overall: 96 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Observed seizure rate was 0.24% for treatment phase and 0.40% for entire study. 8-wk survival analysis performed on patients with a dosing regimen of 300 to 450 mg/d yielded a cumulative rate of 0.36% Rate of seizure for BUP within range of other antidepressants	NR	**Overall attrition rate:** 39% **ITT Analysis** N/A **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Judd et al., 2004[52] **Country and setting:** United States Multicenter **Funding:** Eli Lilly and Co NIMH grants; Roher fund of University of California, San Diego	**Research objective:** To examine efficacy of FLUOX in treatment of outpatients with minor depressive disorder **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 162 **Intervention:** D1: FLUOX: 10-20 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 or older • Diagnosed with minor depression according to NIMH Health Diagnostic Interview Schedule • Healthy with normal physical exam and labs **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Clinically sig medical disease • Investigational drug use with no response or adverse reaction • ECT • Suicidal tendencies • MDD • Dysthmymia • Seizure disorder • Severe allergies • Loss of loved one within past yr	**Mean age (yrs):** Overall: 43.5 **Sex (% female):** Overall: 59.3 **Race (% white):** Overall: 90.1 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 11.7 (3.9) D2: 11.0 (3.9)	Sig greater improvement on 30-item IDS for FLUOX than for PBO (-1.19 vs. -0.61; *P* < 0.02) Statistically greater rate of improvement in FLUOX groups than PBO in 30-item IDS scores (z = 2.40, *P* < 0.02), 17-item HAM-D (z = 2.06, *P* = 0.04), and 21-item HAM-D (z = 2.19, *P* < 0.03). GAF score sig greater in FLUOX group (z = 2.10, *P* < 0.04). At endpoint, 40.5% (FLUOX) vs. 24.1%(PBO) patients were rated as "normal/not at all depressed" on CGI-S (chi sq = 6.63, df = 1, *P* = 0.01)	**Insomnia:** D1: 24.7	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Judge et al., 2002[199] **Country and setting:** Multinational; outpatient **Funding:** Eli Lillly	**Research objective:** To compare mean number of interruption-emergent events during 3 to 5 day PBO interruption period in remitted, depressed patients on maintenance therapy with FLUOX or PAR **Duration of study:** PBO interruption period: 3-5 days, but unclear total duration of observation **Study design:** Open-label, parallel-group study with double-blind, crossover, PBO interruption phase **Overall study N:** 150 **Intervention:** D1: FLUOX: 20-60 mg/d D2: PAR: 20-50 mg/d	**Inclusion criteria:** • Adults 18 and older • Unipolar depression on effective maintenance with FLUOX or PAR • Current maintenance lasting between 4 and 24 mos • MADRS ≤ 12 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Seizure within last yr	**Mean age (yrs):** D1: 41.5 D2: 44.7 **Sex (% female):** D1: 80 D2: 73.3 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	FLUOX group experienced fewer interruption-emergent symptoms (DESS mean diff in change: -2.4 with 95% CI, -3.9 to -1.0; *P* = 0.001) than PAR group Symptoms occuring sig more in PAR patients were: panic, depersonalization, shaking, muscle aches, dyspnoe, stomach cramps, agitation, sleeping problems, dizziness, chills, vomiting, nausea or diarrhea, parasthesia	**Diarrhea:** D2: 10+ **Dizziness:** D2: 33+ **Headache:** D1: 14 D2: 10+ **Insomnia:** D2: 20+ **Nausea:** D2: 20+ **Somnolence (fatigue):** D1: 17 D2: 20+ **Suicidality:** **Sweating (increase):** D2: 20+	**Overall attrition rate:** 6% **ITT Analysis** N/A: Cannot tell if ITT was used; however, attrition was so low that ITT would have made little diff in results **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Kamijima et al., 2006[123] **Country and Setting** Japan; multicenter **Funding** Pfizer, Inc. **Quality Rating** Fair	**Research objective** To evaluate efficacy and tolderability of SER in treating Japanese patients with major depressive disorder using a randomized withdrawal design in patients who had received a response during 8 weeks of open-label SER treatment **Drugs, Doses, and Range** D1: SER 25-100 mg 1 x daily (low to medium dose) D2: PBO Overall: Continuation phase **Study design** RCT **n** 235 **Duration** Randomized evaluation is 16 week continuation phase **Type of depression** MDD	**Inclusion criteria** • Adults (age range): 20-64 years old • Diagnosed with MDD according to DSM-III or -IV: primary MDD determined by DSM-IV; recurrent determined by clinical interview and DSM-IV checklist • HAM-D: 18 or more for acute phase without decrease of 25% or more during 1 week screening period; 13 or less to be included in double-blind phase • CGIS: CGI-I score of 3 or less to be included in double-blind phase • Duration of current depression episode 4 or more weeks • Patients included in double blind phase if met responder criteria (see HAM-D and CGI-I scores above) **Exclusion criteria** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Patients who failed to discontinue or taper off these drugs before receiving study drug • Additional mental illnesses or organic mental disorder not	**Groups similar at baseline** Yes **n =** D1: 117 D2: 118 Overall: 235 **Mean age, years** D1: 40.8 D2: 38.4 Overall: 40 **Sex, % female** D1: 63.2 D2: 62.7 Overall: 63 **Race, % white** D1: 0 D2: 0 Overall: 0 **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** **Mean score at baseline (SD):** D1: 8.3 (3.4) D2: 8.1 (3.3) **Mean score at endpoint (SD):** D1: 6.3 (6.2) D2: 9.7 (7.2) **Mean score change (SD):** D1: -2.0 (NR) D2: 1.6 (NR) Baseline scores reported at beginning at double-blind phase. Compared to PBO group, SER group had a significantly greater change from beginning of double-blind phase to end of double blind phase ($P < 0.001$). **MADRS** NR **CGI-S** **Mean score at endpoint (SD):** NR **Mean score at endpoint (SD):** NR **Number of patients achieving a score of** NR • CGI-I responder rate (proportion of 'much improved' or better compared to open-label baseline) 85.6% in SER	**Overall rate of attrition, %** 26.8 **Attrition rate, %** D1: 18.8 D2: 34.7 **Withdrawals due to adverse events, %** D1: 3.4 D2: 5.9 **Attrition due to lack of efficacy, %** D1: 8.5 D2: 17.8 Attrition due to lack of efficacy was considered as relapse, primary outcome of study **Overall adverse events, %:** D1: 29.9 D2: 31.4 **Cardiovascular, %:** D1: NR D2: 2.5 (decreased blood pressure) **Diarrhea, %:** D1: 2.6 D2: NR **Dizziness, %:** D1: 2.6 D2: 2.5 **Headache, %:** D1: 3.4 D2: NR **Nausea, %:** D1: NR D2: 2.5

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		related to depression (e.g., schizophrenia, bipolar): bipolar disorder, schizophrenia; paranoid disorder; other psychotic disorders; dementia; obsessive-compulsive disorder; post-traumatic stress disorder; panic disorder; dysthymic disorder; social anxiety or generalized anxiety disorder; Axis II personality disorders • Illicit drug and alcohol abuse: within past 6 months • Clinically significant medical disease: • Investigational drug use within last: 4 weeks • ECT within last: 6 months • Suicidal tendencies (acute or other) • Non-responders to adequate trials of antidepressants during current depressive episode • Patients who had HAM-D score of 10 or less from week 2-week 8 during acute phase • Doses were titrated during acute open-label phase. HAM-D score at baseline of open-label phase was 22.2 (3.6)-reported in Q33. • Patients randomized to SER arm continued on		group vs. 67.8% in PBO gropu (P = 0.004). Among subgroup of patients with 'minimally improved' or 'much improved' at start of double-blind phase, percentage with 'very much improved' at end was 45.7% (37/81) in SER arm vs. 27.6% (24/87) in PBO group (P = 0.023) **CGI** NR **QOL scale** Q-LES-Q **Mean score at baseline (SD):** D1: 62.9 (11.2) D2: 64.2 (10.4) **Mean score at endpoint (SD):** D1: 67.4 (15.3) D2: 61.3 (12.6) **Mean score change (SD):** D1: 4.5 (NR) D2: -2.9 (NR) Difference in change from baseline to end of double-blind phase was significant between SER and PBO groups (P < 0.001). At week 24 (completer) sample, then mean score was 70.7 (13.9) for SER and 64.4 (11.3) for PBO (P <0.001) **Adherence**	**Somnolence (fatigue), %:** D1: 3.4 D2: NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		same doses during double-blind continuation phase.		NR **Relapse** • Relapse defined as either: 1) HAM-D score of 18 or greater and a CGI-I of 'no change' or worse, at 2 consecutive visits; or 2) being unable to continue treatment because of insufficient efficacy. • Relapse rate (SER vs. PBO): 8.5% vs. 19.5% (*P* = 0.016). 2 out of 10 patients that relapsed in SER arm met HAM-D/CGI-I criterion. • 5 out of 23 patients that relapsed in PBO arm met HAM-D/CGI-I criterion.	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kasper et al., 2005[54] **Country and setting:** Mulitnational Multicenter **Funding:** ACRAF SpA	**Research objective:** To evaluate efficacy and safety of TRA prolonged release vs. PAR in patients with major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 108 **Intervention:** D1: TRA: (prolonged release) 150-450 mg/d D2: PAR: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • HAM-D score of 18-24 • MADRS < 30 • Depression symptoms at least 1 mo **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT • MDD refractory to treatment • Psychosis or melancholia • High risk of suicide	**Mean age (yrs):** D1: 43.5 D2: 44.3 **Sex (% female):** D1: 58 D2: 68 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline (SE):** D1: 21.0 (0.21) D2: 20.9 (0.21)	No statistically sig diff in responder rates (95% CI): 87.3% (78.5 - 96.1) in TRA group; 90.6% (82.7 - 98.4) in PAR group. (No *P* value reported) No statistically sig diff in remission rates (95% CI): 69.1% (56.9 - 81.3) in TRA group; 67.9% (55.4 - 80.5) in PAR group. (No *P* value reported)	**Overall adverse events:** D1: 34.5 D2: 26.4 **Diarrhea:** D1: 0 D2: 1.9 **Dizziness:** D1: 3.6 D2: 1.9 **Headache:** D1: 7.3 D2: 0 **Insomnia:** D1: 5.5 D2: 5.7 **Nausea:** D1: 1.8 D2: 11.3 **Somnolence (fatigue):** D1: 1.8 D2: 1.9 **Sweating (increase):** D1: 0 D2: 1.9	**Overall attrition rate:** 4.6% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kasper et al., 2005[53] **Country and setting:** Multinational (11 countries) Multicenter (76 general practice and specialist settings) **Funding:** Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmith-Kline, Organon, Servier	**Research objective:** To compare efficacy and tolerability of ESC in a fixed dose of 10 mg with PBO in elderly patients with MDD, using FLUOX at fixed dose of 20 mg as a reference drug **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 518 **Intervention:** D1: PBO D2: ESC: 10 mg D3: FLUOX: 20 mg	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Age 65 or more • MADRS of 22-40 • MMSE 22+ **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use within last 30 days • Current ECT • MADRS score $\geq$ 5 on Item 10 (suicidal thoughts) • Current behavior therapy or psychotherapy • History of severe drug allergy or hypersensitivity • Lack of response to more than one antidepressant treatment (including CIT) during present depressive episode	**Mean age (yrs):** D1: 75 D2: 75 D3: 75 **Sex (% female):** D1: 76 D2: 75 D3: 77 **Race (% white):** D1: 100 D2: 99 D3: 100 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Responders (≥ 50% decrease from baseline in MADRS total score), % D1: 47 D2: 46 D3: 37 P = NS LOCF analysis Remitters (MADRS total score ≤ 12) , % D1: 42 D2: 40 D3: 30 D1 vs D2: P=NS D1 vs D3: *P* < 0.05 LOCF analysis	**Overall AEs:** D1: 2.8 D2: 9.8 D3: 12.2 **Changes in weight (decrease):** D1: 1.1 D2: 1.2 D3: 2.4 **Constipation:** D1: 4.4 D2: 1.2 D3: 4.3 **Diarrhea:** D1: 5.0 D2: 1.7 D3: 4.9 **Dizziness:** D1: 0.6 D2: 2.9 D3: 3.7 **Headache:** D1: 8.3 D2: 5.2 D3: 4.3 **Insomnia:** D1: 2.2 D2: 2.3 D3: 1.8 **Nausea:** D1: 1.7 D2: 6.9 D3: 7.3 **Somnolence (fatigue):** D1: 0.6 D2: 2.3 D3: 0	**Overall attrition rate:** 17.6% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kavoussi et al., 1997[55] Rush et al., 2001[82] Segraves et al., 2000[219] **Country and setting:** United States Multicenter **Funding:** Glaxo Wellcome, Inc	**Research objective:** To compare efficacy and safety of BUP SR and SER, and to determine whether baseline anxiety predicts antidepressant response **Duration of study:** 16 wks **Study design:** RCT **Overall study N:** 248 **Intervention:** D1: BUP: 100-300 mg/d (mean 238 mg/d) D2: SER: 50-200 mg/d (mean 114 mg/d)	**Inclusion criteria:** • Adults 18 to 76 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Stable relationship with normal sexual functioning **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Suicidal tendencies • History/current diagnosis of eating disorders • Known predisposition to seizures	**Mean age (yrs):** D1: 39 D2: 40 **Sex (% female):** D1: 48 D2: 48 **Race (% white):** D1: 93 D2: 94 **Baseline (HAM-A):** D1: 16.6 (5.2) D2: 16.6 (5.2) **Mean HAM-D score at baseline:** D1: 24.8 (4.6) D2: 24.8 (4.6)	HAM-D-21: similar changes in scores over study (both groups showed 50% improvement in scores), no diffs at any point in study CGI-S and CGI-I scores improved steadily throughout treatment phase Response: D1:66% D2: 74% *P* = NR (ns) Remission: D1: 55% D2: 63% *P* = NR (ns)	**Diarrhea:** D1: 3 D2: 22 **Dizziness:** D1: 8 D2: 5 **Headache:** D1: 34 D2: 32 **Insomnia:** D1: 18 D2: 19 **Nausea:** D1: 10 D2: 30 **Somnolence (fatigue):** D1: 2 D2: 13 **Sweating (increase):** D1: 2 D2: 10 **Sexual dysfunction (orgasm in men):** D1: 10 D2: 61 **Sexual dysfunction (orgasm in women):** D1: 7 D2: 41	**Overall attrition rate:** 31.5% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Keller et al., 1998[125] Kocsis et al., 2002[128] **Country and setting:** United States (10) outpatient psychiatric clinics and (2) academic centers **Funding:** Pfizer	**Research objective:** To determine if maintenance therapy with SER can effectively prevent recurrence of depression in patients with chronic major depression or double depression **Duration of study:** 76 wks **Study design:** RCT **Overall study N:** 161 **Intervention:** D1: SER: 50-200 mg/d D2: PBO	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • MDD with or without dysthymic disorder • Chronic depression defined as depression of at least 2 yrs duration • 3 phase study **Exclusion criteria:** NR	**Mean age (yrs):** D1: 40.8 D2: 42.4 **Sex (% female):** D1: 62 D2: 69 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 5.5 (4.2) D2: 6.3 (3.7)	Recurrence %: By strict protocol criteria: D1: 6 D2: 23 (P = 0.002) By consensus agreement: D1: 26 D2: 50 (P = 0.001) Showed first symptoms of recurrence by consensus agreement: D1: 34 D2: 60 (P = 0.001) Patients receiving PBO were 2.18 (1.27, 3.74) times as likely to experience reemergence of depression and 4.07 (1.51, 10.95) times as likely to experience depression recurrence as patients taking SER during maintenance therapy, adjusted for pooled study site, type of depression, and randomization strata (P < 0.02 for both outcomes)	**Overall adverse events:** D1: 80.5 **Changes in weight (increase):** D1: 15.6 **Diarrhea:** D1: 15.6 **Dizziness:** D1: 11.7 **Headache:** D1: 28.6 **Insomnia:** D1: 19.5 **Nausea:** D1: 13 **Sexual dysfunctional (male ejaculation):** D1: 0 **Somnolence (fatigue):** D1: 11.7 **Sweating (increase):** D1: 15.6	**Overall attrition rate:** 63.4% **ITT Analysis** No, time to event of full population **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Kennedy et al., 2000[201] **Country and setting:** Canada Depression clinic **Funding:** Centre for Addiction and Mental Health Foundation	**Research objective:** To evaluate disturbances in sexual drive/desire and arousal/orgasm in depressed patients who completed 8 wks of study **Duration of study:** 14 wks (primary endpoint is 8 wks) **Study design:** Prospective cohort study **Overall study N:** 174 **Intervention:** D1: SER: 50-200 mg/d D2: PAR: 10-80 mg/d D3: VEN: 37.5-375 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Sexual activity within past mo • Major depression with or without other secondary non-psychotic axis I disorders • No antidepressants within 2 wks (or 5 wks for FLUOX) **Exclusion criteria:** • Clinically sig medical disease	**Mean age (yrs):** NR **Sex (% female):** D1: 84.6 D2: 33.3 D3: 61.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Men reported sig greater drug-induced impairment of drive/desire compared with women (mean [SD] = 2.26 (2.02) vs. 1.43(2.12), t = 6.23, df = 107, $P < 0.05$) No signficant diffs between antidepressants among men reporting antidepressant-induced sexual dysfunction On arousal/orgasm scale women showed lower rates of dysfunction on VEN compared to PAR and SER, however, only 1 item of 3 arousal/ orgasm items ("difficulty achieving orgasm") reached statistical significance (chi-sq = 8.51, df = 1, $P < 0.004$). for VEN vs. PAR, VEN introduced sig less difficulty with having an orgasm than PAR (chi-sq = 2.98, df = 1, $P < 0.08$)	NR	**Overall attrition rate:** 38.5% **ITT Analysis** N/A **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Kennedy, 2006[56] **Country and Setting** 15 sites across Canada. Site type not defined **Funding** Boehringer Ingelheim, Canada **Quality rating:** Fair	**Research objective** To evaluate sexual functioning separately in men and women with depression. To compare Sex FX with Investigator-Rated Sexual Desire and Functioning Scale, and to compare antidepressant outcomes with an examination of relation between level of depression and sexual functioning over time. **Drugs, Doses, and Range** D1: BUP (SR 150-400 mg 2 x daily): 150-300mg QD; Low-Medium D2: PAR (10-60 mg 1 x daily): 20-40mg QD; Medium **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **Duration** 8 weeks **Type of depression** MDD **Intervention** BUP SR PAR	**Inclusion criteria:** • Adults (age range): 18-65 • Diagnosed with MDD according to DSM-III or -IV: DSM-IV - Current major depressive episode of at least 4 weeks duration • HAM-D ≥18 • Good physical health • Experienced sexual interest and activity within last month • Willing to complete assessments and questionnaires. **Exclusion criteria:** • Pregnant • Negative pregnancy test. • Women of childbearing potential must use of an acceptable contraceptive method. • Concomitant psychotheraputic or psychotropic medications • Free of any antidepressant use for a minimum of 2 weeks (4 weeks for FLUOX) • No concomitant treatment with psychoactive medication with exception of zopiclone. • Additional mental illnesses or organic mental disorder not related to depression	**Groups similar at baseline** N/A. Baseline demographics are not individually reported. Authors report no difference in demographics, drop out rates or severity of depression. **n = (randomized) = 141** D1: NR D2: NR n (safety population) = 131 D1: 65 D2: 66 **Mean age, years** 37.8 (10.5) **Sex, % female** D1: 43% D2: 52% **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** D1: BUP SR Males D2: PAR Males D3: BUP SR Females D4: PAR Females n at baseline: D1: 37 D2: 32 D3: 28 D4: 34 No. of responders: D1: 24 D2: 19 D3: 15 D4: 18 D2 + D4: 56% D1 + D3: 60% *P* = NR (ns) No. of remitters: D1: 16 D2: 12 D3: 9 D4: 12 D2 + D4: 36% D1 + D3: 38% *P* = NR (ns) Mean score at baseline (SD): D1: 22.8 (2.5) D2: 22.4 (3.6) D3: 21.7 (3.5) D4: 22.1 (3.6) Mean score at endpoint (SD): D1: 9.5 (6.5) D2: 10.7 (7.7) D3: 10.6 (7.3) D4: 10.9 (7.6) Mean score change (SD): D1: -13.3	**Attrition** **Overall attrition, %:** 22 **Attrition rate, %:** D1: 12 D2: 20 **Withdrawals due to adverse events, %** NR **Withdrawals due to lack of efficacy, %** NR **Sexual functioning** Mean change: D1:+ 1.79 D2: - 4.16 **Comments** Attrition rates per treatment arm are calculated without post-randomization exclusions (drop-outs). Authors did not specify from which arms exclusions occurred.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		(e.g., schizophrenia, bipolar): History of bipolar disorder, psychotic disorder or organic disorder. • Drug abuse or dependence within past 12 months. • ECT within last: Suicidal tendencies (acute or other): >3 on HAMD "suicide" item. • More than 2 failed trials of antidepressant medications. **Outcome measures** • HAM-D • QOL scales: Sex FX Scale • IRSD-F		D2: -11.7 D3: -11.1 D4: -11.2 N at baseline does not include exclusions. Could not determine n at baseline; Mean score change was not given and thus calculated by reviewer #1; Authors report only baseline values: BUP SR: 21,8 (2,9); PAR 22,2 (3,6); Authors report significant reduction over time for both treatment groups (P > 0.01) with no significant differences between men and women or treatment arms. **MADRS** No. of responders: D1: 24 D2: 19 D3: 15 D4: 18 Mean score at baseline (SD): D1: 22.8 (2.5) D2: 22.4 (3.6) D3: 21.7 (3.5) D4: 22.1 (3.6) **CGI-S** NR **CGI-I** NR **CGII** No	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				QOL scale Sex FX Intervention: D1: BUP SR Males D2: PAR Males D3: BUP SR Females D4: PAR Females n at baseline: D1: 37 D2: 32 D3: 28 D4: 34 Mean score at baseline (SD): D1: 25.83 (5.83) D2: 24.97 (5.10) D3: 22.86 (5.73) D4: 18.44 (4.91) Mean score at endpoint (SD): D1: 27.62 (5.79) D2: 20.81 (5.66) D3: 23.32 (6.17) D4: 20.76 (5.38) Mean score change (SD): D1: +1.79 D2: -4.16 D3: +0.46 D4: +2.32 Mean score change not reported. Calculated by reviewer #1 Authors report in male PAR patients there was a significant change (deterioration) in sexual functioning. Among women there were significant differences in	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				scores across treatment arms at baseline and endpoint. **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Khan et al., 1998[167] **Country and setting:** United States, multicenter (12 sites) **Funding:** Not reported but 3 authors employed by Wyeth-Ayerst	**Research objective:** To evaluate efficacy of 3 different doses of VEN vs. PBO for treatment of MDD or MDD with associated anxiety **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 403 randomized 353 in modified ITT analysis 346 with associated anxiety **Intervention:** D1: VEN 75 mg/d D2: VEN 150 mg/d D3: VEN 200 mg/d D4: PBO	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-III -R • Minimum HAM-D-21 score of 20 • Depression symptoms for at least 1 mo Note: Anxiety defined as score of 2 or more on HAM-D Anxiety-Psychic Item **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic drugs or ECT • Drug or alcohol dependence (within 2 yrs) • Suicidal • Women with child-bearing potential • Clinically sig medical disease • Decrease of >20% in HAM-D during palcebo washout	**Mean age (yrs):** D1: 43.3 D2: 40.0 D3: 43.6 D4: 40.2 **Sex (% female):** D1: 68 D2: 64 D3: 60 D4: 61 **Race (% white):** NR **Baseline HAM-D:** D1: 24.3 D2: 24.5 D3: 24.8 D4: 25.1 **Baseline HAM-A:** NR	**Anxiety outcomes in patients with anxiety:** All 3 VEN-treated groups had statistically sig improvement in HAM-D Anxiety-Psychic Item and Anxiety-Somatization Factor scores compared to PBO group ($P < 0.05$)	**Dropouts due to dizziness:** D1: 5 D2: 2 D3: 6 D4: 1 **Dropouts due to insomnia:** D1: 5 D2: 3 D3: 5 D4: 0 **Dropouts due to nausea:** D1: 8 D2: 7 D3: 17 D4: 1 **Dropouts due to somnolence:** D1: 7 D2: 4 D3: 4 D4: 0	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Khan, 2007[57] **Country and Setting** 12 independent psychiatric research facilities in U.S. **Funding** Forest Research Institute National Institues of Health **Quality rating:** Fair	**Research objective** To evaluate efficacy and safety of ESC vs. DUL in acute treatment of patients with moderate to severe major depressive disorder. **Drugs, Doses, and Range** D1: ESC (10-20 mg 1 x daily): 10 - 20 mg QD; Low to High (fixed at 10mg/day for first 4 weeks) D2: DUL (40-60 mg 1-2 x daily): 60 mg QD; Medium **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **Duration** 8 weeks **Type of depression** MDD Current depressive episode of at least 12 weeks duration **Intervention** D1: ESC D2: DUL	**Inclusion criteria:** • Adults (age range): 18-80 • DSM-IV • MADRS 26 or more • CGI-S: Minimum score of 4 • MADRS score at baseline also required to be within 25% of score at screening visit. **Exclusion criteria:** • Pregnant • Negative pregnancy test and women with child bearing potential who were not using a medically accepted form of contraception. • Lactating • Concomitant psychotheraputic or psychotropic medications • Use of a depot antipsychotic within 6 months prior to study entry was prohibited, as was use of any benzodiazepine within 4 weeks, or any anti-psychotic, antidepressant or anxiolytic medication within 2 weeks (5 weeks for FLUOX) prior to first administration of double blind study medication. • Additional mental illnesses or organic mental disorder not	**Groups similar at baseline** Yes **n =** D1: 140 D2: 138 **Mean age, years** D1: 41.8 D2: 43 **Sex, % female** D1: 59.1 D2: 63.9 **Race, % white** D1: 78.8 D2: 81.2 **Baseline HAM-A** D1: 16.3 (4.6) D2: 17.1 (5.6) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** MADRS D1: 31 (0.32) D2: 31.6 (0.34) CGI-S D1: 4.5 (0.05) D2: 4.5(0.05)	**HAM-D** D1: ESC (LOCF) D2: DUL (LOCF) n at baseline: D1: 140 D2: 138 No. of responders: D1: 82.96 (61%) D2: 65.52 (52%) *P* = NR No. of remitters: D1: 55.76 (41%) D2: 44.1 (35%) *P* = NR Mean score at baseline (SD): D1: 26.7 (5.0) D2: 26.9 (5.0) Mean score at endpoint (SD): D1: 12.2 D2: 14.2 Mean score change (SD): D1: -14.5 (8.8) D2: -12.7 (9.5) Score at endpoint not reported. Calculated by 1st reviewer. **MADRS** D1: ESC (LOCF) D2: DUL (LOCF) n at baseline: D1: 140 D2: 138 No. of responders: D1: 82.96 D2: 65.52	**Overall adverse events, %:** D1: 80 D2: 80 **Headache, %:** D1: 12 D2: 15 **Insomnia, %:** D1: 9 D2: 20 **Nausea, %:** D1: 15 D2: 23 **Attrition** **Overall attrition, %:** 24 **Attrition rate, %:** D1: 15 D2: 33 **Withdrawals due to adverse events, %** D1: 2 D2: 12 **Withdrawals due to lack of efficacy, %** D1: 1 D2: 1.5 **Comments** Adverse events attrition significant at *P* < 0.01 Additional Attrition: Protocol violation: • ESC: 0 • DUL: 1% Consent withdrawn: • ESC: 2% • DUL: 7% significant at

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		related to depression (e.g., schizophrenia, bipolar) • DSM-IV criteria for any Axis I disorder other than MDD, or bipolar disorder, schizophrenia or any psychotic disorder, obsessive-compulsive disorder, mental retardation or any pervasive developmental disorder or cognitive disorder • Psychotic disorder or psychotic features, or any personality disorder of sufficient severity to interfere with participation in study. • Illicit drug and alcohol abuse • Recent history or current diagnosis of drug or alcohol dependence. • Clinically significant medical disease • History of seizure disorder or any condition that predisposes to risk of seizure, any history of narrow-angle glaucoma, a history of inappropriate antidiuretic hormone secretion syndrome, or a current diagnosis or history of any clinically significant medical illness that had not been stable for at least past year.		No. of remitters: D1: 59.84 D2: 47.88 Mean score at baseline (SD): D1: 26.7 (5.0) D2: 26.9 (5.0) Mean score at endpoint (SD): D1: 13 D2: 15.7 Mean score change (SD): D1: -2.0 (1.2) D2: -1.7 (1.4) ESC (LOCF) significant at *P* >0.05 for score change and responders. Note:Score at endpoint not reported. Calculated by 1st reviewer. **CGI-S** Mean score at baseline (SD): D1: 4.5 (0.5) D2: 4.5 (0.6) Mean score at endpoint (SD): D1: 2.5 D2: 2.8 Score at endpoint not reported. Calculated by 1st reviewer. **CGI-I** D1: ESC (LOCF) D2: DUL (LOCF) **CGII** Yes	*P* < 0.05 vs. ESC Lost to follow-up: • ESC: 8% • DUL: 8% NOTE: Attrition rates were calculated including post-randomization exclusions.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		• Investigational drug use within last: Month • ECT within last: 3 months • Suicidal tendencies (acute or other) • Current suicidal ideation • Suicide attempt within past year. • Previous participation in a clinical study or failed to respond to treatment with either ESC or DUL • Failure to respond to adequate trials of two or more antidepressants • Initiation or termination of any type of psychotherapy within 3 months of current study were not eligible to participate • Initiation or termination of ongoing psychotherpay during study. **Outcome measures** • HAM-D: HAMD-24 Primary Efficacy variable; HAMD-17 Secondary Efficacy variable; HAMD 1 item and subscales. • MADRS • CGI-S or CGI-I • Quality of life scales: Quality of Life Enjoyment and Satisfaction Questionnaire • Others: HAM-A		Intervention: D1: ESC (LOCF) D2: DUL (LOCF) n at baseline: D1: 140 D2: 138 Mean score at endpoint (SD): D1: 2.1 (1.0) D2: 2.3 (1.2) Number of patients achieving a score 1: 97.92 2: 75.6 Number of patients achieving a score of ≤2 significant at $P > 0.05$. **QOL scale** Q-LES-Q Intervention: D1: ESC (LOCF) D2: DUL (LOCF) n at baseline: D1: 140 D2: 138 Mean score at baseline (SD): D1: 44.2 (10.0) D2: 44.3 (9.1) Mean score at endpoint (SD): D1: 32 D2: 33.7 Mean score change (SD): D1: 12.2 (11.3) D2: 10.6 (11.9) Score at endpoint not	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				reported. Calculated by 1st reviewer. **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kiev and Feiger, 1997[58] **Country and setting:** United States Multicenter (2 centers) **Funding:** Solvay Pharmaceuticals, Upjohn	**Research objective:** To compare FLUV and PAR in treatment of outpatients with major depression **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 60 **Intervention:** D1: FLUV: 50-150 mg/d D2: PAR: 20-50 mg/d	**Inclusion criteria:** • Adults 18 to 65 • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 20; minimum score of 2 on "depressed mood" item **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Used a drug within 30 days with anticipated major organ toxicity • Participation in previous FLUV studies • Transportation difficulties	**Mean age (yrs):** D1: 42.7 D2: 39.9 **Sex (% female):** D1: 53 D2: 53 **Race (% white):** D1: 87 D2: 93 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 24.35 D2: 24.36	No statistically sig diff between treatment groups for HAM-D depressed mood item or CGI severity of illness item at each wk or at endpoint No statistically sig treatment diffs in HAM-D retardation and cognitive disturbance factors, HAM-A totoal score or SCL-56 CGI-I mean score at endpoint: D1: 1.93 D2: 2.21	**Cardiovascular adverse events:** D1: 13 D2: 3 **Constipation:** D1: 7 D2: 13 **Diarrhea:** D1: 13 D2: 30 **Dizziness:** D1: 20 D2: 27 **Headache:** D1: 40 D2: 57 **Insomnia:** D1: 30 D2: 20 **Nausea:** D1: 37 D2: 47 **Sexual dysfunction:** D1: 7 D2: 21 **Somnolence (fatigue):** D1: 40 D2: 30 **Sweating (increase):** D1: 10 D2: 33	**Overall attrition rate:** 31% **Overall adverse events:** D1: 97 D2: 100 **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Klysner et al., 2002[127] **Country and setting:** Denmark Single center study - out patient **Funding:** H.Lundbeck A/S	**Research objective:** To compare prophylactic efficacy of CIT and PBO in elderly patients: to evaluate long-term tolerability of CIT **Duration of study:** 48 wks **Study design:** RCT **Overall study N:** 230 in acute 172 entered continuation phase 121 entered maintenance phase **Intervention:** D1: CIT: 20-40 mg/d D2: PBO	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Adults 65 or older • MADRS score of 22 or greater **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • FLUOX within 5 wks • Other antidepressants within 3 days • ECT within last 8 wks • Suicidial tendencies MADRS item 10 ≥ 10 • Severe somatic disorders	**Mean age (yrs):** D1: 74 D2: 75 **Sex (% female):** D1: 82 D2: 72 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Nineteen of 60 patients (32%) using CIT and 41 of 61 patients (67%) using PBO had recurrence. Time to recurrence was sig different between CIT- and PBO-patients, in favour of CIT (log-rank test, $P < 0.0001$)	**Overall adverse events:** D1: 5.4 D2: 12.2 **Diarrhea:** D1: 5 D2: 4.9 **Dizziness:** D1: 1.7 D2: 6.6 **Headache:** D1: 1.7 D2: 6.6 **Insomnia:** D1: 0 D2: 4.9 **Nausea:** D1: 0 D2: 3.3 **Sexual dysfunctional:** D1: 0 D2: 0 **Somnolence (fatigue):** D1: 16.7 D2: 9.8 **Sweating (increase):** D1: 6.7 D2: 4.9	**Overall attrition rate:** 76% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Kocsis et al., 2007;[113] Keller et al., 2007;[126] Keller et al., 2007;[124] Kornstein, 2008;[131] Kornstein et al., 2008;[130] Fava et al., 2008;[254] Fava et al., 2009;[112] Thase et al., 2010[154] **Country and Setting** United States, multicenter **Funding** Wyeth **Quality Rating** Fair	**Research objective** To test long-term efficacy and safety of VEN ER in preventing recurrence in patients with major depression **Drugs, Doses, and Range** D1: VEN 75-300 mg/d (medium dose in acute phase; high dose in continuation phase) D2: FLUOX 20-60 mg/d (medium dose) **Study design** RCT **n** Acute phase 10 weeks VEN ER (75-300 mg/day; mean 161 mg/d; n = 821) or FLUOX (20-60 mg/day; mean 41 mg/d; n = 275). 6-month continuation phase of ongoing therapy with double-blind VEN ER (mean 206 mg/d; n = 530) or FLUOX (mean 49mg/d; n = 185). Maintainence phase 336 (ITT = 324, efficacy = 258) **Duration** 2 years **Type of depression** Recurrent MDD	**Inclusion criteria** • Adults (age range): 18 or older • Diagnosed with MDD according to DSM-III or -IV • HAM-D: 20 or better at screening, 18 or better at randomization • First they were enrolled in double-blind treatment with VEN ER (75 mg/day to 300 mg/day) or FLUOX (20 mg/day to 60 mg/day) for 10 weeks of acute treatment. Responders then received 6 months of continuation treatment. Those who remained responders were then enrolled into a 12-month maintenance period. **Exclusion criteria** • Pregnant • Lactating • Women of childbearing age who were pregnant, breastfeeding, or not using a medically acceptable method of birth control. • Concomitant psychotheraputic or psychotropic medications • Antipsychotic drug, FLUOX, or monoamine oxidase inhibitor within 30 days or any other antidepressant within 14 days; any anxiolytic,	**Groups similar at baseline** No- FLUOX more severly depressed **n =** D1: 781 D2: 266 D3: 530 D4: 185 D5: 129 Overall: 129 **Intervention** D1: Acute VEN D2: Acute FLUOX D3: Continuation VEN D4: Continuation FLUOX D5: Maintainence VEN Overall: Maintainence PBO **Mean age, years** D1: 39.6 D2: 40.0 D3: 40.4 D4: 40.9 D5: 42.6 Overall: 42.0 **Sex, % female** D1: 65 D2: 61 D3: 67 D4: 61 D5: 69 Overall: 67 **Race, % white** 81 Overall: 88 **Baseline HAM-A** Overall **Insomnia, %:**	**HAM-D Responders, n, %:** D1: 612 (79) D2: 210 (79) **Remitters, n, %:** D1: 380 (49) D2: 132 (50) **Mean score at baseline (SD):** D1: 22.6 (SD 3.1) D2: 23.0 (3.2) **Mean score at endpoint (SD):** D1: 9.2 (SE 0.4) D2: 8.9 (0.4) **Mean score change (SD):** NR **Recurrence** • Estimated probability of no recurrence • Primary definition of recurrence-a HAM-D17 > 12, a reduction in HAM-D17 score from acute-phase baseline 50% at 2 consecutive visits or at last valid visit prior to study discontinuation, and meeting DSM-IV criteria for MDD • Month 12 78.3% vs. 75.2% • Month 24 71.9% vs. 55.8% • Secondary definition of recurrence-1 visit with a HAM-D17 > 12 and a HAM-D17 reduction from baseline 50%, and did	**Overall rate of attrition, %** Acute: 27 Continuation: 34 Maintainence: 48.8% **Attrition rate, %** NR **Withdrawals due to adverse events, %** NR **Attrition due to lack of efficacy, %** NR **Intervention** D1: Velafaxine-acute D2: FLUOX- acute D3: Velafaxine-acute and continuation D4: FLUOX- Acute and continuation **Overall adverse events: Weight loss, %:** D1: 2 D2: 4 D3: 2 D4: 4 **Constipation, %:** D1: 14 D2: 7 *P* = 0.002 D3: 16 D4: 7 P < 0.001 **Diarrhea, %:** D1: 11 D2: 15 D3: 13 D4: 17 **Dizziness, %:** D1: 12 D2: 13

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		sedative-hypnotic drug (except chloral hydrate or zaleplon), sumatriptan (and similar agents), or any other psychotropic drug or substance within 7 days; or any nonpsychopharmaco-logic drug with psychotropic effects within 7 days of randomization, unless a stable dose of drug had been maintained for ≥ month. • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Clinically significant medical disease • History or presence of a serious medical disease • Investigational drug use within last: 14 days • ECT within last: 3 months • Suicidal tendencies (acute or other) • Failed an adequate trial of FLUOX, VEN, or VEN ER during current episode of major depression or who were treatment-resistant (had failed ≥3 previous adequate trials of at least 2 classes of antidepressant medication, or ECT, or 2	Overall **Concomitant anergia, %** Overall **Experienced prior depressive episodes, %** Overall	not meet primary definition of recurrence. • Month 12 71.5% vs. 60.5% • Month 24 59.5% vs. 43.3% • Maintenance baseline HAM-D VEN XR 4.9 (3.5) vs. PBO 4.3 (3.3) **MADRS** **Mean score at baseline (SD):** NR **Mean score at endpoint (SD):** D1: 1.9 (0.04) D2: 1.9 (0.07) **Mean score change (SD):** NR **CGI-S** **Mean score at endpoint (SD):** D1: 2.3 (0.05) D2: 2.3 (0.07) **QOL scale** SF-36 Physical/Mental **Mean score at endpoint (SD):** D1: 53.2 (0.3)/40.9 (0.5) D2: 53.3 (0.5)/41.3 (0.8) **Another QOL scale** Q-LES-Q **Mean score at baseline (SD):** D1: 781 D2: 266 **Mean score at endpoint**	D3: 17 D4: 16 **Headache, %:** D1: 28 D2: 29 D3: 34 D4: 32 **Insomnia, %:** D1: 22 D2: 20 D3: 25 D4: 22 **Nausea, %:** D1: 20 D2: 19 D3: 22 D4: 20 **Somnolence (fatigue), %:** D1: 16 D2: 17 D3: 18 D4: 19 **Sweating-increased, %:** D1: 13 D2: 12 D3: 17 D4: 15

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		adequate trials of psychotherapy in past 3 years) • Known hypersensitivity to VEN or FLUOX • History or presence of a serious medical disease, cancer, seizure disorder, bipolar disorder, eating disorder (if not remitted for 5 years), primary Axis I disorder other than MDD or substance dependence/abuse within 6 months, significant Axis II disorder, any psychotic disorder, or current postpartum depression; those who were a serious suicide risk; those who had clinically significant abnormalities on prestudy medical assessments		**(SD):** D1: 55.6 (0.5) D2: 55.9 (0.7) **Adherence** NR **Recurrence** • KaplaneMeier estimated probability of not experiencing a recurrence was 71.9% VEN vs. 55.8% FLUOX. *P* = 0.399 • Cox multiple regression analysis, treatment-by-time interaction was observed using primary definition of recurrence *P* = 0.034 risk for recurrence varied differently over time for 2 treatments For randomized PBO-controlled recurrence prevention: • First year mainteance probability of recurrence VEN (n = 129) 23.1% (95% CI, 15.3-30.9) vs. PBO (n = 129) 42.0% (95% CI, 31.8-52.2) *P* = 0.005 • Second year maintainence probability of recurrence VEN (n = 43) 8.0% (95% CI, 0.0-16.8) vs. PBO (n = 40) 44.8% (95% CI, 27.6-62.0) P < 0.001 • Combined 2-year maintenance phase probability of recurrence	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
				VEN (n = 129) 28.5% (95% CI, 18.3-38.7) vs. PBO (n = 129) 47.3% (95% CI, 36.4-58.2) *P* = 0.005 • Over 2 year maintainence period probability of remaining well was VEN 67% vs. PBO 41% *P* = 0.007	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Kornstein et al., 2006[129] **Country and Setting** United States, 28 centers **Funding** Forest Research Insitute **Quality Rating** Fair	**Research objective** Examine efficacy of maintenance treatment with esctialopram in preventing depression recurrence in patients who previously responded to treatment with another SSRI antidepressant **Drugs, Doses, and Range** D1: ESC 10-20 mg/day, mean 15.5 mg/day (Low-Medium –High dose) D2: PBO **Study design** RCT **n** 139 **Duration** 52 Weeks **Type of depression** Recurrent Major depressive disorder	**Inclusion criteria** • Adults (age range): 18-81 yrs • HAM-D: minimum score of 2 on item 1 • MADRS: total score ≥ 22 • Acute phase for current MDE **Exclusion criteria** • Pregnant • Women of childbearing potential required to practice a reliable method of birth control. • Lactating • Concomitant psychotheraputic or psychotropic medications • Concomitant psychotropic medication. • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Bipolar disorder, schizophrenia or any psychotic disorder, obsessive-compulsive disorder, mental retardation, or any pervasive developmental or cognitive disorder. • Any Axis I disorder other than MDD (including dysthymic disorder). • History of any psychotic disorder. Exhibition of any psychotyic features. Significant personality	**Groups similar at baseline** Yes **n =** D1: 73 D2: 66 **Mean age, years (SD)** D1: 42.0 (11.3) D2: 43.7 (12.4) **Sex, % female** D1: 79.5 D2: 78.8 **Race, % white** D1: 87.7 D2: 86.4 **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, mean (SD)** Number of previous MDEs, D1: 4.7 (3.1) D2: 5.8 (6.0)	**HAM-D** **Mean score at baseline (SD):** D1: 5.2 (4.0) D2: 5.2 (3.8) **Mean score at endpoint (SD):** D1: 4.7 D2: 5.0 **Mean score change (SD):** D1: -0.5 (5.9) D2: -0.2 (3.6) **Comments?** Mean at endpoint not given (SD). Calculated by reviewer #1. **MADRS** **Mean score at baseline (SD):** D1: 4.7 (4.0) D2: 4.9 (3.6) **Mean score at endpoint (SD):** D1: 4.8 D2: 4.6 **Mean score change (SD):** D1: 0.1 (5.8) D2: -0.3 (3.0) Mean at endpoint not given (SD). Calculated by reviewer #1. **CGI-S** **Mean score at baseline (SD):** D1: 1.5 (0.6) D2: 1.6 (0.7) **Mean score at endpoint (SD):**	**Overall rate of attrition, %** 65 **Attrition rate, %** D1: 49 D2: 82 **Withdrawals due to adverse events, %** D1: 4 D2: 9 **Attrition due to lack of efficacy, %** D1: 5 D2: 12 **Overall adverse events, %:** At 14 days: D1: 21 D2: 41 **Cardiovascular, %:** D1: 1.4 D2: 0 **Weight gain (SD:** Change at endpoint D1: 2.9 lb (10.3) D2: 1.2 lb (10.2) **Dizziness, %:** At 14 days: D1: 0 D2: 18.2 At maintenance phase D1: 3 D2: 20 **Headache, %:** At 14 days: D1: 1.4 D2: 1.5 At maintenance phase:

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		disorders. • Illicit drug and alcohol abuse: within previous 6 months. • Clinically significant medical disease: abnormal or clinically significant findings on physical examination, lab test, and 12-leac electrocardiogram • Suicidal tendencies (acute or other): suicide risk; score at least 5 on MADRS item 10 (suicidality)		Change at endpoint D1: 1.5 D2: 1.5 **Mean score change (SD):** D1: 0.0 (0.9) D2: 0.1 (0.3) Mean at endpoint not given (SD) calculated by reviewer **CGI-I** **Mean score at endpoint (SD):** Change at endpoint D1: 0.0 (0.6) D2: -0.1 (0.3) • Mean at endpoint not given (SD) calculated by reviewer **QOL scale** NR **Adherence** NR **Recurrence** • Time to recurrence was significantly longer for ESC-treated pts, mean (SD) of 252 (134) days and median of 357 days vs PBO treatment , mean (SD) 130 (135) days and median of 58 days [hazard ratio (HR) = 0.26, 95% CI, 0.13 to 0.52, *P* < 0.001] • Cumulative rates of recurrence were lower for ESC arm (27%) vs PBO (65%) in figure 3. After censoring all recurrence events occurring within 14 days	D1: 11 D2: 6 **Suicidality, %:** D1: 0 D2: 1.5

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
				of start of double-blind treatment, results remained statistically significant (HR = 0.29, *P* < 0.001) in favor of ESC.	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Kranzler et al., 2006[238] **Country and Setting** United States, multicenter (13 investigative sites), outpatient setting **Funding** Pfizer Parmaceuticals supported conduct of this study NIH grant supported mauscript preparation. **Quality Rating** Fair	**Research objective** To evaluate safety and efficacy of SER in patients with co-occurring MDD and alcohol dependence. **Intervention Drugs, Doses, and Range** D1: Group A: SER 50-200mg/day (low-high dose) D2: Group A: PBO D3: Group B: SER 50-200mg/day (low-high dose) D4: Group B: PBO **Study design** RCT **n** 345 randomized (328 provided postbaseline information) **Duration** 10 weeks **Type of depression** Major depressive disorder	**Inclusion criteria** • Adults (age range): 21 to 65 years • Diagnosed with MDD according to DSM-III or -IV: modified DSM; except that symptoms could have occurred during a period of heavy alcohol use • HAM-D: total score of ≥ 17 on 17-item HAM-D • Current DSM-IV diagnosis of AD; had to have drunk an average of ≥ 18 drinks weekly for men or ≥ 14 drinks weekly for women and at least one heavy drinking day (i.e., ≥ 5 drinks on one occation for men and ≥ 4 drinks for women) per week during month before screening **Exclusion criteria** • Pregnant: or of childbearing potential not using an effective method of contraception • Lactating • Clinically significant medical disease • Clinically significant co-occuring psychiatric or medical diagnoses including dependence on any psychoactive substance other than alcohol or nicotine during preceding year	**Groups similar at baseline** No, statistically significant differences for: Group A PBO older, reported more drinks/wk during pre-txt period, had higher CGI depression score than Group A SER; Group B SER patients--greater percentage of family history **n =** D1: 89 D2: 100 D3: 70 D4: 69 **Mean age, years (SD)** D1: 41.7 (9.4) D2: 44.0 (8.0) D3: 41.8 (9.4) D4: 42.9 (9.2) **Sex, % female** D1: 34 D2: 36 D3: 34 D4: 42 **Race, % white** D1: 93.3 D2: 88.0 D3: 94.3 D4: 97.1 **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR	**HAM-D** **Responders, %:** D1: 64 D2: 47 (D1 vs. D2 *P* = 0.022) D3: 58 D4: 77 (D3 vs. D4 *P* = 0.018) **Remitters:** NR **Mean score at baseline (SD):** D1: 20.3(2.8) D2: 20.9 (4.0) D3: 12.6 (2.8) D4: 12.5 (2.9) **Mean score at endpoint:** NR **Mean score change:** D1: 10.8 (SD 6.5) D2: 9.6 (SD 7.8) D3: 6.0 (SD, 5.4) D4: 7.2 (SD, 5.7) **MADRS** NR **CGI-S** NR **CDI-I** NR **CGI** **Mean score at baseline (SD):** D1: 4.3 (0.7) D2: 4.5 (0.8) (D1 vs. D2 *P* = 0.04) D3: *3.7 (0.5) D4: *3.7 (0.6) (D3 vs. D4 ,	**Overall rate of attrition, %** 38.7 **Attrition rate, %** D1: 41.6 D2: 44 D3: 44.3 D4: 21.7 **Withdrawals due to adverse events, %** NR **Attrition due to lack of efficacy, %** NR **Overall adverse events, %:** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		• Suicidal tendencies (acute or other) • Treatment with disulfiram, naltrexone, or psychotropic medication, serum aminotransferase levels or other measures of hepatic function that were greater than 250% of normal • Two groups of patients were randomized separately to receive SER or PBO: group A had HAM-D scores of ≥ 17, and group B had scores = < 16.	**Experienced prior depressive episodes, %** NR	*P* = 0.74) **Mean score at endpoint:** NR **Mean score change:** NR **Comments?** **QOL scale** NR **Adherence (≥ 80% of doses taken)** D1: 74.4% D2: 73.8% D3: 75.7% D4: 76.5%	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Lee et al., 2007[61] **Country and Setting** Multinational, Investigational settings **Funding** Eli Lilly and Boehringer Ingelheim **Quality rating:** Fair	**Research objective** The object was to compare efficacy and tolerability of DUL with PAR in a predominantly Asian cohort of patients with MDD. **Drugs, Doses, and Range** D1: DUL (40-60 mg 1-2 x daily): 60 mg 1 x daily; medium D2: PAR (10-60 mg 1 x daily): 20 mg 1 x daily; medium **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** Yes **Study design** RCT **Duration** 8 weeks **Type of depression** MDD **Intervention** D1: DUL 60 mg/day D2: PAR 20 mg/day	**Inclusion criteria:** • Adults (age range): at least 18 years of age • Diagnosed with MDD according to DSM-III or -IV • HAM-D: greater than or equal to 15 • CGIS: greater than or equal to 4 **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Current DSM-IV diagnosis other than MDD, previous psychotic disorder diagnosis, dysthymic disorder within past 2 years, anxiety disorder as a primary diagnosis within past year, axis II disorder that would interfere with protocol compliance • History of substance abuse; history of hepatic dysfunction, current jaundice, or positive hepatitis B surface antigen (Dane particle; HBsAg) or positive hepatitis C surface antibody (HCAb) • ECT within last: within 1 year • Suicidal tendencies (acute or other)	**Groups similar at baseline** Yes **n =** D1: 238 D2: 240 **Mean age, years** D1: 39.0 (13.95) D2: 38.0 (15.27) **Sex, % female** D1: 65.5 D2: 73.8 **Race, % white** D1: 7.1 D2: 4.6 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** Of those randomized, 91.0% were East Asian. At baseline, mean weight for patients in DUL group (60.2 kg) was significantly higher than that observed in PAR group (58.3 kg).	**HAM-D** No. of responders: D1: 144 (60%) D2: 157 (65%) *P* = 0.296 No. of remitters: D1: 117 (49%) D2: 121 (50%) *P* = 0.855Mean score at baseline (SD): D1: 21.1 (4.12) D2: 21.2 (4.04) Mean score at endpoint (SD): D1: 6.91 D2: 7.68 Mean score change (SD): D1: -14.19 D2: -13.52 **MADRS** NR No. of responders: D1: 144 D2: 157 Mean score at baseline (SD): D1: 21.1 (4.12) D2: 21.2 (4.04) Mean score change (SD): D1: -1.51 D2: -1.55 **CGI-S** D1: DUL 60 mg/day D2: PAR 20 mg/day n at baseline: D1: 238 D2: 240	**Overall adverse events, %:** D1: 78.1 D2: 70.3 **Constipation, %:** D1: 14.8 D2: 11.2 **Dizziness, %:** D1: 21.0 D2: 18.4 **Headache, %:** D1: 11.3 D2: 12.1 **Nausea, %:** D1: 37.0 D2: 24.6 **Vomiting, %:** D1: 8.0 D2: 5.8 **Attrition** **Overall attrition, %:** 26% **Attrition rate, %:** D1: 30.3 D2: 23.8 **Withdrawals due to adverse events, %** D1: 8.4 D2: 7.1 **Withdrawals due to lack of efficacy, %** D1: 0.4 D2: 0.4 **Comments** The primary reasons for discontinuation were due to patient decision and adverse events.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		• Lack of response of current episode to 2 or more adequate courses of antidepressant therapy • History of lack of response to an adequate trial of PAR for treatment of depression • Alanine aminotransaminase level greater than or equal to 2-fold upper limit of normal, psychotherapy, started light therapy or phototherapy within 6 weeks of study entry **Outcome measures** • HAM-D: 17-Item HAM-D total score • CGI-S • HAM-D subscales-Anxiety/Somatization, Retardation, Sleep, Core and Maier, HAM-A, PGI, SSI, and VAS scales		Mean score at baseline (SD): D1: 4.4 (0.61) D2: 4.5 (0.65) Mean score at endpoint (SD): D1: 2.89 (0.51 S.E.) D2: 2.95 (0.49 S.E.) The mean score at enpoint for each treatment group was based on adjusted means from MMRM analysis pooled across all visits. **CGI-I** NR **CGII** No **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** Adherence **Rate of adherence or compliance** Refill adherence over a 1-year period was greater with BUP XL than BUP SR. percentage of patients with ≥1 refill over 1 year was 60.1% with BUP XL compared with 51.3% with BUP SR (*P* < 0.0001). Percentage of patients with ≥ 2 **Additional Results:** • BUP XL was associated	proportion of patients that discontinued due to patient decision was significantly higher in DUL group (n = 42, 17.6%), compared with PAR group (n = 26, 10.8%).

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				with significantly greater likelihood of refilling a prescription than BUP SR ($P > 0.0001$). • Persistence was considered to be maintained if days of medication supply from previous prespcription plus a 30-day grace period exceeded number of days between previous prescription date and current prescription fill date. • The medication possession ratio over a 9-month period was 1.5-fold higher for BUP XL (0.26) than it was for BUP SR (0.16), a finding that suggests that those on XL formulation were likely to remain on BUP for 50% longer than those on SR formulation.	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Leinonen et al., 1999[62] **Country and setting:** Multinational **Funding:** Clinical research grant from NV Organon, Oss, Netherlands	**Research objective:** To compare andtidepressant, anxiolytic, and QOL effects of MIR and CIT **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 270 **Intervention:** D1: MIR: 15-60 mg/d D2: CIT: 20-60 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 22 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 1 to 4 wks • ECT within last 3 mo • Suicidal tendencies • Present depressive episode >12 mos • Non-responders to antidepressant treatment • Fast PBO-responders	**Mean age (yrs):** D1: 42.1 D2: 41.1 **Sex (% female):** D1: 66.9 D2: 57.1 **Race (% white):** NR **Baseline (HAM-A):** D1: 21.1 D2: 20.9 **Mean HAM-D score at baseline:** NR	Responders by CGI criterion = 85.3% (MIR) vs. 88.7% (CIT) (*P* = 0.59) CGI-QOL scale: 77.1% (MIR) vs. 62.4% (CIT) of patients showed any degree of improvement (*P* = 0.039) Q-LES-Q: both groups improved; no statistically sig diff between groups; estimate of treatment diff = -0.01 (95% CI, -2.65 to -2.63, *P* = 0.99)	**Changes in weight (increase):** D1: 15.3 D2: 4.5 **Diarrhea:** D1: 2.9 D2: 6.0 **Dizziness:** D1: 8.8 D2: 4.5 **Headache:** D1: 9.5 D2: 14.3 **Nausea:** D1: 10.2 D2: 20.2 **Somnolence (fatigue):** D1: 8 D2: 6 **Sweating (increase):** D1: 2.2 D2: 15.0	**Overall attrition rate:** 19.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Lenox-Smith et al. 2008[132] **Country and Setting** Multinational (Europe and Australia), inpatient and outpatient **Funding** Wyeth **Quality Rating** Fair	**Research objective** To compare efficacy and safety of VEN ER and CIT in treatment of moderate-to-severe depression in patients who did not experience a treatment response to an SSRI other than CIT and to investigate effects of severity of de **Drugs, Doses, and Range** D1: VEN 75-375 mg 2-3 x daily, mean 191 mg (medium dose) D2: CIT 20-60 mg 1 x daily, mean 51 mg (high dose) **Study design** RCT **n** 406 **Duration** NR **Type of depression** One failed SSRI	**Inclusion criteria** • Adults (age range): 18-65 • Diagnosed with MDD according to DSM-III or -IV: DSM-IV • HAM-D: 20 or more **Exclusion criteria** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse • Clinically significant medical disease • Suicidal tendencies (acute or other) • Seizure disorder	**Groups similar at baseline** Yes **n =** D1: 200 D2: 206 **Mean age, years** D1: 42 D2: 43 **Sex, % female** D1: 69.0 D2: 64.1 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** **Mean score at baseline (SD):** D1: 28.6 (5.7) D2: 28.8 (5.4) **Mean score at endpoint (SD):** NR **Mean score change (SD):** D1: -17.0 D2: -16.5 *P* = 0.4778 Baseline HAM-D 31 or less, there were no statistical differences but in Baseline HAM-D > 31 at endpoint HAM-D was Ven 14.25 vs. Cit 17.78 *P* = 0.0121 Remission rates presented in figure only, with text saying no difference between groups. **MADRS** **Mean score at baseline (SD):** D1: 30.8 (5.7) D2: 30.9 (6.1) **Mean score at endpoint (SD):** D1: NR D2: NR *P* = 0.5002 **Mean score change (SD):** NR **CGI-S** **Mean score at baseline (SD):**	**Overall rate of attrition, %** 22.7 (92/406) **Attrition rate, %** D1: 24.5 D2: 20.9 **Withdrawals due to adverse events, %** D1: 5.5 D2: 5.3 **Attrition due to lack of efficacy, %** D1: 11 D2: 7 **Overall adverse events, %:** D1: 57.8 D2: 63.4 **Constipation, %:** D1: 6.0 D2: 2.9 **Dizziness, %:** D1: 8.5 D2: 5.4 **Headache, %:** D1: 15.6 D2: 15.6 **Nausea, %:** D1: 14.1 D2: 16.6 **Sweating-increased, %:** D1: 3.5 D2: 5.9

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
				NR **Mean score at endpoint (SD):** Data NR *P* = 0.3014 **Mean score change (SD):** Mild , % D1: 3.0 D2: 5.4 Moderate, % D1: 24.0 D2: 35.0 Marked, % D1: 45.0 D2: 38.8 Severe, % D1: 24.5 D2: 20.9 Extremely Severe, % D1: 0.5 D2: 1.0 For patients baseline HAM-d greater than 31 change on CGI-S D1: 1.94 D2: 1.53 *P* = 0.0359 **CGI-I** Significantly more VEN ER patients had a CGI-I score of 1 at week 12 (*P* = 0.024) **QOL scale** NR **Adherence** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Lepine et al., 2004[133] **Country and setting:** France Psychiatric centers (83 sites) **Funding:** Pfizer	**Research objective:** To determine whether SER prevents recurrence of major depressive disorder among patients with recurrent depression who had been treated to remission with medications other than SER **Duration of study:** 20 mos 18 mos double-blind phase **Study design:** RCT **Overall study N:** 299 **Intervention:** D1: SER 50 D2: SER 100 D3: PBO	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • At least 3 documented episodes in previous 4 yrs • Treated for at least 4 mos, currently in full remission **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder	**Mean age (yrs):** D1: 47.3 D2: 48.0 D3: 45.5 **Sex (% female):** D1: 60.0 D2: 77.7 D3: 73.7 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Recurrences were sig lower in SER groups compared with PBO (SER, 50 mg: 16 [16.8%] of 95; SER, 100 mg: 16 [17.0%] of 94; PBO: 33 [33.3%] of 99). Patients treated with SER also had sig longer time until recurrence compared with PBO-treated patients	**Overall adverse events:** D1: 76 D2: 80 D3: 71 **Headache:** D1: 11.2 D2: 7.1 D3: 7.8 **Insomnia:** D1: 12.2 D2: 11.2 D3: 12.6 **Nausea:** D1: 6.1 D2: 10.2 D3: 4.9 **Somnolence (fatigue):** Asthenia D1: 6.1 asthenia- 9.2 D2: 5.1 asthenia- 10.2 D2: 6.8 asthenia-5.8	**Overall attrition rate:** 41.1% **ITT Analysis** Yes **Quality rating:** Good

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Lepola et al., 2003[63] **Country and setting:** Europe and Canada Primary care **Funding:** H. Lundbeck A/S	**Research objective:** Efficacy and tolerability of ESC compared to CIT and PBO in depression in primary care setting **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 315 **Intervention:** D1: CIT: 20-40 mg/d (mean 28.4) D2: ESC: 10-20 mg/d (mean 14.0) D3: PBO	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 22 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 43 D2: 43 D3: 43 **Sex (% female):** D1: 69.4 D2: 74.8 D3: 72.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Sig more ESC patients responded to treatment at study endpoint on MADRS scale than CIT patients (63.7% vs. 52.6%; *P* = 0.021) Sig more ESC than CIT-treated patients were in remission at endpoint (52.1% vs. 42.8%; *P* = 0.036) ESC was numerically better than CIT at all time points on all 3 efficacy scales Analysis of time to response showed that ESC–treated patients were responders 8.1 days faster than CIT-treated patients	**Overall adverse events:** D1: 59.7 D2: 69.7 D3: 65 **Diarrhea:** D1: 3.2 D2: 6.5 D3: 7.5 **Insomnia:** D1: 1.9 D2: 6.5 D3: 4.4 **Nausea:** D1: 9.1 D2: 17.4 D3: 14.4 **Sexual dysfunction :** D1: 0 D2: 5.1 (male impotence) D3: 0 **Somnolence (fatigue):** D1: 1.3 D2: 5.2 D3: 3.1 **Suicidality:** D1: 1.9 D2: 7.7 D3: 5.6	**Overall attrition rate:** 7% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Lesperance et al., 2007[239] **Country and Setting** Canada, multicenter (9 academic centers) **Funding** CIHR Clinical Trials Program grant, Foundation du Centre Hospitalier de l'Universite' de Montreal, and Foundation de l'Institute de Cardiologie de Montreal **Quality Rating** Fair	**Research objective** To document short-term efficacy of a selective-serotonin reuptake inhibitor (CIT) and IPT in reducing depressive symptoms in patients with CAD and major depression **Intervention Drugs, Doses, and Range** D1: Clinical Management + IPT and CIT 20-40 mg/day (low-medium dose) D2: Clinical Management + IPT and PBO D3: Clinical Management Alone and CIT 20-40 mg/day (low-medium) D4: Clinical Management Alone and PBO **Study design** RCT **n** 284 with CAD **Duration** 12 weeks **Type of depression** MDD	**Inclusion criteria** • Adults (age range): ≥ 18 years • HAM-D: have a 20 or higher on centralized, telephone-administered 24-item HAM-D • DSM-IV for current major depression • Be depressed for 4 weeks or longer • Established CAD based on hospital chart evidence of a previous acute myocardial infaction or cardiac revascularization or coronary angiography showing 50% blockage or more in at least 1 major coronary artery **Exclusion criteria** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Bipolar disorder or major depression with psychotic features • Illicit drug and alcohol abuse • Suicidal tendencies (acute or other) • Depression due to a general condition (based	**Groups similar at baseline** Yes **n =** D1: 67 D2: 75 D3: 75 D4: 67 **Mean age, years (SD)** D1: 58.6 (10.44) D2: 59.4 (9.28) D3: 57.3 (7.83) D4: 57.3 (8.95) **Sex, % female** D1: 38.8 D2: 24.0 D3: 9.3 D4: 28.4 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** Recurrent depression D1: 33 (49.3) D2: 42 (56.0) D3: 34 (45.3) D4: 27 (40.3) Almost half of participants had previous depression; only significant difference	**HAM-D** **# of responders:** D1: 22 D2: 28 D3: 42 D4: 29 CIT vs. PBO 75 vs. 57 **# of remitters:** D1: 24 D2: 16 D3: 27 D4: 16 CIT vs. PBO 51 vs. 32 **Mean score at baseline (SD):** D1: 28.8 (6.39) D2: 30.0 (6.43) D3: 29.6 (6.43) D4: 30.3 (7.64) **Mean score at endpoint:** NR **Mean score change:** D1: 13.7 (9.98) D2: 10.5 (9.96) D3: 16.1 (9.96) D4: 12.6 (9.97) CIT vs. PBO 14.99 (9.99) vs. 11.6 (9.99) *P* = 0.005 **MADRS** NR **CGI-S** NR **CGI-I** NR **CGI** NR	**Overall rate of attrition, %** 19.0 **Attrition rate, %** D1: 11.9 D2: 21.3 D3: 13.3 D4: 29.9 **Withdrawals due to adverse events, %** D1: *1.5 D2: *4.0 D3: *2.7 D4: *1.5 **Attrition due to lack of efficacy, %** D1: 0 D2: 5.3 D3: 0 D4: 17.9 **Diarrhea, %:** D1: 49.3 D2: 23.9 **Dizziness, %:** D1: 48.6 D2: 30.3 **Sexual dysfunction, %:** D1: 21.1 D2: 7.0 **Somnolence (fatigue), %:** D1: 43.7 D2: 25.4 **Sweating-increased, %:** D1: 39.4 D2: 23.9

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		on clinical judgment) • Current use of anti-depressants, litium, or anticonvulsants for mood disorder • Previous absence of response to CIT or IPT • 2 or more previous unsuccessful treatments for index depression episode • Lifetime history of early termination (<8 weeks) of CIT or 2 other SSRIs because of adverse events • MMSE score of less than 24 and clinician judgment that patients would not adhere to study regimen • Patients with coronary artery bypass graft surgery planned duing next 4 months • Canadian Cardiovascular Society Angina Class of 4 (severe limitations) • Participating in other trials • Unable to speak English or French	involved a lower proportion of females randomized to clinical management alone vs. to IPT	**QOL scale** NR **Adherence** Rate of adherence or compliance 94%	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Li et al., 2008[240] **Country and Setting** China, university hospital **Funding** National Science Foundation of Shandong Province, People's Republic of China **Quality Rating** Fair	**Research objective** To evaluate efficacy and tolerability of herbal drug, FEWP compared with FLUOX and PBO, in patients affected by post-stroke depression **Intervention Drugs, Doses, and Range** D1: FLUOX 20-40 mg/day (low-medium dose) D2: PBO Note: Overall data includes D1 and D2 plus FEWP groups **Study design** RCT **n** 150 (ITT NR) **Duration** 8 weeks **Type of depression** MDD; Minor depression	**Inclusion criteria** • HAM-D: over 20 • Presence of recent (less than 6 weeks) single ischemic or hemorrhagic stroke documented by cerebral computed tomograph scanning or MRI • Presence of major or minor depression • Lack of treatment with antidepressants 2 weeks prior to study **Exclusion criteria** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • History of psychiatric illness other than depression • Illicit drug and alcohol abuse: chronic alcoholism • MMSE score <23 • Severe aphasia • Abnormal thyroid function • Epilepsy	**Groups similar at baseline** No, percent of females **n =** D1: 60 D2: 30 Overall: 150 **Mean age, years** D1: 69.2 D2: 67.8 Overall: NR **Sex, % female** D1: 58.3 D2: 43.3 Overall: NR **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Weeks since Stroke (SD)** D1: 4.75 (0.70) D2: 4.82 (0.67)	**HAM-D** **# of responders:** At week 8 D1: 39 D2: 6 **# of remitters:** NR **Mean score at baseline (SD):** D1: 25.5 (3.1) D2: 24.3 (2.9) **Mean score at endpoint (SD):** D1: 14.5 (2.4) D2: 18.7 (3.9) **Mean score change (SD):** D1: -11.0 (NR) D2: -5.6 (NR) **MADRS** NR **CGI-S** NR **CGI-I** NR **CGI** NR **QOL scale** NR **Adherence** NR	**Overall rate of attrition, %** 2.7 **Attrition rate, %** D1: 3.3 D2: 6.7 **Withdrawals due to adverse events, %** D1: 0.0 D2: 0.0 **Attrition due to lack of efficacy, %** NR **Overall adverse events, %:** D1: 16.7 D2: 16.7 **Insomnia, %:** D1: 6.7 D2: 6.7 **Nausea, %:** D1: 10.0 D2: 10.0

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Lin et al., 2008[134] **Country and Setting** Taiwan, public mental hospital **Funding** Variety of Taiwanese public institutions including-Kai-Suan Psychiatric Hospital, National Science Council. National Health Research Institutes, Committee on Chinese Medicine and Pharmacy, Department of Health, etc. **Quality Rating** Fair	**Research objective** To compare VEN and FLUOX treatment in long-term outcome measure, time to rehospitalization. **Drugs, Doses, and Range** D1: VEN 75-375 mg 2-3 x daily, mean 116.5 mg (Low dose) D2: FLUOX 20 mg 1 x daily, mean 25.1mg (Low dose) **Study design** Observational **n** 202 **Duration** One year followup **Type of depression** Improved at time of discharge (CGI-I of 1 or 2)	**Inclusion criteria** • Concomitant condition (e.g., alcoholism, anxiety, stroke)- most were allowed except as noted in exclusion criteria • Diagnosed with MDD, CGI-I of 1 or 2 • Tolerability to VEN or FLUOX **Exclusion criteria** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): Schizophrenia and bipolar, • Illicit drug and alcohol abuse • ECT within last: While in hospital for current episode • TRD	**Groups similar at baseline** Yes **n =** D1: 122 D2: 80 **Mean age, years** D1: 44.4 D2: 43.7 **Sex, % female** D1: 73.8 D2: 73.7 **Race, % Han Chinese** D1: 100 D2: 100 **Baseline HAM-A, %** Comorbid anxiety disorder D1: 24.6 D2: 21.3 **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** NR **MADRS** NR **CGI-S** NR **CGI-I** NR **CGI** NR **QOL scale** Rate of hospitalization in year following discharge from hospital following treatmnt for depression. **QOL scale** **Mean score at baseline (SD):** D1: 122 D2: 80 Rehospitalized, (%) D1: 53 (43.4) D2: 37 (46.2) **Adherence** NR	**Overall rate of attrition, %** 25.7% either LTF or shifted drug **Attrition rate, %** Either LTF or shifted drug D1: 27 D2: 23.8 **Withdrawals due to adverse events, %** NR **Attrition due to lack of efficacy, %** NR **Additional comments** NR **Overall adverse events, %:** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Lopez-Ibor, 1993[203] **Country and setting:** Spain Database analysis **Funding:** NR	**Research objective:** Effect of PAR on suicidality in depressed patients **Duration of study:** Up to 6 wks **Study design:** **Database analysis** **Overall study N:** 4668 **Intervention:** D1: PAR D2: PBO	**Inclusion criteria:** • Depressed patients in a clinical trial **Exclusion criteria:** • NR	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	PAR and active control were sig better than PBO in reducing suicidal thoughts and behavior from wk 1 onwards	N/A	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Lustman et al., 2006[135] **Country and Setting** United States, outpatient clinics (multicenter) **Funding** National Institutes of Health **Quality Rating** Fair	**Research objective** To determine whether maintenance therapy with SER hydrochloride prevents recurrence of major depression in patients with diabetes **Intervention Drugs, Doses, and Range** D1: SER 25-200 mg/day (low-high dose) D2: PBO **Study design** RCT **n** 152 **Duration** up to 52 weeks **Type of depression** Major depressive disorder	**Inclusion criteria** • 18-80 years of age • HAM-D: 15 or greater (or have a total score of 14 or greater on BDI) • Type 1 or type 2 diabetes • Total score of 14 or greater on BDI • Patients who recovered from depression during induction phase were randomized into maintenance phase **Exclusion criteria** • History of bipolar depression or any psychotic disorder • Illicit drug and alcohol abuse • Suicidal or homicidal ideation or history of attempted suicide • Medical contraindication to SER treatment	**Groups similar at baseline** No, **n =** D1: 79 D2: 73 **Mean age (SD)** D1: 50.5 (11.7) D2: 55.3 (12.5) *P* < 0.05 **Sex, % female** D1: 58.2 D2: 61.6 **Race, % white** D1: 78.5 D2: 83.6 **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 100 D2: 100	**HAM-D** **Mean score at baseline of maintenance phase (SD):** D1: 3.3 (2.7) D2: 4.0 (3.5) **Mean score at endpoint (SD):** NR **Mean score change (SD):** NR Recurrences occurred in 65 patients; more than three fourths of recurrences (50/65 patients) occurred early, ie, in first 4 mongths following randomization (nonrecurrence = 87). Maintenance of response greater with SER: HR, 0.51, 95% CI, 0.31-0.85 *P* = 0.02 **MADRS** NR **CGI-S** NR **Intervention** **CGI-I** NR **CGI** NR **QOL scale** NR **Adherence** Rate of compliance, %	**Overall rate of attrition, %** 14.5 **Attrition rate, %** D1: 19 D2: 10 **Withdrawals due to adverse events, %** 0.66 **Attrition due to lack of efficacy, %** NR **Overall adverse events, %:** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
				94.1 (9 of 152 patients withdrew due to noncompliance)	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Lyketsos et al, 2003[241] **Country and setting:** US, 3 psychiatric outpatient clinics **Funding:** Depression in Alzheimer's disease study from NIMH	**Research objective:** To assess efficacy and safety of SER for treatment of major depression in Alzheimer disease and to evaluate effect of depression reduction on activities of daily living, cognition, and nonmood behavioral disturbance **Duration of study:** 12 wks (after 1-wk single-blind PBO phase) **Study design:** RCT **Overall study N:** 44 **Intervention:** D1: PBO D2: SER: up to 150 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Probable alzheimer disease by National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders Association • MMSE of 10 • Current residence in a community setting (home or assisted living) **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Use of SER contraindicated in opinion of study psychiatrist	**Mean age (yrs):** D1: 79.9 D2: 75.5 **Sex (% female):** D1: 50 D2: 83 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 21.8 (5.4) D2: 23.7 (6.4)	9 SER patients (38%) were full responders and 11 (46%) were partial responders compared with 3 (20%) and 4 (15%) PBO patients (P = 0.007) SER was statistically sig superior to PBO as measured by both Cornell Scale for Depression in Dementia (P = 0.002) and Hamilton Depression Rating Scale (P = 0.01)	NR	**Overall attrition rate:** 18.2% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Mackay et al., 1997;[204] Mackay et al., 1999;[205] Mackay et al., 1999[206] **Country and setting:** UK General practice **Funding:** Reported as "many pharmacetical companies"	**Research objective:** To compare safety and side-effect profiles of 4 SSRIs, FLUV, FLUOX, SER and PAR in a cohort study **Duration of study:** N/A **Study design:** Cross sectional – prescription event monitoring **Overall study N:** 74,626 **Intervention:** D1: FLUV D2: FLUOX D3: SER D4: PAR Study 1999: D5: Venlafaxine D6: Nefazodone	**Inclusion criteria:** • Patients prescribed SSRIs **Exclusion criteria:** None	**Survey Response rate:** 54.6% to 64.1% **Mean age (yrs):** D1: 51 D2: 50 D3: 49 D4: 49 D5: 48 D6: 45 **Sex (% female):** D1: 70.1 D2: 69.8 D3: 68.6 D4: 67.5 D5: 65.0 D6: 62.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	FLUV had considerably higher incidence of side-effects associated with its use than other 3 SSRIs **Incidence rate:** D1: 17.6 D2: 7.0 D3: 6.2 D4: 7.6 D5: NR D6: NR 36% of GPs expressing an opinion reported FLUV as effective, compared with approximately 60% for FLUOX, SER, and PAR The most common reason for stopping treatment was nausea/vomitting for all 4 SSRIs	**Rate of Occurrence per 1000 patient-month of treatment** **Nause/Vomitting:** D1: 127.2 D2: 26.3 D3: 34.6 D4: 52.9 D5: 71.9 D6: 46.1 **Headache:** D1: 25.1 D2: 12.5 D3: 13.1 D4: 13.1 D5: 20.2 D6: 25.1 **Dizziness:** D1: 25.5 D2: 6.7 D3: 8.7 D4: 11.5 D5: 19.9 D6: 31.9 Patients with 2 or more diagnostic features of the serotonin syndrome: (percentage of cohort D1: NR D2: 0.2 D3: 0.3 D4: 0.4 D5: 0.4 D6: 0.4	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Mao et al., 2008[64] **Country and Setting** China, multicenter **Funding** Xian-Janssen Pharmaceutical Company **Quality rating:** Fair	**Research objective** Assess efficacy and tolerability of ESC in Chinese pts with moderate to severe depression **Drugs, Doses, and Range** D1: ESC (10-20 mg 1 x daily): 10mg/day D2: FLUOX (20 mg 1 x daily): **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** Yes **Study design** RCT **Duration** 8wks **Type of depression** MDD **Intervention** D1: ESC D2: FLUOX	**Inclusion criteria:** • Adults (age range): between 18 and 65 years • Diagnosed with MDD according to DSM-IV • HAM-D: ≥ 18 • CGIS: ≥ 4 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Other current primary diagnosis of Axis I or anxiety disorder in last year, ever had a diagnosis of bipolar, psychosis, schizoaffective disorder • Illicit drug and alcohol abuse: with last year • Clinically significant medical disease: cardiovascular, hepatic, renal, respiratory, hematological, endocrinological, or neurological disease, or clinically significant laboratory abnormality • Suicidal tendencies (acute or other) • Pts taking St. Johns Wort or any other Chinese herbal meds for depression **Outcome measures** • HAM-D	**Groups similar at baseline** No- more men randomized to treatment with ESC **n =** D1: 123 D2: 117 **Mean age, years** D1: 37.1 D2: 40.7 **Sex, % female** D1: 47 D2: 62 **Race, % white** Han Chinese: D1: 99 D2: 96 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** **Outpatients/Inpatients** Both **Baseline mean HAM-A > 25?** No **Mean age at baseline** Less than 65 years **Mean HAM-D at baseline**	**HAM-D** D1: ESC D2: FLUOX n at baseline: D1: 123 D2: 117 No. of responders: Week 2: D1: 13 D2: 14 Week 4: D1: 55 D2: 14 Week 8: D1: 94(80%) D2: 89(79%) *P* > 0.05 No. of remitters: Week 2: D1: 6 D2: 5 Week 4: D1: 31 D2: 5 Week 8: D1: 64(46%) D2: 62(55%) *P* = NR Mean score at baseline (SD): D1: NOT ITT D2: NOT ITT Mean score at endpoint (SD): D1: NOT ITT D2: NOT ITT Mean score change (SD): D1: NOT ITT	**Overall adverse events, %:** D1: 44.7 D2: 47.0 **Dizziness, %:** D1: 9.8 D2: 7.7 **Headache, %:** D1: 6.0 D2: 6.8 **Nausea, %:** D1: 12.0 D2: 13.7 **Attrition** **Overall attrition, %:** 13.3 **Attrition rate, %:** D1: 12.2 D2: 14.5 **Withdrawals due to adverse events, %** D1: 4.9 D2: 4.3 **Withdrawals due to lack of efficacy, %** D1: 0.8 D2: 3.4 **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		• MADRS • CGI-S or CGI-I	Greater than 17 (moderate to severe)	D2: NOT ITT **MADRS** D1: ESC D2: FLUOX n at baseline: D1: 123 D2: 117 No. of responders: Week 2: D1: 13 D2: 14 Week 4 D1: 55 D2: 58 Week 8 D1: 94 D2: 89 No. of remitters: Week 2: D1: 17 D2: 18 Week 4 D1: 54 D2: 48 Week 8 D1: 93 D2: 86 Mean score at baseline (SD): D1: NOT ITT D2: NOT ITT Mean score at endpoint (SD): D1: NOT ITT D2: NOT ITT **CGI-S** Means and change scores NOT Reported for ITT,	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				remitters* (CGI-S ≤2) at endpont: ESC: 77; FLUOX: 85 (*calculated from Ns = 118, 113) **CGI-I** NR **CGII** Yes Number of patients achieving a score 1: means and change scores NOT Reported for ITT, Responders* (CGI-I ≤ 2) at endpont: ESC: 87; FLUOX: 97 (*calculated from Ns = 118, 113) **QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Martinez et al., 2005[207] **Country and setting:** UK General practice research database (clinical primary care records in UK) **Funding:** Medicines and Healthcare Products Regulatory Agency	**Research objective:** To compare risk of non-fatal self harm and suicide in patients taking SSRIs with that of patients taking tricyclic antidepressants, as well as between different SSRIs and different tricyclic **Duration of study:** 1995 to 2001 **Study design:** Nested case-control study **Overall study N:** 146,095 **Intervention:** D1: CIT D2: FLUOX D3: FLUV D4: PAR D5: SER	**Inclusion criteria:** • Age < 90 • First prescription for antidepressants between 1/1/1995 and 12/31/2001 **Exclusion criteria:** • None	**Mean age (yrs):** 31 of patients in age cohort 31 to 45 yrs old **Sex (% female):** Overall: 65 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	No diff in risk of non-fatal self harm among different SSRIs (P = 0.35) No diff in risk of self-harm between SSRIs and tricyclic antidepressants (OR, 0.99; 95 %CI, 0.86 to 1.14) No diff in risk of suicide between SSRIs and tricyclic antidepressants (OR, 0.57; 95% CI, 0.26 to 1.25)	N/A	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Good

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Martinez et al, 2010[208] **Country and Setting** United Kingdom, general medical practices **Funding** Wyeth **Quality rating:** Fair	**Research objective** Using a population based observational approach to assess risk of out-of-hospital haemodynamically significant significant acute ventricular tachyarrhythmia or sudden cardiac death associated with VEN use relative to use of FLUOX, CIT, or dosulepin in patients treated for depression or anxiety. **Drugs, Doses, and Range** D1: CIT (20-60 mg 1 x daily): dosage NR D2: FLUOX (10-80 mg 1-2 x daily): dosage NR D3: VEN (75-375 mg 2-3 x daily): dosage NR D4: Other (augmentation): Dosulepin, dosage NR **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** Observational **Duration** January 1995-Februarty 2005 -cohort entry period and until occurrence of outcome, death, transfer out of practice or practice's last collection date before data extraction for study began **Type of depression**	**Inclusion criteria:** • Adults (age range): 18-89 years on date of incident prescription • Diagnosed with MDD according to DSM-III or -IV • Permanent registration status with a participating general practice, had at least a one year longitudinal record before incident prescription, had an acceptable patient status for data quality, and originated from a general practice which was up to standard for at least a year before incident prescription **Exclusion criteria:** • Clinically significant medical disease • History of life threatening ventricular tachyarrhythmia, cardioversion, aborted cardiac arrest, or implantation of a cardiac defibrillator • Patients with a congenital conduction disorder or advanced cardiomyopathy before cohort entry or at any time during follow-up were als excluded **Outcome measures** NR – adverse events reported	**Groups similar at baseline** No- cases generally had a higher prevalence of cardiovascular related comorbidity, particularly diabetes, acute myocardial infarction, congestive heart failure, rheumatoid arthritis, epilepsy, and schizophrenia, as well as use of NSAID **n =** D1: 568 D2: 14,812 **Mean age, years** D1: 72.9 D2: 72.9 **Sex, % female** D1: 54.6 D2: 54.6 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** D1: NR D2: NR **Experienced prior depressive episodes, %** D1: 100 D2: 100 **Comments:** Characteristics of cases and controls in year	**HAM-D** NR **MADRS** NR **CGI-S** NR **CGI-I** NR **CGII** No **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	**Cardiovascular, %:** D1: Adjusted odds ratio (95% CI): VEN only 18 (3.2); vs. FLUOX 63 (11.1); vs. CIT 39 (6.9); vs. any three (including dosulepin) 137 (24.1) D2: Adjusted odds ratio (95% CI): VEN only 544 (3.7); vs. FLUOX 1281 (8.6) **Attrition** **Overall attrition, %:** NR **Attrition rate, %:** NR **Withdrawals due to adverse events, %** NR **Withdrawals due to lack of efficacy, %** NR **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
	Clinical record for depression or anxiety **Intervention** D1: Cases D2: Controls		before index date. **Outpatients/Inpatients** Outpatients **Baseline mean HAM-A > 25?** NR **Mean age at baseline** Equal to or greater than 65 years **Mean HAM-D at baseline** NR		

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year McCall et al. 2010[169] **Country and Setting** USA, Outpatient clinics and sleep labs **Funding** NIH, Sepracor & Mini Mitter **Quality rating:** Fair	**Research objective** Patients experiencing insomnia after one week of FLUOX were randomly assigned to either double-blind ESZ 3 mg or PBO at bedtime **Drugs, Doses, and Range** D1: FLUOX 20-40 mg/day + ESZ D2: FLUOX 20-40 mg/day + PBO **Fixed dose** **Dosages equivalent** No, PBO study **Study design** RCT **Duration** 8 weeks **Type of depression** • MDE	**Inclusion criteria:** • Adults 18-70 yrs • Diagnosed with MDE according to DSM-IV • Sleep latency > 30 min and sleep efficiency 85% or less at least 4 nights/week or insomnia 4 nights/week **Exclusion criteria:** • Clinically significant medical disease • Daytime sleepiness • Habitual snoring • Substance abuse • Significant restless leg syndrome • BMI > 35	**Groups similar at baseline** Yes **n =** D1: 30 D2: 30 **Mean age, years** D1: 44.9 D2: 38.0 **Sex, % female** D1: 66.7 D2: 66.7 **Race, % white** D1: 73.3 D2: 80.0	**HAM-D** Mean score at baseline (SD): D1: 27.3 (3.3) D2: 26.9 (4.5) Response D1: 80% D2: 38% $P < 0.01$ Remission D1: 32% D2: 19% P = NS **Q-Les-Q** Mean score at baseline (SD): D1: 38.8 (7.2) D2: 38.6. (6.7) Endpoint 8 weeks D1: 50.2 (8.11) D2: 46.9 (9) ESZ had lower (better) DLRF scores (0.81 ± 0.64) than those receiving PBO (1.2 ± 0.72), P = 0.01. effect size for DLRF was 0.62, indicating a moderate effect. **Is adherence reported?** NR **Rate of adherence or compliance** NR	**Attrition** **Overall attrition, %:** 15 **Attrition rate, %:** D1: 16.7 D2: 13.3 **Withdrawals due to adverse events, %** NR **Withdrawals due to lack of efficacy, %** NR **Comments** 46% ESZ experienced unpleasant taste

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year McGrath et al., 2006[136] **Country and Setting** United States, multicenter **Funding** National Institute of Mental Health; State of New York **Quality Rating** Fair	**Research objective** To examine predictors in relapse in patients with major depressive disorder maintained on FLUOX vs. PBO **Drugs, Doses, and Range** D1:FLUOX 10-80 mg 1-2 x daily, average dose: 45.8 mg/day (medium dose) D2: PBO **Study design** RCT **n** 262 **Duration** 12 week open-label phase; 52 week continuation/ maintenence phase **Type of depression** MDD	**Inclusion criteria** • Diagnosed with MDD according to DSM-III or -IV: established using Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition • Patients who responded to fluxoetine during 12-week open-label phase **Exclusion criteria** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): Illicit drug and alcohol abuse: in previous 6 months • Clinically significant medical disease: • Unstable physical disorder • History of seizures; neurological disorder; • Taking medications that may cause or exacerbate depression • Evidence of hypothyroidism • History of nonresponse to an adequate trial of a SSRI • 570 patients underwent 12-week open-label acute phase. • Doses were titrated and adjusted by clinician.	**Groups similar at baseline** NR **n =** D1: 131 D2: 131 Overall: Patients randomized **Mean age, years** D1: NR D2: NR Overall: 38.2 **Sex, % female** D1: NR D2: NR Overall: 55.3 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR Overall: Mean HAM-D score at baselineline was 17.1 (4.1) and at randomization, 4.9 (3.1)	**HAM-D** NR **MADRS** NR **CGI-S** NR **CGI-I** NR **CGI** NR **QOL scale** NR **Adherence** NR **Relapse** • FLUOX treatment was a significant predictor of lower relapse rate (hazard ratio = 0.383; 95% CI, 0.198-0.742; *P* = 0.004). • Continuation and maintenance FLUOX treatment associatd with continued remission (hazard ratio 1.73 (95% CI, 1.20-2.51). • Relapse rate at end of continuation phase, 6 months after randomization in FLUOX vs. PBO: 35.2% vs. 61.8%; after 1 year (representing maintenance): 45.9% vs. 72.0%. • Chronicity, symptom severity, a neuovegetativ	**Overall rate of attrition, %** 32.4 **Attrition rate, %** D1: 38.9 D2: 26.0 **Withdrawals due to adverse events, %** NR **Attrition due to lack of efficacy, %** NR • *P* = 0.035 for differential attrition • Most common reasons for attrition: 30.6% (of those who left study) had inadequate adherence; 14.1% loss to follow-up; 7.1% side effects. • Patients that dropped out due to worsening of symptoms were not considered in attrition. **Overall adverse events, %:** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		mean HAM-D baseline score was 17.7 (4.5). 292 patients responded to treatment and 262 of these patients were randomized for 52-week continuation/maintainenc e phase to assess relapse. Patients in double blind phase remained on same dose they had responded to during acute phase.		symptom pattern, and female gender were all assciated wit a significantly greater risk of relapse, with no difference observed between FLUOX and PBO on these factors.	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: McPartlin et al., 1998[65] **Country and setting:** UK Multicenter (43 general practice sites) **Funding:** Wyeth-Ayerst International	**Research objective:** To evaluate efficacy and safety of VEN XR and PAR for treatment of depression in general practice **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 361 **Intervention:** D1: VEN: XR 75 mg/d D2: PAR: 20 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Symptoms of depression at least 14 days • Minimum baseline MADRS score of 19 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days • ECT within last 30 days • Suicidal tendencies • Hypersensitive to or previous treatment with VEN or PAR	**Mean age (yrs):** D1: 45 D2: 44 **Sex (% female):** D1: 68.3 D2: 68.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23 (4) D2: 23 (4)	No sig diffs in outcome measures between treatment groups Global response NR Remission rates (6 or less on MADRS) were 54% for VEN XR and 52% for PAR Both treatment groups produced sig improvements on QOL scale without showing diffs between groups	**Overall adverse events:** D1: 70 D2: 70 **Constipation:** D1: 9.9 D2: 6.8 **Diarrhea:** D1: 4.4 D2: 5.1 **Dizziness:** D1: 16.6 D2: 9.6 **Headache:** D1: 8.8 D2: 11.9 **Insomnia:** D1: 5.5 D2: 4.5 **Nausea:** D1: 25.4 D2: 24.9 **Somnolence (fatigue):** D1: 5.5 D2: 5.6 **Sweating (increase):** D1: 2.2 D2: 6.2	**Overall attrition rate:** 27.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Mehtonen et al., 2000[66] **Country and setting:** Scandinavia Multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** Efficacy and safety of SER and VEN in outpatients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 147 **Intervention:** D1: VEN: 75-150 mg/d D2: SER: 50-100 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease	**Mean age (yrs):** D1: 44.1 D2: 41.0 **Sex (% female):** D1: 65 D2: 67 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25.5 (3.5) D2: 25.8 (4.5)	Both treatment groups showed sig reductions of MADRS, CGI, and HAM-D scores from baseline to wk 8 Response rates (decrease of 50% on HAM-D) were higher for VEN at wk 6 (74% vs. 59%; *P* = 0.04) and at endpoint (83% vs. 68%; *P* = 0.05) Remission rates (HAM-D < 10) at endpoint were higher for VEN treated group (68% vs. 45%; *P* = 0.008) No sig diffs were noted in response rates on MADRS and CGI scales Remission rates for patients who increased dose was higher for VEN group (67% vs. 36%; *P* < 0.05)	**Diarrhea:** D1: 8.0 D2: 13.9 **Headache:** D1: 28.0 D2: 29.2 **Nausea:** D1: 36.0 D2: 29.2 **Sexual dysfunction :** D1: 8.0 D2: 5.6 **Somnolence (fatigue):** D1: 6.7 D2: 11.1 **Sweating (increase):** D1: 18.7 D2: 11.1	**Overall attrition rate:** 19% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Meijer et al., 2002[209] **Country and setting:** The Netherlands Multicenter (109 psychiatrists in general hospitals, regional institutes of mental health, or private practices) **Funding:** Pfizer, Inc	**Research objective:** To evaluate safety profile of SER vs. other SSRIs directly following introduction of SER to Dutch market **Duration of study:** 12 mo observation period **Study design:** Cohort study **Overall study N:** 1,251 **Intervention:** D1: SER D2: Other SSRIs (FLUOX FLUV PAR)	**Inclusion criteria:** • All patients with a new SER prescription; consecutive patients taking FLUOX, FLUV, or PAR used as controls **Exclusion criteria:** • No additional exclusion criteria were applied	**Mean age (yrs):** 41 (median) **Sex (% female):** 64.1% **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	2.2 AEs per SER patient vs. 2.1 AEs per other SSRIs patient 73.4% of SER patients and 75.0% of other SSRI patients reported an AE Diarrhea was reported more frequently by SER patients than patients taking other SSRIs ($P < 0.05$) Abdominal pain was reported more frequently by other SSRI users ($P < 0.05$) No sig diffs in SAE reporting found between SER patients (5.0%) and patients using other SSRIs (4.6%) Suicide attempt: SER: 0.9% vs. other SSRIs: 1.2%	**Overall adverse events:** D1: 73.4 D2: 75 **Cardiovascular adverse events:** D1: 3.2 D2: 2.2 **Diarrhea:** D1: 14 D2: 6.8 **Dizziness:** D1: 11.4 D2: 11.8 **Headache:** D1: 19.3 D2: 17.1 **Insomnia:** D1: 8 D2: 5.9 **Nausea:** D1: 24.3 D2: 27 **Sexual dysfunctional (male ejaculation):** D1: 2.1 D2: 3.7 **Sweating (increase):** D1: 13.4 D2: 11.7	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Michelson et al., 1999[137] **Country and setting:** United States Academic centers (5 sites) **Funding:** Eli Lilly	**Research objective:** To assess changes in weight during long-term treatment with FLUOX or PBO **Duration of study:** 50 wks **Study design:** RCT **Overall study N:** 839 acute phase 395 remission phase **Intervention:** D1: FLUOX: 20 mg/d D2: PBO	**Inclusion criteria:** • Adults 18+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 **Exclusion criteria:** • None reported	**Mean age (yrs):** D1: 40.8 D2: 42.2 **Sex (% female):** D1: 68.3 D2: 73.3 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	No diff in weight change between FLUOX and PBO groups after 50 wks (1.6 kg vs. 1.6 kg)	**Changes in weight (increase):** D1: 1.6kg D2: 1.6kg	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Moak et al., 2003[242] **Country and setting:** USA Single center **Funding:** National Institute on Alcohol Abuse and Alcoholism	**Research objective:** Comparison of SER and PBO in conjunction with CBT in treatment of depressed alcoholics **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 82 **Intervention:** D1: SER: 50-200 mg/d D2: PBO	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 17 • Alcoholism (alcohol dependence or abuse) • Dysthymia • Primary major depression episode of dysthymic disorder or a clear family hisory of affective disorder without comorbid substance abuse in a first degree relative **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Current suicidal ideation or plan • Treatment resistant depression	**Mean age (yrs):** D1: 41 D2: 42 **Sex (% female):** D1: 39 D2: 39 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 19.4 (2.6) D2: 18.8 (2.4)	Subjects who received SER had fewer drinks per drinking day than subjects who received PBO, but other drinking outcomes were not different between 2 treatment groups. In female subjects, treatment with SER was associated with less depression at end of treatment compared with PBO. Less drinking during study was associated with improved depression outcomes	NR	**Overall attrition rate:** 28% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Montejo et al., 2001[210] **Country and setting:** Spain Multicenter **Funding:** Bristol-Myers Squibb	**Research objective:** Incidence of sexual dysfunction associated with anti-depressant agents **Duration of study:** Carried out between April 1995 and February 2000 **Study design:** Prospective cohort study **Overall study N:** 1,022 **Intervention:** CIT FLUOX FLUV MIR NEF PAR SER VEN	**Inclusion criteria:** • Normal sexual functioning prior to taking antidepressants • Treatment with antidepressant alone or combine with benzodiazepine • Previous regular and satisfactory sexual practices • Occurrence of sexual dysfunction within 2 mos after introduction of antidepressant **Exclusion criteria:** • Prior sexual dysfunction • Combination of antidepressant and neuroleptic treatment • Treatment with hormones or any other drug capable of interfering with sexual intercourse • Sig intercurrent diseases affecting sexual function • Substance abuse	**Mean age (yrs):** Overall: 39.8 **Sex (% female):** Overall: 60 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Overall incidence of sexual dysfunction was 59.1% Incidence of overall sexual dysfunction: FLUOX, 57.7% SER, 62.9% FLUV, 62.3% PAR, 70.7% CIT, 72.7% VEN, 67.3% MIR, 24.4% NEF, 8% Men had a higher frequency of sexual dysfunction (62.4%) than women (56.9%), although women had higher severity	N/A	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Montgomery and Rasmussen, 1992[140] **Country and setting:** NR Multicenter (18) **Funding:** H Lundbeck A/S employs second author	**Research objective:** A total of 147 patients who had responded in a PBO-controlled study to 6 wks treatment of an episode of DSM-III-R major depression with either 20 mg or 40 mg CIT were randomized double-blind to continue on same dose of CIT or to receive PBO during a 24-wk study of efficacy of CIT in prevention of relapse **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 147 **Intervention:** D1: CIT: 20 mg/d D2: CIT: 40 mg/d D3: PBO	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • MADRS of at least 22 in initial study • Had response to CIT (20 or 40 mg) resulting in MADRS score of 12 or less **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotherapeutic or psychotropic medications • Duration of depression more than 12 mos	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	CIT 20 and 40 mg groups showed a sig advantage in relapse(overall 10.5% ciotalopram 20 8% and CIT 40 12%) compared with PBO (31%) ($P < 0.05$) and in survival analysis of time to relapse ($P = 0.01$ and $P = 0.02$, respectively)	NR	**Overall attrition rate:** 26.5% for reasons other than relapse **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Montgomery and Dunbar1993[139] **Country and setting:** NR (UK) 5 psychiatric outpatient centers **Funding:** Second author is with SmithKline Beecham NR	**Research objective:** Efficacy of PAR in relapse prevention and prophylaxis of depression **Duration of study:** 1 year **Study design:** RCT **Overall study N:** 135 **Intervention:** D1: PAR: 20-30 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Recurrence of at least 3 episodes **Exclusion criteria:** • Pregnant • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Neuroleptics	**Mean age (years):** D1: 45.9 D2: 48.3 **Sex (% female):** D1: 79 D2: 78 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 5.5 (1.9) D2: 5.7 (1.8)	PAR 16% vs. PBO 43% in reappearance of depression ($P < 0.01$) and in time to reappearance ($P < 0.001$) over 1-year study. Sig advantage was seen for PAR 3% vs. PBO 19% in first 4mos in relapse prevention ($P < 0.01$) and in time to relapse ($P < 0.005$), and later period of treatment in preventing recurrence PAR 14% vs. PBO 30% ($P < 0.05$)	**Dizziness** D1: 4 Vertigo **Insomnia:** D1: 13 **Nausea:** D1: 8 **Suicidality:** D1: 1 Suicide **Sweating (increase):** D1: 5	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Montgomery et al., 2004[67] **Country and setting:** Mulitnational Primary care **Funding:** H. Lundbeck A/S	**Research objective:** To compare efficacy and tolerability of ESC to VEN XR in primary care patients with MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 293 **Intervention:** D1: ESC: 10-20 mg/d (12.1) D2: VEN: 75-150 mg/d (95.2)	**Inclusion criteria:** • Adults 18 to 85 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** D1: 49 D2: 47 **Sex (% female):** D1: 73 D2: 71 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 19.9 D2: 20.4	Rates of respone and remission-equal numbers in both groups of responders and remitters Endpoint (%): Responders D1: 77.4 D2: 79.6 Remitters D1: 69.9 D2: 69.7	**Overall adverse events:** D1: 67 D2: 71 **Constipation:** D1: 2 D2: 6 **Nausea:** D1: 17 D2: 26 **Sweating (increase):** D1: 6 D2: 12.5	**Overall attrition rate:** 14% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Montgomery et al., 2004[138] **Country and setting:** United States and Europe Psychiatric centers (31 sites) **Funding:** Wyeth Research	**Research objective:** Long-term efficacy and safety of prophylactic VEN treatment in patients with recurrent major depression **Duration of study:** 12 mos double-blind phase **Study design:** RCT **Overall study N:** 235 (ITT = 225) **Intervention:** D1: VEN: 100-200 mg/d D2: PBO	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Hypersensitivity to VEN • HAM-D score > 12 after acute and continuation treatment	**Mean age (yrs):** D1: 43.8 D2: 43.5 **Sex (% female):** D1: 71 D2: 67 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Survival analysis determined a 22% cumulative probability of recurrence in VEN-treated patients after 12 mos compared with 55% for PBO group ($P < 0.001$) More than twice as many PBO-treated patients (48%) as VEN-treated patients (21%) discontinued treatment because of lack of efficacy ($P < 0.001$)	**Overall adverse events:** TAES D1: 80 D2: 79 **Diarrhea:** D1: 12 D2: 7 **Dizziness:** D1: 17 D2: 25 **Headache:** D1: 27 D2: 21 **Nausea:** D1: 19 D2: 14 **Somnolence (fatigue):** Asthenia D1: 11 D2: 7	**Overall attrition rate:** 63% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Moore et al., 2005[68] **Country and setting:** France Psychiatric and general practice **Funding:** H. Lundbeck A/S	**Research objective:** Efficacy of ESC vs. CIT in outpatients **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 294 (ITT = 280) **Intervention:** D1: ESC: 20 mg/d D2: CIT: 40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS of at least 30 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse	**Mean age (yrs):** D1: 44.1 D2: 46.2 **Sex (% female):** D1: 81.7 D2: 72 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Responders: (50% decrease in MADRS) D1: 76.1 D2: 61.3 (*P* = 0.008) Remitters (%): D1: 54 D2: 43 (*P* = 0.04); NNT for remission: 9 MADRS-S D1: -9.9 D2: -8.6 (*P* < 0.05) CGI-S D1: -2.3 D2: -2.12 (*P* = 0.65) Overall discontinuation was sig higher in CIT (10.6%) than ESC (4.3%) group (*P* = 0.005)	**Overall adverse events:** D1: 14.8 D2: 16.4 **Changes in weight (increase):** D1: 1.4 D2: 1.3 **Dizziness:** D1: 0.7 D2: 1.3 **Headache:** D1: 4.2 D2: 5.3 **Insomnia:** D1: 1.4 D2: 0.7 **Nausea:** D1: 3.5 D2: 3.9 **Sexual dysfunction :** D1: 0 D2: 0.7 **Somnolence (fatigue):** D1: 0 D2: 2.0	**Overall attrition rate:** 7.5% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Munizza et al., 2006[69] **Country and Setting** Italy, multicenter **Funding** ACRAF SpA **Quality rating:** Fair	**Research objective** Evaluate efficacy and safety of TRA vs. SER in txt of MDD **Drugs, Doses, and Range** D1: SER 50-100mg/day D2: TRA 150-450mg/day **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** **Study design** RCT **N** 122 **Duration** 6wks **Type of depression** MDD	**Inclusion criteria:** • Adults (age range): 18-65 • Diagnosed with MDD according to DSM-IV • HAM-D: HAMD17 score 18-24 • MADRS: < 30 • Other: depression symptoms lasting ≥ 1 month, not receiving txt for current phase of illness **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications: benzodiazepines allowed • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): bipolar, any psychotic or mental disorder due to a general medical condition • Illicit drug and alcohol abuse • Clinically significant medical disease • ECT within last: current • Suicidal tendencies (acute or other) • Treatment refractory depression	**Groups similar at baseline** **n =** D1: 62 D2: 60 **Mean age, years** D1: 45 D2: 46.9 **Sex, % female** D1: 59.7 D2: 70.0 **Race, % white** NR **Baseline HAM-A** D1: NR (graph only) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 72.6 D2: 71.7	**HAM-D** n at baseline: D1: 62 D2: 60 (*only 59 included in analysis, NOT ITT) No. of responders: At 1 week: D1: 3 D2: 1 At 3 week: D1: 17 D2: 14 At 6 week: D1: (74%) D2: 37 (63%) *P* = NR (ns) No. of remitters: At 1 week: D1: 1 D2: 0 At 3 weeks: D1: 7 D2: 2 At 6 weeks: D1: 37 (60%) D2: 29 (49%) *P* = NR (ns) Mean score at baseline (SD): D1: 21.7 (0.22) D2: 21.9 (0.22) (N = 59) Mean score at endpoint (SD): D1: Day 42: 8.6 (0.93) D2: 9.5 (0.82) (N = 59) Mean score change (SD): D1: -12.9 (1.15) D2: -11.5 (1.08) (N = 59)	**Overall adverse events, %:** Patients report AE(s): D1: 41.9 D2: 43.3 **Cardiovascular, %:** Palpitation: D1: 1.6 D2: 1.7 **Weight gain, %:** D1: no changes compared to baseline D2: no changes compared to baseline **Weight loss, %:** D1: no changes compared to baseline D2: no changes compared to baseline **Diarrhea, %:** D1: 3.3 D2: 5.0 **Dizziness, %:** D1: 19.4 D2: 13.3 **Headache, %:** D1: 1.6 D2: 8.3 **Insomnia, %:** D1: 4.8 D2: 5.0 **Nausea, %:** D1: 9.7 D2: 15.0 **Vomiting, %:** D1: 4.8 D2: 3.3 **Attrition**

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		Outcome measures • HAM-D • MADRS • CGI-S or CGI-I • Others: HAM-A		**MADRS** D1: TRA D2: SER n at baseline: D1: 62 (*only 60 include in analysis, NOT ITT) D2: 60 (*only 59 include in analysis, NOT ITT) No. of responders: Week 1 D1: 3 D2: 1 Week 3 D1: 17 D2: 14 Week 6 D1: 46 D2: 37 Mean score at baseline (SD): D1: 21.7 (0.22) D2: 21.9 (0.22) (N = 59) Mean score at endpoint (SD): D1: 9.0 (0.99) (N = 60) D2: 10.5 (1.04) (N = 59) Mean score change (SD): D1: NR - graph only/Not ITT D2: NR - graph only/Not ITTI **CGI-S** D1: TRA D2: SER n at baseline: D1: 62 (analysis includes 60) D2: 60 (analysis includes	**Overall attrition, %:** 10.7 **Attrition rate, %:** D1: 8.1 D2: 13.3 **Withdrawals due to adverse events, %** D1: 3.2 D2: 10.0 **Withdrawals due to lack of efficacy, %** D1: 1.6 D2: 0 **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				59) Mean score at baseline (SD): D1: NR - graph only/Not ITT D2: NR - graph only/Not ITT Mean score at endpoint (SD): D1: NR - graph only/Not ITT D2: NR - graph only/Not ITT **CGI-I** D1: TRA D2: SER **CGII** Yes Intervention: D1: TRA D2: SER n at baseline: D1: 62 (analysis includes 60) D2: 60 (analysis includes 59) Mean score at endpoint (SD): D1: NR - graph only/Not ITT D2: NR - graph only/Not ITT Number of patients achieving a score 1: NR - graph only/Not ITT 2: NR - graph only/Not ITT **QOL scale** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				Is adherence reported? NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Murray et al., 2005[255] **Country and setting:** Sweden, outpatients (4 stroke centers) **Funding:** Pfizer AB Sweden	**Research objective:** To evaluate efficacy and safety of SER in post-stroke depression **Duration of study:** 26 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** D1: SER: 50-100 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Stroke (according to WHO criteria), hospitalized during acute phase of index stroke • Minor depression according to DSM-IV and MADRS ≥ 10 and time criteria (symptoms should have been present during same 2 wk period) **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Sig risk of suicide • Severe impairment of ability to communicate • Current use of opiate analgesics	**Mean age (yrs):** D1: 70.7 D2: 70.7 **Sex (% female):** D1: 48.4% D2: 55.7% **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	HAM-D responders (percent of those who completed 26 wks of treatment) D1: 76% D2: 78% % remission (defined as a MADRS score < 10) (percent of those who completed 26 wks of treatment) D1: 81% D2: 87% Improvement in QOL at wk 26 was sig better in SER treated patients ($P < 0.05$)	**Changes in weight (decrease):** D1: 17.4 D2: 13.3 **Changes in weight (increase):** D1: 15.2 D2: 15.6 **Constipation:** D1: 14.5 D2: 9.3 **Diarrhea:** D1: 23.6 D2: 9.3 **Dizziness:** D1: 14.5 D2: 13.0 **Headache:** D1: 14.5 D2: 16.7 **Nausea:** D1: 21.8 D2: 14.8 **Sweating (increase):** D1: 16.4 D2: 17.0	**Overall attrition rate:** 44% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Nemeroff et al., 1995[70] **Country and setting:** United States Multicenter **Funding:** Solvay Pharmaceuticals	**Research objective:** Comparison of efficacy and safety of FLUV and SER in treatment of depression **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 95 **Intervention:** D1: SER: 50-200 mg/d (137.1) D2: FLUV: 50-150 mg/d (123.8)	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • HAM-D depressed mood item of at least 2 • Covi anxiety score less than Raskin score • Minimum score of 8 on Raskin Depression Scale **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Patients itolerant of SSRI side effects	**Mean age (yrs):** D1: 41.2 D2: 38.5 **Sex (% female):** D1: 60.9 D2: 61.2 **Race (% white):** D1: 84.8 D2: 98.0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.15 (2.77) D2: 24.57 (3.66)	Both treatment groups resulted in sig improvements of depression scores compared to baseline No sig diff in efficacy between treatment groups	**Overall adverse events:** D1: 93.5 D2: 85.7 **Diarrhea:** D1: 23.9 D2: 14.3 **Dizziness:** D1: 15.2 D2: 12.2 **Headache:** D1: 32.6 D2: 26.5 **Insomnia:** D1: 34.8 D2: 26.5 **Nausea:** D1: 21.7 D2: 30.6 **Sexual dysfunction :** D1: 28 D2: 10 **Somnolence (fatigue):** D1: 17.4 asthenia-13 D2: 24.5 asthenia-6.1 **Sweating (increase):** D1: 10.9 D2: 6.1	**Overall attrition rate:** 28% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Nemeroff et al., 2007[71] **Country and Setting** United States (13 centers) **Funding** Wyeth Research **Quality rating:** Fair	**Research objective** To compare VEN to FLUOX for MDD. **Drugs, Doses, and Range** • FLUOX (10-80 mg 1-2 x daily): 20mg/d to 60mg/d (mean 41 (SD 17) mg/day; medium) • VEN (75-375 mg 2-3 x daily): 75mg/d to 225mg/d (mean 142 (SD 64) mg/day; low) **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** Yes **Study design** RCT **N** 206 **Duration** 6 weeks **Type of depression** MDD **Intervention** D1: VEN D2: FLUOX D3: PBO	**Inclusion criteria:** • Adults (age range): 18-75 • HAM-D: ≥ 20 • Symptoms at least 1 month **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications: astemizole, cisapride, sumatriptan, terfenadine, any monoamine oxidase inhibitor, PAR, or SER within 14 days • Any other antidepressant, anxiolytic, sedative-hypnotic drug (except chloral hydrate), or any other psychotropic drug within 7 days of start of double-blind treatment; any other drug with psychotropic effects within 7 days of start of double-blind treatment period unless a stable dose of drug had been maintained for at least 1 month (3 months for thyroid or hormonal medications) before study day 1. • Additional mental illnesses or organic mental disorder not related to depression	**Groups similar at baseline** Yes **n =** D1: 102 D2: 104 D3: 102 **Mean age, years** D1: 40.1 D2: 37.9 D3: 40.4 **Sex, % female** D1: 65 D2: 69 D3: 56 **Race, % white** D1: 91 D2: 93 D3: 92 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 49 D2: 41 D3: 38 **Comments:** Prior deperessive episodes = % who have taken prior antidepressant medications **Outpatients/Inpatients** Outpatients	**HAM-D** D1: VEN D2: FLUOX D3: PBO n at baseline: D1: 102 D2: 104 D3: 102 No. of responders: D1: 51 (53%) D2: 45 (45%) *P* = NR (ns) D3: 37 No. of remitters: D1: 31 (32%) D2: 32 (28%) *P* = NR (ns) D3: 22 Mean score at baseline (SD): D1: 23.5 (3.2) D2: 23.7 (3.2) D3: 23.7 (3.3) Remission based on HAM-D-21, results for HAMD-D-17 31;28;22 **MADRS** D1: VEN D2: FLUOX D3: PBO n at baseline: D1: 102 D2: 104 D3: 102 No. of responders: D1: 51 D2: 45 D3: 37	**Constipation, %:** D1: 10 D2: 2 D3: 5 **Diarrhea, %:** D1: 9 D2: 13 D3: 9 **Dizziness, %:** D1: 13 D2: 8 D3: 3 **Headache, %:** D1: 36 D2: 24 D3: 33 **Insomnia, %:** D1: 22 D2: 15 D3: 14 **Nausea, %:** D1: 40 D2: 22 D3: 8 **Vomiting, %:** D1: 11 D2: 5 D3: 2 **Attrition** **Overall attrition, %:** 25 **Attrition rate, %:** D1: 24 D2: 18 D3: 24 **Withdrawals due to adverse events, %** D1: 12

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		(e.g., schizophrenia, bipolar): Illicit drug and alcohol abuse: w/in past year • Clinically significant medical disease: Investigational drug use within last: w/in 30 days • ECT within last: 3 months • Suicidal tendencies (acute or other) • History of nonresponse to VEN or FLUOX • Received study drug w/in past 6 months **Outcome measures** • HAM-D • MADRS • CGI-S and CGI-I • QOL scales: GLF Total Score, Activities Questionnaire Total Score, Cognitive Functioning, General Health, Vitality	**Baseline mean HAM-A > 25?** NR **Mean age at baseline** Less than 65 years **Mean HAM-D at baseline** Greater than 17 (moderate to severe)	Mean score at baseline (SD): D1: 23.5 (3.2) D2: 23.7 (3.2) D3: 23.7 (3.3) **CGI-S** D1: VEN D2: FLUOX D3: PBO n at baseline: D1: 102 D2: 104 D3: 102 Mean scores not reported. A significant between-groups difference in CGI-S scores At week 6 D1: F(1, 281): 6.26, *P:* 0.013 D2: F(1, 281): 4.49, *P:* 0.035) D1 and D2 vs D3: F(2, 281): 3.65, *P*: 0.027 AND: There were no statistically significant differences between VEN and FLUOX therapy groups on either CGI measure (CGI-S: D1 vs D2: F(1, 281) = 0.16, *P:* 0.689; CGI-I: D1 vs D2:F(1, 282) = 0.46, *P:* 0.499 **CGI-I** Number of patients achieving a score	D2: 7 D3: 3 **Withdrawals due to lack of efficacy, %** D1: 4 D2: 4 D3: 6 **Comments** Based on mITT population, 10 PRE not included in this population.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				1: 59 2: 54 3: 38 **QOL scale** GLF n at baseline: D1: 102 D2: 104 D3: 102 Mean score at endpoint (SD): D1: 55.7 (11.0) D2: 52.8 (9.8) D3: 50.9 (11.5) GLF was only one of QOL scales used that demonstrated a statistical difference between VEN and FLUOX **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** N/A **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Newhouse et al., 2000[40] Finkel et al., 1999[39] **Country and setting:** United States Outpatient **Funding:** NR	**Research objective:** To assess efficacy of SER vs. FLUOX on depressive symptoms in patients aged 60 or older and 70 or older **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 75 (n = 236 in full trial, subgroup analysis of 75 patients who were 70 or older) **Intervention:** D1: SER: 50-100 mg/d D2: FLUOX: 20-40 mg/d	**Inclusion criteria:** • Minimum HAM-D score of 18 • Age ≥ 60 overall; ≥ 70 for subgroup analysis **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Failure to respond to either ECT or adequate antidepressant trials	**Overall/Subgroup** **Mean age (yrs):** D1: 68/74 D2: 67/75 **Sex (% female):** D1: 63/57 D2: 51/49 **Race (% white):** D1: 96/95 D2: 100/100 **Baseline (HAM-A):** D1: NR D2: NR **Mean HAM-D score at baseline:** D1: 25.1/24.2 D2: 25.0/25.4	**Overall:** No sig diffs in SER and FLUOX on primary efficacy measures Responders: SER: 73% FLUO: 71% *P* = NR (ns) Remitters: SER: 45% FLUOX: 46% *P* = NR **Sugroup analysis:** Sig more responders in SER group (*P* = 0.027): 58.5% (SER) vs. 42.4% (FLUOX) Psychological Health subscale: SER group improved from 46.0 (9.2) to 51.4 (8.8) and FLUOX group improved from 43.0 (7.0) to 45.3 (9.3). No data given on total Q-LES-Q scores	**Overall adverse events:** D1: 88/93 D2: 89/94 **Nausea:** D1: 14.7/16.7 D2: 18.6/15.2	**Overall attrition rate:** 32.2% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Nierenberg et al, 2007;[72] Pigott et al, 2007[256] **Country and Setting** 36 psychiatric clinical settings in U.S. **Funding** Eli Lilly **Quality rating:** Fair	**Research objective** To compare speed of onset of antidepressant efficacy for DUL and ESC. **Drugs, Doses, and Range** D1: DUL (40-60 mg 1-2 x daily): 60 mg QD; medium D2: ESC (10-20 mg 1 x daily): 10 mg QD; low D3: PBO **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** No **Study design** RCT **N** 547 **Duration** 8 weeks **Type of depression** MDD **Intervention** D1: DUL 60 mg QD D2: ESC 10 mg QD D3: PBO	**Inclusion criteria:** • Adults (age range): 18-79 • Diagnosed with MDD according to DSM-III or -IV • MADRS: ≥ 22 • CGIS: ≥ 4 **Exclusion criteria:** • Pregnant: HCG test at screening • Lactating: Concomitant psychotheraputic or psychotropic medications: central nervous systems activity • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): bipolar, schizo, Axis II disorder • Illicit drug and alcohol abuse: within last 6 mos. • Clinically significant medical disease • ECT within last: year • Suicidal tendencies (acute or other): decided by investigator • Other: anxiety within last 6 mos. • TRD **Outcome measures** • HAM-D: 20% decrease from baseline • CGI-S or CGI-I: 17% decrease from baseline	**Groups similar at baseline** Yes **n =** D1: 273 D2: 274 D3: 137 **Mean age, years** D1: 41.1 D2: 43.3 D3: 42.5 **Sex, % female** D1: 63.4 D2: 67.9 D3: 63.5 **Race, % white** D1: 75.5 D2: 77.4 D3: 82.5 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** No. of responders: D1: 117 D2: 112 D3: 44 No. of remitters: D1: 101 D2: 88 D3: 37 Mean score at baseline (SD): D1: 17.6 (4.8) D2: 17.8 (5.1) D3: 17.7 (5.2) Mean score at endpoint (SD): D1: 10.01 D2: 10.58 D3: 11.73 Mean score change (SE): D1: -7.61 (0.42) D2: -7.22 (0.40) D3: -5.97 (0.58) **MADRS** No. of responders: D1: 117 D2: 112 D3: 44 Mean score at baseline (SD): D1: 17.6 (4.8) D2: 17.8 (5.1) D3: 17.7 (5.2) Mean score change (SD): D1: -1.44 (SE) D2: -1.36 (SE) D3: -1.08 (SE) **CGI-S** D1: DUL	**Overall adverse events, %:** D1: 85.7 D2: 81.0 D3: 78.1 **Constipation, %:** D1: 23 D2: 16 D3: 8 **Diarrhea, %:** D1: 32 D2: 33 D3: 11 **Dizziness, %:** D1: 26 D2: 20 D3: 7 **Headache, %:** D1: 53 D2: 55 D3: 20 **Insomnia, %:** D1: 22 D2: 21 D3: 9 **Nausea, %:** D1: 65 D2: 33 D3: 12 **Vomiting, %:** D1: 20 D2: 6 D3: 1 **Attrition** **Overall attrition, %:** 27.9 **Attrition rate, %:** D1: 31

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		• HAM-A total score		D2: ESC D3: PBO n at baseline: D1: 273 D2: 274 D3: 137 Mean score at baseline (SD): D1: 4.2 (0.7) D2: 4.2 (0.7) D3: 4.2 (0.7) Mean score at endpoint (SD): D1: 2.76 D2: 2.84 D3: 3.12 **CGI-I** NR **CGII** No **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** Adherence **Rate of adherence or compliance** Number of unused capsules was recorded at all post-baseline visits. **Additional Results:** NR	D2: 24 D3: 29 **Withdrawals due to adverse events, %** D1: 7.3 D2: 5.1 D3: 5.8 **Withdrawals due to lack of efficacy, %** D1: 3.3 D2: 1.5 D3: 5.1 **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year O'Connor et al. 2010[245] SADHART-CHF **Country and Setting** US, multicenter **Funding** NIMH **Quality rating:** Fair	**Research objective** To evaluate the safety and efficacy of sertraline in patients with depression and HF. **Drugs, Doses, and Range** D1: SER 50-200 mg/d D2: PBO **Flexible dose** **Dosages equivalent** N/A **Study design** RCT **Duration** 12 weeks **Type of depression** MDD	**Inclusion criteria:** • 45 years of age or older • left ventricular ejection fraction ≤45% (within previous 6 months) • NYHA functional class II to IV HF symptoms • Met DSM-IV criteria for MDD **Exclusion criteria:** • significant cognitive • impairment, alcohol or drug dependence within year; • psychoses, bipolar disorder, severe personality disorder,; • active suicidal ideation; • life-threatening comorbidity (estimated 50% mortality within 1 year) • Current use of antipsychotic or antidepressant medication	**Groups similar at baseline - Yes** **n =** D1: 234 D2: 235 **Mean age, years** D1: 62.9 D2: 61.4 **Sex, % female** D1: 43.2 D2: 37.9 **Race, % white** D1: 56.0 D2: 57.9 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %**	**HAM-D** Mean score at baseline (SD): D1: 18.3 (5.5) D2: 18.3 (5.4) Mean score change (SD): D1: -7.1 (0.5 D2: -6.8 (0.5) *P* = 0.89 **Is adherence reported?** NR **Rate of adherence or compliance** NR Composite cardiovascular score worsened, improved, or was unchanged (%): D1: 29.9, 40.6%, 29.5%, D2: 31.1, 43.8, 25.1 *P* = 0.78	**Attrition** **Overall attrition, %:** 38 **Attrition rate, %:** D1: 41 D2: 35 **Withdrawals due to adverse events, %** D1: 11.5 D2: 6 *P* = 0.03 **Withdrawals due to lack of efficacy, %** NR **Dizziness, %:** D1: 9.8 D2: 4.9 *P* = NR **Nausea, %:** D1: 21.9 D2: 2.4 *P* = NR **Serious AEs:** **Cardiovascular:** D1: 3.56 D2: 37.1 *P* = 0.79

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Olfson and Marcus, 2008[213] **Country and Setting** United States, (data provided for all 50 states by Centers for Medicare and Medicaid Services, Baltimore, Md.) **Funding** Grants from NARSAD, American Foundation for Suicide Prevention, and Agency for Healthcare Research and Quality **Quality rating:** Fair	**Research objective** To estimate relative risk of suicide attempts in child and adult outpatients initiating antidepressants for major depressive episodes compared to those not treated with antidepressant (includes SSRIs but not all antidepressants described or differentiated). **Drugs, Doses, and Range** NR **Fixed dose** NR **Flexible dose** NR **Dosages equivalent** No **Study design** Observational **Duration** Over a 2-year period, with suicide cases measrued withing first 120 days after index diagnosis **Type of depression** MDE **Intervention** Depressed Adults with suicide attempts	**Inclusion criteria:** • Adults (age range): *included 6-64, but performed a separate analyses on patients 19 to 64 years • Patients who had a first outpatient treatment claim for a major depressive episode (first listed ICD-9-CM: 296.2, 296.3, OR 296.5) during study period and were continuously eligible for Medicaid services for at least 90 days before and 120 days after index claim. **Exclusion criteria:** • Pregnant • Claim for pregnancy during 90 days prior to index diagnosis date • Lactating • Concomitant psychotheraputic or psychotropic medications • Antipsychotic medication • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): Other psychoses, mental retardation, or dementia/delirium during 90 days prior to index diagnosis date	**Groups similar at baseline** NA **n =** D1: 185 **Mean age, years** D1: 31.6 **Sex, % female** D1: 68.3 **Race, % white** D1: 78.9 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 100* **Comments:** • Adult age range, 19 to 64 years • At their index diagnosis date, a majority of adult suicide attempt cases were diagnosed with single or recurrent episodes of major depression and with moderate or severe without psychosis symptom severity • Results reported based on type of major depressive episode, subtype • Major depression,	**HAM-D** NR **MADRS** NR **CGI-S** NR **CGI-I** NR **CGII** No **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** Adherence **Rate of adherence or compliance** Withdrawl due to protocol violation was reported. Based on number of patients in safety population (N: 1051) and number of withdrawls due to protocol violation, compliance was 98.6%. **Additional Results:** NR	**Attrition** **Overall attrition, %:** NR **Attrition rate, %:** NR **Withdrawals due to adverse events, %** NR **Withdrawals due to lack of efficacy, %** NR **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		• ECT within last: during 90-day period prior to index diagnosis date • Suicidal tendencies (acute or other): received treatment for a suicide attempt during 90-day period prior to index diagnosis date • Fifth digit of index MDE claim indicating partial (5) or full (6) remission, unspecified illness severity (0), or was absent • Filled a prescription for an antidepressant medication or mood stabilizer • Received any inpatient treatment for a mental disorder during 90-day period prior to index diagnosis date • Patients who had any claim for major depression, single episodes occurring in context of major depression, single episodes (ICD-9-CM 296.2) • Major depression, recurrent episodes (296.3); and bipolar disorder, currently depressed (296.5) or any other mention of bipolar disorder (ICD-9-CM 296.0, 296.1, 296.4, 296.6-296.8) or depression (ICD-9-CM 298.0, 300.4, 309.1,	single episode (31.4%) • Major depression, recurrent (63.2%) • Bipolar disorder, depressed (5.4%). **Outpatients/Inpatients** Outpatients **Baseline mean HAM-A > 25?** NR **Mean age at baseline** Less than 65 years **Mean HAM-D at baseline** NR		

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		311) during 90 days prior to index diagnosis. **Outcome measures** • The outcome variable for study was presence or absence of a suicide attempt, which was defined by ICD-9- CM 950-959			

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Owens et al., 2008[73] **Country and Setting** United States, Multicenter (7 clinical research centers) **Funding** GlaxoSmithKline NIH **Quality rating:** Fair	**Research objective** The secondary objective of study was to look at clinical efficacy measures of PAR CR and VEN XR. **Drugs, Doses, and Range** D1: PAR (CR 12.5-75 mg 1 x daily): week 1: 12.5 mg 1 x daily, low; week 2: 25 mg 1 x daily, medium; week 3: 50 mg 1 x daily, high; week 4: 50 mg 1 x daily, high; week 5: 62.5 mg 1 x daily, high; week 6: 62.5 mg 1 x daily, high; week 7: 75 mg 1 x daily, high; week 8: 75 mg 1 x daily, high D2: VEN XR (75-225 mg 1 x daily): week 1: 75 mg 1 x daily, low; week 2: 150 mg 1 x daily, medium; week 3: 225 mg 1 x daily, medium; week 4: 225 mg 1 x daily, medium; week 5: 300 mg 1 x daily, medium; week 6: 300 mg 1 x daily, medium; week 7: 375 mg 1 x daily, high; week 8: 375 mg 1 x daily, high **Fixed dose** No **Flexible dose** No **Dosages equivalent** No **Study design**	**Inclusion criteria:** • Adults (18 - 65 years of age; Diagnosed with MDD according to DSM-III or -IV: diagnosis made by principle investigator using (MINI)- a structured diagnostic interview for DSM-IV; MADRS **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Clinically significant medical disease • Suicidal tendencies (acute or other) • Clinical predominant axis I disorder other than MDD • History of unresponsiveness to either PAR or VEN or exhibited prior hypersensivity/ intolerance to either PAR CR or VEN XR • Prior non-response to SSRIs • Baseline evaluation that would preclude administration of PAR CR or VEN XR,concurrent psychotherapy **Outcome measures** • MADRS: Change from	**Groups similar at baseline** NR **n =** D1: 40 D2: 41 **Mean age, years** NR **Sex, % female** NR **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** The article included overall percent of females in study. On 86 patients randomized, 64% were female subjects. All other demographic and baseline characteristics are available upon request.	**HAM-D** NR **MADRS** D1: PAR CR D2: VEN XR n at baseline: D1: 40 D2: 41 No. of remitters: D1: 17(46%) D2: 24 (63%) *P* = 0.17 Mean score at endpoint (SD): D1: 11.9 D2: 11.3 Mean score change (SE): D1: -16.7 (8.59) D2: -17.3 (8.99 *P* = 0.784 **CGI-S** D1: PAR CR D2: VEN XR n at baseline: D1: 40 D2: 41 Mean score at baseline (SD): D1: 4.4 D2: 4.6 Mean score at endpoint (SD): D1: 2.7 D2: 2.6 **CGI-I** D1: PAR D2: VEN **CGII**	**Overall adverse events, %:** D1: 4.8 D2: 9.1 **Attrition** **Overall attrition, %:** 25.60% **Attrition rate, %:** D1: 23.8 D2: 27.3 **Withdrawals due to adverse events, %** D1: 4.8 D2: 9.1 **Withdrawals due to lack of efficacy, %** NR **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
	RCT **N** 86 **Duration** 8 weeks **Type of depression** MDD **Intervention** D1: PAR CR D2: VEN XR	baseline in MADRS total score at week 8 LOCF endpoint. • CGI-S or CGI-I: Proportion of CGI-I responders defined as a score of 1 or 2 on CGI-S		Yes Intervention: D1: PAR D2: VEN n at baseline: D1: 40 D2: 41 Mean score at endpoint (SD): N/A The study examined percent off CGI-I response rates (LOCF). study found that CGI-I response rate was 78.9% for VEN and 67.5% for PAR. **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Patris et al., 1996[74] **Country and setting:** France Multicenter (general practices) **Funding:** NR	**Research objective:** To compare CIT with FLUOX treatment in patients with unipolar major depression treated in general practice **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 357 **Intervention:** D1: CIT: 20 mg/d D2: FLUOX: 20 mg/d	**Inclusion criteria:** • Adults 18 to 73 • Diagnosed with MDD according to DSM-III or -IV • MADRS at least 22 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Dysthymia or cyclothmia • MAOI treatment within last 2 wks	**Mean age (yrs):** D1: 44 D2: 43 **Sex (% female):** D1: 79 D2: 76 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No diff in mean MADRS at endpoint or in mean change from baseline; mean change: D1: -20.7 D2: -19.4 Responders (reduction in score from baseline > 50%) at endpoint: D1: 78% D2: 76% Remitters (MADRS ≤ 12) at endpoint: D1: 75% D2: 86% (*P* = 0.26)	**Overall adverse events:** D1: 50 D2: 52 **Changes in weight (decrease):** D1: 3.5 D2: 8.2 **Constipation:** D1: 1.2 D2: 3.3 **Diarrhea:** D1: 3.5 D2: 0 **Headache:** D1: 3.5 D2: 3.8 **Insomnia:** D1: 4.6 D2: 5.4 **Nausea:** D1: 9.8 D2: 7.6	**Overall attrition rate:** 12.6% **ITT analysis:** No **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Perahia et al., 2006[75] **Country and Setting** Multinational, outpatient setting **Funding** Eli Lilly and Company; Boehringer Ingelheim **Quality rating:** Fair Although article stated that subjects were randomized, randomization process was not described. Therefore, it was not clear if subjects were adequately randomized. Also, method of allocation concealment was not reported; therefore, it could not be determined if allocation concealment was adequate.	**Research objective** To assess for efficacy and sefety of DUL doses of 80 and 120 mg/day in treatment of MDD. **Drugs, Doses, and Range** D1: DUL: 40 mg 2 x daily D2: DUL: 60 mg 2 x daily D3: PAR: 20 mg 1 x daily D4: PBO **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** No **Study design** RCT **N** 293 **Duration** 32 weeks **Type of depression** MDD	**Inclusion criteria:** • Adults (age range): at least 18 years • Diagnosed with MDD according to DSM-III or -IV • HAM-D: HAM-D total score greater than or equal to 15 • CGIS: greater than or equal to 4 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse • Clinically significant medical disease: cardiovascular, hepatic, renal, respiratory, hematological, endocrine, or neurological disease, or clinically significant laboratory abnormality • Investigational drug use within last • Suicidal tendencies (acute or other) • Lack of response to at least two adequate courses of antidepressant therapy (at least 4 weeks' duration) within therapeutic dose range during their current	**Groups similar at baseline** Yes **n =** D1: 99 D2: 93 D3: 103 D4: 97 **Mean age, years** D1: 44.7 (10.1) D2: 46.5 (12.7) D3: 44.0 (10.8) D4: 45.8 (10.6) **Sex, % female** D1: 65.7 D2: 66.7 D3: 74.8 D4: 71.1 **Race, % white** 100 **Baseline HAM-A** D1: 18.8 (4.4) D2: 19.3 (4.9) D3: 19.5 (5.7) D4: 19.9 (5.1) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** No. of responders: D1: 55 D2: 64 D3: 76 D4: 65 No. of remitters: D1: 33 D2: 41 D3: 41 D4: 42 Mean score at baseline (SD): D1: 20.6 (3.7) D2: 21.3 (3.0) D3: 21.4 (4.4) D4: 21.0 (3.4) Mean score at endpoint (SD): D1: 9.8 D2: 9.2 D3: 9 D4: 9.1 Mean score change (SD): D1: -10.8 (0.5) D2: -12.1 (0.5) D3: -12.4 (0.5) D4: -11.9 (0.5) Number of responders and number of remitters caluated using given estimated probability of response (MMRM analysis) and estimated probability of remission for each treatment group. mean change in HAM-D total (SD) during continuation phase for	**Overall adverse events, %:** D1: 14.1 D2: 21.5 D3: 35.0 D4: 30.9 **Constipation, %:** D1: 5.1 D2: 4.3 D3: 3.9 D4: 2.1 **Headache, %:** D1: 6.1 D2: 2.2 D3: 4.9 D4: 5.2 **Insomnia, %:** D1: 0.0 D2: 3.2 D3: 5.8 D4: 6.2 **Nausea, %:** D1: 1.0 D2: 6.5 D3: 8.7 D4: 6.2 **Vomiting, %:** D1: 0.0 D2: 1.1 D3: 2.9 D4: 2.1 **Attrition** **Overall attrition, %:** 11 % rate of attrition based on acute therapy phase. rate of attrition for continuation phase was 17%. **Attrition rate, %:** D1: 9

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		MDD episode. **Outcome measures** • HAM-D: mean change from baseline in HAM-D 17 total score after 8 weeks of treatment • MADRS • CGI-S • PGI scale • SDS • VAS) for pain • SSI		each treatment group was as follows: D1: -2.3 (5.1) D2: -3.3 (3.9) D3: -2.5 (4.7) D4: -3.6 (4.3). The patiented treated with DUL (both groups) had significantly greater improvement in 17-Item HAM-D total scores at week 8 compared with PBO-treated patients. **MADRS** D1: PBO D2: DUL 40 mg BID D3: DUL 60 mg BID D4: PAR 20 mg QD No. of responders: D1: 55 D2: 64 D3: 76 D4: 65 No. of remitters: D1: 33 D2: 41 D3: 41 D4: 42 Mean score at baseline (SD): D1: 20.6 (3.7) D2: 21.3 (3.0) D3: 21.4 (4.4) D4: 21.0 (3.4) Mean score at endpoint (SD): D1: 10.4 D2: 9.2 D3: 8.7 D4: 9.1	D2: 11 D3: 13 D4: 11 **Withdrawals due to adverse events, %** D1: 1 D2: 2 D3: 2 D4: 1 **Withdrawals due to lack of efficacy, %** D1: 4 D2: 3 D3: 2 D4: 1 **Comments** The attrition rates for continuation phase are as follows: Attrition rate (%) D1: 12.7 D2: 18.3 D3: 23.5 D3: 12.9 Withdrawls due to adverse events (%) D1: 1.4 D2: 2.8 D3: 3.7 D4: 0 Attrition due to lack of efficacy (%) D1: 1.4 D2: 1.4 D3: 4.9 D4: 2.9.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				Mean score change (SD): D1: -1.7 (0.1) D2: -2.0 (0.1) D3: -2.0 (0.1) D4: -2.1 (0.1) Patients treated with DUL 60 mg BID showed significantly greater improvement on MADRS scale compared with PBO-treated patients. number of responders and number of remitters were caluated using given estimated probability of response (MMRM analysis) and estimated probability of remission for each treatment group. mean change in MADRS (S.D.) during continuation phase for each treatment group was as follows: PBO: -4.0 (5.0), DUL 40 mg BID: -4.0 (4.8), DUL 60 mg BID: -2.5 (5.9), and PAR 20 QD: -3.9 (5.1). **CGI-S** D1: PBO D2: DUL 40 mg BID D3: DUL 60 mg BID D4: PAR 20 mg QD n at baseline: D1: 99 D2: 93 D3: 103 D4: 97 Mean score at baseline (SD): D1: 4.23 (0.67) D2: 4.30 (0.48)	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				D3: 4.30 (0.65) D4: 4.26 (0.58) Mean score at endpoint (SD): D1: 2.53 D2: 2.3 D3: 2.3 D4: 2.16 Patients treated with DUL 60 mg BID had significantly greater improvement on CGI-S scale compared with PBO-treated patients. mean change in CGI-S during continuation phase for each treatment group was as follows: PBO: -0.5 (1.0), DUL 40 mg BID: -0.6 (0.8), DUL 60 mg BID: -0.6 (1.0), and PAR 20 mg QD: -0.6 (0.8). **CGI-I** NR **CGII** No **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** Authors also utilized IRSD-F. Reports given were to validate Sex FX	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				scale by examining correlations between Sex FX total and overall satisfaction scores and IRSD-F total score. A statistically significant negative correlation was found for both men and women between IRSD-F total and Sex FX scores reflecting inverse relation between function on Sex FX and dysfunction on IRSD-F.	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Perahia et al., 2006[115]; Fava et al., 2006[114] **Country and Setting** Multinational (France, Italy, Spain and USA), multicenter **Funding** Eli Lilly **Quality Rating** Fair	**Research objective** DUL vs. PBO in efficacy, safety and tolerability in prevention of relapse of MDD **Drugs, Doses, and Range** D1: DUL 60 mg/day D2: PBO **Study design** RCT **n** 533 in 12 week open label treatment, responders were randomized to DUL (136) or PBO (142) for 26 weeks **Duration** 26 weeks **Type of depression** MDD	**Inclusion criteria** • Adults (age range): at least 18 yrs old • Diagnosed with MDD according to DSM-III or -IV: DSM-IV • HAM-D: 18 or more on 17 item • CGIS: 4 or more • At least 1 other MDE before episode that was being experienced at time of entry **Exclusion criteria** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Current and primary Axis I disorder other than MDD • Anxiety disorder as a primary diagnosis within 1 year of entry to study • Treatment-resistant depression • Clinically significant medical disease • Suicidal tendencies (acute or other) • Serious suicidal risk Note: patients that reacted poorly to 60 mg of DUL could have their dosage reduced for first 2 weeks	**Groups similar at baseline** Yes **n =** Acute phase DUL: 533 D1: 136 D2: 142 **Mean age, years** Acute phase DUL: 43.4 D1: 45.7 D2: 44.8 **Sex, % female** Acute phase DUL: 71.9 D1: 67.6 D2: 77.5 **Race, % white** Acute phase DUL: 89.9 D1: 94.1 D2: 93.0 **Baseline HAM-A** Overall **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** NR **Outpatients/Inpatients** Outpatients **Baseline mean HAM-A > 25?** No	**HAM-D** **Responders, n:** Acute phase DUL: 347 **Remitters, n:** Acute phase DUL: 270 **Mean score at baseline (SD):** D1: 4.9 (2.44) D2: 4.6 (2.44) Acute phase DUL: 23.7 (3.6) **Mean score at endpoint (SD):** D1: 2.92 D2: 7.82 **Mean score change (SD):** Relapse per protocol D1: 23 D2: 39, $P <= 0.05$ Per investigator D1: 29 D2: 59, $P <= 0.001$ **MADRS** NR **CGI-S** **Mean score at baseline (SD):** D1: 1.4 (0.48) D2: 1.4 (0.48) **Mean score at endpoint (SD):** D1: 0.57 D2: 1.47 **CGI-I** NR **QOL scale** NR	**Overall rate of attrition, %** 25.2% discontinued (not counting relaps group that switched treatments-31.3% switched to rescue DUL) **Attrition rate, %** D1: 24.3 D2: 26.1 **Withdrawals due to adverse events, %** D1: 3.7 D2: 3.5 **Attrition due to lack of efficacy, %** D1: 0.7 D2: 2.1 Lack of efficacy is patient reported, as opposed to relapse group that entered rescue **Overall adverse events, %:** NR **Cardiovascular, %:** Acute phase DUL: 0- there were no clinically significant changes in BP or heart rate **Headache, %:** Acute: 20 **Insomnia, %:** Acute phase DUL: 11 **Nausea, %:** Acute: 36 **Vomiting, %:** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
			Mean age at baseline Less than 65 years **Mean HAM-D at baseline** Greater than 17 (moderate to severe)	**Adherence** NR	**Sexual dysfunction, %:** NR **Somnolence (fatigue), %:** Acute: 14 **Suicidality, %:** Acute phase DUL: 1 person at 16 days **Sweating-increased, %:** Acute phase DUL: NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Perahia et al., 2009[141] **Country and Setting** Multinational, multicenter **Funding** Eli Lilly and Company, Boehringer Ingelheim GmbH **Quality Rating** Fair	**Research objective** To assess efficacy of DUL 60-120 mg once daily vs. PBO in prevention of depressive recurrence in outpatients with recurrent major depressive disorder **Drugs, Doses, and Range** D1: DUL 60 mg-120 mg (medium-high dose) D2: PBO **Study design** RCT **n** 288 **Duration** 52 weeks **Type of depression** Recurrent MDDr	**Inclusion criteria** • Adults (age range): 18 years old and over • Diagnosed with MDD according to DSM-III or -IV: • Diagnosis confirmed via MINI, more than 3 episodes of depression within past 5 years and achieved remission between 3 episodes; • Stable and off antidepressants at least 2 months prior to onset of presenting episode • HAM-D: 18 or greater • CGIS: 4 or greater • Met response critieria during 10 week open label acute treatment phase and 24 week open label continuation phase of DUL treatment (60-120 mg/day), which included HAM-D ≤ 9, CGI-S ≤ 2, and did not meet MDD criteria as assessed by MINI **Exclusion criteria** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): bipoloar	**Groups similar at baseline** Yes **n =** D1: 142 D2: 146 Overall: 288 **Mean age, years** D1: 48.0 D2: 47.1 Overall: 47.5 **Sex, % female** D1: 74.6 D2: 68.5 Overall: 71.5 **Race, % white** D1: 97.9 D2: 97.9 Overall: 97.9 **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 100 D2: 100 Overall: 100 **Comments:** • Overall **Outpatients/Inpatients** Outpatients **Baseline mean HAM-A > 25?**	**HAM-D** **Mean score at baseline (SD):** D1: 4.49 (2.51) D2: 4.12 (2.52) **Mean score at endpoint (SD):** D1: 4.36 (0.57) D2: 1.40 (0.53) **Mean score change (SD):** NR • Open label acute treatment phase baseline: 23.07 (3.57) • Open label continuation treatment phase baseline: 6.65 (2.06) **MADRS** NR **Mean score at baseline (SD):** D1: 1.46 (0.50) D2: 1.49 (0.52) **Mean score at endpoint (SD):** D1: 2.34 (0.11) D2: 1.72 (0.11) **Mean score change (SD):** • Open label acute treatment phase baseline: 4.49 (0.60) • Open label continuation treatment phase baseline: 1.83 (0.39) **CGI-S** **Mean score at endpoint (SD):** D1: 0.84 (0.10)	**Overall rate of attrition, %** 21.5 **Intervention** D1: PBO D2: DUL **Attrition rate, %** D1: 18.3 D2: 24.7 **Withdrawals due to adverse events, %** D1: 2.1 D2: 4.1 **Attrition due to lack of efficacy, %** D1: 30.3 D2: 9.6 **Overall adverse events, %:** D1: 62.7 D2: 61.0 **Weight gain, %:** D1: 7.0 D2: 10.3 **Dizziness, %:** D1: 6.3 D2: 3.4 **Headache, %:** D1: 7.7 D2: 8.9 **Hepatotoxicity, %:** D1: high bilirbuin level: 7.7 D2: 8.9 **Insomnia, %:** D1: 6.3 D2: 4.8 **Somnolence (fatigue), %:**

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		disorder, schizophrenia, psychotic disorders • Illicit drug and alcohol abuse: excludes nicotine and caffieine; includes benzodiazepines • Clinically significant medical disease: serious medical illness likely to require hospitalization and/or use of prohibited drugs • Investigational drug use within last: prior treatment history with DUL • Suicidal tendencies (acute or other) • Dysthmia • Any anxiety disorder as a primary diagnosis wihtin past year • An Axis II disorder that would interfere with compliance • Taking any excluded medications (includes centrally acting medications such as antidepressants and antipsychotics) within 7 days prior to visit 2 • Treatment with a MAO inhibitor within 14 days prior to study onset • Treatment with FLUOX within 30 days prior to study onset Abstracted data from double blind maintainence phase of study although study contains data from	NR **Mean age at baseline** Less than 65 years **Mean HAM-D at baseline** Greater than 17 (moderate to severe)	D2: 0.24 (0.10) **QOL scale** SF-36 mental component and physical component scale **Mean score at baseline (SD):** NR **Mean score at endpoint (SD):** NR **Mean summary score change (SD):** Mental: D1: -5.74 (1.20) D2: -1.11 (1.11) Physical: D1: 0.33 (0.76) D2: -0.45 (0.70) • SDS global functioning • PGI-I • SQ-SS • VAS for pain **Adherence** NR **Recurrence** • Recurrence rate at any time (PBO vs. DUL): 33.1% vs. 14.4% ($P < 0.001$) • Rate of loss of response at any time: 46.5% vs. 30.1% ($P = 0.003$) • Remission at end-point: 56.3% vs. 68.3% ($P = 0.025$)	D1: 2.8 D2: 5.5 **Suicidality, %:** D1: 0 D2: 0

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		open label acute and continuation phases Note that answer to question 33 refers to HAMD-17 score at beginning of open-label acute phase.			

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Perry et al., 1989[76] **Country and setting:** United States **Funding:** NR	**Research objective:** To compare clinical efficacy of FLUOX and TRA in patients with major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 40 **Intervention:** D1: FLUOX: 20-60 mg/d D2: TRA: 50-400 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Duration of illness ≥ 1 mo • Outpatient • Unipolar **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease • Investigational drug use within last 4 wks • Suicidal tendencies • Hypertensive patient using guanethidine, reserpine, clonidine, or methyldopa	**Mean age (yrs):** D1: 42 D2: 39 **Sex, male:female ratio** D1: 9:12 D2: 10:9 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline (SD):** D1: 23.2 (2.8) D2: 23.6 (3.0)	At endpoint no sig diffs in health outcomes between FLUOX and TRA	**Overall adverse events:** Reported 2+ events, % D1: 43 D2: 37 **Cardiovascular adverse events:** D1: 0 D2: 11 **Diarrhea:** D1: 14 D2: 0 **Dizziness:** D1: 14 D2: 21 **Headache:** D1: 29 D2: 26 **Nausea:** D1: 24 D2: 26 **Somnolence (fatigue):** D1: 19 D2: 37	**Overall attrition rate:** 20% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Petrakis et al., 1998[246] **Country and setting:** US Teaching hospital **Funding:** National Institute on Drug Abuse	**Research objective:** To evaluate efficacy of FLUOX in treating depression in methadone-maintained opioid addicts **Duration of study:** 3 mos **Study design:** RCT **Overall study N:** 44 **Intervention:** D1: FLUOX: 20-60 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 14 • Methadone-maintained opioid addiction • > 8 on BDI; medically healthy **Exclusion criteria:** • Additional mental illnesses or organic mental disorder	**Mean age (yrs):** D1: 35.4 D2: 33.3 **Sex (% female):** D1: 39.1 D2: 33.3 **Race (% white):** D1: 91.3 D2: 85.7 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 14 (4.9) D2: 14.9 (5.8)	In entire sample, BDI and HAM-D scores decreased sig in both groups (Z score = 2.37; *P* = 0.01; Z score = 5.85, *P* < 0.01); no sig diffs between PBO and FLUOX treated patients. Among subjects with major depression (n = 31), there were no sig diffs in rate of change of depressive symptoms by treatment group over time Concomitant heroin use and ASI scores decreased sig for both groups (z = 2.92, *P* < 0.01; z = 2.66, *P* < 0.01); no sig diff between groups	NR	**Overall attrition rate:** 15.9% **ITT Analysis** No **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events	Analysis Quality Rating
Author: Philip et al., 2000[216] **Country and setting:** Autralia, Germany; outpatient private practice **Funding:** Not reported	**Research objective:** To compare emergent sexual effects of moclobemide and SSRIs during acute and maintenance therapy in routine practice **Duration of study:** 6 mo **Study design:** Prospective cohort study **Overall study N:** 268 **Intervention:** D1: FLUOX: 20-60 mg/d D2: FLUV: 50-300 mg/d D3: PAR: 10-50 mg/d D4: SER: 50-150 mg/d D5: Other: moclobemide 300-1200 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Depressive disorder of at least mild severity • On either moclobemide or SSRI (FLUOX, FLUV, PAR, SER) • Interested in sexual activity **Exclusion criteria:** • No combination therapy	**Mean age (yrs):** Overall: 42 **Sex (% female):** Overall: 49.8 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Incidence of sexual function impairment was 61.5% (Phys-SFR) with SSRIs. Male erection and ejacualation impaired in 44.3% and 39.3% of SSRI group, respectively. No statistical diff between each SSRI Higher rates in SSRI's vs. moclobemide	NR	**Overall attrition rate:** 27.2% **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Poirier and Boyer, 1999[142] **Country and setting:** France inpatients and outpatients **Funding:** Wyeth-Lederle	**Research objective:** To compare efficacy and safety of PAR and VEN in patients with treatment resistant depression **Duration of study:** 4 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** D1: PAR: 30-40 mg/d D2: VEN: 200-300 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Depression duration less than 8 mos • For current episode, history of resistance to 2 previous antidepressant treatments, 2nd of which had to have been prescribed by investigator prior to study • Adults 19 to 60 • HAM-D $\geq$ 18 **Exclusion criteria:** • Pregnant/Lactating • Suicidal tendencies • Illicit drug or alcohol abuse • Concomitant psychotheraputic or psychotropic medications • ECT • Additional mental illnesses or organic mental disorder not related to depression • VEN or PAR during current episode	**Mean age (yrs):** D1: 42.5 D2: 44.1 **Sex (% female):** D1: 73.8 D2: 69.4 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 24.6 (3.9) D2: 24.5 (4.1)	HAM-D Response: VEN 45% PAR 36% (*P* = 0.07) HAM-D Remission: VEN 37% PAR 18% (*P* = 0.02) Mean change in HAM-D: VEN -11.1 (8.5) PAR -10.2 (6.8) (*P* = 0.55) CGI-I improvement (1 or 2): VEN 73% PAR 84% (*P* = 0.39)	Overall adverse events: D1: 69 D2: 63 Diarrhea: D1: 2.9 D2: 4.2 Headache: D1: 6.7 D2: 4.2 Insomnia: D1: 4.8 D2: 1.0 Nausea: D1: 14.3 D2: 15.6 Somnolence (fatigue): D1: 2.9 D2: 9.4	**Overall attrition rate:** 11.4% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rabkin et al., 2004[247] **Country and setting:** US Outpatient **Funding:** Lilly (provided tablets); Pharmacia and Upjohn (provided coded vials) National Institute of Mental Health	**Research objective:** To determine whether testosterone and FLUOX is superior to PBO for depression, fatigue, or both **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** D1: FLUOX: 20-60 mg/d D2: PBO Testosterone 200-400 mg biwkly	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • HIV seropositive • Dysthymia • Male • Negative PSA • Agreement of primary healthcare provider **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use within last 5 wks • ECT • Suicidal tendencies • Psychotherapy started in last mo • Use of anabolic steroids • Current/anticipated change in ARV regimen within 4 wks • Unprotected intercourse with partners of unknown or negative HIV status	**Mean age (yrs):** D1: 40 D2: 41 **Sex (% female):** D1: 0 D2: 0 **Race (% white):** D1: 21.7 D2: 23.1 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 18.2 (4.5) D2: 16.8 (3.3)	No statistically different outcomes between treatment groups. HAM-D response (52% [FLUOX] vs. 51% [PBO] [*P* = 0.66]) and remission (50% [FLUOX] vs. 51% [PBO] [*P* = 0.59]) rates	**Changes in weight (decrease):** D1: 9 **Diarrhea:** D1: 4 **Headache:** D1: 9 **Insomnia:** D1: 4 **Nausea:** D1: 7 **Sexual dysfunctional (male ejaculation):** D1: 6 **Somnolence (fatigue):** D1: 7	**Overall attrition rate:** 26.8% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Rapaport et al., 1996[77] **Country and setting:** United States, multicenter **Funding:** Solvay Pharmaceuticals, Inc.; Upjohn Company	**Research objective:** To compare efficacy, safety, and tolerance of FLUV and FLUOX in a depressed outpatient population **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** D1: FLUV: 100-150 mg; endpoint mean = 101.85 (25.22) D2: FLUOX: 20-80 mg; endpoint mean = 34.17 (18.84)	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Minimum score of 2 on depressed mood item at screening and baseline visits (HAM-D) **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Previous treatment with FLUOX or FLUV • History of seizure disorder	**Mean age (yrs):** D1: 40.0 D2: 38.6 **Sex (% female):** D1: 62 D2: 63.2 **Race (% white):** D1: 92.2 D2: 98 **Baseline (HAM-A):** D1: 16.0 D2: 16.2 **Baseline HAM-D:** D1: 25.2 D2: 25.6	No statistically sig diffs observed between 2 groups on any efficacy parameter Medications were well tolerated, with only 2 patients in each group terminated because of side effects. FLUV was associated with less nausea than FLUOX	**Headache:** D1: 50 D2: 53 **Insomnia:** D1: 36 D2: 28 **Nausea:** D1: NR D2: 42.5 *P* = 0.030 **Suicidality:** D1: 2 D2: 2 **Vomiting** D1: 4 D2: 13	**Overall attrition rate:** 16% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rapaport et al., 2003[78] **Country and setting:** US and Canada Multicenter (31) **Funding:** GlaxoSmithKline	**Research objective:** Efficacy and safety of PAR CR and IR vs. PBO in late life depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 310 **Intervention:** D1: PAR CR 12.5-50 D2: PAR IR 10-40 mg/d D3: PBO	**Inclusion criteria:** • Adults > 59 yrs • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • ECT within last 3 mos • Suicidal tendencies • History of brief depressive episodes with spontaneous remission • Neuological disorders contributing to secondary depression • Dementia • MMSE ≤ 24	**Mean age (yrs):** D1: 70.4 D2: 70.1 D3: 69.4 **Sex (% female):** D1: 48.1 D2: 56.6 D3: 63.3 **Race (% white):** D1: 96.2 D2: 95.3 D3: 94.5 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 22.1(3.45) D2: 22.3(3.15) D3: 22.1(3.0)	PAR CR and IR were more effective than PBO, with mean +/- SD endpoint HAM-D total scores of 10.0 +/- 7.41 (*P* = 0.007) and 10.0 +/- 7.10 (*P* = 0.003), respectively, compared with 12.6 +/- 7.34 for PBO. Response (a score of 1 or 2 on CGI-I scale) was achieved by 72% of PAR CR patients (*P* < 0.002 vs. PBO), 65% of PAR IR patients (*P* = 0.06 vs. PBO), and 52% of PBO patients. Remission, defined as HAM-D total score ≤ 7, was achieved by 43% of PAR CR patients (*P* = 0.009 vs. PBO), 44% of PAR IR patients (*P* = 0.01 vs. PBO), and 26% of PBO patients	**Insomnia:** D1: 9.6 D2: 14.2 D3: 8.3	**Overall attrition rate:** 24.4% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rapaport et al., 2004[143] **Country and setting:** United States Multicenters (53 sites) **Funding:** Forest Labs	**Research objective:** Evaluation of efficacy and safety of continuation ESC treatment **Duration of study:** 36 wks **Study design:** RCT **Overall study N:** 274 **Intervention:** D1: ESC: 10-20 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 to 81 • Diagnosed with MDD according to DSM-III or -IV • MADRS of 22 or more **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Suicidial tendencies	**Mean age (yrs):** D1: 42.9 D2: 41.8 **Sex (% female):** D1: 60.2 D2: 62.4 **Race (% white):** D1: 86.7 D2: 84.9 **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 7.7 (4.6) D2: 6.6 (4.6) (P < = 0.05)	Time to depression relapse was sig longer (P = 0.013) and cumulative rate of relapse was sig lower in patients who received ESC (26% ESC vs. 40% PBO; hazard ratio = 0.56; P = 0.01). ESC-treated subjects had sig lower depression ratings than PBO-treated patients	**Headache:** D1: 8.8 D2: 8.6 **Insomnia:** D1: 5.5 D2: 7.5 **Nausea:** D1: 5.5 D2: 4.3	**Overall attrition rate:** 55% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Raskin, 2007;[171] Raskin, 2008;[170] Raskin, et al., 2008;[257] Wohreich et al., 2009;[251] Wise et al., 2007[258] **Country and Setting** United States; multicenter **Funding** Eli Lilly and Company, Boehringer Ingelheim Corporation **Quality rating:** Fair	**Research objective** To compare time to antidepressant and painful symptom response for DUL vs. PBO in elderly patients with MDD. **Drugs, Doses, and Range** D1: DUL (40-60 mg 1-2 x daily): 60 mg; medium D2: PBO **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** Yes **Study design** RCT **Duration** 8 weeks **Type of depression** Recurrent MDD **Intervention** D1: PBO D2: DUL	**Inclusion criteria:** • Adults (age range): 65 years old or greater • Diagnosed with MDD according to DSM-III or -IV; HAM-D: 18 or greater on visits 1 and 2; MMSE Score of 20 or greater, with or without mild dementia; at least one previous episode of major depression **Exclusion criteria:** • Previous diagnosis of psychotic disorder; psychological condition • Clinically significant medical disease • Current primary Axis I diagnosis other than MDD or mild dementia • Moderate to severe dementia • Mental retardation **Outcome measures** • HAM-D • Quality of life scales: VAS overall pain severity • GDS	**Groups similar at baseline** Yes **n =** D1: 104 D2: 207 Overall: 311 **Mean age, years** D1: 73.3 D2: 72.6 Overall: NR **Sex, % female** D1: 57.7 D2: 60.4 Overall: NR **Race, % white** D1: 78.8 D2: 77.8 Overall: NR **Baseline HAM-A** NR Overall: NR **Insomnia, %** NR Overall: NR **Concomitant anergia, %** NR Overall: NR **Experienced prior depressive episodes, %** D1: 100 D2: 100 Overall: 100 **Comments:** NR	**HAM-D** No. of responders: D1: 16 D2: 86 (*P* >0.001) No. of remitters: D1: 15 D2: 67 (*P:* 0.009) Mean score at baseline (SD): Screening: D1: 22.0 (3.6) D2: 22.4 (3.8) Pre-randomization: D1: 18.9 (4.5) D2: 18.8 (4.8) Percent of Responders D1: 15.6 D2: 41.9 Percent of Remission D1: 15.3 D2: 32.5 Used n = 104 for PBO and n = 207 for DUL. PBO referenced DUL hazard ratios for HAMD-17 response was 2.03 (*P:* 0.002) and for remission 2.01 (*P:* 0.006). HAMD response, remission, and total scores - all treatment-by-comorbidity interactions *P*s: NS[258] GDS total scores - all treatment-by-comorbidity interactions *P*s: NS[258] **MADRS** No. of responders:	**Diarrhea, %:** D1: 1.9 D2: 8.2 **Nausea, %:** D1: 3.8 D2: 12.6 **Attrition** **Overall attrition, %:** 22.2 **Attrition rate, %:** D1: 23.1 D2: 21.7 **Withdrawals due to adverse events, %** D1: 9.7 D2: 8.7 **Withdrawals due to lack of efficacy, %** D1: 9.6 D2: 2.9 **Comments** • Attrition is for discontinuation during acute therapy phase. • Discontinuation due to AEs –all treatment-by-comorbidity interactions *P* = NS[259]

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				D1: 16 D2: 86 (*P* >0.001) Mean score at baseline (SD): D1: Screening: 22.0 (3.6); pre-randomization: 18.9 (4.5) D2: 22.4 (3.8); 18.8 (4.8) **CGI-S** All treatment-by-comorbidity interactions *P*s: NS[258] **CGI-I** NR **CGII** No **QOL scale** VAS overall pain severity Mean score at baseline (SD): D1: 33.53 (28.4) D2: 30.10 (25.8) Percent that demonstrated a sig increase in VAS overall pain response- PBO: 32.4%; DUL: 41.9% (*P:* 0.331). Response defined as a 50% or greater reduction of VAS overall pain. The PBO-referenced DUL hazard ratio for time to 50% reduction in overall pain was 1.75 (*P:* 0.024) for patient with moderate to severe pain. VAS*Baseline difference by subgroups[258]	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				Headache pain - all treatment-by-comorbidity interactions *P:* NS Shoulder pain - all treatment-by-comorbidity interactions *P:* NS Overall pain - arthritis (DUL -7.97 vs. PBO 1.29, *P:* 0.052) vs. no arthritis (DUL -1.27 vs. PBO -6.13, *P:* 0.241), interaction variable *P:* 0.037; vascular (DUL 1.81 vs. PBO 11.59, *P:* 0.059) vs. no vascular (DUL -7.79 vs. PBO -7.13, *P:* 0.868), interaction variable *P:* 0.077; all other treatment-by-comorbidity interactions *P:* NS Interference with daily activities - arthritis (DUL -4.85 vs. PBO 3.52, *P:* 0.067) vs. no arthritis (DUL -1.53 vs. PBO -6.75, *P:* 0.198), interaction variable *P:* 0.057; all other treatment-by-comorbidity interactions *P:* NS Back pain - arthritis (DUL -8.79 vs. PBO 5.96, *P* < 0.001) vs. no arthritis (DUL –2.08 vs. PBO -6.64, *P:* 0.227), interaction variable *P:* 0.001; all other treatment-by-comorbidity interactions *P:* NS Time in pain while awake - vascular (DUL -2.05 vs. 10.01, *P:* 0.048) vs. no	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				vascular (DUL -8.28 vs. PBO -5.30, *P:* 0.477) interaction 0.090; all other treatment-by-comorbidity interactions *P:* NS **Another QOL scale** SF-36 physical*(Baseline differences) and mental components[258] all treatment-by-comorbidity interactions *P:* NS **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Ravindran et al., 2000[79] **Country and setting:** Canada and Europe Multicenter **Funding:** Pfizer, Inc	**Research objective:** To determine safety, tolerability, and efficacy of SER vs. PBO in treatment of dysthymia **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 310 **Intervention:** D1: SER: 50-200 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 or older • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 12 • Dysthymia • Duration ≥ 5 yrs **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder	**Mean age (yrs):** D1: 46.0 D2: 44.2 **Sex (% female):** D1: 65.8 D2: 67.8 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 19.2 (6.98) D2: 18.6 (6.62)	Number of responders sig higher in SER group HAM-A: D1: 51.9 D2: 33.8% (*P* = 0.001) MADRS: D1: 53.2% D2: 37.5% (*P* = 0.006) CGI-I: D1: 60.1% D2: 39.5%, (*P* < 0.001) Number of remitters was also sig higher in SER group 33.8% vs. 21.6% (*P* = 0.02) BQOL showed sig greater improvements in 8 of 9 domains in SER group	**Overall adverse events:** D1: 75.3 D2: 64.5 **Constipation:** D1: 6.3 D2: 3.3 **Diarrhea:** D1: 12.7 D2: 7.2 **Dizziness:** D1: 12.7 D2: 3.9 **Headache:** D1: 30.4 D2: 33.6 **Insomnia:** D1: 22.2 D2: 16.4 **Nausea:** D1: 20.9 D2: 17.8 **Sexual dysfunction :** D1: 9.3 D2: 0 **Somnolence (fatigue):** D1: 11.4 fatigue-7.0 D2: 7.2 fatigue-2.6 **Sweating (increase):** D1: 13.9 D2: 2	**Overall attrition rate:** 24.2% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Reimherr et al., 1998[144] **Country and setting:** United States 5 outpatient psychiatric clinics **Funding:** Lilly Research Laboratories	**Research objective:** To determine prospectively optimal length of therapy in long-term, PBO-controlled continuation study of patients who responded to acute FLUOX treatment for major depression **Duration of study:** 50 wks **Study design:** RCT **Overall study N:** 395 (randomized) **Intervention:** D1: FLUOX 20 mg/d 14 wks D2: FLUOX 20 mg/d 38 wks D3: FLUOX 20 mg/d 50 wks D4: PBO	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Type II bipolar disorder **Exclusion criteria:** • Type I bipolar disorder	**Mean age (yrs):** D1: 40.1 D2: 40.3 D3: 40.3 D4: 40.5 **Sex (% female):** D1: 64.9 D2: 70 D3: 62.7 D4: 80.2 **Race (% white):** D1: 97.9 D2: 96 D3: 93.1 D4: 87.5 **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 20.5 (3.4) D2: 20.5 (3.6) D3: 20.5 (3.6) D4: 21.5 (3.7)	Relapse rates lower among patients who continued to take FLUOX compared with those transferred to PBO in both first interval, after 24 total wks of treatment (FLUOX, 26.4%; PBO, 48.6%, $P < 0.001$), and second interval, after 38 total wks of treatment (FLUOX, 9.0%; PBO, 23.2% $P < 0.04$) In third interval, after 62 total wks of treatment, rates were not sig different between groups (FLUOX, 10.7%; PBO, 16.2% $P = 0.54$)	NR	**Overall attrition rate:** N/A **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Reynolds et al., 2006[145] **Country and Setting** United States; university-based clinic **Funding** National Institute of Mental Health; National Center for Minority Health and Health Disparities **Quality Rating** Fair	**Research objective** To assess whether long-term antidepressant treatment with PAR would affect recurrence of depression in those 70 years old or older **Drugs, Doses, and Range** • PAR (10-60 mg 1 x daily): Acute phase: 10 mg/day (low) titrate to max of 40 mg/day (medium). Dose tapered down during maintainence phase. • PBO • monthly psychotherapy; • monthly clinical management sessions **Study design** RCT **n** 116 **Duration** 2 years **Type of depression** Major depressive disorder	**Inclusion criteria** • Adults (age range): 70 years old and older • Diagnosed with MDD according to DSM-III or -IV: DSM-IV (nonpsychotic and nonbipolar) • HAM-D: at least 15 • Folstein Mini-Mental State Exam score of at least 17 **Exclusion criteria** Before double blind maintaince phase of study (n = 116); study started with 195 patients on acute treatment. 151 patients with clinical response (HAM-D score of 0-10 for 3 weeks) had 16 weeks of continued treatment and 116 patients that maintained efficacy were randomized. 38 of patients were receiving augmented pharmacotherapy (BUP, nortriptyline, or lithium) and 19 randomized to PAR arm continued augmented pharmacotherapy. other 19 randomized to PBO did not continue augmented pharmacotherapy.	**Groups similar at baseline** Yes **n =** D1: 28 D2: 35 D3: 35 D4: 18 **Intervention** D1: PAR + psychotherapy D2: PAR + clinical management D3: PBO + psychotherapy D4: PBO + clinical management **Mean age, years** D1: 77.6 D2: 77.0 D3: 77.4 D4: 74.8 **Sex, % female** D1: 68 D2: 60 D3: 71 D4: 56 **Race, % white** D1: 93 D2: 91 D3: 94 D4: 94 **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior**	**HAM-D** **Intervention** D1: PAR + psychotherapy D2: PAR + clinical management D3: PBO + psychotherapy D4: PBO + clinical management **n at baseline:** D1: 28 D2: 35 D3: 35 D4: 18 **Responders, n:** N/A **Remitters, n:** N/A **Mean score at baseline (SD):** D1: 6.0 (2.9) D2: 4.9 (2.7) D3: 5.5 (2.7) D4: 5.8 (2.2) **Mean score at endpoint (SD):** NR **Mean score change (SD):** NR Baseline scores reported are scores at randomization (start of maintenance). Recurrence defined as a major depressive episode was defined by DSM-IV criteria and a HAM-D score of at least 15. This was confirmed by a geriatric	**Overall rate of attrition, %** 21.6 **Intervention** D1: PAR + psychotherapy D2: PAR + clinical management D3: PBO + psychotherapy D4: PBO + clinical management **Attrition rate, %** D1: 32.1 D2: 20.0 D3: 17.1 D4: 16.7 **Withdrawals due to adverse events, %** D1: 10.7 D2: 2.9 D3: 0.0 D4: 0.0 **Attrition due to lack of efficacy, %** N/A **Overall adverse events, %:** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc.	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
			depressive episodes, % D1: 43 D2: 40 D3: 40 D4: 39 **Comments:** NR **Outpatients/Inpatients** Outpatients **Baseline mean HAM-A > 25?** NR **Mean age at baseline** Equal to or greater than 65 years **Mean HAM-D at baseline** Greater than 17 (moderate to severe)	psychiatrist. Rate of recurrence (D1, D2, D3, D4, respectively): 35%; 37%; 68%; 58%. **MADRS** NR **CGI-S** NR **CGI-I** NR **CGI** NR **QOL scale** NR **Adherence** Rate of non-compliance, % D1: 3.6 D2: 2.9 D3: 0.0 D4: 0.0 **Recurrence** Both PAR+ psychotherapy and PAR+clinical management were superior to PBO+psychotherapy (P = 0.03; P = 0.03; respectively) and PBO+clinical management (P = 0.05; P = 0.06; respectively). relative risk of recurrence in PBO arm was 2.4 times that of PAR arm (95% CI, 1.4-4.2).	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Rickels et al.2010[146] **Country and Setting** Multinational, multicenter **Funding** Wyeth - Pfizer **Quality rating:** Fair	**Research objective** efficacy and safety of desvenlafaxine with placebo in reducing relapse rate in patients with major depressive disorder **Drugs, Doses, and Range** OL: 12 week open label phase desvenlafaxine 200 or 400 mg/d D1: Desvenlafaxine 200 or 400 mg/d D2: Placebo **Flexible dose** **Dosages equivalent - No** **Study design** Open label for 12 weeks followed with RCT of 6 months **Duration** 6 months **Type of depression** • MDD	**Inclusion criteria:** • Male and female outpatients, • 18 to 75 years of age, • primary diagnosis of MDD , single or recurrent episode, symptoms for at least 30 days • HAM-D_{17} > 20, score at least 2 on item 1 (depressed mood) • CGI-S > 4 7 **Exclusion criteria:** • substance use disorders; • desvenlafaxine at any time in the past, • venlafaxine within 90 days, or known hypersensitivity • risk of suicide based on clinical judgment; • pregnant, breast-feeding, or planning to become pregnant during the study; • current manic episodes, PTSD, OCD, or clinically important personality disorder; • depression associated with an organic mental disorder due to a general medical condition or neurological disorder; seizure disorder; or clinically important medical disease	**Groups similar at baseline** **n =** OL: 594 D1: 190 D2: 185 **Mean age, years** OL: 41.9 D1: 42.7 D2: 42.8 **Sex, % female** OL: 68 D1: 67 D2: 68 **Race, % white** OL: 85 D1: 89 D2: 87 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** **Comments:** NR	**HAM-D** Mean score at baseline (SD): OL: 24.2 (3.0) D1: 5.6 (3.2) D2: 5.4 (3.2) % patients relapsing during 6 month RCT : D1: 24% (45/189) D2: 42% (78/185) *P* < 0.001 Remission at 6 months): D1: 69% D2: 44% *P* < 0.001 **CGI-S** Mean score at baseline (SD): OL: 4.51 (0.61) D1: 1.6 (0.7) D2: 1.7 (0.7) **CGI-I** NR **QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR	**Attrition** **Overall attrition, %:** OL: 30 D1: 31 D2: 55 **Attrition rate, %:** OL: 30 D1: 31 D2: 55 **Withdrawals due to adverse events, %** OL: 116/594 D1: 11% 21/190) D2: 18% (33/185) **Withdrawals due to lack of efficacy, % (n)** OL: NR D1: 15% (88) D2: 32% (28) **TEAEs, %:** OL: 90% D1: 73% D2: 82%

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Robert et al., 1995[147] **Country and setting:** France, multicenter outpatient trial **Funding:** NR	**Research objective:** To evaluate whether there was therapeutic benefit in continuation treatment for patients with depression who had responded favorably to CIT **Duration of study:** 6 mos (24 wks) **Study design:** RCT **Overall study N:** 226 **Intervention:** D1: CIT: 20-60 mg/d D2: PBO	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • MADRS < 12 after 8 wks on CITor PBO **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Depression lasted for >3 mos	**Mean age (yrs):** D1: 49.5 D2: 46.5 **Sex (% female):** D1: 69% D2: 73% **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 4.7 (3.6) D2: 5 (3.4)	# relapses (defined as a MADRS>25 and clinical judgment of investigator): D1: 21 (13.8%) D2: 18 (24.3%) *P* = 0.04	**Constipation:** D1: 15 D2: 5	**Overall attrition rate:** N/A **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Rosenberg et al., 2010[248] **Country and Setting** US; Multicenter (5 memory clinics) **Funding** NIMH **Quality rating:** Fair	**Research objective** Assess the efficacy and tolerability of sertraline for depression in AD **Drugs, Doses, and Range** D1: SER 50-100 mg/d D2: PBO **Flexible dose** Yes **Dosages equivalent** N/A **Study design** RCT **Duration** 12 weeks **Type of depression** MDD	**Inclusion criteria:** • Adults • Met DSM-IV criteria for dementia of AD • MMSE scores from 10-26 • Met criteria for depression of Alzheimers Disease (3 or more symptoms within a 2-week period, one of which must be depressed mood or anhedonia, with the addition of irritability as possible symptom) **Exclusion criteria:** • Taking psychotics, antidepressants or benzodiazepines	**Groups similar at baseline** **n =** D1: 67 D2: 64 **Mean age, years** D1: 6.5 D2: 78.2 Overall 77.3 **Sex, % female** D1: 59.7 D2: 48.4 **Race, % white** D1: 73.1 D2: 60.9 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes before cognitive symptoms, %** D1: 22.4 D2: 29.7	**HAM-D** NR **MADRS** NR **CGI-S** NR **CGI-I** NR OR of being at or better than a given CGIC category for SER vs. PBO: 1.01 (95% CI: 0.52-1.97), *P* = 0.98 **CSDD Difference** 1.20 (-1.65 to 4.05) **Remission, %:** CSDD score ≤6 and mADCS-CGIC ≤2 D1: 33 D2: 19 OR 2.06 (95% CI: 0.84-5.04), *P* =0.11 **Rate of adherence or compliance, % (95% CI):** D1: 83.1 (78.1-88.1) D2: 90.1 (86.3-93.8) *P* = 0.03	**Attrition** **Overall attrition, %:** 16 **Attrition rate, %:** D1: 18 D2: 14 **Withdrawals due to adverse events, %** D1: 7.5 D2: 4.7 **Diarrhea, n:** D1: 34 D2: 19 *P* = 0.02 **Dizziness, n:** D1: 39 D2: 19 *P* = 0.001 **Dry mouth, n:** D1: 30 D2: 17 *P* = 0.04 **Headache, n:** D1: 29 D2: 22, *P* = 0.37 **Indigestion, n:** D1: 23 D2: 11 *P* = 0.03 **Serious AEs, n:** D1: 19.7 D2: 11.1 *P* = 0.23

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rossini et al., 2005[80] **Country and setting:** Italy One inpatient center **Funding:** NR	**Research objective:** To compare efficacy and tolerability of FLUV and SER in elderly patients **Duration of study:** 7 wks (after a 7-day single-blind PBO washout) **Study design:** RCT **Overall study N:** 93 **Intervention:** D1: FLUV: 200 mg/d (100mg twice daily) D2: SER: 150 mg/d (75mg twice daily)	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 21 • 59 yrs of age and older • MDD diagnosed by MD using unstructured interviews and medical records according to DSM-IV, and after a best estimate procedure **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • MMSE score <23 • Nonreversible MAOI or slow release neuroleptics within 1 mo of study • Bipolar patients had to be on mood stabilizers • Depression or bipolar disorder due to a medical condition or induced by a substance	**Mean age (yrs):** D1: 67.80 D2: 68.24 **Sex (% female):** D1: 61.5 D2: 82.2 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 31.23 (5.12) D2: 29.23 (3.45)	HAM-D: No sig diff in final response rates found between 2 treatment groups, 55.6% (25/45) and 71.8% (28/39) for SER and FLUV (P = 0.12). Repeated-measures analysis of variance on HAM-D scores revealed a sig different decrease of depressive symptoms between 2 treatment groups, favoring FLUV (P = 0.007)	NR	**Overall attrition rate:** 4.5% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rudolph and Feiger, 1999[81] **Country and setting:** United States Multicenter (12 outpatient psychiatric practices) **Funding:** Wyeth-Ayerst International	**Research objective:** Comparison of efficacy and tolerability of VEN XR to FLUOX **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 203 **Intervention:** D1: VEN: XR 75-225 mg/d D2: FLUOX: 20-60 mg/d D3: PBO	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression • Illicit drug and alcohol abuse • Bipolar disorder	**Mean age (yrs):** D1: 40 D2: 40 D3: 40 **Sex (% female):** D1: 73 D2: 69 D3: 64 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25 D2: 26 D3: 25	No sig diff between VEN and FLUOX treatment on 21-HAM-D or MADRS at endpoint in LOCF analysis At wk 8 of LOCF, 57% of VEN group and 50% of FLUOX group (*P* = NR) were HAM-D responders At end of treatment 37% of VEN group and 22% of FLUOX ($P \leq 0.05$) group were in remission (HAM-D score ≤ 7) At endpoint in LOCF analysis, VEN patients showed a sig diff from PBO in MADRS, CGI, and HAM-D depressed mood item FLUOX patients only showed a sig diff in HAM-D depressed mood item	**Changes in weight (decrease):** D1: 9 D2: 10 **Diarrhea:** D1: 14 D2: 19 **Dizziness:** D1: 26 D2: 6 **Nausea:** D1: 36 D2: 20 **Somnolence (fatigue):** D1: 8 D2: 12 **Sweating (increase):** D1: 10 D2: 8	**Overall attrition rate:** 23% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rush et al., 2006[148] Rush et al, 2006,[149] Trivedi et al. 2006,[156] Fava et al. 2006,[260]* Nierenberg et al. 2006,[261]* McGrath et a. 2006,[262]* Fava et al. 2008[254]* Rush et al. 2008,[263]* Warden et al. 2009[264]* **Country and setting:** United States Primary and psychiatric public and private practices **Funding:** NIMH *Supplemental Data	**Research objective:** To compare remission rates among antidepressant treatment strategies in patients with major depressive disorder and anxiety that did not respond or tolerate CIT (only level 2 and 3 medication arms abstracted) **Duration of study:** 14 wks for each treatment interval **Study design:** RCT **Overall study N:** Level 1; 3671 Level 2: 1439 Switch: 727 Augment: 565 Level 3: 359 Switch: 226 Augment: 133 Level 4: 105 **Intervention:** **Level 2** ***Switch*** **D1:** Bupropion: SR 150-400 mg/d **D2:** Sertraline: 50-200 mg/d **D3:** Venlafaxine: XR 37.5-375 mg/d ***Augment*** **D4:** Citalopram plus bupropion SR 200-400 mg/d **D5:** Citalopram plus	**Inclusion criteria:** • Adults 18 and over • QIDS-C-16 > 5 **Exclusion criteria:** • NR	**Mean age (yrs):** **D1:** 41.9 **D2:** 42.6 **D3:** 41.1 **D4:** 40.8 **D5:** 41.5 **D6:** 45.1 **D7:** 44.8 **D8-11:** 40.6 **D12-15:** 43.2 Sex (% female): **D1:** 56.9 **D2:** 55.0 **D3:** 64.0 **D4:** 61.6 **D5:** 55.9 **D6:** 51.2 **D7:** 42.1 **D8-11:** 60.9 **D12-15:** 56.2 Race (% white): **D1:** 74.9 **D2:** 78.2 **D3:** 74.4 **D4:** 79.2 **D5:** 76.9 **D6:** 76.0 **D7:** 80.7 **D8-11:** 85.5 **D12-15:** 80.8 Baseline HAM-A: NR Baseline HAM-D: **D1:** 18.5 (7.7) **D2:** 19.3 (6.9) **D3:** 18.9 (7.3) **D4:** 15.4 (6.8) **D5:** 16.2 (7.3) **D6:** 18.6 (5.9)	HAM-D Remission at end of study: **Level 2** **Switch strategy** **D1:** 21.3% **D2:** 17.6% **D3:** 24.8% (*P* = 0.16) **Augmentation strategy** **D4:** 29.7% **D5:** 30.1% (*P* = 0.93) **Level 3** **Switch strategy** **D6:** 19.8% **D7:** 12.3% (*P*=0.27) **Augmentation strategy** **D8-11:** 15.9% **D12-15:** 24.7% *(P* = 0.43) QIDS SR Remission / Response % **Level 1 (N=3,671)** 36.8 / 48.6 **Level 2 (N=1,439)** **Switch strategy** (N=727) 27.0 / 27.3 **D1:** (N=239) 25.5 / 26.1 **D2:** (N=238) 26.6 / 26.7 **D3:** (N=250) 25.0 / 28.2 (*P* > 0.05) **Augmentation strategy** (N=565) 35.0 / 29.9 **D4:** (N=279) 39.0 / 31.8 **D5:** (N=286) 32.9 / 26.9 (*P* = 0.13) **Level 3 (N=359)** **Switch strategy** (N=226) 10.7 / 15.6 **D6:** (N=116) 12.9 / 17.2 **D7:** (N=110) 8.3 / 13.9 (*P* = 0.45 / 0.57) **Level 3** **Augmentation strategy**	Serious AEs **Level 2** **Switch strategy** **D1:** 2.1% **D2:** 4.2% **D3:** 2.4% **(***P* > 0.05) **Augment strategy** **D4:** 3.6% **D5:** 4.2% **(***P* > 0.05) **Level 3** **Switch strategy** **D6:** 2.5% **D7:** 3.5% (*P* = 0.65) **Augment strategy** **D8-11:** 7.2% **D12-15:** 4.1% (*P* = 0.66) Serious Psychiatric AEs **Level 2** **Switch strategy** **D1:** 0.4% **D2:** 1.3% **D3:** 0.8% **(***P* > 0.05) **Augment strategy** **D4:** 1.1% **D5:** 2.1% **(***P* > 0.05) **Level 3** **Switch strategy** **D6:** 0.8% **D7:** 3.5% (*P* = 0.16) **Augment strategy** **D8-11:** NR **D12-15:** NR	Intolerance rate % - Proportion of participants who left the level prior to 4 weeks for any reason and those who left thereafter whose exit form indicated intolerance Level 1 (N=3,671) 16.3 Level 2 (N=1,439) 19.5 Switch strategy (N=789) 22.6 D1: (N=239) 27.2 D2: (N=238) 21.0 D3: (N=250) 21.2 (*P* > 0.05) Augmentation strategy (N=650) 15.8 D4: (N=279) 12.5 D5: (N=286) 20.6 (*P* < 0.0009) Level 3 (N=359) 25.9 Switch strategy (N=226) 32.3 D6: (N=116) 32.8 D7: (N=110) 31.8 Augmentation strategy (N=133) 15.0 D8-11: (N=63) 20.6 D8: (N=18) 22.2 D9: (N=24) 8.3 D10: (N=14) 45.5 D11: (N=10) 20.0 D12-15: (N=70) 10.0 D12: (N=8) 12.5 D13: (N=37) 8.1 D14: (N=10) 10.0 D15: (N=15) 13.3 Features associated with Level 2 remission Odds ratio (95%CI) Age range, y 18-25 y -- 1 [Reference]

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
	buspirone 15-60 mg/d **Level 3** ***Switch*** **D6:** Nortriptyline 75-150 mg/d **D7:** Mirtazapine 15-60 mg/d ***Augment*** **D8-11: Lithium** **D8:** Bupropion SR plus Lithium 450-900 mg/d **D9:** Citalopram plus Lithium 450-900 mg/d **D10:** Sertraline plus Lithium 450-900 mg/d **D11:** Venlafaxine plus Lithium 450-900 mg/d **D12-15 Thyroid** **D12:** Bupropion SR plus Thyroid 50 mcg/d **D13:** Citalopram plus Thyroid 50 mcg/d **D14:** Sertraline plus Thyroid 50 mcg/d **D15:** Venlafaxine plus Thyroid 50 mcg/d		**D7:** 19.8 (7.0) **D8-11:** 19.0 (6.6) **D12-15:** 17.2 (6.2)	(N=133) 20.5 / 20.5 **D8-11:** (N=63) 13.2 / 16.2 **D12-15:** (N=70) 24.7 / 23.3 (*P* = 0.22 / 0.19) NonAnxious vs. Anxious HAM-D Remission **D1:** 33.9% vs. 10.2% **D2:** 28.5% vs. 8.3% **D3:** 36.4% vs. 12.1% **D4-D15:** NR QIDS-SR Remission **D1:** 36.4% vs. 12.5% **D2:** 35.7% vs. 19.6% **D3:** 35.6% vs. 11.3% **D4-D15:** NR		26-35 y D1: 1.27 (0.40-4.03) D2: 1.36 (0.45-4.13)* D3: 3.06 (1.10-8.51)* 36-50 y D1: 1.79 (0.61-5.26)* D2: 1.17 (0.42-3.27) D3: 1.25 (0.45-3.48) 51-75 y D1: 1.35 (0.44-4.12)* D2: 0.83 (0.28-2.47) D3: 1.63 (0.58-4.59)* Male sex (vs female) D1: 0.89 (0.49-1.61) D2: 1.25 (0.70-2.23) D3: 0.79 (0.43-1.45) White race (vs nonwhite) D1: 2.32 (1.07-5.05)* D2: 1.97 (0.90-4.32)* D3: 1.75 (0.85-3.62)* Hispanic ethnicity D1: 2.03 (0.83-4.95)* D2: 1.64 (0.71-3.76)* D3: 0.76 (0.29-1.96)* *Clinical significance *P* ≤ 0.20 **ITT Analysis** Yes **Quality rating:** Good Effectiveness trial

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rush et al., 2006[148] **Country and setting:** United States Primary and psychiatric public and private practices **Funding:** NIMH	**Research objective:** To compare remission rates among three antidepressants in patients with major depressive disorder that did not respond or tolerate an SSRI (CIT) **Duration of study:** 14 wks **Study design:** RCT **Overall study N:** 727 **Intervention:** D1: BUP: SR 150-400 mg/d D2: SER: 50-200 mg/d D3: VEN: XR 37.5-375 mg/d	**Inclusion criteria:** • Adults 18 and over • QIDS-C-16 > 5 **Exclusion criteria:** • NR	**Mean age (yrs):** D1: 41.9 D2: 42.6 D3: 41.1 Sex (% female): D1: 56.9 D2: 55.0 D3: 64.0 Race (% white): D1: 74.9 D2: 78.2 D3: 74.4 Baseline HAM-A: NR Baseline HAM-D: D1: 18.5 (7.7) D2: 19.3 (6.9) D3: 18.9 (7.3)	HAM-D Remission at end of study: D1: 21.3% D2: 17.6% D3: 24.8% (*P* = 0.16) QIDS-SR-16 Remission: D1: 25.5% D2: 26.6% D3: 25.0% (*P* = NR; ns) QIDS-SR-16 Response: D1: 26.1% D2: 26.7% D3: 25.0% (*P* = NR; ns)	NR	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Good Effectiveness trial

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schatzberg et al., 2002[83] **Country and setting:** United States Mutli-center (recruited from advertising, private practice, routine intake at clinics and other healthcare facilities) **Funding:** Organon Pharmacueticals	**Research objective:** To compare efficacy and tolerability of MIR with PAR in elderly patients with MDD **Duration of study:** 8 wk acute phase, optional 16 wk continuation phase **Study design:** RCT **Overall study N:** 255 **Intervention:** D1: MIR: 15 mg/d up to 45 mg/d D2: PAR: 20 mg/d up to 40 mg/d	**Inclusion criteria:** • Adults 65 or older • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 18 • MMSE above 25% for age and educational level **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 6 mos • Suicide attempts • MAOIs within 14 days, other psychotropic drugs or herbals within 7 days • PAR or MIR for current depressive episode • Patients requiring drugs for memory deficit • Patients who did not respond to or tolerate MIR or PAR during a previous depressive episode	**Mean age (yrs):** D1: 71.7 D2: 72.0 **Sex (% female):** D1: 50% D2: 53% **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 22.2 (3.5) D2: 22.4 (3.5)	CGI-I responders (CGI-I of much or very much improved) At endpoint, n (%) D1: 80 (64.0) D2: 68 (57) chi square 1.23 *P* = 0.267	**Overall adverse events:** D1: 79.7 D2: 82.5 **Changes in weight (increase):** D1: 10.9 D2: 0 **Constipation:** D1: 11.7 D2: 11.1 **Diarrhea:** D1: 14.8 D2: 17.5 **Dizziness:** D1: 15.6 D2: 14.3 **Headache:** D1: 15.6 D2: 24.6 **Insomnia:** D1: 11.7 D2: 11.1 **Nausea:** D1: 6.3 D2: 19.0 **Somnolence (fatigue):** D1: 30.5 D2: 29.4 **Sweating (increase):** D1: 6.3 D2: 13.5	**Overall attrition rate:** 26.8% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Schatzberg and Roose, 2006[249] **Country and Setting** United States, Multicenter (21 university-affiliated and private research clinics) **Funding** Pharmaceutical company or other commercial source (please list name): Wyeth Research **Quality Rating** Fair	**Research objective** To compare efficacy of VEN IR and FLUOX with PBO in a sample of patients over age of 65 with depression. **Intervention Drugs, Doses, and Range** D1: VEN 37.5-225 mg/day (low - high) D2: FLUOX 20-60 mg/day low -high) D3: PBO **Study design** RCT **n** 300 **Duration** 8 weeks **Type of depression** Major depressive disorder unipolar depression (single or recurrent, nonpsychotic)	**Inclusion criteria** • Adults (age range): 65 years and older • HAM-D: 21-item HAM-D score ≥ 20 at initial visit • Not living in a residential setting • Unipolar (single or recurrent, nonpsychotic), with a current episode of at least 4 weeks in duration **Exclusion criteria** • Concomitant psychotheraputic or psychotropic medications: within prior 30 days • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse within past year • Clinically significant medical disease • Investigational drug use within last: 30 days • ECT within last: 3 months • Suicidal tendencies (acute or other) • MMSE score = < 18 • FLUOX or VEN in past six months • Astemizole, cisapride, sumatriptan, terfenadine, PAR, SER, or any	**Groups similar at baseline** Yes **n =** D1: 104 D2: 100 D3: 96 **Mean age, years** D1: 71 D2: 71 D3: 71 **Sex, % female** D1: 56 D2: 45 D3: 46 **Race, % white** D1: 93 D2: 93 D3: 93 **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** **# of responders:** Reported in figure **Remitters, %:** D1: 27 D2: 20 D3: 24 *P* = 0.549 **Mean score at baseline (SD):** D1: 24 D2: 24 D3: 23 **Mean score at endpoint:** NR **Mean score change:** NR **MADRS** **# of responders:** Reported in figure **# of remitters:** NR **Mean score at baseline:** D1: 26 D2: 27 D3: 27 **Mean score at endpoint:** NR **Mean score change:** NR **CGI-S** **Mean score at baseline:** NR **Mean score at endpoint:** NR	**Overall rate of attrition, %** 30% **Attrition rate, %** D1: 35.6 D2: 30 D3: 4 **Withdrawals due to adverse events, %** D1: 27 D2: 19 D3: 9.4 **Attrition due to lack of efficacy, %** NR **Overall adverse events, %:** D1: 26 D2: 19 D3: 9.4 **Weight loss, %:** D1: 0.98 D2: 6 D3: 3.1 **Constipation, %:** D1: 21.6 D2: 10 D3: 4.2 **Diarrhea, %:** D1: 11.8 D2: 1 D3: 14.6 **Dizziness, %:** D1: 16.7 D2: 8 D3: 5.2 **Headache, %:**

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
		monoamine oxidase inhibitor within 14 days • Used any other antidepressant, anxiolytic, or sedative-hypnotic durg (except choloral hydrate) • Known hypersensitivity to VEN or FLUOX		**Mean score change:** NR **CGI-I** **QOL scale** NR **Adherence** NR	D1: 25.5 D2: 8 D3: 22.9 **Insomnia, %:** D1: 9.8 D2: 11 D3: 4.2 **Nausea, %:** D1: 44.1 D2: 23 D3: 14.6 **Vomiting, %:** D1: 8.8 D2: 2 D3: 2 **Sexual dysfunction, %:** D1: 8.8 D2: 8 D3: 1.0 **Somnolence (fatigue), %:** D1: 11.8 D2: 10 D3: 5.2

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schmidt et al., 2000[84] Dinan et al., 2001[109] Schmidt et al., 2002[150] **Country and setting:** United States Multicenter **Funding:** Eli Lilly	**Research objective:** To assess efficacy of FLUOX 20 mg daily vs. FLUOX 90 mg wkly vs. PBO in continuation treatment of MDD **Duration of study:** 25 wks **Study design:** RCT **Overall study N:** 501 **Intervention:** D1: FLUOX 90 mg/wk D2: FLUOX 20 mg/wk D3: PBO	**Inclusion criteria:** • Minimum HAM-D score of 18 • Diagnosed with MDD according to DSM-III or -IV • Adults 18 or older • CGI-S > 4 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Clinically sig medical disease	Mean age (yrs): D1: 40.9 D2: 41.7 D3: 42 Sex (% female): D1: 68.4 D2: 70.9 D3: 63.9 Race (% white): D1: 91.6 D2: 86.8 D3: 91.0 Baseline HAM-A: NR Mean HAM-D score at baseline: NR	Relapse rates 25 wks, %: D1: 37 D2: 26 D3: 50	Diarrhea: D1: 8.4 D2: 1.6 D3: 4.9 Dizziness: D1: 5.3 D2: 5.8 D3: 4.9 Headache: D1: 10.5 D2: 12.2 D3: 9.0 Insomnia: D1: 7.4 D2: 5.3 D3: 4.1 Nausea: D1: 6.3 D2: 4.2 D3: 7.4 Somnolence (fatigue): D1: 8.4 D2: 10.6 D3: 8.2	**Overall attrition rate:** N/A **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Schneeweiss et al. 2010[218] **Country and Setting** Canada, Population-based health care utilization data **Funding** NIMH **Quality rating:** Good	**Research objective** NR **Drugs, Doses, and Range** D1: CIT D2: FLUOX D3: FLUV D4: PAR D5: SER D6: VEN D7: MIR, NEF, and TRA **Fixed dose** N/A **Dosages equivalent** N/A **Study design** Observational – retrospective cohort **Duration** 287,543 mean follow-up 0.49 person-years **Type of depression** • MDD	**Inclusion criteria:** • All residents of British Columbia, Canada, • 18 years and older who initiated use of an AD between January 1, 1997, and December 31, 2005. Initiation was defined as filling an AD prescription without having filled 1 in preceding year. • We considered only first treatment episode during study period • Evidence of depression as indicated by a diagnosis recorded during 2 office visits or as a hospital discharge diagnosis during 6 months prior to through 2 months after initiation date **Exclusion criteria**: • Existing bipolar disorder	**Groups similar at baseline** **n =** D1: 45,522 D2: 22,207 D3: 9,690 D4: 74,780 D5: 36,135 D6: 35,732 D7: 28,316 **Mean age, years** Overall: 46 **Sex, % female** Overall: 56% **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** NR	**HAM-D** N/A **CGI-S** **CGI-I** NR **QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR	**Attrition** **Overall attrition, %:** **Attrition rate, %:** N/A **Withdrawals due to adverse events, %** N/A **Withdrawals due to lack of efficacy, %** N/A Risk of suicide and suicide attempt compared with FLUOX initiation: D1: HR=1.00 (95% CI, 0.63-1.57); D3: HR =0.98 (95% CI, 0.63-1.51) D4: HR =1.02 (95% CI, 0.77-1.35); D5: HR =0.75 (95% CI, 0.53-1.05). Compared with SSRIs as a drug class, other classes including SNRIs, TCAs tricyclic agents, and other newer and atypical agents had a similar risk.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schone and Ludwig, 1993[85] and Geretsegger et al., 1994[233] **Country and setting:** Austria and Germany 6 centers **Funding:** SmithKline, Beecham	**Research objective:** Comparison of efficacy and safety with PAR and FLUOX in geriatric outpatients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 106 **Intervention:** D1: PAR: 20-40 mg/d D2: FLUOX: 20-60 mg/d	**Inclusion criteria:** • Adults 65 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Serious risk of suicide • Improvement of more than 20% on HAM-D during PBO run-in period (3-7 days)	**Mean age (yrs):** D1: 74.3 D2: 73.7 **Sex (% female):** D1: 83 D2: 90 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 24.2 D2: 26.0	No sig diff in mean changes on HAM-D or MADRS HAM-D responders at wk 6 (i.e., reduction > 50% from baseline HAM-D21) sig greater in PAR group than FLUOX group (P=0.03) MADRS responders at wk 6 (i.e., reduction > 50% from baseline MADRS) sig greater in PAR than FLUOX (P=0.04) No sig diff between treatment groups in proportion of responders on CGI-S Mean changes from baseline SCAG total score: D1:-14.5 D2:. -8.9 SCAG Cognitive dysfunction factor scores: D1: -2.9 D2: -0.6. HAM-D cognitive factor scores: D1: -1.5 D2: -1.0.	**Overall adverse events:** D1: 61 D2: 77 **Constipation:** D1: 5.6 D2: 3.8 **Diarrhea:** D1: 1.9 D2: 11.5 **Dizziness:** D1: 7.4 D2: 3.8 **Headache:** D1: 7.4 D2: 5.8 **Insomnia:** D1: 9.3 D2: 13.5 **Nausea:** D1: 9.3 D2: 11.5 **Somnolence (fatigue):** D1: asthenia 1.9 D2: asthenia 7.7 **Sweating (increase):** D1: 7.4 D2: 7.7	**Overall attrition rate:** 17% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Sechter et al., 1999[86] **Country and setting:** France Multicenter (45) **Funding:** Pfizer, Inc	**Research objective:** Comparison of efficacy and safety in patients being treated with SER and FLUOX with MDD **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 238 **Intervention:** D1: SER: 50-150 (mean = 76.5) D2: FLUOX: 20-60 (mean = 33.6)	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Epilepsy • FLUOX or lactose allergy	**Mean age (yrs):** D1: 43.4 D2: 42.5 **Sex (% female):** D1: 66.7 D2: 68.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Response was observed in 74% in SER patients vs. 64% in FLUOX patients on HAM-D, $P = 0.11$ No diff in QOL (SIP)	**Constipation:** D1: 1 D2: 2 **Diarrhea:** D1: 3 D2: 2 **Headache:** D1: 5 D2: 7 **Nausea:** D1: 23 D2: 17 **Somnolence (fatigue):** D1: 5 D2: 6	**Overall attrition rate:** 29.2% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Shelton, 2006[87] **Country and Setting** Eight U.S. sites (type not reported) **Funding** Pfizer, Inc. **Quality rating:** Fair	**Research objective** To compare efficacy, safety, and tolerability of SER and VEN XR in outpatients with MDD. **Drugs, Doses, and Range** D1: SER (25-200 mg 1 x daily): 50-150mg QD; Low-Medium; Maximum dose as tolerated. D2: VEN XR (75-225 mg 1 x daily): 75-225 mg QD; Low-High; Maximum dose as tolerated. **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **N** 160 **Duration** 8 weeks **Type of depression** MDD **Intervention** SER VEN XR	**Inclusion criteria:** • Adults (age range): 18 - older • Diagnosed with MDD according to DSM-III or -IV: DSM-IV • Single episode or recurrent w/o psychotic features. • HAM-D: ≥ 18 on HAM-D17 and ≥ 2 on item 1 (depressed mood). **Exclusion criteria:** • Pregnant: Positive pregnancy test excluded participant. • Lactating: Concomitant psychotheraputic or psychotropic medications • Use of an antidepressant within 2 weeks of baseline (4 weeks for FLUOX) • Use of any psychotropics within 1 week of baseline (except zolpidem or zopiclone) • Use of benzodiazepines taken on a regular, daily basis within 4 weeks of baseline • Monoamine oxidase inhibitors within 14 days of baseline evaluation. • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia,	**Groups similar at baseline** Yes **n =** D1: 82 D2: 78 **Mean age, years (SD)** D1: 41.2 (12.0) D2: 37.2 (11.6) **Sex, % female** D1: 46 D2: 61 **Race, % white** D1: 83 D2: 84 **Baseline HAM-A (SD)** D1: 15.7 (5.1) D2: 16.0 (4.4) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 51 D2: 52 **Comments:** NR	**HAM-D** D1: SER D2: VEN XR n at baseline: D1: 82 D2: 78 No. of responders: D1: 45 (55%) D2: 49 (65%) *P* = 0.22 No. of remitters: D1: 31 (38%) D2: 37 (49%) *P* = 0.168 Mean score at baseline (SD): D1: 22.1 (2.9) D2: 22.4 (2.9) Mean score at endpoint (SD): D1: 10.8 (6.4) D2: 9.7 (6.4) Mean score change (SD): D1: -11.3 D2: -12.7 Mean score change was not reported; Calculated by reviewer 1 **MADRS** No. of responders: D1: 45 D2: 49 Mean score at baseline (SD): D1: 22.1 (2.9) D2: 22.4 (2.9)	**Overall adverse events, %:** D1: 80 D2: 79 **Diarrhea, %:** D1: 31 D2: 25 **Dizziness, %:** D1: 23 D2: 42 **Headache, %:** D1: 22 D2: 32 **Insomnia, %:** D1: 26 D2: 20 **Nausea, %:** D1: 17 D2: 17 **Sexual dysfunction, %:** D1: 21 D2: 23 **Attrition** **Overall attrition, %:** 20 **Attrition rate, %:** D1: 23 D2: 17 **Withdrawals due to adverse events, %** D1: 1 D2: 4 **Withdrawals due to lack of efficacy, %** D1: NR D2: NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		bipolar) • Current or past diagnosis of bipolar disorder or any psychotic disorder • Current diagnosis of delirium or dementia • A mental condition rendering patient unable to understand study • Schizoid, schizotypal, or borderline personality disorder. • Illicit drug and alcohol abuse • Alcohol or Ddependence or abuse within last 6 months. • Clinically significant medical disease • Any serious and/or unstable medical condition • Abnormal baseline laboratory finding considered indicative of conditions that might affect study results • Impaired hepatic function • Impaired renal function • History of seizure disorder. • Investigational drug use within last: 90 days • ECT within last: 30 days • Suicidal tendencies (acute or other): Score of 3 or 4 on suicide item of HAMD. • Previous non-response		Mean score change (SD): D1: -1.5 D2: -1.8 **CGI-S** D1: SER D2: VEN XR n at baseline: D1: 82 D2: 78 Mean score at baseline (SD): D1: 4.1(0.5) D2: 4.2 (0.5) Mean score at endpoint (SD): D1: 2.6 (1.1) D2: 2.4 (1.1) Mean score change was not reported; Calculated by reviewer 1 **CGI-I** D1: SER D2: VEN XR **CGII** Yes Intervention: D1: SER D2: VEN XR n at baseline: D1: 82 D2: 78 Mean score at endpoint (SD): D1: 2.3 (1.1) D2: 2.0 (1.1) Number of patients achieving a score	**Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		to SER, VEN XR, or to 2 antidepressants in current episode • Use of herbal and/or homeopathic remedies within 2 weeks of baseline • History of intolerance or hypersensitivity to SER and/or VEN XR • Likelihood of requiring treatment during study period with drugs not permitted by study protocol. **Outcome measures** • HAM-D • CGI-S and CGI-I • QOL scales: Q-LES-Q • HAM-A		1: 50 2: 57 345 The authors state that 75% of VEN group were rated as much or very much improved on CGI-I - as n for VEN is 76 after baseline, this n was used to calculate number of patients (by reviewer #2) **QOL scale** Q-LES-Q Intervention: D1: SER D2: VEN XR n at baseline: D1: 82 D2: 78 Mean score at baseline (SD): D1: 0.53 (0.10) D2: 0.51 (0.08) Mean score at endpoint (SD): D1: 0.69 (0.12) D2: 0.67 (0.12) Mean score change (SD): D1: +0.16 D2: +0.16 Mean score change was not reported; Calculated by reviewer 1 **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or**	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				compliance NR	

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Silverstone and Ravindran, 1999[88] Silverstone and Salinas, 2001[172] **Country and setting:** Canada Multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** Comparison of VEN XR and FLUOX in outpatients with depression and anxiety **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 249 **Intervention:** D1: PBO D2: VEN: 75-225 mg/d (could be increased to 150 mg/d on day 14 and 225 mg/d on day 28) D3: FLUOX: 20-60 mg/d (could be increased to 40 mg/d on day 14 and 60 mg/d on day 28)	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Depression for 1 mo before study **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug • ECT within last 30 days • Suicidal tendencies	**Mean age (yrs):** D1: 41.6 D2: 41.1 D3: 43.2 **Sex (% female):** D1: 64 D2: 60 D3: 57.6 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 27.6 (5.1) D2: 27.0 (4.6) D3: 27.1 (4.5)	No statistical comparisons between FLUOX and VEN (just PBO) At wk 12 response rates were 67% for VEN and 62% for FLUOX (*P* = NR) HAM-D scores in VEN and FLUOX groups dropped sig when compared with PBO VEN had sig more HAM-A responders at wk 12 than FLUOX HAM-D remission rate in VEN group was sig compared to PBO at wks 3, 4, 6, 8, 12 and final HAM-D remission rate in FLUOX group was sig compared to PBO at wks 8, 12, and final Patients in VEN group showed a sig decrease in HAM-D and HAM-A scores compared to PBO ($P < 0.05$) With Comorbid GAD vs. not with GAD HAM-D Remission FLUOX 33% vs. 48% VEN 41% vs. 48% PBO 12% vs. 25%	**Changes in weight (decrease):** D2: 10 D3: 7 **Dizziness:** D2: 38 D3: 18 **Insomnia:** D2: 32 D3: 25 **Somnolence (fatigue):** D2: 13 D3: 14 **Sweating (increase):** D2: 10 D3: 10	**Overall attrition rate:** 32% **With Comorbid GAD vs. not with GAD** D1: 28% vs. 44% D2: 29% vs. 29% **D3: 36% vs. 23%** **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

				HAM-A remission FLUOX 36% vs. 33% VEN 31% vs. 47% PBO 12% vs. 28%		
Study Characteristics	**Research Objective Duration Study Design**	**Inclusion/Exclusion**	**Baseline Characteristics**	**Health Outcome Results**	**Adverse Events (%)**	**Analysis and Quality Rating**
Author: Simon et. al., 2004[151] **Country and setting:** United States Multicenter study **Funding:** Wyeth	**Research objective:** To evaluate efficacy of VEN XR in prevention of relapse of depression by continuation treatment **Duration of study:** 8 wk acute phase; 6 mo continuation phase **Study design:** RCT **Overall study N:** 318 entered relapse prevention study (490 in acute phase) **Intervention:** D1: VEN XR 75-225 mg/d D2: PBO	**Inclusion criteria:** • Adults 18+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of >20 • No greater than 20% decrease in HAM D between evaluations **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Investigational drug use • Suicidial tendencies • Seizure • Antipsychotic medication • FLUOX within 30 days	**Mean age (yrs):** D1: 43 D2: 41 **Sex (% female):** D1: 102 (66%) D2: 86 (62%) **Race (% white):** NR **Baseline HAM-A:** N/A **Baseline HAM-D:** D1: 6.5 D2: 6.4	HAM-D At day 56 D1: 6.5 D2: -6.4 MADRS At day 56 D1: 74 D2: -7.2 Relapse rates, % At 6 months D1: 28 D2: 52 *P* < 0.001	**Overall adverse events:** D1: 97% D2: 93% **Cardiovascular adverse events:** D1: 6% D2: 2% **Constipation:** D1: 7% D2: 3% **Sexual dysfunction:** D1: 5% D2: 2% **Sweating (increase):** D1: 11% D2: 5%	**Overall attrition rate:** 62% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Simon et al., 2006[220] **Country and Setting** United States, large insured population **Funding** Grants from NIMH **Quality rating:** Fair	**Research objective** To evaluate risk of suicide death and serious suicide attempt in relation to initiation of antidepressant treatment. **Drugs, Doses, and Range** **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** Observational **Duration** 10.5 years **Type of depression** • MDD • Dysthmia • Diagnosis of unipolar MDD, dysthymia, or despressiver disorder not otherwise specified (ICD-9 code 311) **Intervention** Antidepressant Prescription	**Inclusion criteria:** • Dysthymia • Outpatient antidepressant prescription filled between Jan. 1, 1992, and June 30, 2003 • No antidepressant prescription filled in previous 180 days • Unipolar MDD, dysthymia, or depressive disorder not otherwise specified during 30 days before or 30 days after index prescription • Limited to persons enrolled in GHC health plan during 6 months before index prescription. **Exclusion criteria:** NR **Outcome measures** NR	**Groups similar at baseline** N/A **n =** D1: 65103 **Mean age, years** D1: 44 (SD: 18)* **Sex, % female** D1: 69.5%* **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** **Comments:** *Results are based on overall study population (ages 5 to 105 years). A total of 9,520 members contributed 2 treatment epsodes to sample, and 1,916 members contributed more than 2 episodes. **Outpatients/Inpatients** Both **Baseline mean HAM-A > 25?** NR **Mean age at baseline** Less than 65 years	**HAM-D** NR **MADRS** NR **CGI-S** NR **CGI-I** NR **CGII** No **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** • Risk of suicide death during first 6 months after initial antidepressant prescription (suicide deaths per 100,000) • Results were presented in a figure. results (approximately) are as follow: age 18-30: 62 per 100,000; age 31-50: 30 per 100,000; age > 50: 56 per 100,000. 95 % CIs were also reported, but only in graph. • Risk of suicide attempt during first 6 months	**Attrition** **Overall attrition, %:** Rate of attrition was not reported. There were 31 suicide deaths during 6-month follow-up period (0.048%). It could not be determined if 31 suicide deaths included individuals under age of 18. **Attrition rate, %:** NR **Withdrawals due to adverse events, %** NR **Withdrawals due to lack of efficacy, %** NR **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
			Mean HAM-D at baseline NR	after initial antidepressant prescription (suicide attempts per 100,000) • Results were presented in a figure. Results (approximately) are as follow: • age 18-30: 149 per 100,000; • age 31-50: 75 per 100,000; • age > 50: 48 per 100,000. • 95 % confidence intervals were reported, but only in graph. Rates of suicide death during first 6 months after initial antidepressant prescription (by month), rates of suicide attempts during 3 months before and 6 months after initial antidepressant prescription (by month), and rates of suicide attempts during 4 weeks before and 4 weeks after initial antidepressant prescription (by week) were also reported. However, results on overall study population (adults + children and adolescents) and/or children and adolescents-not just adults.	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Sir et al., 2005[89] **Country and setting:** Australia and Turkey Clinics (Turkey 7 and Australia 6) **Funding:** Pfizer, Inc	**Research objective:** Test for diffs between SER and VEN XR on measures of QOL.Test for efficacy diffs on measures of depressive symptoms and tolerability, including discontinuation symptoms **Duration of study:** 8 wks then up to 2 wks discontinuation **Study design:** RCT **Overall study N:** 163 **Intervention:** D1: SER: 50-150 mg/d D2: VEN: 75-225 mg/d	**Inclusion criteria:** • Adults 18 or older • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Non-response to an adequate trial of 2 ADs in current episode	**Mean age (yrs):** D1: 37.3 D2: 36.8 **Sex (% female):** D1: 72.2 D2: 66.7 **Race (% white):** D1: 96.2 D2: 100 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.4 (4.4) D2: 23.5 (4.4)	Efficacy: No sig diff exists in terms of efficacy between VEN and SER. HAM-D responders: D1: 70.9% D2: 70.9% (*P* = 0.95) HAM-D remitters: D1: 59.5% D2: 54.4% (*P* = 0.47) Discontinuation of SER is associated with fewer discontinuation-emergent symptoms than for discontinuation of VEN Change in Q-LES-Q: D1: 16.8 + 1.77 D2: 17.5 + 14.5 (*P* = 0.74)	**Dizziness:** D1: 32.9 D2: 26.2 **Headache:** D1: 44.3 D2: 32.1 **Insomnia:** D1: 35.4 D2: 27.4 **Nausea:** D1: 51.9 D2: 47.6 **Somnolence (fatigue):** D1: 21.5 D2: 26.2 **Sweating (increase):** D1: 31.6 D2: 21.4	**Overall attrition rate:** 23% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Soares et al. 2010[152] **Country and Setting** Multinational (Chile, Argentina, Colombia, Mexico and USA) and Multicenter (72) **Funding** Wyeth - Pfizer **Quality rating:** KQ1 and KQ4 Poor KQ2 Fair	**Research objective** the efficacy, safety, and tolerability of desvenlafaxine and escitalopram for major depressive disorder (MDD) in postmenopausal women **Drugs, Doses, and Range** D1: flexible-dose desvenlafaxine (100-200 mg/d) D2: flexible-dose escitalopram (10-20 mg/d) **Flexible dose** **Dosages equivalent - yes** **Study design** 8 week RCT (6 month continuation phase for responders) **Duration 8 weeks + 26 weeks** **Type of depression** • MDD	**Inclusion criteria:** • between 40 and 70 years of age with a • primary diagnosis of MDD • MADRS 22 or more **Exclusion criteria:** • treatment with or had known hypersensitivity to desvenlafaxine; or venlafaxine or citalopram or escitalopram; • risk of suicide based on clinical judgment; • current psychoactive substance abuse or dependence, manic episodes, PTSD; OCD; bipolar or psychotic disorder, or clinically important personality disorder; • seizure disorder; • clinically important medical disease; • formal CBT or IPT within 30 days; • used prohibited treatments, including hormone products, within 4 weeks to 6 months	**Groups similar at baseline** **n =** D1: 224 (137) D2: 237 (160) **Mean age, years** D1: 56 (56) D2: 56 (56) **Sex, % female** 100% **Race, % white** D1: 79 (80) D2: 82 (81)	**HAM-D** Mean score at baseline (SD): D1: 23 (4) D2: 23 (4) Mean score at endpoint (6 months): D1: 10.67 (6.56) D2: 9.41 (7.32) D3: Mean score change (SD): D1: -12.33 (0.44) (-16.44(6.65)) D2: -13.59 (0.42) (-15.68 (6.30) Response at 8 weeks D1: 137/299 (45.8%) D2: 160/308 (51.9%) Among responders, ongoing response at 52 weeks D1: 25/137 (18%) D2: 32/160 (20%)	**Attrition** **Overall attrition, %:** 16 **Attrition rate, %:** D1: 17.2% (19.2%) D2: 14.4% (19.7%) **Withdrawals due to adverse events, %** D1: 6.1% (6.4%) D2: 4.3% (5.8%) **Withdrawals due to lack of efficacy, %** D1: 1% (0.58%) D2: 1% (0.53%) **Adverse Events n (%)** Desvenlafaxine vs. Escitalopram Acute phase Headache 76 (26) vs. 85 (28) Dry mouth 83 (28) vs. 60 (20) Nausea 74 (25) vs. 61 (20) Constipation 52 (18) vs. 28 (9) Somnolence 42 (14) vs. 48 (16) Diarrhea 26 (9) vs. 49 (16) Sweating 43 (15) vs. 33 (11) Insomnia 33 (11) vs. 39 (13) Dizziness 33 (11) vs. 28 (9) Abdominal pain 29 (10) 21 (7) Continuation Phase Headache 67 (39) vs.74 (39) Dry mouth 51 (30) vs. 48 (26) Nausea 48 (28) vs.46 (25) Diarrhea 20 (12) vs. 47 (25) Constipation 43 (25) vs. 21 (11) Insomnia 29 (17) vs. 40 (21) Somnolence 28 (16) vs. 39 (21) Sweating 33 (19) vs. 29 (15) Infection 20 (12) vs.35 (19) Abdominal pain 31 (18) vs. 24 (13)

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
					Pain 28 (16) vs. 27 (14) Asthenia 27 (16) vs. 23 (12) Arthralgia 26 (15) vs. 29 (15) Accidental injury 17 (10) vs. 27 (14) Dizziness 22 (13) vs. 22 (12) Weight gain 13 (8) vs. 24 (13) Flu syndrome 22 (13) vs. 12 (6) Back pain 21 (12) vs. 19 (10) Dyspepsia 17 (10) vs. 21 (11) Upper respiratory tract infection 11 (6) vs. 19 (10)

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Stang et al. 2007[221] **Country and Setting** USA **Funding** GlaxoSmithKline **Quality rating:** Fair	**Research objective** To assess impact of dosing frequency (once daily with BUP XL vs. twice daily with BUP SR) on adherence to BUP therapy. **Drugs, Doses, and Range** D1: BUP (SR 150-400 mg 2 x daily): dose range NR D2: BUP XL (150-450 mg 1 x daily): dose range NR **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** **Study design** Observational **Duration** October 2004 to October 2005 **Type of depression** Documented diagnosis of depression during study period was not requirement for inclusion - study is based on prescription data **Intervention** D1: BUP XL D2: BUP SR	**Inclusion criteria:** • Patients of any age in US with prescription for BUP XL or BUP SR were identified from prescription database maintained by Cataline Health Resource. **Exclusion criteria:** **Outcome measures** • Refill adherence • Persistance	**Groups similar at baseline** N/A only data on percentage of females and age reported **n =** D1: 257049 D2: 12468 **Mean age, years** Females D1: 42.6 D2: 47.3 Males D1: 42.3 D2: 45.0 **Sex, % female** D1: 69 D2: 67 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** NR	**HAM-D** NR **MADRS** NR **CGI-S** NR **CGI-I** NR **CGII** No **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** Refill adherence over 1-year period was greater with BUP XL than BUP SR. The percentage of patients with >=1 refill over 1 year was 60.1% with BUP XL compared with 51.3% with BUP SR ($P < 0.0001$). Percentage of patients with >=2 refills over 1 year was 47.9 for BUP XL and 34.0 for BUP SR; percentages for >=3 refills over 1 year was 40.0 for BUP XL and 21.7 for BUP SR; percentages for >=4 refills over 1 year was 33.9 for BUP XL and 15.5	**Attrition** **Overall attrition, %:** N/A **Attrition rate, %:** NR **Withdrawals due to adverse events, %** NR **Withdrawals due to lack of efficacy, %** NR **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				for BUP SR; percentages for >=5 refills over 1 year was 29.9 for BUP XL and 11.5 for BUP SR; percentage of patients with >=6 refills over 1 year was 25.3% with BUP XL compared with 9.5% with BUP SR. Refill adherence over time was calculated as percentage of patients with >= 1, 2, 3, 4, 5, and 6+ refills from October 2004 to October 2005. BUP XL was associated with significantly greater likelihood of refilling a prescription than BUP SR (*P*<0.0001). Persistence was considered to be maintained if days of medication supply from previous prescription plus a 30-day grace period exceeded number of days between previous prescription date and current prescription fill date. medication possession ratio over a 9-month period was 1.5-fold higher for BUP XL (0.26) than it was for BUP SR (0.16), a finding that suggests that those on XL formulation were likely to remain on BUP for 50% longer than those on SR formulation. **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Strik et al., 2000[250] **Country and setting:** Netherlands Hospitals (2) **Funding:** Eli Lilly Dutch Prevention Fund; Maastricht University Hospital Research Fund	**Research objective:** To investigate efficacy and safety of FLUOX in patients with depression after first MI **Duration of study:** Maximum of 25 wks (acute phase 9 wks; continuation phase 16 wks) **Study design:** RCT **Overall study N:** 54 **Intervention:** D1: FLUOX: 20-60 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 to 75 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 17 • 3 to 12 mos post-MI **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease • Right ventricular filling pressure > 30 mmHG; ATVI < 20 cm	**Mean age (yrs):** D1: 54.1 D2: 58.7 **Sex (% female):** D1: 22.2 D2: 37.0 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 22.0 (3.5) D2: 21.2 (3.7)	At 9 wks mean HAM-D-17 score FLUOX - 8.34(5.87) vs. PBO 5.84(5.92) (*P* = 0.06) but mildly depressed patients in FLUOX group had endpoint HAM-D scores sig different (by 5.4 points) than PBO (*P* = 0.01). At wk 25- responder rates 48% (FLUOX) vs. 26% (PBO) (*P* = 0.05) and remission rates 26% (FLUOX) vs. 14.8% (PBO)(*P* = 0.60)	**Cardiovascular adverse events:** D1: 18.5 D2: NR	**Overall attrition rate:** 25.9% **ITT Analysis** Yes **Quality rating:** Good

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Terra and Montgomery, 1998[153] **Country and setting:** France Multicenter, outpatient **Funding:** NR	**Research objective:** To evaluate efficacy of FLUV in reducing risk of new episodes of depression **Duration of study:** 1 yr **Study design:** RCT **Overall study N:** 204 (number enrolled in double-blind prophylactic treatment phase) **Intervention:** D1: FLUV: 100 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Acute phase: MADRS>25 • History of at least 2 episodes of major depression in previous 5 yrs **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications, but benzos and hypnotics were also allowed during acute/continuation phases if started more than 3 mos before start • Clinically sig medical disease • ECT within last 2 wks • Epilepsy or history of convulsions, • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse	**Mean age (yrs):** D1: 44.5 D2: 45.0 **Sex (% female):** D1: 70 D2: 77.7 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Incidence of recurrence was lower in FLUV (12.7%) than PBO (35.1%) ($P < 0.001$) Highly sig diff between FLUV and PBO in distribution of time to recurrence ($P < 0.001$). time to recurrence sig longer for FLUV and PBO (181 vs. 96 days, $P < 0.005$)	**Changes in weight (decrease):** D1: 1 **Headache:** D1: 5 **Sexual dysfunction:** D1: 0 **Somnolence (fatigue):** D1: 4	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Thapa et al., 1998[222] **Country and setting:** United States 53 rest homes **Funding:** CDC and FDA	**Research objective:** To compare rate of falls between nursing home residents using SSRIs and TCAs **Duration of study:** N/A **Study design:** Observational **Overall study N:** Cohort- 2,428 **Intervention:** D1: Non-users (847) D2: TCAs (665) D3: SSRIs (612) D4: TRA (304)	**Inclusion criteria:** • Adults 65 or older • Nursing home residents who were new users of antidepressants, in facility more than 30 days **Exclusion criteria:** NR	**Mean age (yrs):** D1: 83 D2: 82.1 D3: 82.1 D4: 82.2 **Sex (% female):** D1: 75.9 D2: 75.2 D3: 74 D4: 73 **Race (% black):** D1: 13.2 D2: 5.1 D3: 5.9 D4: 6.6 **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Rate of falls per 100 person-yr PAR- 301 RR, 95% CI, 2.3 (2.1-2.6) Adjusted RR, 1.7 (1.5-1.9) FLUOX- 314 RR, 95% CI, 2.4 (2.1-2.8) Adjusted RR, 1.8 (1.6-2.1) SER- 342 RR, 95% CI, 2.6 (2.3-3.0) Adjusted RR, 1.8 (1.5-2.1) TRA- 244 RR, 95% CI, 1.9 (1.7-2.1) Adjusted RR, 1.2 (1.0-1.4)	NR	**Overall attrition rate:** N/A **ITT Analysis** N/A Retrospective Cohort **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Thase et al., 1996[60] Kocsis et al., 1997[59] **Country and setting:** United States Multicenter (17 United States centers) **Funding:** NR	**Research objective:** To evaluate safety and efficacy of SER and IMI in treating dysthymia **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 416 **Intervention:** D1: SER: 50-200 mg/d D2: Imipramine: 50-300 mg/d D3: PBO	**Inclusion criteria:** • Adults 25 to 65 • Minimum HAM-D score of 12 • Dysthymia • Early onset dysthmia • Duration ≥ 5 yrs • Depression symptom-free mos ≤ 2 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies • Previous nonresponse to at least 2 adequate antidepressant trials • Concurrent MDD	**Mean age (yrs):** D1: 42 D2: 42 D3: 42 **Sex (% female):** D1: 65 D2: 65 D3: 65 **Race (% white):** D1: 95 D2: 95 D3: 95 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 12.7 (4) D2: 13.4 (3.8) D3: 12.7 (3.9)	SER group showed sig more responders than PBO (59.0% vs. 44.3%; $P < 0.02$) A sig greater proportion of patients in SER group increased in psychosocial functioning compared to PBO (61% vs. 45%; $P = 0.01$) as measured by Global Assessment of Functioning Score of 71 or more Sig improvements in family relationships, marital relationships, and parental role functioning Sig more SER patients than PBO patients were classified as harm avoidance responders ($P = 0.001$)	**Cardiovascular adverse events:** D1: 4 D2: 9 D3: 2 **Constipation:** D1: 16 D2: 40 D3: 9 **Diarrhea:** D1: 21 D2: 7 D3: 10 **Dizziness:** D1: 14 D2: 28 D3: 16 **Headache:** D1: 41 D2: 39 D3: 46 **Insomnia:** D1: 24 D2: 12 D3: 17 **Nausea:** D1: 27 D2: 26 D3: 20 **Somnolence (fatigue):** D1: 23 D2: 32 D3: 12 **Sweating (increase):** D1: 12 D2: 28 D3: 6	**Overall attrition rate:** 24.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Thase et al., 2001[155] **Country and setting:** United States Multicenter (12) Outpatient **Funding:** Organon Inc	**Research objective:** Evaluate efficacy and safety of mirazapine in continuation phase therapy **Duration of study:** Acute Phase- 8-12 wks Continuation Phase- up to 40 wks **Study design:** RCT **Overall study N:** • 410 for open-label • 156 randomized to continuation treatment **Intervention:** D1: MIR: 15-45 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 and up • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use	**Mean age (yrs):** D1: 40.1 D2: 40.7 **Sex (% female):** D1: 52.6 D2: 48.8 **Race (% white):** D1: 93.4 D2: 86.3 **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 5.0 (4.0) D2: 7.7 (6.7)	Relapse rates during 40-wk double blind continuation phase were 19.7% for MIR and 43.8% for PBO ($P < 0.001$) Between group diff in distribution of relapse risk over time was statistically sig ($P < 0.001$) Mean HAM-D for MIR was 6.1(7.2) and for PBO 10.7(8.8)	**Overall adverse events:** D1: 36 D2: 30 **Cardiovascular adverse events:** D1: 21 D2: 23 **Changes in weight (increase):** D1: 7.9 D2: 7.3 **Dizziness:** D1: 3 D2: 4 **Headache:** D1: 12 D2: 16 **Somnolence (fatigue):** D1: 4 D2: 1	**Overall attrition rate:** 46% in acute phase 11.8% in continuation phase **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Tignol, 1993[90] **Country and setting:** France Multicenter **Funding:** SmithKline Beecham Pharmaceuticals	**Research objective:** To compare PAR and FLUOX in treatment of inpatients with major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 178 **Intervention:** D1: PAR: 20 mg D2: FLUOX: 20 mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS total score of 24 or more • Hospital inpatient at screening and for first 2 wks of trial **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 6 mos • ECT within last 3 mos • Suicidal tendencies • Receiving oral anticoagulant • Severe drug allergy/reaction in past	**Mean age (yrs):** D1: 43.0 D2: 44.7 **Sex (% female):** D1: 64 D2: 75 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	A reduction of 50% or more in MADRS scores among 75% of PAR and 78% of FLUOX patients. MADRS scores fell to ≤ 11 among 67% of PAR and 64% of FLUOX patients After 6 wks of treatment, CGI-S scores were 1 or 2 among 78% of PAR and 73% of FLUOX patients	**Nausea:** D1: 4 D2: 10	**Overall attrition rate:** 1.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Tourian et al., 2009[91] **Country and Setting** USA; Multicenter (21) **Funding** Wyeth Pharmaceuticals **Quality rating:** Fair	**Research objective** To compare efficacy and tolerability of fixed-dose DES 50 and 100 mg/d with PBO for MDD. **Drugs, Doses, and Range** • DES (50 mg 1 x daily): 50 or 100 mg/day • DUL (40-60 mg 1-2 x daily): 60 mg/day • PBO **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** Yes **Study design** RCT **N** 474 **Duration** 8 weeks **Type of depression** Acute Recurrent MDD **Intervention** D1: DES 50 D2: DES 100 D3: DUL 60 D4: PBO	**Inclusion criteria:** • Adults (age range): 18 years or more • Diagnosed with MDD according to DSM-III or -IV • HAM-D: 20 or more, HAM-D item,1 (depressed mood): 2 or more • CGIS: 4 or more (moderately ill) **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse • Clinically significant medical disease • Investigational drug use within last: 30 days • Suicidal tendencies (acute or other): significant risk of suicide **Outcome measures** • HAM-D • MADRS • CGI-S or CGI-I	**Groups similar at baseline** Yes **n =** D1: 148 D2: 150 D3: 157 D4: 160 **Mean age, years** D1: 41 D2: 39 D3: 39 D4: 39 **Sex, % female** D1: 69 D2: 66 D3: 66 D4: 58 **Race, % white** D1: 75 D2: 73 D3: 75 D4: 76 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** NR **Outpatients/Inpatients** Outpatients **Baseline mean HAM-A >**	**HAM-D** Mean score at baseline (SD): D1: 23 (3) D2: 23 (3) D3: 23 (2) D4: 24 (3) Mean score change (SD): D1: -9.8, *P:* 0.198 D2: -10.5, *P:* 0.028 D3: -10.3, *P:* 0.047 D4: -8.7 **MADRS** n at baseline: D1: 143 D2: 145 D3: 152 D4: 156 Mean score at baseline (SD): D1: 23 (3) D2: 23 (3) D3: 23 (2) D4: 24 (3) Mean score change (SD): D1: -1.3 *P:* 0.248 D2: -1.4 *P:* 0.011 D3: -1.4 *P:* 0.026 D4: -1.1 **CGI-S** NR **CGI-I** Mean score at endpoint (SD): D1: 2.6 *P:* 0.154 D2: 2.4 *P:* 0.004 D3: 2.5 *P:* 0.011 D4: 2.8 (P-values=drug vs.	**Constipation, %:** D1: 6 D2: 7 D3: 11 D4: 3 **Insomnia, %:** D1: 11 D2: 14 D3: 19 D4: 3 **Nausea, %:** D1: 22 D2: 23 D3: 31 D4: 9 **Vomiting, %:** D1: 1 D2: 4 D3: 8 D4: 2 **Attrition** **Overall attrition, %:** 22% **Attrition rate, %:** D1: 19 D2: 22 D3: 24 D4: 24 **Withdrawals due to adverse events, %** D1: 5 D2: 7 D3: 13 D4: 6 **Withdrawals due to lack of efficacy, %** NR **Comments** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
			25? NR **Mean age at baseline** Less than 65 years **Mean HAM-D at baseline** Greater than 17 (moderate to severe)	placebo) **QOL scale** NR **Another QOL scale** NR **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Tylee et al., 1997[92] **Country and setting:** UK **Funding:** Wyeth-Ayerst International	**Research objective:** Safety and efficacy of VEN and FLUOX in depression treated in general practice **Duration of study:** 12 wks + 7 day post follow-up **Study design:** RCT **Overall study N:** 341 **Intervention:** D1: VEN: 75 mg/d D2: FLUOX: 20 mg/d	**Inclusion criteria:** • Adults 18 or older • MDD diagnosis according to DSM-III or -IV • Depressive symptoms for more than 2 wks **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • ECT within last 1 mo • Suicidal tendencies	**Mean age (yrs):** D1: 43.5 D2: 45.5 **Sex (% female):** D1: 67.8 D2: 74.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	MADRS, HAM-D, and CGI scores decreased sig for both treatment groups but there were no sig diffs between treatment groups MADRS, HAM-D, or CGI responders: FLUOX: 62.8% VEN: 55.1% (*P* = NR (ns)) MADRS remitters (MADRS ≤ 6): FLUOX: 34.1% VEN: 35.4% (*P* = NR (ns)) No sig diffs in effects on sleep	**Overall adverse events:** D1: 80.7 D2: 71.8 **Diarrhea:** D1: 4.1 D2: 6.5 **Dizziness:** D1: 11.1 D2: 6.5 **Headache:** D1: 11.1 D2: 17.1 **Nausea:** D1: 34.5 D2: 18.2 **Somnolence (fatigue):** D1: 7.0 D2: 4.7 **Sweating (increase):** D1: 5.8 D2: 1.2	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Tzanakaki et al., 2000[93] **Country and setting:** Greece and Italy Hospitalized and day care **Funding:** Wyeth-Ayerst International	**Research objective:** Efficacy and tolerability of VEN and FLUOX in patients with major depression and melancholia **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 109 **Intervention:** D1: VEN: 225 mg/d D2: FLUOX: 60 mg/d	**Inclusion criteria:** • Adults 18 to 64 • Outpatient or hospitalized • MDD with melancholia according to DSM-IV • MADRS of 25 or more • Depression symptoms for one mo or more **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days • ECT within last 30 days • Suicidal tendencies	**Mean age (yrs):** D1: 47 D2: 49 **Sex (% female):** D1: 75 D2: 83 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 27.8 (5.6) D2: 27.1 (5.6)	At 6 wks, 65% of patients with VEN and 58% with FLUOX had ≥ 50% reduction in MADRS score, and 70% with VEN and 62% with FLUOX had a CGI-I score of 1 or 2. A CGI-I score of 1 was observed in 51% of patients with VEN and 32% with FLUOX (P = 0.018). Final HAM-D score < 7 was attained in 41% of VEN and 36% of FLUOX patients **Depression outcomes in melancholia:** Response rates were similar for FLUOX-treated group (58%) and VEN group (65%; P = NR). Remission rates were similar for FLUOX (36%) and VEN (41%; P = NR)	**Overall adverse events:** D1: 49.1 D2: 46.3 **Constipation:** D1: 7.3 D2: 1.9 **Dizziness:** D1: 5.5 D2: 0 **Headache:** D1: 5.5 D2: 1.9 **Insomnia:** D1: 12.7 D2: 1.9 **Nausea:** D1: 5.5 D2: 14.8 **Sweating (increase):** D1: 5.5 D2: 3.7	**Overall attrition rate:** 22% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Ushiroyama et al., 2004[94] **Country and Setting** Japan, Menopause Center of OB/GYN Clinic of Osaka Medical College **Funding** NR **Quality Rating** Fair	**Research objective** To compare FLUV vs. PAR in depressed patients in menopause transition **Intervention Drugs, Doses, and Range** D1: FLUV 50 mg/day D2: PAR 20 mg/day **Study design** RCT **n** 105 **Duration** Three months **Type of depression** Major depressive disorder	**Inclusion criteria** • Adults (age range): Women in perimenopause • Diagnosed with MDD according to DSM-III or -IV: HAM-D: at least 13 **Exclusion criteria** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse	**Groups similar at baseline** Yes **n =** D1: 53 D2: 52 **Intervention** D1: FLUV D2: PAR **Mean age, years** D1: 51.1 D2: 51.4 **Sex, % female** D1: 100 D2: 100 **Race, % white** D1: 0 D2: 0 **Baseline HAM-A** D1: 16.1 D2: 15.5 **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**HAM-D** **Mean score at baseline (SD):** D1: 25.2 (2.2) D2: 24.0 (2.3) **Mean score at endpoint (SD):** D1: 9.3 (5.5) D2: 10.1 (5.5) *P* = 0.45 **Mean score change (SD):** D1: 15.9 D2: 13.9 **HAM-A** **Mean score at baseline (SD):** D1: 16.1 D2: 15.5 **Intervention** **Mean score at endpoint (SD):** D1: 6.5 (4.5) D2: 7.0 (3.7) *P* = 0.531 **Mean score change (SD):** NR **MADRS** NR **CGI-S** NR **CGI-I** NR **CGI** NR **QOL scale**	**Overall rate of attrition, %** 25 **Attrition rate, %** D1: 18.9 D2: 30.8 **Withdrawals due to adverse events, %** D1: 9.4 D2: 5.8 **Attrition due to lack of efficacy, %** NR **Overall adverse events, %:** NR

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Design, Sample Size, Duration, Type of Depression	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
				VAS **Mean score at baseline (SD):** D1: 88.1 (9.1) D2: 87.6 (10.1) **Mean score at endpoint (SD):** D1: 33.1 (21.7) D2: 42.8 (24.8) *P* = 0.0338 **Mean score change (SD):** NR • Significant difference between groups was observed in percentage change only for hot flashes: -81.1 (18.8) vs. -66.8 (23.3); *P* < 0.01 **Adherence** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Van Moffaert et al., 1995[95] **Country and setting:** Belgium, Multicenter trial (15 psychiatric centers, in- and out-patient) **Funding:** Pfizer	**Research objective:** To evaluate comparative efficacy and tolerability of SER and FLUOX in acute and continuation treatment of MDD **Duration of study:** 8 wks acute phase, responders and partial responders could continue in 24 wk continuation phase **Study design:** RCT **Overall study N:** 165 **Intervention:** D1: SER: 50-100 mg/d D2: FLUOX: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 80 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal ideation • MADRS score greater than 40 • Concomitant serotonergic drugs (including lithium and carbamazepine)	**Mean age (yrs):** D1: 46.1 D2: 48.4 **Sex (% female):** D1: 66.3 D2: 65.9 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 24.5 D2: 23.2	**ACUTE PHASE** % responders/partial responders at end of acute phase (defined as ≥ 50% reduction in HAM-D or MADRS, or a score ≤ 10 on HAM-D, and much/very much improved on CGI-GI and a CGI-S within nonmental illness range) : SER = 71% FLUOX = 77% **CONTINUATION PHASE** Relapse rates SER = 10% FLUOX = 13% Response rate (see defintion above) SER = 81% FLUOX = 80%	**Overall adverse events:** D1: 48 D2: 54 **Cardiovascular adverse events:** D1: 4 D2: 4	**Overall attrition rate:** 17% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: van Moffaert et al., 1995[96] **Country and setting:** Belgium Psychiatric centers (6 sites) **Funding:** NV Organon	**Research objective:** Safety and efficacy of MIR and TRA in depressed hospital patients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 200 **Intervention:** D1: MIR: 24-72 mg/d D2: TRA: 150-450 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT • Suicidal tendencies 3 mos • > 6 episodes of depression requiring hospitalization	**Mean age (yrs):** D1: 46.1 D2: 46.3 **Sex (% female):** D1: 69 D2: 71 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	MIR had sig higher response rates on HAM-D at study endpoint than TRA (61% vs. 51%; *P* = NR (ns)) MIR was also more efficacious on other outcome scales (MADRS, Beck, Brief Psychiatric Rating Scale total score, General Psychiatric Impression Global Assessment Scale) but not all diffs reached statistical significance	NR	**Overall attrition rate:** 24.5% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Vanelle et al., 1997[97] **Country and setting:** France, Psychiatric centers **Funding:** NR	**Research objective:** To investigate whether FLUOX is effective in treatment of dysthymia **Duration of study:** 6 mos (Phase 1 = 3 mos, Phase 2 = 3 mos) **Study design:** RCT **Overall study N:** 140 (randomized) **Intervention:** D1: FLUOX: 20 mg/d (Phase I), 20-40 mg/d (Phase II) D2: PBO	**Inclusion criteria:** • Adults 18 or older • Minimum HAM-D score of 16 • Dysthymia • Dysthymia not secondary to any other axis I disorder **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • MDD, other types of depression • Uncontrolled serious somatic disease • FLUOX for depressive disorder which had not been effective • Received a psychotropic drug during previous wk (except for authorized benzodiazepines) • Requiring one of following during study: neuroleptic, lithium, or other mood regulator	**Mean age (yrs):** NR **Sex (% female):** D1: 76.9 D2: 73.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 20.5 (3.1) D2: 20.9 (3.0)	# of responders at mo 3 (>50% decrease in HAM-D associated with a score of 1 (very much improved) or 2 (much improved) on CGI-I), FLUOX = 42 PBO = 14 (*P* = 0.03) Remission n at mo 3 (HAM-D $\leq$ 7), FLUOX = 32, PBO = 10 (*P* = 0.07) # of responders at mo 6: FLUOX = 33 PBO = 9 (*P* = 0.48) Remission n at mo 6: FLUOX: 29 PBO: 4 (*P* = 0.01) Increase in GAF scores by mo 3 sig greater in FLUOX (*P* = 0.02); mean score indicated return to functioning level compatible with normal social and relational life (mean GAF score = 70) No sig change in GAF scores from mo 3 to 6 for either treatment group	**Overall adverse events:** D1: 38.5% D2: 44.9%	**Overall attrition rate:** 22.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Ventura et al, 2007[98] **Country and Setting** multicenter (8 Centers). United States **Funding** Forest Laboratories **Quality rating:** Fair .	**Research objective** Comparison of efficacy and tolerability of a fixed dose of ESC with SER **Drugs, Doses, and Range** D1: ESC (10-20 mg 1 x daily): 10 mg QD; Low D2: SER (25-200 mg 1 x daily): 50-200 mg QD; Low, Medium, or High **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **N** 215 **Duration** 8 week + 1 week lead-in **Type of depression** MDD **Intervention** ESC SER	**Inclusion criteria:** • Adults (age range): 18-80 • Diagnosed with MDD according to DSM-III or -IV: DSM-IV • MADRS: ¡Ý22 at both screening and baseline • CGIS: Concomitant condition (e.g., alcoholism, anxiety, stroke) **Exclusion criteria:** • Pregnant • Negative pregnancy test • Women of childbearing potential not on accepted form of contraception • Lactating • Concomitant psychotheraputic or psychotropic medications • Use of a depot neruoleptic within 6 months. • Use of any neuroleptic, antidepressant, or anxiolytic medication within 2 week (5 weeks for FLUOX). • Treatment with either ESCalopam or SER. • Failure to respond to adequate trials of any two SSRIs. • Any psychotropic Dexcept zaleplon or zolpidem for sleep. • Additional mental	**Groups similar at baseline** Yes **n =** D1: 107 D2: 108 **Mean age, years** D1: 40.6 D2: 38.1 **Sex, % female** D1: 54.8% D2: 60.2% **Race, % white** D1: 82.7% D2: 89.8% **Baseline HAM-A** D1: 15.9 (0.5 SE) D2: 15.6 (0.5 SE) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** Use of sleep medication, % D1: 9.6 D2: 7.4	**HAM-D** D1: ESC D2: SER n at baseline: D1: 104 D2: 107 No. of responders: D1: 75 (72%) D2: 74 (69%) *P* = NR (ns) No. of remitters: D1: 51 (49%) D2: 57 (53%) *P* = NR (ns) Mean score at baseline (SE): D1: 26.8 (0.5) D2: 26.8 (0.4) Mean score at endpoint (SD): D1: 9.9 D2: 10.7 Mean score change (SE): D1: -16.9 (0.7) D2: -16.1 (0.8) End point scores not given and calculated by reviewer #1 **MADRS** D1: ESC D2: SER n at baseline: D1: 104 D2: 107 No. of responders: D1: 75 D2: 74	**Overall adverse events, %:** D1: 49% D2: 62% **Diarrhea, %:** D1: 13% D2: 23% **Headache, %:** D1: 13% D2: 10% **Insomnia, %:** D1: 14% D2: 17% **Nausea, %:** D1: 17% D2: 17% **Sexual dysfunction, %:** Libido decreased: D1: 10 D2: 14 Ejaculation disorder: D1: 23 D2: 23 **Attrition** **Overall attrition, %:** 16% **Attrition rate, %:** D1: 17% D2: 14% **Withdrawals due to adverse events, %** D1: 2 D2: 4 **Withdrawals due to lack of efficacy, %** D1: 0 D2: 0

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) Following were all listed as exclusion criteria: • Primary Axis I disorder other than MDD • history of any DSM-IV defined psychotic disorder • DSM-IV criteria for bipolar disorder, schizophrenia, obsessive-compulsive disorder, mental retardation, or pervasive development disorder. • Current psychotic disorder, personality disorder of sufficient severity to interfere with participation. • Illicit drug and alcohol abuse: Dependency as defined by DSM-IV. • Clinically significant medical disease • Findings from physical examination, laboratory test, and ECG were required to be normal or clinically insignificant. • Investigational drug use within last month. • Suicidal tendencies (acute or other) **Outcome measures** • HAM-D: HAMD baseline; HAMD anxiety		No. of remitters: D1: 60 D2: 62 Mean score at baseline (SE): D1: 26.8 (0.5) D2: 26.8 (0.4) Mean score at endpoint (SD): D1: 10.4 D2: 10.6 Mean score change (SE): D1: -2.1 (0.1) D2: -2.1 (0.1) End point scores not given and calculated by reviewer #1 **CGI-S** D1: ESC D2: SER n at baseline: D1: 104 D2: 107 Mean score at baseline (SE): D1: 4.2 (0.04) D2: 4.2 (0.04) Mean score at endpoint (SD): D1: 2.1 D2: 2.1 Mean score change (SD): End point scores not given and calculated by reviewer #1 **CGI-I** D1: ESC D2: SER	**Comments** • Loss to follow-up 5% for each arm. • Protocol violation 4% for each arm. • Consent withdrawn: ESC 4%; SER 2%. • Other ESC 1%.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		subscale • MADRS • CGI-S and CGI-I • Quality of life scales: Quality of Life Enjoyment and Satisfaction Questionnaire • Others: HAM-A; CES-D		**CGII** Yes Intervention: D1: ESC D2: SER n at baseline: D1: 107 D2: 108 Mean score at endpoint (SE): D1: 1.8 (0.1) D2: 1.8 (0.1) **QOL scale** Q-LES-Q Intervention: D1: ESC D2: SER n at baseline: D1: 107 D2: 108 Mean score at baseline (SE): D1: 43.6 (0.8) D2: 41.8 (0.8) Mean score at endpoint (SD): D1: 56.3 D2: 57 Mean score change (SE): D1: 12.7 (1.2) D2: 15.2 (1.3) End point scores not given and calculated by reviewer #1 **Another QOL scale** NR	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				Is adherence reported? Rates NR	

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Versiani, 2005[99] **Country and setting:** Europe and South America, multicenter (30 sites) **Funding:** Organon	**Research objective:** To compare efficacy and tolerability of MIR and FLUOX in severe MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 299 randomized; 292 included in analysis **Intervention:** D1: FLUOX 20-40 mg/d D2: MIR 30-60 mg/d	**Inclusion criteria:** • Adults 18 to 65 • MDD according to DSM-IV • Minimum HAM-D-17 score of 25 **Exclusion criteria:** • Current depression episode duration >12 mos • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic drugs • Investigational drug use within 30 days • ECT within 3 mos • Alcohol or substance abuse (within 6 mos) • Pregnant or lactating • Clinically sig medical disease • Suicidal risk • Response during PBO washout (25% improvement in HAM-D-17)	**Mean age, years** D1: 47 D2: 43 **Sex (% female)** D1: 69 D2: 74 **Race (% white)** NR **Baseline HAM-D (SD)** D1: 28 (3) D2: 29 (3) **Baseline HAM-A** NR	No sig diff in percent of responders at day 56, remission: (MIR: 40.1% vs. FLUOX: 41.4 %) Both treatment groups showed 18 point improvement on Q-LES-Q **Sleep outcomes:** Scores on Leeds Sleep Evaluation Questionnaire improved similarly for both groups	**Overall adverse events:** D1: 45 D2: 50 **Changes in weight (increase):** D1: 1.3 D2: 6.9 **Dizziness:** D1: 12.8 D2: 9 **Headache:** D1: 18.8 D2: 19.3 **Insomnia:** D1: 8.7 D2: 4.8 **Nausea:** D1: 24.1 D2: 15.9 **Somnolence:** D1: 9.4 D2: 13.8	**Overall attrition rate:** 14% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Wade et al., 2007[100] **Country and Setting** Multinational, Multicenters (psychiatric outpatient and general practice settings) **Funding** H. Lundbeck A/S **Quality rating:** Fair	**Research objective** The objective was to examine efficacy and tolerability of ESC compared to DUL in patients with moderate to severe MDD patients over 24 weeks, with a secondary enpoint at 8 weeks. **Drugs, Doses, and Range** D1: ESC 20 mg/day (Primary Analysis- endpoint at 24 weeks) D2: DUL 60 mg/day (Primary Analysis- endpoint at 24 weeks) D3: ESC 20 mg/day (Seconday Analysis - endpoint at 8 weeks) D4: DUL 60 mg/day (Secondary **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** No **Study design** RCT **Duration** 24 weeks **Type of depression** MDD **Intervention** ESC 20 mg/day DUL 60 mg/day	**Inclusion criteria:** • Adults (age range): 18 - 65 years of age • Diagnosed with MDD according to DSM-III or -IV • MADRS: total score greater than or equal to 26 • CGIS: greater than or equal to 4 • Other: Patients with a secondary current comorbid anxiety disorder could be included, except obsessive-compulsive disorder, post traumatic stress disorder, or panic disorder **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications: (except zolpidem, zolpiclone and zaleplon used episodically for insomnia) within 2 weeks prior to baseline or during study • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): bipolar disorder, psychotic disorder or features,	**Groups similar at baseline** Yes **n =** D1: 141 D2: 146 **Mean age, years** D1: 43.3 (11.6) D2: 44.5 (11.0) **Sex, % female** D1: 74.1 D2: 70.2 **Race, % white** D1: 94.4 D2: 97.4 **Baseline HAM-A** D1: 22.1 (7.6) D2: 21.9 (6.5) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** Base on intent-to-treat population (ESC, n = 141, DUL, n = 146)	**HAM-D** No. of responders: D1: 109 (77%) D2: 106 (73%) *P* = NR (ns) D3: 94 D4: 81 No. of remitters: D1: 94 (67%) D2: 87 (60%) *P* = NR (ns) D3: 69 D4: 62 Mean score at baseline (SD): D1: 22.7 (5.1) D2: 22.7 (4.7) D3: 22.7 (5.1) D4: 22.7 (4.7) Mean score at endpoint (SD): D1: 7.13 D2: 8.47 D3: 9.93 D4: 11.19 Mean score change (SD): D1: -15.6 D2: -14.2 D3: -12.8 D4: -11.5 D1/2 results at 24 weeks, D3/4 results at 8 weeks. mean HAMD- 17 total scores improved steadily from baseline to week 24 for ESC and DUL, with statistically significant (p <0.05) separation at weeks 1,2, and 16 in	**Overall adverse events, %:** D1: 77.6 D2: 74.8 **Constipation, %:** D1: 2.8 D2: 8.6 **Diarrhea, %:** D1: 7.7 D2: 7.3 **Dizziness, %:** D1: 9.1 D2: 15.9 **Headache, %:** D1: 23.1 D2: 16.6 **Insomnia, %:** D1: 4.9 D2: 12.6 **Nausea, %:** D1: 24.5 D2: 31.8 **Vomiting, %:** D1: 5.6 D2: 7.3 **Sexual dysfunction, %:** D1: 4.9 D2: 6.6 **Attrition** **Overall attrition, %:** 23% **Attrition rate, %:** D1: 22.2 D2: 24.5 **Withdrawals due to adverse events, %**

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		current eating disorders (anorexia nervosa, bulimia), mental retardation, any pervasive developmental disorder or cognitive disorder • Illicit drug and alcohol abuse within 12 months prior to baseline • ECT within last 6 months • Suicidal tendencies (acute or other) • Receiving formal, behaviour therapy or systematic psychotherapy • History of lactose intolerance • History of hypersensitivity or non-response to CIT, or ESC, or DUL, or with increased intra-ocular pressure, or at risk of acute narrow-angle glaucoma **Outcome measures** • HAM-D • MADRS: adjusted mean change in MADRS total score from baseline to 24 weeks • CGI-S or CGI-I • Quality of life scales: MOS 36 - Item Health Survey (SF-36) • Others: HAM-A, Sheehan Disability Scale (SDS)		favour of ESC. **MADRS** No. of responders: D1: 109 D2: 106 D3: 94 D4: 81 No. of remitters: D1: 103 D2: 102 D3: 79 D4: 70 Mean score at baseline (SD): D1: 22.7 (5.1) D2: 22.7 (4.7) D3: 22.7 (5.1) D4: 22.7 (4.7) Mean score at endpoint (SD): D1: 9.1 D2: 10.4 D3: 13.0 D4: 14.7 Mean score change (SD): D1: -2.7 D2: -2.5 D3: -2.2 D4: -2.0 D1/2 results at 24 weeks, D3/4 results at 8 weeks. Analyses were based on intent-to-treat. Superiority to DUL was significant at week 24 (treatment diffeerence of 2.21l ANCOVA, one-sided, *P* = 0.011). **CGI-S**	D1: 9.0 D2: 17.2 **Withdrawals due to lack of efficacy, %** D1: 4.9 D2: 1.3 **Comments** Calculations were based on number of patients randomized to each treatment group (ESC, n-144 and DUL, n= 151). Significantly more patients withdrew due to adverse events from DUL group than from ESC group (9.0%).

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				Mean score at baseline (SD): D1: 4.8 (0.7) D2: 4.8 (0.7) D3: 4.8 (0.7) D4: 4.8 (0.7) Mean score at endpoint (SD): D1: 2.11 D2: 2.28 D3: 2.65 D4: 2.79 D1/2 results at 24 weeks, D3/4 results at 8 weeks. **CGI-I** n at baseline: D1: 141 D2: 146 D3: 141 D4: 146 Mean score at endpoint (SD): D1: 1.76 D2: 1.99 D3: 1.99 D4: 2.23 D1/2 results at 24 weeks, D3/4 results at 8 weeks. There was a statistically significant difference in favour of ESC on CGE-E at week 8, but not at week 24. **QOL scale** MOS 36-item Health Survey (SF-36) scale Intervention: D1: ESC 20 mg/day D2: DUL 60 mg/day	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				n at baseline: D1: 141 D2: 146 Mean score at baseline (SD): D1: 32.5 D2: 32.5 Mean score at endpoint (SD): D1: 61.8 D2: 62.0 Analyses were based on patients scoring ≤ 50 on bodily pain dimension of SF-36. SF-36 was used at baseline, week 6, week 12 and week 24. No significant difference on any of 8 subscales of SF-36 between treatment groups. **Is adherence reported?** NR **Rate of adherence or compliance** NR **Additional Results:** • At week 24, HAM-A total score was 7.7 for ESC-treated patients and 8.6 for DUL-treated patients. • HAM-A scores at week 1 were significantly different (18.8 for ESC vs.19.9 for DUL, $P < 0.05$). • On SDS scale, mean score at baseline for ESC-treated patients	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				was 20.5 for patients in treatment groups. • Patients in ESC mean score at endpoint at 24 weeks was 7.58, and mean score for patients in DUL group was 9.95. mean scores at week 8 for ESC-treated patients and DUL-treated patients were 10.10 and 12.57, respectively. • SDS total scores were significantly better for ESC treatment group at both week 8 and week 24. • SDS subscale scores were statistically significant for patients treated with ESC vs. DUL at week 8 for social and family subscales, and at week 24 for work subscale. • At week 24, patients treated with ESC showed statistically significant decreases from baseline of 5.0 and 3.7 mmHg, respectively, in seated systolic (baseline of 125.8 mmHg) and diastolic (baseline of 79.0 mmHg) blood pressure. • Patients treated with ESC had a non-stastically significant decrease in pulse rate of 1.0 bpm from baseline (93.4 bpm),	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				and patients treated with DUL showed a statistically significnt increase in seated pulse rate of 2.7 bpm.	

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Weihs et al., 2000[101] Doraiswamy et al., 2001[230] **Country and setting:** United States Multicenter **Funding:** Glaxo Wellcome	**Research objective:** Comparison of efficacy and safety of BUP and PAR with PAR in treatment of MDD in elderly **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** D1: BUP: 100-300 mg/d (197) D2: PAR: 10-40 mg/d (22)	**Inclusion criteria:** • Adults 60+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** D1: 69.2 D2: 71.0 **Sex (% female):** D1: 54 D2: 60 **Race (% white):** D1: 98 D2: 90 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	No sig diffs in any outcome measures between treatment groups (LOCF and observed) Response rates $\geq$ 50% reduction in HAM-D) were similar in both groups: BUP SR: 71%, PAR: 77% No sig diffs in Quality of Life scales (QLDS, SF-36) between treatment groups at endpoint; overall sig improvement in QLDS and QOL at day 42 ($P < 0.0001$)	**Constipation:** D1: 4 D2: 15 **Diarrhea:** D1: 6 D2: 21 **Dizziness:** D1: >10 D2: >10 **Headache:** D1: 35 D2: 19 **Insomnia:** D1: >10 D2: >10 **Nausea:** D1: >10 D2: >10 **Somnolence (fatigue):** D1: 6 D2: 27	**Overall attrition rate:** 16% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Weihs et al., 2002[157] **Country and setting:** United States outpatient, mulitcenter **Funding:** GlaxoSmithKline	**Research objective:** To evaluate safety and efficacy of BUP SR for decreasing risk for relpase of depression in patients who responded to BUP SR **Duration of study:** Up to one yr (52 wks) **Study design:** RCT **Overall study N:** 828 in open label phase; 423 entered double-blind phase **Intervention:** D1: BUP: 300 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 to 18 and older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use • Suicidial tendencies • Propensity for seizures	**Mean age (yrs):** D1: 39.4 D2: 39.9 **Sex (% female):** D1: 66 D2: 64 **Race (% white):** D1: 88 D2: 86 **Baseline HAM-A:** NR **Baseline HAM-D:** NR	423 patients were randomized to continuation treatment A statistically sig diff in favor of BUP SR (37% relapse) over PBO (52% relapse) was seen in time to treatment intervention for depression when survival curves were compared (log-rank test, $P = 0.004$) Statistically sig separation between BUP SR and palcebo began at double-blind wk 12 ($P < 0.05$) AEs in BUP SR-treated patients accounted for 9% and 4% of discontinuations from open-label and double-blind phases, respectively	**Overall adverse events:** D1: 54 D2: 46 **Cardiovascular adverse events:** D1: mean sbp -1.1 D2: Mean sbp +2.1 **Changes in weight (decrease):** D1: -2.5 lbs D2: 0 **Constipation:** D1: 1 D2: 1 **Diarrhea:** D1: 1 D2: 5 **Dizziness:** D1: 1 D2: 3 **Headache:** D1: 16 D2: 13 **Insomnia:** D1: 3 D2: 3 **Nausea:** D1: 4 D2: 2	**Overall attrition rate:** 75.7% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Weisler et al., 1994[102] **Country and setting:** Country NR, appears to be United States 2 private psychopharma-cology clinics **Funding:** Burroughs Wellcome Co	**Research objective:** To compare safety and efficacy of BUP and TRA **Duration of study:** 6 wks (after a 1 wk single-blind PBO lead-in to eliminate PBO responders and PBO nontolerators) **Study design:** RCT **Overall study N:** 124 **Intervention:** D1: BUP: 225-450 mg/d D2:TRA: 150-400 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Episode of 4 wks to 2 yrs • Clinically approrpiate for therapy **Exclusion criteria:** • Pregnant/Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Male with a history of priapism or being treated with medications associated with priapism • Prior treatment with BUP or TRA, currently taking digoxin or phenytoin	**Mean age (yrs):** D1: 40.2 D2: 40.8 **Sex (% female):** D1: 52.4 D2: 65.6 **Race (% white):** D1: 90.5 D2: 90.2 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25.8 (NR) D2: 25.0 (NR)	HAM-D (LOCF) Center 1 BUP: at day 42, BUP stat sig better than TRA ($P < 0.01$) When centers were combined, no statistically sig diffs between TRA and BUP were observed Responder analysis (responder ≥ 50% reduction in HAM-D score between baseline and discontinuation) D1: 33 (55.9%) D2: 21 (40.4%) Remitters (>50% reduction and a HAM-D score<10) D1: 27 (46%) D2: 16 (31%) CGI-I responders D1: 34 (57.6%) D2: 24 (46.2%) Compliance D1: 94.7% D2: 90.1%	**Constipation:** D1: 9.68 D2: 11.67 **Diarrhea:** D1: 4.84 D2: 11.67 **Dizziness:** D1: 20.97 D2: 30.00 **Headache:** D1: 33.87 D2: 23.33 **Insomnia:** D1: 14.52 D2: 5.00 **Nausea:** D1: 11.29 D2: 6.67 **Somnolence (fatigue):** D1: 8.06 D2: 45.00 **Sweating (increase):** D1: 9.68 D2: 5.00	**Overall attrition rate:** 40.3% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Wheatley et al., 1998[103] **Country and setting:** Multinational Multicenter **Funding:** NV Organon	**Research objective:** To compare efficacy and tolerability of MIR and FLUOX in depressed inpatients and outpatients **Duration of study:** 6 wks (after a 3-7 day single-blind, PBO washout period) **Study design:** RCT **Overall study N:** 133 **Intervention:** D1: MIR: 15-60 mg/d D2: FLUOX: 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 75 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 21 • HAM-D item 1 (depressed mood) score ≥ 2 • Depressive episode duration 2 wks to 12 mos **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Nonresponders to antidepressant treatment	**Mean age (yrs):** D1: 47.2 D2: 47.5 **Sex (% female):** D1: 55 D2: 58.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 26.0 (4.4) D2: 26.1 (4.3)	HAM-D responders at endpoint (≥ 50% improvment) MIR ~65% (n = 39) FLOU ~45% (n = 28) (*P* = NS) Remission from depression (HAM-D < 7 at endpoint): MIR 23.3% FLUOX 25.4% (*P* = 0.39) CGI responders (much or very much approved): MIR 63.3% FLUOX 54.0% (*P* = 0.677) Q-LES-Q estimated treatment diff (MIR minus FLUOX): 2.14 95% CI, (-2.30, 6.58) (*P* = 0.348)	**Dizziness:** D1: 7.6% D2: 9.0% **Headache:** D1: 9.1% D2: 17.9% **Nausea:** D1: 3.0% D2: 10.4% **Somnolence (fatigue):** D1: 18.2% **D2: 13.4%** Weight gain: D1: +1.84 (+/- 2.52) D2: - 0.54 (+/-2.32) *P* = 0.0001	**Overall attrition rate:** 28.6% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Whyte et al., 2003[225] **Country and setting:** Australia Hospital (Hunter Area Toxicology Service Database) **Funding:** NR	**Research objective:** To assess toxicity in overdose of VEN and SSRIs compared to TCAs **Duration of study:** Taken from database records between November 1994 and April 2000 **Study design:** Cohort study of prospectively collected data **Overall study N:** 538 (284 VEN and other SSRI records) **Intervention:** D1: VEN D2: Other SSRIs	**Inclusion criteria:** • First time admissions for overdose with an SSRI or TCA **Exclusion criteria:** • Patients who took a MAOI • Patients ingesting more than one drug of interest • Second and subsequent admissions for deliberate DSPs	**Mean age (yrs):** D1: 36 D2: 29 **Sex (% female):** D1: 68.6 D2: 67 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	Overdosing and seizure experience on VEN: D1: 13.7% D2: 1.3% ($P < 0.001$) Overdosing required ICU admission: D1: 29.4% D2: 7.3% ($P < 0.01$) No other sig diffs between VEN and SSRI overdoses	NR	**Overall attrition rate:** N/A **ITT Analysis** NR **Quality rating:** Good

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Williams et al., 2000[104] **Country and setting:** United States Multicenter, primary care clinics **Funding:** Hartford and MacArthur Foundations	**Research objective:** To compare effectiveness of PAR vs. PBO vs. behavioral treatment for dysthymia or minor depression in primary care patients older than 60 yrs **Duration of study:** 11 wk **Study design:** RCT **Overall study N:** 415 **Intervention:** D1: PAR: 10-40, individually titrated D2: PBO	**Inclusion criteria:** • Minimum HAM-D score of 10 • Dysthymia • Age 60+ **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Severe Suicidal tendencies • MMSE <24 • Current depression treatment	**Mean age (yrs):** D1: 71 D2: 71 **Sex (% female):** D1: 39 D2: 45 **Race (% white):** D1: 82.5 D2: 75.7 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	Mean decrease in HSCL-D-20: D1: 0.61 (*P* = 0.05) D2: 0.40 (*P* = 0.05) Behavior Therapy 0.52 (*P* = 0.05) *P* = 0.004 for PAR vs. PBO PAR only statistically and clinically sig better than PBO for subjects with dysthymia and high baseline mental health function HAM-D results NR for ITT population	NR	**Overall attrition rate:** 25.1% **TT Analysis:** Yes **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Wilson et al, 2003[158] **Country and setting:** UK, outpatient clinic(s) **Funding:** NR	**Research objective:** To examine efficacy of SER in preventing recurrence of depression in older people living in community **Duration of study:** 8 wk treatment phase and a 16-20 wk continuation phase (open-label SER) 100 wk randomized, double-blind phase (SER and PBO) (article focuses on results of this maintenance phase) **Study design:** RCT **Overall study N:** 113 (randomised to double-blind phase) **Intervention:** D1: SER: 50-100 mg/d D2: PBO	**Inclusion criteria:** • Adults 65+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Geriatric Mental State AGECAT depression level 3 or greater **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medicationsIllicit drug and alcohol abuse • Clinically sig medical diseaseSuicidial tendencies: sig suicidal or delusional experiences • MMSE ≤ 11 • Concomitant drugs excluded include psychotropic drugs, warfarin, and anticonvulsants	**Mean age (yrs):** D1: 76.6 D2: 76.8 **Sex (% female):** D1: 66.1 D2: 75.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 20.7 (3.7) D2: 20.3 (3.3)	Analysis of recurrence Kaplan Meier analysis, SER vs PBO, log rank test = 1.55, df = 1 (*P* = 0.21) Cumulative survival function SER = 39%, median survival 92 wks; PBO = 31%, median survival 48 wks Reduction in risk of recurrence: 8.4% over 100 wks (SER vs. PBO) % with recurrence in first 26 wks and wks 27-52, respectively: SER = 57%, 16% PBO = 60%, 32% Cox regression model predicting recurrence: hazard ratio (95% CI) included variables: SER vs. PBO = 1.21 (0.704, 2.082)	NR	**Overall attrition rate:** 72.6% **ITT Analysis** Not applicable: recurrence trial **Quality rating:** Fair

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Yevtushenko, 2007[105] **Country and Setting** Eight psychiatric out-patient clinics across Federation of Russia **Funding** ARBACOMLLC – Russian pharmaceutical company. **Quality rating:** Good Fair	**Research objective** To compare efficacy and tolerability of ESC and CIT in outpatients with MDD (MDD). **Drugs, Doses, and Range** D1: CIT: 10 mg QD (D2: CIT 20 mg QD D3: ESC: 10 mg QD **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** Yes **Study design** RCT **Duration** 6 weeks **Type of depression** MDD **Intervention** ESC CIT 10 mg CIT 20 mg	**Inclusion criteria:** • Adults (age range): 23 to 45 • Diagnosed with MDD according to DSM-III or -IV: DSM-IV • MADRS: Total Score ≥ 25 • Opinion of treating psychiatrist, potential benefit from treatment with 1 or other study drugs **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Oral antipsychotic drugs or MAOIs w/in 2 weeks • Depot antipsychotic preparation within 6 months • SSRI, SNTR, or TCA within 1 week or FLUOX within 5 weeks • Mania or any bipolar disorder, schizophrenia, or any psychotic disorder, or display of any psychotic features, • OCD, mental retardation or any pervasive developmental disorder, • Eating disorder (anorexia nervosa or bulimia nervosa), or dementia	**Groups similar at baseline** Yes **n =** D1: 109 D2: 111 D3: 110 **Mean age, years** D1: 35.19 D2: 34.79 D3: 35.12 **Sex, % female** D1: 61.1% D2: 57.5% D3: 56.5% **Race, % white** D1: 100% D2: 100% D3: 100% **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 14.8% D2: 9.4% D3: 9.3% **Comments:** MADRS total score, mean (SE) 34.78(0.34) MADRS total score, mean (SE) 35.40(0.32) MADRS total score, mean (SE)35.70 (0.37)	**HAM-D** NR **MADRS** D4: ESC Subgroup D5: CIT 10 mg Subgroup; CIT 20 mg Subgroup n at baseline: D3: 109 D1: 111 D2: 110 D4: 66 D5: 65; 78 No. of remitters: D3: 97 D1: 27 D3: 55 D4: NR D5: NR Mean score at endpoint (SD): D3: 6.08 D1: 15.29 D2: 10.51 D4: 6.58 D5: 16.68; 11.26 Mean score change (SE): D3: -2.60 (0.10) D1: -1.61 (0.10) D2: -2.05 (0.10) D4: -2.63 (0.12) D5: -1.53 (0.12); -1.92 (0.11) NOTE: A subgroup of patients with severe depression defined as having a baseline MADRS total score of ≥ 35 is included in above table. ESC arm significantly greater at $P < 0.001$.	**Overall adverse events, %:** D1: 6.5 D2: 15.1 D3: 17.6 **Dizziness, %:** D1: 0 D2: 0 D3: 0.9 **Headache, %:** D1: 0.9 D2: 1.9 D3: 3.7 **Nausea, %:** D1: 1.9 D2: 4.7 D3: 6.5 **Sexual dysfunction, %:** D1: 0.9 D2: 0.9 D3: 0.9 **Attrition** **Overall attrition, %:** 2.40% **Attrition rate, %:** D1: 1% D2: 5% D3: 2% **Withdrawals due to adverse events, %** D1: 0 D2: 0 D3: 0 **Withdrawals due to lack of efficacy, %** D1: 0 D2: 0 D3: 0

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
		• Alcohol or drug abuse within previous 12 months • Other serious illnesses or sequela of serious illness • ESC or CIT usage within 60 days • Severe drug allergies or hypersensitivity • Inability to comply with protocol • Undergoing treatment with antiparkinsonian compound, barbiturate, chloral hydrate, lithium, anticonvulsant, or hypnotic and anxiolytic. **Outcome measures** • MADRS: Primary efficacy measure. A secondary efficacy measure was reported in changes from baseline in total score in a subgroup of severely depressed patients (MADRS total score ≥35) • Also MADRS core depressions subscale score in overall population and severely depressed subgroup. This data was not abstracted but is available, if needed. • CGI-S or CGI-I: Secondary efficacy measure. Changes from baseline to end of study.		Difference between two CIT groups significant at $P > 0.001$ NOTE: Mean score at endpoint was not reported and thus calculated by 1st reviewer. Note: primary definition of remission MADRS total score ≤ 12 (see numbers in question 55). Remission rates with secondary definition (MADRS total score ≤ 10): ESC 21, CIT 10mg 31, CIT 20mg 31. **CGI-S** D1: ESC D2: CIT 10 mg D3: CIT 20 mg D4: ESC Subgroup D5: CIT 10 mg Subgroup; CIT 20 mg Subgroup n at baseline: D3: 109 D1: 111 D2: 110 D4: 66 D5: 65; 78 All were found significant, baseline vs. endpoint, at $P > 0.001$ No report given of baseline or endpoint scores. **CGI-I** D1: ESC D2: CIT 10 mg D3: CIT 20 mg **CGII**	**Comments** Attrition: Seven participants withdrew consent and one patient withdrew due to recurrence of a pre-existing condition.

Evidence Table 1. Randomized controlled trials and observational studies (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion Outcome Measures	Population Characteristics	Health Outcome Results	Adverse Events
				Yes Intervention: D1: ESC D2: CIT 10 mg D3: CIT 20 mg n at baseline: D3: 109 D1: 111 D23: 110 Endpoint changes in score from baseline as follows: D3:+1.58 (SE 0.09) D1: +2.35 (0.10) D2: +1.80 (0.09). **QOL scale** NR **Another QOL scale** NR **Rate of adherence or compliance** Potentially non-compliant patients were not included. No methods were specifically employed to assess compliance. No deviations were reported.	

Evidence Table 2. Systematic evidence reviews and meta-analyses

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Aursnes et al., 2005[174] **Country and setting:** NR **Funding:** None	**Study design:** Pooled analysis **Number of Patients:** 1,466 **Studies Included:** 16 studies with unpublished data	**Included Studies:** Clinical data on PAR as presented to world's drug regulatory agencies in 1989 **Included Populations** NR **Interventions:** PAR vs. PBO, no other info provided	**Study Results:** 7 suicide attempts in patients on drug and 1 in a patient on PBO. Probability of increased intensity of suicide attempts per yr in adults taking PAR was 0.90 with a "pessimistic" prior, and somewhat less with 2 more neutral priors	NR	**Publication Bias:** No **Heterogeneity:** No	**Standard Method of Study Appraisals:** NR **Quality Rating:** Fair

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Barbui et al., 2009[175] **Country and setting:** US **Funding:** Fondazione Cariverona **Aims of Review:** To quantify the risk of completed or attempted suicide among people in different age groups with depression after exposure to SSRIs. **Quality Rating:** Good	**Study design:** Systematic Review **Number of Patients:** NR **Studies Included:** Gibbons et al., 2007 Olfson et al., 2006. Olfson and Marcus, 2008 Rahme et al., 2008 Sondergard et al., 2007 Sondergard et al., 2006 Tiihonen et al., 2006 Valuck et al., 2004	**Characteristics of Included Studies:** Observational cohort and case–control studies in any language that reported data on completed or attempted suicide among people exposed to SSRIs and among those who were not exposed to antidepressants; studies that reported relative risk [RR] estimates suitable for re-analysis; studies that used International Classification of Disease (ICD,ninth or tenth revision) definitions of completed or attempted suicide **Characteristics of Included Populations** Either sex and any age with a diagnosis of major depression. **Characteristics of Interventions:** Observational cohort (6)and case– control studies (2)	**Study Results:** The risk was decreased among adults (OR 0.57,95% CI, 0.47–0.70). Among people aged 65 or more years, exposure to SSRIs had a protective effect (OR 0.46, 95% CI, 0.27–0.79). Sensitivity analyses did not change these findings. In particular, for studies that used completed suicide as an outcome, decreased risk among adults (OR 0.66, 95% CI, 0.52–0.83) and older people (OR 0.53, 95% CI, 0.26–1.06). Among adults, no individual antidepressant was significantly associated with completed or attempted suicide. Random-effect meta-analysis of the risk of suicide attempt and completion associated with the use of individual antidepressants compared with no exposure to any antidepressants. Citalopram OR 0.87 (0.58–1.29) Fluoxetine OR (95% CI) 0.83 (0.32–2.14) Fluvoxamine OR (95% CI) 1.39 (0.66–2.92) Paroxetine OR (95% CI) 0.91 (0.52–1.58) Sertraline OR (95% CI) 0.46 (0.09–2.23) Venlafaxine OR (95% CI) 1.32 (0.74–2.35)	**Adverse Events:** N/A

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Brambilla et al., 2005[176] **Country and setting**: NR **Funding:** Multinational **Research objective:** To assess frequency of side-effects in FLUOX compared to other SSRIs, TCAs and other anti-depressants	**Study design:** Meta-analysis **Number of Patients:** 15,920 **Studies Included:** 131 studies	**Included Studies:** • All studies with random assigned patients that received FLUOX or any other anti-depressant • Cross-over studies and those with patients with concomitant medical illness were excluded **Included Populations** Patients with MDD **Interventions:** • FLUOX vs. tricyclic antidepressant (65 studies) • FLUOX vs. SSRI (22 studies) • FLUOX vs. another AD (44 studies)	**Study Results:** • 59.4% of patients treated with FLUOX and 59.3% of patients treated with other SSRIs experienced AEs.RR, 1.00 95% CI, 0.95, 1.04 • FLUOX less withdrawals due to side effects than TCAs and other related Ads RR, 0.61 95% CI, 0.52, 0.71 but not in comparison to other SSRIs RR, 1.04 95% CI, 0.84, 1.29 • FLUOX had less side effects (50.9%) than TCAs (60.3%) RR, = 0.84 95% CI, 0.76 to 0.94(*P* = 0.03) • FLUOX patients had more activating and GI adverse effects and less cholinergic side effects than other ADs	NR	**Publication Bias:** Yes **Heterogeneity**: Yes	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Yes **Quality Rating:** Good

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Bush et al., 2005[229] **Country and setting:** Multinational **Funding:** AHRQ **Research objective:** To examine role of depression post-MI	**Study design:** Systematic review **Number of Patients:** NR **Studies Included:** Studies (86) have examined depression or depressive symptoms in patients after MI and focuses on prevalence, clinical significance, treatment, and methods of evaluating condition	**Included Studies:** See above **Included Populations** Patients suffering from myocardial infarction and depression **Interventions:** SSRIs and therapy	**Study Results:** In post-MI patients with depression, selective serotonin reuptake inhibitors improve depression and some surrogate markers of cardiac risk, but no studies of sufficient power address question of whether treatment improves survival	**Adverse Events:** NR	**Publication Bias:** Yes **Heterogeneity:** Yes	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** MEDLINE®, Cochrane CENTRAL Register of Controlled Trials (Issue 1, 2003), Cochrane Database of Methodology Reviews (CDMR®), Cumulative Index of Nursing and Allied Health Literature (CINAHL®), Psychological Abstracts (PsycINFO®), and EMBASE **Quality Rating:** Fair

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Cipriani et al., 2010[178] **Country and setting:** Multinational **Funding:** Cochrane **Aims of Review:** 1) the efficacy of sertraline in comparison with other antidepressive agents in alleviating the acute symptoms of MDD 2) the acceptability of treatment with sertraline in comparison with other antidepressive agents 3)e the adverse effects of sertrali **Quality Rating:** Good	**Study design:** Systematic Review and Meta-analysis **Number of Patients:** See adverse events **Studies Included:**	**Characteristics of Included Studies:** Mostly RCTs that compared sertraline to another drug **Characteristics of Included Populations** Patients aged 18 or older, of both sexes with a primary diagnosis of major depression **Characteristics of Interventions:** Sertraline (as monotherapy). Comparator interventions All other antidepressive agents in the treatment of acute depression, including: 1) conventional tricyclic ADs (TCAs) 2) heterocyclic ADs (e.g. maprotiline) 3) SSRIs (fluoxetine, fluvoxamine, citalopram, paroxetine, escitalopram) 4) newer antidepressants (SNRIs such as venlafaxine, duloxetine, milnacipran; MAOIs or newer agents such as mirtazapine, bupropion, reboxetine; and non-conventional ADs, such as herbal products - e.g. hypericum).	**Study Results:** See Aes	**Adverse Events:** Constipation - sertraline vs paroxetine (OR 0.31, 95% CI, 0.16 to 0.58, P = 0.0002; 2 trials, 545 participants) diarrhoea - sertraline vs. escitalopram (OR 2.10, 95% CI, 1.22 to 3.61, P = 0.007; 2 trials, 489 participants) or paroxetine (OR 2.51, 95% CI, 1.66 to 3.80, P<0.0001; 2 trials, 545 participants) Urinary problems - sertraline vs. paroxetine (OR0.09, 95%CI 0.01 to 0.68, P = 0.02; 1 trial, 353 participants) paroxetine, sertraline vs paroxetine anorgasmia (OR 0.19, 95% CI, .04 to 0.89, p = 0.03; 1 trial, 353 participants) ejaculation disorder (OR 0.29, 95% CI, 0.14 to 0.60, p = 0.0009; 2 trials, 545 participants) or tremor (OR 0.55, 95% CI, 0.32 to 0.94, p = 0.03, 2 trials, 545 participants Constipation - Sertraline vs. venlafaxine (OR 0.05, 95% CI, 0.00 to 0.85, P = 0.04; 1 trial, 89 participants) Diarrhoea - sertraline vs. bupropion (OR 3.88, 95%CI 1.50 to 10.07, P = 0.005; 3 trials, 727 participants), or mirtazapine (OR 2.74, 95% CI, 1.52 to 4.97, P = 0.0009; 2 trials, 596 participants) d) Dry mouth - sertraline vs. venlafaxine (OR 0.02, 95% CI, 0.00 to 0.33, P = 0.006; 1 trial, 89 participants) Insomnia - sertraline vs. mirtazapine (OR 2.72, 95% CI, 1.15 to 6.43, P = 0.02; 2 trials,

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
				596 participants) Nausea - sertraline vs. bupropion (OR 2.14, 95% CI, 1.12 to 4.08, P = 0.02; 3 trials, 727 participants), or mirtazapine (OR 3.68, 95% CI, 2.10 to 6.45, P<0.00001; 2 trials, 596 participants) Sleepiness/drowsiness - sertraline vs. bupropion (OR 5.10, 95% CI, 2.53 to 10.31, P<0.00001; 3 trials, 727 participants); vs. mirtazapine (OR 0.33, 95% CI, 0.20 to 0.54, P<0.00001; 2 trials, 596 participants) mirtazapine vs sertraline appetite increase (OR 0.20, 95% CI, 0.09 to 0.46, p = 0.0002; 2 trials, 596 participants,fatigue (OR 0.44, 95% CI, 0.25 to 0.77, p = 0.004; 2 trials, 596 participants (see Analysis 31.4) and weight gain (OR 0.18, 95% CI, 0.09 to 0.37, p<0.00001; 2 trials, 596 participants, and gastrointestinal symptoms or dyspepsia (OR 3.54, 95% CI, 1.52 to 8.23, p = 0.003; 1 trial, 250 participants, headache (OR 1.53, 95% CI, 1.01 to 2.30, p = 0.04; 2 trials, 596 participants, libido decrease (OR 5.44, 95% CI, 1.17 to 25.19, p = 0.03; 1 trial, 346 participants, sweating increase (OR 4.86, 95% CI, 1.04 to 22.85, p = 0.05; 1 trial, 346 participants nefazodone vs. sertraline dizziness (OR 0.17, 95%CI 0.06 to 0.44, p = 0.0003; 1 trial

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: CSM Expert Working Group, 2004[183] **Country and setting:** UK **Funding:** Not reported **Research objective:** Evaluating safety of SSRI antidepressants (CIT, ESC, FLUOX, FLUV, MIR, PAR, SER, VEN)	**Study design:** Systematic review **Number of Patients:** NR **Studies Included:** All published and unpublished trials including output from GPRD- 477 studies **Intervention:** D1: VEN D2: Other SSRIs	**Characteristics of Included Studies:** • Studies that included safety information on suicide, withdrawal, and dose response **Characteristics of Included Populations** • Individuals taking SSRIs **Characteristics of Interventions:** SSRIs	**Study Results:** Suicide No diffs in risk among second-generation antidepressants Withdrawal Based on observational studies, spontaneous reporting data, and clinical trials data, experts concluded that discontinuation syndromes occur most commonly with PAR and VEN and least commonly with FLUOX	N/A	**Publication Bias:** No- however review was designed to eliminate publication bias **Heterogeneity**: Yes	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** Clinical trial data from pharmaceutical companies, spontaneous reporting data, GPRD, expert evidence, regular searches of published literature **Quality Rating:** Good

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Fergusson et al., 2005[190] **Country and setting:** Canada **Funding:** Canadian Institutes of Health Research **Research objective:** To establish if an association exists between SSRI use and suicide attempts	**Study design**: Systematic review **Number of Patients:** 36,445 **Studies Included**: 345 RCTs	**Included Studies:** RCTs comparing an SSRI with either PBO or an active non-SSRI **Included Populations** • All patients included in trials comparing SSRIs to either PBO or non-SSRI control • No age, gender, or diagnosis restrictions **Interventions:** Patients randomized to either an SSRI, PBO, or non-SSRI control for any clinical condition	**Study Results:** A sig increase in odds of suicide attempts was found in patients receiving SSRIs compared to patients receiving PBO (OR, 2.28 (95% CI, 1.144 - 4.55) *P* = 0.02) No diffs in actual suicides between SSRIs and PBO were found (OR, 0.95; 95%CI, 0.24-3.78) No sig diff found in odds of suicide attempts between patients receiving SSRIs and patients receiving tricyclic antidepressants (OR, 0.88 (95% CI, 0.54 - 1.42)	NR	**Publication Bias:** NR **Heterogeneity:** Yes	**Standard Method of Study Appraisals:** Yes--independent review of all citations by 3 authors **Comprehensive Search Strategy:** Yes Systematic literature search to identify all RCTs of SSRIs indexed on Medline between 1967 and 2003; search of Cochrane Collaboration's register of controlled trials for trials produced by Cochrane depression, anxiety, and neurosis group; reviewed biliographies of 3 systematic reviews to identify relevant trials and reports **Quality Rating:** Good

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Greist et al., 2004[193] **Country and setting:** US (6 studies); Europe (2 studies) **Funding:** Eli Lilly **Research objective:** To assess incidence, severity and onset of nausea among MDD patients treated with DUL	**Study design:** Pooled analysis **Number of Patients:** 2,345 **Studies Included:** • Detke et al., 2002[162] • Detke et al., 2002[163] • Goldstein et al., 2002[44] • Goldstein et al., 2004[265] • 4 unpublished studies submitted for FDA approval of DUL	**Included Studies:** Double-blind, randomized, PBO or active-controlled trials of DUL **Included Populations** Adult outpatients with MDD **Interventions:** • Duloxetine (40-120 mg/d) vs. Placebo (8 studies) • Duloxetine (40-120 mg/d) vs. Paroxetine (20 mg/d) (4 studies) • Duloxetine (120 mg/d) vs. Fluoxetine (20 mg/d) (2 studies)	**Study Results:** No sig diffs in nausea between DUL (40-120 mg/d), PAR (20 mg/d) (14.4% vs. 12%, *P* -NR), and FLUOX (20mg) (17.1% vs. 15.7%, *P* -NR) No sig diffs between DUL (120 mg/d) and FLUOX (20 mg/d) (17.1% vs. 15.7%, *P* -NR) Sig more DUL- than PBO-treated patients reported nausea (19% vs. 6.9%, *P* < 0.001) Incidence of treatment-emergent nausea dudring 6-mo continuation of DUL (80 mg/d or 120 mg/d) was similar to PBO (2.1% vs. 1.3% vs. 1.6%) Following abrupt discontinuation after 8 mos of treatment, nausea was reported by 1.6% of DUL (120 mg/d) patients vs. 0% for those receiving DUL (80 mg/d) and 0% for PBO	NR	**Publication Bias**: No **Heterogeneity**: No	**Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** No; analysis of all published and unpublished trials **Quality Rating:** Fair

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Gunnell et al., 2005[194] **Country and setting:** Multinational **Funding:** NR **Research objective**: To investigate whether SSRIs are associated with an increased risk of suicide related outcomes in adults	**Study design:** Meta-analysis **Number of Patients:** 40,826 **Studies Included:** • Published and unpublished data submitted by pharmaceutical companies to MHRA (2004) • 342 PBO controlled trials included in report – citations not given in bibliography	**Included Studies:** Randomized, PBO controlled trials of SSRIs (CIT, ESC, FLUOX, FLUV, PAR, and SER) submitted by pharmaceutical companies **Included Populations** Adult patients with various indications included in trials comparing SSRIs to PBO **Interventions:** Patients randomized to either SSRI or PBO	**Study Results:** No sig diff was found between SSRI treatment and PBO treatment in odds ratios for suicide (OR, 0.85 CI, 0.2 to 3.4), or suicidal thought (OR, 0.77 CI, 0.37 to 1.55) Non-fatal self harm (OR, 1.57 CI, 0.99 to 2.55) was more common in SSRI-treated than in PBO treated patients but did not reach statistical significance. For non-fatal self-harm NNH is 759	NR	**Publication Bias:** Yes **Heterogeneity:** Yes, vaguely	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** No (published and unpublished data submitted by pharmaceutical companies; review does not include studies from sources other than pharmaceutical companies) **Quality Rating:** Good

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Kasper et al., 2009[200] **Country and setting:** NR **Funding:** H. Lundbeck A/S **Aims of Review:** To analyze pooled data from two previous studies comparing escitalopram to paroxetine for the long-term treatment of MDD. **Quality Rating:** Fair	**Study design:** Post-hoc pooled analysis of data from two 6-month RCTs in patients with MDD. **Number of Patients:** 777 **Studies Included:** Baldwin, D.S., Cooper, J.A., Huusom, A.K., Hindmarch, I., 2006. A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder. Int. Clin. Psychopharmacol. 21, 159–169. Boulenger, J.P., Huusom, A.K., Florea, I., Baekdal, T., Sarchiapone, M., 2006. A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients. Curr. Med. Res. Opin. 22, 1331–1341.	**Characteristics of Included Studies:** -RCTs -24-week and 27-week trials -Compared escitalopram to paroxetine **Characteristics of Included Populations** -Treatment groups had a mean age of 44.6 + or - 13.2 yrs -Baseline MADRS total score of 32.8 + or - 4.7 -Women comprised approx 70% of each group -No significant or clinically relevant differences at baseline between patients treated with escitalopram or paroxetine **Characteristics of Interventions:** Escitalopram 10-20 mg/d Paroxetine 20-30 mg/d	**Study Results:** see adverse events (KQ4 only)	**Adverse Events:** -No differences in weight gain between treatmetn groups -There were no statistically significant differences between treatment groups -Headache and nausea were the most frequent AEs (~20%) -The most common AEs (>10 patients in total) reported during the taper period were: -dizziness (escitalopram 12, paroxetine 15) -headache (escitalopram6, paroxetine 11) -nausea (escitalopram 4, paroxetine 7) -depression (escitalopram 7, paroxetine 4)

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Khan et al., 2003[202] **Country and setting:** US **Funding:** NR **Research objective:** Compare suicide rates among depressed patients	**Study design:** Meta-analysis **Number of Patients:** 48,277 **Studies Included:** • Pooled analysis of FDA clinical trial data from 1985-2000 for 9 SSRIs • 2000 publication reports on 1987 to 1997 (same data)	**Included Studies:** FDA clinical trial data **Included Populations** • Major depression according to DSM-III-R criteria • Minimum score of 18 or 20 on HAM-D-17 or HAM-D-21 **Interventions:** FLUOX SER PAR CIT FLUV NEF MIR BUP VEN Imipramine Amitrptyline Maprotiline TRA Mianserin Dothiepin	**Study Results:** No statistically sig diff in suicide rates between SSRIs, other antidepressants, and PBO ($P > 0.05$) Absolute Suicide Rate • SSRI: 0.15% (0.10-0.20% 95% CI) • "Other": 0.20% (0.09-0.27% 95% CI) • PBO: 0.10% (0.01-0.19% 95% CI) • $P > 0.05$ for diff Suicide Rate by Patient Exposure Yrs (PEY) • SSRI: 0.59%/PEY (0.31-0.87 95% CI) • "Other": 0.76%/PEY (0.49-1.03 95% CI) • PBO: 0.45%/PEY (0.01-0.89 95% CI) • $P > 0.05$ for diff	NR	**Publication Bias:** NR **Heterogeneity**: No	**Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** No **Quality Rating:** Fair

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Krebs et al., 2008[168] **Country and setting:** Conducted in USA, studies involved are multinational **Funding:** Agency for Healthcare Research and Quality **Aims of Review:** The effect of newer antidepressants on pain in patients with depression. **Quality Rating:** Good	**Study design:** Systematic Review and Meta-analysis **Number of Patients:** 2,352 **Studies Included:** seven published trials21–27 and one unpublished trial (Eli Lilly and Co.: Clinical Study Summary: Study F1J-MC-HMAT, Study Group A: Eli Lilly and Co., 2004; 21. Brannan SK, Mallinckrodt CH, Brown EB, et al: Duloxetine 60 mg once daily in the treatment of painful physical symptoms in patients with major depressive disorder. J Psychiatr Res 2005; 39:43–53 22. Detke MJ, Lu Y, Goldstein DJ, et al: Duloxetine, 60 mg once daily, for major depressive disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2002; 63:308–315 23. Detke MJ, Lu Y, Goldstein DJ, et al: Duloxetine 60 mg once-daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res 2002; 36:383–390 24. Detke MJ, Wiltse CG, Mallinckrodt CH, et al: Duloxetine in the acute and long-term treatment of major depressive disorder: a	**Characteristics of Included Studies:** Trials of second-generation antidepressants that enrolled depression patients and reported pain outcomes **Characteristics of Included Populations** Adolts with depression **Characteristics of Interventions:** second-generation antidepressants, duloxetine and paroxetine	**Study Results:** duloxetine versus paroxetine (WMD:-0.8 mm; 95% confidence interval [CI]:-3.8 to 2.3; negative values favor paroxetine).WMD for duloxetine versus placebo: 5.2 mm; 95% CI: 2.7–7.7; WMD for paroxetine versus placebo: 5.8 mm;95% CI: 2.2–9.4).	**Adverse Events:** N/A

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
	placebo- and paroxetine-controlled trial. Eur Neuropsychopharmacol 2004; 14:457–470 25. Dickens C, Jayson M, Sutton C, et al: The relationship between pain and depression in a trial using paroxetine in sufferers of chronic low back pain. Psychosomatics 2000; 41:490–499 26. Goldstein DJ, Lu Y, Detke MJ, et al: Duloxetine in the treatment of depression: a double-blind, placebo-controlled comparison with paroxetine. J Clin Psychopharmacol 2004; 24:389–399 27. Perahia DGS, Wang F, Mallinckrodt CH, et al: Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetinecontrolled trial. Eur Psychiatry 2006; 21:367–378			

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Nieuwstraten and Dolovich, 2001[212] **Country and setting:** Canada **Funding:** NR	**Study design:** Meta-analysis **Number of Patients:** 1,332 **Studies Included:** • Kavoussi RJ et al. 1997 • Segraves RT, et al. 2000 • Weihs KL, et al. 2000 • Croft H, et al. 1999 • ColemanCC, et al. 1999 • Feighner JP, et al. 1991	**Included Studies:** • RCTs • Study durations: 6 to 16 wks • Median 7 wks **Included Populations** • Age: 36 to 70 yrs • Proportion of females: 48.0% to 61.8% **Interventions:** BUP vs. SER (3 trials) BUP vs. PAR (1 trial) BUP vs. FLUOX (1 trial)	**Study Results:** Results of HAM-D scores and CGI-I scores could not be pooled due to unavailability of data; weighted mean diffs of CGI-S and HAM-A scores not sig different between BUP and SSRIs	**Adverse Events:** Nausea, diarrhea, and somnolence occurred sig less frequently in BUP group compared to SSRI group RR, nausea: 0.6 (95%CI, 0.41-0.89), diarrhea: 0.31 (95%CI, 0.16-0.57), somnolence: 0.27 (95% CI, 0.15-0.48). Satisfaction with sexual function was sig less in SSRI group RR, 1.28 (95% CI, 1.16-1.41)	**Publication Bias:** No **Heterogeneity:** Yes- indirectly	**Standard Method of Study Appraisals:** Yes **Quality Rating:** Good **Comprehensive Search Strategy:** Yes

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Pedersen, 2005[214] **Country and setting:** Denmark **Funding:** Drug Development, H. Lundbeck A/S	**Study design:** Retrospective cohort study **Number of Patients:** 4091 **Studies Included:** 12 PBO-controlled studies and 2 relapse prevention studies	**Included Studies:** Studies are from adult clinical database at H. Lund **Included Populations** Adult outpatients with MDD (2,277) or anxiety (371) **Interventions:** ESC and PBO	**Study Results:** MADRS item 10 (suicidal thoughts): ESC patients had fewer suicidal thoughts than PBO from wks 1 ($P < 0.05$) to 8 ($P < 0.001$) Suicides in PBO-controlled studies: ESC n = 0 Rate = 0 Incidence = 0 PBO n = 1 Rate = 0.003 Incidence = 0.1 Non-fatal self harm in PBO controlled studies: ESC n = 5 Rate = 0.011 Incidence = 0.2 PBO n = 1 Rate = 0.003 Incidence = 0.1	NR	**Publication Bias:** No **Heterogeneity:** No	**Standard Method of Study Appraisals:** Yes **Quality Rating:** Fair **Comprehensive Search Strategy:** No

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Perahia et al., 2005[215] **Country and setting:** NR **Funding:** Eli Lilly and Company **Research objective:** To characterize DEAEs of DUL hydrochloride	**Study design:** Pooled analysis (9 trials: 6 short-term treatment trials, 2 extension trials and 1 open trial) **Number of Patients:** 3,624 **Studies Included:** 9 multicenter clinical trials assessing efficacy and safety of DUL in treatment of major depressive disorder	**Characteristics of Included Studies:** • Conducted in US, Europe, and Latin America • 8 studies randomized, double blind, PBO controlled trials, examining 8-9 wks of acute treatment (2 had 26-wk PBO-controlled extension phase and grouped as long-term treatment) • 1 study was a 52-wk open-label trial **Characteristics of Included Populations** • Depression defined by DSM-IV • Baseline total HAMD-17≥15 • Baseline CGI-S >+4 **Characteristics of Interventions:** • DUL (40-120 mg/d) • DUL discontinued, followed by lead-out phase of 1 or 2 wks • PBO-controlled trials, PBO given during lead-out phase	**Study Results:** In 6-study pooled analysis, significanlty more DUL patients (44.3%) had > 1 DEAE than PBO (22.9%) (*P* = NR). Dizziness most common symptom in all groups analyzed. Mild, moderate, and severe DEAEs were 39.8%, 50.6%, and 9.6% for DUL vs. 46%, 48.9%, and 5.0% for PBO. Withdrawal due to DEAEs occured in 3.1% of DUL patients and 0% of PBO. A higher, but nonlinear, incidence of DEAEs was seen with 120 mg/d compared to lower doses In 2 long-term studies, significanlty more DUL patients (9.1%) had > = 1 DEAE than PBO-treated (2.0%) (*P* = NR). Mild, moderate, and severe DEAEs were 70.6%, 26.5%, and 2.9% for DUL group. No difference in DEAEs between 80 and 120 mg/d groups. 47.5% of DEAEs resolved prior to final contact with study patients. In open label study 50.8% reported ≥1 DEAE	**Adverse Events:** Events registered as DEAEs if they occured for first time or worsened following discontinuation of treatment. Observation period for DEAEs was 2 wks	**Publication Bias:** No **Heterogeneity:** No	**Standard Method of Study Appraisals:** Not described **Comprehensive Search Strategy:** Not described **Quality Rating:** Fair

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Vanderburg et al., 2009[223] **Country and setting:** Multinational **Funding:** Pfizer Inc. **Aims of Review:** To identify possibly suicide-related adverse events in Pfizer-sponsored, phases 2 through 4, placebo-controlled, completed studies of sertraline in adult patients and evaluate the risk of suicidality with sertraline versus placebo. **Quality Rating:** Fair	**Study design:** Pooled analysis **Number of Patients:** 19,923 MDD only 3857 **Studies Included:** 126 studies conducted between the mid-1980s and the mid-2000s, Pfizer-sponsored, phases 2 through 4, placebo-controlled, completed studies of sertraline - MDD only 19 studies	**Characteristics of Included Studies:** Placebo controlled RCTs **Characteristics of Included Populations** Any patients that were included in studies **Characteristics of Interventions:** Sertraline or placebo	**Study Results:** Four cases of completed suicides among 10,917 sertraline-treated subjects yielded an incidence of 0.04% (95% CI, 0.01-0.09) and 3 cases among 9,006 placebo treated subjects yielded an incidence of 0.03% (95% CI, 0.01-0.10). No statistically significant differences between sertraline and placebo in any of the individual categories or combined suicidality risk category across all performed analyses.	**Adverse Events:** Suicidality: • All conditions: Sertraline 19 (0.29%) 95% CI, 0.17-0.45 vs. placebo 29 (0.53%) (95% CI, 0.35-0.76); RR, 0.55 (95% CI, 0.31-0.97) • MDD only: Sertraline 5 (0.23%) (95% CI, 0.07-0.54) vs. placebo 8 (0.47%) (95% CI, 0.21-0.93); RR, 0.46 (95% CI, 0.16 to 1.48)

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
Author, Year Vestergaard et al. 2008[224] **Country and Setting** Denmark National Hospital Discharge Registry **Funding** Danish Medical Research Council **Quality rating:** Good	**Research objective** Risk of fractures in users of antidepressants **Drugs, Doses, and Range** D1: Cases 124, 655 D2: Controls 373, 962 age and gender matched **Fixed dose** N/A **Dosages equivalent** N/A **Study design** Case control observational **Duration** January 1, 2000 to December 31, 2000 **Type of depression** • MDD	**Inclusion criteria:** • Cases: All subjects who had sustained a fracture between January 1, 2000, and December 31, 2000 (n = 124,655). • Controls: randomly selected 3 for each case matched by yr of birth; selected using incidence-density sampling technique; i.e., controls had to be alive and at risk for fracture diagnosis at time corresponding case was diagnosed.	**Groups similar at baseline** **n =** D1: 124,655 D2: 373,962 **Mean age, yrs** D1: 43.44 D2: 43.44 **Sex, % female** D1: 51.8 D2: 51.8 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** NR	**Risk of fractures by length of drug use** CIT • 6 mos or less: 1.58 (1.45-1.71)* • 6 mos to a yr: 1.67 (1.53-1.83)* • 1.1 to 2.5 yrs: 1.22 (1.15-1.29)* • More than 2.5 yrs 1.15 (1.10-1.19)* FLUOX • 6 mos or less: 1.31 (1.05-1.65)* • 6 mos to a yr: 1.29 (1.00-1.66)* • 1.1 to 2.5 yrs: 1.14 (1.00-1.30)* • More than 2.5 yrs: 1.08 (1.02-1.14)* FLUV • 6 mos or less: 0.73 (0.22-2.43) • 6 mos to a yr: 0.43 (0.12-1.56) • 1.1 to 2.5 yrs: 1.17 (0.67-2.05) • More than 2.5 yrs: 1.12 (0.87-1.45) PAR • 6 mos or less: 1.24 (1.02-1.50)* • 6 mos to a yr: 1.19 (0.96-1.46) • 1.1 to 2.5 yrs: 1.24 (1.11-1.39)* • More than 2.5 yrs: 1.04 (0.96-1.12)	**Attrition** N/A Conditional OR of fracture depending on dose: CIT • DDD < 0.251: OR, 1.11 (95% CI, 1.06-1.16)* • DDD 0.251- 0.5: OR, 1.31 (95% CI, 1.21-1.41)* • DDD >0.5 OR, 1.38 (95% CI, 1.33-1.44)* FLUOX • DDD < 0.251: OR, 1.06 (95% CI, 1.00-1.13)* • DDD 0.251-0.5: OR, 1.16 (95% CI, 1.01-1.33)* • DDD > 0.5 OR, 1.20 (95% CI, 1.09-1.32)* FLUV • DDD < 0.251: OR, 1.04 (95% CI, 0.78-1.40) • DDD 0.251-0.5: OR, 1.46 (95% CI, 0.84-2.56) • DDD > 0.5: OR, 0.95 (95% CI, 0.61-1.49) PAR • DDD < 0.251: OR, 1.08 (95% CI, 0.99-1.17) • DDD 0.251-0.5: OR, 1.12 (95% CI, 0.94-1.33) • DDD > 0.5: OR, 1.21 (955 CI 1.10-1.33)* SER • DDD < 0.251: OR, 1.04 (95% CI, 0.97-1.11) • DDD 0.251-0.5: OR,

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics	Research Objective, Intervention, Duration, etc	Inclusion/Exclusion	Population Characteristics	Health Outcome Results	Adverse Events
				SER • 6 mos or less: 1.09 (0.95-1.25) • 6 mos to a yr: 1.35 (1.17-1.56)* • 1.1 to 2.5 yrs: 1.08 (1.00-1.18) More than 2.5 yrs: 1.10 (1.03-1.17)* * 2*P* < 0.05	1.08 (95% CI, 0.95-1.23) • DDD > 0.5: OR, 1.25 • (95% CI, 1.16-1.34)* DDD = defined daily dose * = 2*P* < 0.05

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Wise et al., 2006 [226] **Country and setting:** Conducted in USA, studies involved are multinational **Funding:** Eli Lilly and Co. **Aims of Review:** To assess the effect of duloxetine on body weight of patients with major depressive disorder (MDD) **Quality Rating:** Quality rating for the reporting of adverse events: Fair Overall quality rating: Fair	**Study design:** Meta-analysis **Number of Patients:** Acute studies = 2,878 Long-term studies = 2,316 **Studies Included:** all 10 phase II and III registration studies of duloxetine in the treatment of MDD performed by Eli Lilly and Company, study durations: 8 - 52 weeks	**Characteristics of Included Studies:** Except for study 10 and the acute phase of study 9 (a relapse-prevention study), all studies were randomized, double-blind, controlled (with placebo, fluoxetine, and/or paroxetine used as comparators). **Characteristics of Included Populations** 1. Acute Studies: Gender, F (%)- placebo = 68.2; Duloxetine = 66.8; Fluoxetine 20 mg qd = 60.0; Paroxetine 20 mg qd = 63.8; and Acute Uncontrolled Duloxetine 60 mg qd = 71.9; Age, mean (SD)- placebo = 42.2 (12.9); Duloxetine = 42.7 (12.2); Fluoxetine 20 mg qd = 39.7 (11.6); Paroxetine 20 mg qd = 43.2 (12.0); Acute Uncontrolled Duloxetine 60 mg qd = 43.4 (12.7); Ethnicity, white (%)- placebo = 86.7; Duloxetine = 89.2; Fluoxetine 20 mg qd = 82.9; Paroxetine 20 mg qd = 89.1; and Acute Uncontrolled Duloxetine 60 mg qd = 89.9; weight, mean (SD) kg - placebo = 78.3 (20.0); Duloxetine = 79.7 (20.7); Fluoxetine 20 mg qd = 82.3 (20.8); Paroxetine 20 mg qd = 77.8 (22.4); and Acute Uncontrolled Duloxetine 60 mg qd = 82.1 (22.3) 2. Long-term studies: Gender, F (%)- (Study 5 and 6) placebo	**Study Results:** Acute Placebo-Controlled Dataset: Duloxetine-treated patients (pooled doses) versus placebo (-0.5 kg vs. 0.2 kg, P < .001). Repeated analysis revealed no consistent relationship between duloxetine dose and weight change. The incidence of PCS (potentially clinically significant) weight loss (more or equal to 7%) from baseline to endpoint or any time were significantly greater for duloxetine-treated than for placebo-treated patients P = 0.035 and 0.010 resprectively). Acute fluoxetine-controlled and paroxetine-controlled datasets: The mean change in weight from baseline to endpoint for duloxetine-treated compared with fluoxetine-treated patients(-0.7 kg vs. -0.6 kg). In studies that compared duloxetine with paroxetine, ts (-0.3 kg vs. -0.2 kg). Long-term treatment datasets: Pooling the arms of studies 5 and 6, the mean changes in weight from baseline to the end of the acute phase ranged across the 4 treatment groups from -0.17 to 0.18 kg for all randomnly assigned patients and from -0.06 to 0.19 kg for the patients who entered the continuation phase. The least squares mean weight change from baseline to endpoint for patients freated with duloxetine at a dose of 40mg bid vs. placebo-treated patients (0.7 kg vs. 0.1 kg). Weight changes in duloxetine 60mg bid-treated patients (0.9kg) and	**Adverse Events:** Treatment-emergent weight-related adverse events were report in acute placebo-controlled studies (studies 1-8). Duloxetine-treated patients reported the treatment emergent weight-related adverse events of appetite decreased (P < .001) and anorexia (p = .001) significantly more often than did placebo-treated patients. A lower percentage of duloxetine-treated patiens (1.1%) compared with placebo-treated patients (1.4%) reported appetite increased (n.s.). The incidences of weight-related events were similar across duloxetine doses. Anorexia was the only weight-related event reported as a reason for treatment discontinuation (duloxetine, 0.1%; placebo, 0.0%). [Appetite decreased was reported in 1.9 % (n = 15) of placebo patients, compared to 5.9 % (n = 67) in duloxetine patients (p < .001). Appetite increased in 1.4% (n = 11) of placebo patients and 1.1 % (n = 12) of duloxetine patients (p = .637. Anorexia was reported in 0.1 % (n = 1) of placebo patients and 1.7 % (n = 19) of duloxetine patients (p = .001)] Among long-term studies, no significant differences between treatment groups were seen in the incidence of treatment-emergent weight-related adverse events. No patients discontinued from the studies due to appetite

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
		= 69.8%; Duloxetine 40 mg bid = 70.2; Duloxetine 60 mg bid = 75.0; and Paroxetine 20 mg qd = 69.4; (Study 9) placebo = 77.5 and Duloxetine 60 mg qd = 67.6; (Study 10) Duloxetine 40-60 mg bid = 72.6; Age, mean (SD)- (Study 5 and 6) placebo = 44.2 (11.1); Duloxetine 40 mg bid = 44.8 (12.0); Duloxetine 60 mg bid = 44.3 (10.7); and Paroxetine 20 mg qd = 44.0 (10.8); (Study 9) placebo = 44.8 (11.9) and Duloxetine 60 mg qd = 45.7 (12.7); (Study 10) Duloxetine 40-60 mg bid = 44.4 (13.2); Ethnicity, white (%)- (Study 5 and 6) placebo = 100; Duloxetine 40 mg bid = 100; Duloxetine 60 mg bid = 99.5; and Paroxetine 20 mg qd = 100; (Study 9) placebo = 93.0 and Duloxetine 60 mg qd = 94.1; (Study 10) Duloxetine 40-60 mg bid = 42.2; weight, mean (SD) kg -(Study 5 and 6) placebo = 69.3 (14.4); Duloxetine 40 mg bid = 70.9 (14.4); Duloxetine 60 mg bid = 72.4 (17.4); and Paroxetine 20 mg qd = 69.7 (14.1); (Study 9) placebo = 80.9 (22.2) and Duloxetine 60 mg qd = 83.3 (22.1); (Study 10) Duloxetine 40-60 mg bid = 70.3 (17.4) **Characteristics of Interventions:** Study 1 and 2 [acute, 8 wks]: duloxetine 20-60 mg bid vs. fluoxetine 20 mg qd. vs. placebo; Study 3 and 4 [acute,	paroxetine 20mg qd-treated patients (1.0) kg versus placebo-treated patients (0.1kg, P <= 0.05 for each). The treatment groups did not differ significantly in the rates of PCS weight loss at endpoint or any time, whereas the rates of PCS weight gain at endpoint versus placebo (dulox 40mg bid vs. placebo P <= 0.05, dulox 60mg bid and parox 20 mg qd vs. placebo P <= 0.001, respectively).	decreased, appetite increase, or anorexia. In the long-term uncontrolled dataset (study 10), anorexia (0.1%) was the only treatment-emergent weight related adverse event reported as a reason for treatment discontinuation. [studies 5 and 6: appetite decreased was reported in 0 of placebo patients, 1.6% (n=3) of duloxetine 40mg bid patients, 1.5% (n=3) of duloxetine 60mg bid patients, 0 in paroxetine 20mg qd patients; appetite increased was reported in 0 of placebo patients, 0.5% (n=1) of duloxetine 40mg bid patients, 0 of duloxetine 60mg bid patients, 0.5% (n=1) in paroxetine 20mg qd patients; anorexia was reported in 1.0% (n=2) of placebo patients, 1.6% (n=3) of duloxetine 40mg bid patients, 0.5% (n=1) of duloxetine 60mg bid patients, 1.1% (n=2) in paroxetine 20mg qd patients; study 10: appetite decreased was reported in 8.1% (n=104), appetite increased was reported in 3.9% (n=50) and anorexia was reported in 8.1% (n=104)]

Evidence Table 2. Systematic evidence reviews and meta-analyses (continued)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
		8 wks]: duloxetine 20 mg bid vs. duloxetine 40 mg bid vs. paroxetine 20 mg qd vs. placebo; study 5 and 6 [acute, 8 wks + long-term continuation, 26 wks]: duloxetine 40 mg bid vs. duloxetine 60 mg bid vs. paroxetine 20 mg qd vs. placebo; study 7 and 8 [acute, 9 wks]: duloxetine 60 mg qd vs. placebo; study 9 [acute, 12 wks]: duloxetine 60 mg qd; study 9 [long-term continuation, 26 wks]: duloxetine 60 mg qd vs. placebo; and study 10 [long-term, 52 wks]: duloxetine 40-60 mg bid		

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Appendix D. Poor-Quality Studies

Characteristics of Studies with Poor Internal Validity

To assess the quality (internal validity or risk of bias) of studies, we used predefined criteria based on those described in the AHRQ Methods Guide for Comparative Effectiveness Reviews (ratings: good, fair, poor).[1] Elements of quality assessment for trials included, among others, the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; overall and differential loss to follow-up; and the use of intention-to-treat analysis. We assessed observational studies based on the potential for selection bias (methods of selection of subjects and loss to follow-up), potential for measurement bias (equality, validity, and reliability of ascertainment of outcomes), adjustment for potential confounders, and statistical analysis.

In general terms, a "good" study has the least bias and results are considered to be valid. A "fair" study is susceptible to some bias but probably not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A "poor" rating indicates significant bias (stemming from, e.g., serious errors in design, analysis reporting large amounts of missing information, or discrepancies in reporting) that may invalidate the study's results.

To systematically rate studies, we designed and used a structured data abstraction form. Trained reviewers abstracted data from each study and assigned an initial quality rating. A second reviewer read each abstracted article, evaluated the accuracy, completeness, and consistency of the data abstraction, and independently rated the quality. If differences in quality ratings could not be resolved by discussion, a third senior reviewer was involved. The full research team talked regularly during the article abstraction period to discuss global issues related to the data abstraction process. The following lists all the studies reviewed and rated as poor quality, with their design and primary reasons for the final rating.

Study	Design	Primary Reasons for Poor Quality Rating
Aguglia et al., 1993[2]	RCT	High LTF
Amini et al., 2005[3]	RCT	No ITT analysis
Ashman et al., 2009[4]	RCT	No ITT analysis
Brown, et al., 2005[5]	RCT	No ITT analysis
Byerley, et al., 1988[6]	RCT	No ITT analysis
Claghorn, 1992[7]	RCT	No ITT analysis
Claghorn, et al., 1996[8]	RCT	High LTF and no ITT analysis
Claghorn and Lesem, 1995[9]	RCT	High LTF
Clerc et al., 1994[10]	RCT	High differential attrition
Cohn, et al., 1990[11]	RCT	No ITT analysis
Cohn and Wilcox, 1992[12]	RCT	No ITT analysis
Corrigan, et al., 2000[13]	RCT	High differential attrition
Croft, et al., 2002[14]	RCT	High LTF
Dube, et al., 2010[15]	RCT	High LTF
Dunbar, et al., 1993[16]	RCT	No ITT analysis
Dunbar, et al., 1991[17]	RCT	High LTF
Elliott, et al., 1998[18]	RCT	High LTF
Evans, et al., 1997[19]	RCT	High LTF

Study	Design	Primary Reasons for Poor Quality Rating
Fabre, et al., 1996[20]	RCT	High LTF
Fabre, 1992[21]	RCT	High differential attrition
Fabre, et al., 1995[22]	RCT	High LTF
Fabre and Putman, 1987[23]	RCT	High LTF
Falk et al., 1989[24]	RCT	High LTF
Fava, et al., 1997[25]	RCT	No ITT analysis
Fava, et al., 2005[26]	RCT	High LTF
Feighner, et al., 1998[27]	RCT	High LTF
Feighner, 1992[28]	RCT	High LTF
Feighner;Boyer, 1992[29]	RCT	High LTF
Feighner, et al., 1993[30]	RCT	High LTF
Ferrando et al., 1997[31]	RCT	No ITT analysis
Flament and Lane, 2001[32]	RCT	No ITT analysis
Garakani et al., 2008[33]	RCT	No ITT analysis
Gastpar et al., 2006[34]	RCT	No ITT analysis
Goldstein et al., 2004[35]	RCT	High LTF
Grigoriadis et al., 2003[36]	Observational	No ITT analysis
Gülseren et al., 2005[37]	RCT	No ITT analysis
Hegerl, et al., 2010[38]	RCT	High attrition
Kasper, et al., 2010[39]	Pooled analysis	No systematic literature search
Lapierre, et al., 1987[40]	RCT	No ITT analysis
March, et al., 1990[41]	RCT	No ITT analysis
McGrath, et al., 2000[42]	RCT	High differential attrition
Mesters et al., 1993[43]	RCT	No ITT analysis
Montgomery et al., 2007[44] Montgomery, et al., 2008[45]	Systematic Review	Publication bias
Muijen, et al., 1988[46]	RCT	No ITT analysis
Nyth, et al., 1992[47]	RCT	No ITT analysis
Oslin et al., 2003[48]	RCT	High attrition
Petracca, et al., 2001[49]	RCT	No ITT analysis
Pettinati, et al., 2010[50]	RCT	High attrition
Ravindran, et al., 1995[51]	RCT	High attrition
Reimherr, et al., 1998[52]	RCT	High attrition
Rickels, et al., 1992[53]	RCT	No ITT analysis
Rickels and Case, 1982[54]	RCT	No ITT analysis
Rickels, et al., 1994[55]	RCT	High attrition, no ITT
Roscoe et al., 2005[56]	RCT	No ITT analysis
Rosenbaum et al., 1998[57]	Observational	No ITT analysis
Roth, et al., 1990[58]	RCT	No ITT analysis
Roy-Byrne, et al., 2000[59]	RCT	High attrition
Rudolph, et al., 1998[60]	RCT	High attrition
Schmitz et al., 2001[61]	RCT	High LTF
Schweizer, et al., 1991[62]	RCT	High attrition
Smith and Glaudin, 1992[63]	RCT	High attrition
Smith, et al., 1990[64]	RCT	High attrition
Spielmans, 2008[65]	Systematic Review	No quality assessment of included studies, lack of clear and comprehensive search strategy
Stahl et al., 2000[66]	RCT	High attrition
Thase et al., 2001[67]	Pooled analysis	No systematic literature search

Study	Design	Primary Reasons for Poor Quality Rating
Thase et al., 2006[68]	RCT	High LTF
Tollefson et al., 1994[69] Beasley et al., 1991[70]	Meta-analysis	No systematic literature search
Trkulja, 2010[71]	RCT	No dual literature review
Vartiainen and Leinonen, 1994[72]	RCT	High attrition, no ITT
Wade et al., 2003[73]	RCT	High LTF
Wagner et al., 1998[74]	RCT	No ITT analysis
Weintraub, et al., 2010[75]		High attrition and imputations
Wernicke, et al., 1987[76]	RCT	No ITT analysis
Winokur et al., 2003[77]	RCT	No ITT analysis
Zanardi et al., 1996[78]	RCT	High LTF

ITT, intent to treat analysis; LTF, loss to followup; RCT, randomized controlled trial.

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Appendix E. Studies Included in Mixed-Treatment Comparisons and Meta-analyses

Studies Included in Mixed Treatment Comparisons and Meta-Analyses (based on change in HAM-D)

Trial	Drug	Dosage	Number randomized	Number of responders[a]	Quality Rating
Alves et al., 1999[1]	Fluoxetine	20-40 mg/d	47	35	Fair
	Venlafaxine	75-150 mg/d	40	35	
Benkert et al., 2000[2]	Paroxetine	15-45 mg/d	136	66	Fair
	Mirtazapine	20-40 mg/d	139	74	
Bennie et al., 1995[3]	Fluoxetine	20-40 mg/d	144	63	Fair
	Sertraline	50-100 mg/d	142	73	
Bielski et al., 2004[4]	Venlafaxine	225 mg/d	100	47	Fair
	Escitalopram	20 mg/d	98	59	
Blumenthal et al., 2007[5b]	Placebo	NA	49	16	Fair
	Sertraline	50-200 mg/d	49	19	
Boulenger et al., 2006[6b]	Escitalopram	10-20 mg/d	232	175	Fair
	Paroxetine	20-40 mg/d	227	146	
Boyer et al., 2008[7]	Placebo	NA	161	40	Fair
	Desvenlafaxine	50 mg/d, 100 mg/d	324[c]	205[c]	
Brannan et al., 2005[8]	Placebo	NA	141	54	Fair
	Duloxetine	60 mg/d	141	55	
Chouinard et al., 1999[9]	Fluoxetine	20-80 mg/d	101	67	Fair
	Paroxetine	20-50 mg/d	102	67	
Cohn et al., 1996[10]	Placebo	NA	42	15	Fair
	Nefazodone	200-600 mg/d	39	25	
Coleman et al., 1999[11]	Placebo	NA	124	66	Fair
	Bupropion	150-400 mg/d	122	78	
	Sertraline	50-200 mg/d	118	66	
Coleman et al., 2001[12]	Placebo	NA	152	73	Fair
	Bupropion	150-400 mg/d	150	76	
	Fluoxetine	50-200 mg/d	154	83	
Croft et al., 1999[13]	Placebo	NA	121	55	Fair
	Bupropion	150-400 mg/d	120	77	
	Sertraline	50-200 mg/d	119	79	
De Nayer et al., 2002[14]	Fluoxetine	20 mg/d	73	34	Fair
	Venlafaxine	75 mg/d	73	48	
De Wilde et al., 1993[15]	Fluoxetine	20-60 mg/d	50	26	Fair
	Paroxetine	20-40 mg/d	50	25	
Detke et al., 2002[16]	Placebo	NA	139	49	Fair
	Duloxetine	60 mg/d	128	64	
Detke et al., 2002[17]	Placebo	NA	122	26	Fair
	Duloxetine	60 mg/d	123	54	
Detke et al., 2004[18]	Placebo	NA	93	41	Fair
	Duloxetine	80mg/d, 120 mg/d	188[c]	126[c]	
	Paroxetine	20 mg/d	86	63	
Dierick et al., 1996[19]	Fluoxetine	20 mg/d	161	95	Fair
	Venlafaxine	75-150 mg/d	153	107	
Fava et al., 1998[20]	Placebo	NA	19	10	Fair
	Fluoxetine	20-80 mg/d	54	31	
	Paroxetine	20-50 mg/d	55	32	
Fava et al., 2002[21]	Paroxetine	20-60 mg/d	96	64	Fair
	Fluoxetine	20-60 mg/d	92	57	
	Sertraline	50-200 mg/d	96	70	
Feiger et al., 1996[22]	Sertraline	50-200 mg/d	82	41	Fair
	Nefazodone	100-600 mg/d	78	42	

Trial	Drug	Dosage	Number randomized	Number of responders[a]	Quality Rating
Feiger et al., 2009[23]	Placebo	NA	121	36	Good
	Desvenlafaxine	200-400 mg/d	123	46	
Feighner et al., 1991[24]	Fluoxetine	20-80 mg/d	62	35	Fair
	Bupropion	225-450 mg/d	61	37	
Fontaine et al., 1994[25]	Placebo	NA	45	14	Fair
	Nefazodone	100-500 mg/d	90	41	
Gagiano, 1993[26]	Fluoxetine	20-60 mg/d	45	27	Fair
	Paroxetine	20-40 mg/d	45	30	
Goldstein et al., 2002[27]	Placebo	NA	70	24	Fair
	Duloxetine	40-120 mg/d	70	32	
	Fluoxetine	20 mg/d	33	15	
Haffmans et al., 1996[28]	Fluvoxamine	100-200 mg/d	109	31	Fair
	Citalopram	20-40 mg/d	108	33	
Halikas et al., 1995[29]	Mirtazapine	5-35 mg/d	50	25	Fair
	Trazodone	40-280 mg/d	50	20	
	Placebo	NA	50	18	
Hicks et al., 2002[30]	Paroxetine	20-40 mg/d	20	16	Fair
	Nefazodone	400-600 mg/d	20	11	
Hong et al., 2003[31]	Fluoxetine	20-40 mg/d	66	30	Fair
	Mirtazapine	15-45 mg/d	66	35	
Hypericum Depression Trial Study Group, 2002[32]	Placebo	NA	116	13	Good
	Sertraline	50-100 mg/d	111	26	
Kasper et al., 2005[33]	Trazodone	150-450 mg/d	55	48	Fair
	Paroxetine	20-40 mg/d	53	48	
Khan et al., 2007[34]	Duloxetine	60 mg/d	138	66	Fair
	Escitalopram	10-20 mg/d	140	83	
Lee et al., 2007[35]	Duloxetine	60 mg/d	238	144	Fair
	Paroxetine	20 mg/d	240	157	
Liebowitz et al., 2007[36]	Placebo	NA	122	39	Good
	Desvenlafaxine	100-200 mg/d	125	52	
Lydiard et al., 1989[37]	Placebo	NA	18	5	Fair
	Fluvoxamine	100-300 mg/d	18	9	
Lydiard et al., 1997[38]	Placebo	NA	129	43	Fair
	Sertraline	50-200 mg/d	132	65	
Mao et al., 2008[39]	Fluoxetine	20 mg/d	117	89	Fair
	Escitalopram	10 mg/d	123	94	
Mehtonen et al., 2000[40]	Venlafaxine	75-150 mg/d	75	49	Good
	Sertraline	50-100 mg/d	72	41	
Munizza et al., 2006[41]	Sertraline	50-100 mg/d	60	37	Fair
	Trazodone	150-450 mg/d	62	46	
Nemeroff and Thase, 2007[42]	Placebo	NA	102	37	Fair
	Fluoxetine	20-60 mg/d	104	45	
	Venlafaxine	75-225 mg/d	102	51	
Newhouse et al., 2000[43]	Fluoxetine	20-40 mg/d	119	84	Fair
	Sertraline	50-100 mg/d	117	85	
Nierenberg et al., 2007[44]	Placebo	NA	137	44	Fair
	Duloxetine	40-60 mg/d	273	117	
	Escitalopram	10-20 mg/d	274	112	
Olie et al., 1997[45]	Placebo	NA	129	45	Fair
	Sertraline	50-200 mg/d	129	70	
Perahia et al., 2006[46]	Placebo	NA	99	51	Fair
	Duloxetine	80mg/d, 120 mg/d	196[c]	129[c]	
	Paroxetine	20 mg/d	97	59	
Reimherr et al., 1990[47]	Placebo	NA	150	49	Fair
	Sertraline	20-200 mg/d	149	77	
Rickels et al., 1989[48]	Placebo	NA	56	12	Fair
	Paroxetine	10-50 mg/d	55	24	

Trial	Drug	Dosage	Number randomized	Number of responders[a]	Quality Rating
Rudolph and Feiger, 1999[49]	Placebo	NA	98	41	Fair
	Fluoxetine	20-60 mg/d	103	52	
	Venlafaxine	75-225 mg/d	100	54	
Rush et al., 2001[50]	Sertraline	50-200 mg/d	126	93	Fair
	Bupropion	100-300 mg/d	122	81	
Sechter et al., 1999[51]	Fluoxetine	20-60 mg/d	120	35	Fair
	Sertraline	50-150 mg/d	118	48	
Septien-Velez et al., 2007[52]	Placebo	NA	126	48	Good
	Desvenlafaxine	200mg/d, 400mg/d	249[c]	142[c]	
Shelton et al., 2006[53]	Venlafaxine	75-225 mg/d	78	49	Fair
	Sertraline	50-150 mg/d	82	45	
Sir et al., 2005[54]	Venlafaxine	75-225 mg/d	84	56	Good
	Sertraline	50-150 mg/d	79	56	
Thase, 1997[55]	Placebo	NA	102	29	Fair
	Venlafaxine	75-225mg/d	95	53	
Tollefson et al., 1993[56]	Fluoxetine	20 mg/d	335	121	Fair
	Placebo	NA	336	91	
Tourian et al., 2009[57]	Placebo	NA	164	61	Fair
	Duloxetine	60 mg/d	159	74	
	Desvenlafaxine	50mg/d, 100 mg/d	315[c]	132[c]	
van Moffaert et al., 1995[58]	Trazodone	150-450 mg/d	100	51	Fair
	Mirtazapine	24-72 mg/d	100	61	
Ventura et al., 2007[59]	Escitalopram	10 mg/d	107	75	Fair
	Sertraline	50-200 mg/d	108	74	
Wade et al., 2007[60]	Duloxetine	60 mg/d	151	81	Fair
	Escitalopram	20 mg/d	144	94	
Weihs et al., 2000[61]	Bupropion	100-300 mg/d	48	34	Fair
	Paroxetine	10-40 mg/d	52	40	
Weisler et al., 1994[62]	Trazodone	150-400 mg/d	61	21	Fair
	Bupropion	225-450 mg/d	63	33	
Wernicke et al., 1988[63]	Placebo	NA	78	18	Fair
	Fluoxetine	5-40 mg/d	285	132	

[a] Calculated based on number of patients randomized
[b] Data was received from authors
[c] Arms of the same drug with different dosage are summed together

Twenty studies[64-83] met inclusion criteria for the mixed-treatment comparison, but did not report sufficient HAM-D information for our analysis.

Studies Included in KQ1 Meta-Analysis (based on change in HAM-D)

Trial	Drug	Dosage	Number randomized	Number of responders[a]	Quality Rating
Alves et al., 1999[1]	Fluoxetine	20-40 mg/d	47	35	Fair
	Venlafaxine	75-150 mg/d	40	35	
Bennie et al., 1995[3]	Fluoxetine	20-40 mg/d	144	63	Fair
	Sertraline	50-100 mg/d	142	73	
Chouinard et al., 1999[9]	Fluoxetine	20-80 mg/d	101	67	Fair
	Paroxetine	20-50 mg/d	102	67	
De Nayer et al., 2002[14]	Fluoxetine	20 mg/d	73	34	Fair
	Venlafaxine	75 mg/d	73	48	
De Wilde et al., 1993[15]	Fluoxetine	20-60 mg/d	50	26	Fair
	Paroxetine	20-40 mg/d	50	25	
Detke et al., 2004[18]	Placebo	NA	93	41	Fair
	Duloxetine	80mg/d, 120 mg/d	188[c]	126[c]	
	Paroxetine	20 mg/d	86	63	
Dierick et al., 1996[19]	Fluoxetine	20 mg/d	161	95	Fair
	Venlafaxine	75-150 mg/d	153	107	
Fava et al., 1998[20]	Placebo	NA	19	10	Fair
	Fluoxetine	20-80 mg/d	54	31	
	Paroxetine	20-50 mg/d	55	32	
Fava et al., 2002[21]	Paroxetine	20-60 mg/d	96	64	Fair
	Fluoxetine	20-60 mg/d	92	57	
	Sertraline	50-200 mg/d	96	70	
Gagiano, 1993[26]	Fluoxetine	20-60 mg/d	45	27	Fair
	Paroxetine	20-40 mg/d	45	30	
Lee et al., 2007[35]	Duloxetine	60 mg/d	238	144	Fair
	Paroxetine	20 mg/d	240	157	
Mehtonen et al., 2000[40]	Venlafaxine	75-150 mg/d	75	49	Good
	Sertraline	50-100 mg/d	72	41	
Newhouse et al., 2000[43]	Fluoxetine	20-40 mg/d	119	84	Fair
	Sertraline	50-100 mg/d	117	85	
Perahia et al., 2006[46]	Placebo	NA	99	51	Fair
	Duloxetine	80mg/d, 120 mg/d	196[c]	129[c]	
	Paroxetine	20 mg/d	97	59	
Rudolph and Feiger, 1999[49]	Placebo	NA	98	41	Fair
	Fluoxetine	20-60 mg/d	103	52	
	Venlafaxine	75-225 mg/d	100	54	
Sechter et al., 1999[51]	Fluoxetine	20-60 mg/d	120	35	Fair
	Sertraline	50-150 mg/d	118	48	
Shelton et al., 2006[53]	Venlafaxine	75-225 mg/d	78	49	Fair
	Sertraline	50-150 mg/d	82	45	
Silverstone and Ravindran, 1999[84]	Fluoxetine	20-60	119	74	Fair
	Venlafaxine	75-225	122	82	
Sir et al., 2005[54]	Venlafaxine	75-225 mg/d	84	56	Good
	Sertraline	50-150 mg/d	79	56	

Studies Included in KQ1 Meta-Analysis (based on change in MADRS)

Trial	Drug	Dosage	Number randomized	Number of responders[a]	Quality Rating
Burke et al., 2002[85]	Escitalopram	10 mg/d, 20 mg/d	244	122	Fair
	Citalopram	40 mg/d	125	57	
Colonna et al., 2005[86]	Escitalopram	10 mg/d	175	104	Fair
	Citalopram	20 mg/d	182	96	
Lepola et al., 2003[87]	Escitalopram	10-20 mg/d	155	99	Fair
	Citalopram	20-40 mg/d	160	84	
Moore et al., 2005[88]	Escitalopram	20 mg/d	142	105	Fair
	Citalopram	40 mg/d	152	87	
Unpublished Study SCT MD-02[89]	Escitalopram	10 – 20 mg/d	125	57	Fair
	Citalopram	20-40 mg/d	123	61	
Yevtushenko et al., 2007[90]	Escitalopram	10 mg/d	109	103	Fair
	Citalopram	20 mg/d	110	90	

Studies Included in KQ4 Meta-Analysis: Nausea and Vomiting

Trial	VEN n	SSRI n	VEN n nausea	SSRI n nauseea	VEN n nausea+ vomiting	SSRI n nausea+ vomiting	Quality Rating
Alves et al., 1999[1]	40	47	13	13	19	14	Fair
Ballus et al., 2000[80]	41	43	11	4	17	5	Fair
Bielski et al., 2004[4]	100	98	24	6	24	6	Fair
Clerc et al., 1994[91]	34	34	3	4	3	4	Poor
Costa e Silvia, 1998[92]	196	186	57	35	57	35	Fair
De Nayer et al., 2002[14]	73	73	21	16	21	16	Fair
Dierick et al., 1996[19]	153	161	43	23	43	23	Fair
McPartlin et al., 1998[82]	183	178	46	44	56	56	Fair
Mehtonen et al., 2000[40]	75	72	27	21	27	21	Good
Nemeroff and Thase, 2007[42]	100	102	40	22	51	27	Fair
Rudolph and Feiger, 1999[49]	100	103	36	21	36	21	Fair
Schatzberg and Roose, 2006[93]	102	100	46	23	55	25	Fair
Silverstone and Ravindran, 1999[84]	128	121	52	39	50	39	Fair
Shelton et al., 2006[53]	78	82	12	12	12	12	Fair
Sir et al., 2005[54]	84	79	40	41	40	41	Good
Tylee et al., 1997[94]	171	170	59	31	81	40	Fair
Tzanakaki et al., 2000[95]	55	54	3	8	3	11	Fair

Studies Included in KQ4 Meta-Analysis: Overall Loss to Follow-up

VENLAFAXINE VS. SSRIs					
Trial	Total #	VEN # LTF	Total #	SSRIs # LTF	Quality Rating
Alves et al., 1999[1]	40	10	47	9	Fair
Ballus et al., 2000[80]	41	16	43	11	Fair
Bielski et al., 2004[4]	100	34	98	26	Fair
Clerc et al., 1994[91]	34	6	34	12	Poor
Costa e Silvia, 1998[92]	196	29	186	18	Fair
De Nayer et al., 2002[14]	73	24	73	29	Fair
Dierick et al., 1996[19]	153	38	161	40	Fair
McPartlin et al., 1998[82]	183	48	178	52	Fair
Mehtonen et al., 2000[40]	75	16	72	12	Good
Montgomery et al., 2004[76]	145	19	148	21	Fair
Nemeroff et al., 2007[42]	102	24	104	19	Fair
Owens et al., 2008[96]	44	12	42	10	Fair
Rudolph and Feiger, 1999[49]	100	19	103	29	Fair
Schatzberg and Roose, 2006[93]	104	37	100	30	Fair
Shelton et al., 2006[53]	78	11	82	19	Fair
Silverstone and Ravindran, 1999[84]	128	37	121	32	Fair
Sir et al., 2005[54]	84	25	79	13	Good
Tylee et al., 1997[94]	171	47	170	46	Fair
MIRTAZAPINE VS. SSRIs					
Trial	Total #	MIR # LTF	Total #	SSRIs # LTF	Quality Rating
Behnke et al., 2003[77]	176	41	170	32	Fair
Benkert et al., 2000[2]	139	30	136	33	Fair
Blier et al., 2009[97]	21	0	19	2	Fair
Hong et al., 2003[31]	66	30	66	22	Fair
Leinonen et al., 1999[98]	137	18	133	8	Fair
Schatzberg and Roose, 2006[93]	128	29	126	39	Fair
Versiani, 2005[75]	147	16	152	21	Fair
Wheatley et al., 1998[69]	66	17	67	21	Fair
BUPROPION VS. SSRIs					
Trial	Total #	BUP # LTF	Total #	SSRIs # LTF	Quality Rating
Coleman et al., 2001[12]	150	56	154	57	Fair
Coleman et al., 1999[11]	122	27	118	43	Fair
Croft et al., 1999[13]	120	36	119	39	Fair
Feighner et al., 1991[24]	61	16	62	18	Fair
Kavoussi et al., 1997[99]	122	35	126	43	Fair
Kennedy, 2006[100]	65	8	66	13	Fair
Weihs et al., 2000[61]	48	8	52	8	Fair
DULOXETINE VS. SSRIs					
Trial	Total #	DUL # LTF	Total #	SSRIs # LTF	Quality Rating
Detke et al., 2004[18]	188	21	86	10	Fair
Goldstein et al., 2002[27]	70	24	33	12	Fair
Khan et al., 2007[34]	138	46	140	21	Fair
Lee et al., 2007[35]	238	72	240	57	Fair
Nierenberg et al., 2007[44]	273	85	274	66	Fair
Perahia et al., 2006[46]	200	23	97	11	Fair
Wade et al., 2007[60]	151	37	144	32	Fair
NEFAZODONE VS. SSRIs					
Trial	Total #	NEF # LTF	Total #	SSRIs # LTF	Quality Rating
Baldwin et al., 1996[73]	105	28	101	28	Fair
Feiger et al., 1996[22]	78	19	82	20	Fair
Hicks et al., 2002[30]	20	5	20	3	Fair
Rush et al., 1998[101]	64	11	61	10	Fair
TRAZODONE VS. SSRIs					
Trial	Total #	TRAZ # LTF	Total #	SSRIs # LTF	Quality Rating
Beasley et al., 1991[102]	61	20	65	23	Fair
Kasper et al., 2005[33]	55	5	53	0	Fair

VENLAFAXINE VS. SSRIs					
Trial	Total #	VEN # LTF	Total #	SSRIs # LTF	Quality Rating
Munizza et al., 2006[41]	62	5	60	8	Fair
Perry et al., 1989[68]	19	4	21	4	Fair

Studies Included in KQ4 Meta-Analysis: Loss to Follow-up Due to Adverse Events

VENLAFAXINE VS. SSRIs					
Trial	Total #	VEN # disc. AEs	Total #	SSRIs # disc. AEs	Quality Rating
Allard et al., 2004[103]	76	6	75	3	Fair
Alves et al., 1999[1]	40	3	47	1	Fair
Ballus et al., 2000[80]	41	6	43	3	Fair
Bielski et al., 2004[4]	100	16	98	4	Fair
Clerc et al., 1994[91]	34	1	34	5	Poor
Costa e Silvia, 1998[92]	196	14	186	7	Fair
De Nayer et al., 2002[14]	73	8	73	9	Fair
Dierick et al., 1996[19]	153	14	161	7	Fair
McPartlin et al., 1998[82]	183	22	178	29	Fair
Mehtonen et al., 2000[40]	75	12	72	5	Good
Montgomery et al., 2004[76]	145	16	148	11	Fair
Nemeroff et al., 2007[42]	102	12	104	7	Fair
Owens et al., 2008[96]	44	4	42	2	Fair
Rudolph and Feiger, 1999[49]	100	6	103	9	Fair
Schatzberg and Roose, 2006[93]	104	28	100	19	Fair
Shelton et al., 2006[53]	78	3	82	1	Fair
Silverstone and Ravindran, 1999[84]	128	13	121	8	Fair
Sir et al., 2005[54]	84	5	79	3	Good
Tylee et al., 1997[94]	171	36	170	24	Fair
MIRTAZAPINE VS. SSRIs					
Trial	Total #	MIR # disc. AEs	Total #	SSRIs # disc. AEs	Quality Rating
Behnke et al., 2003[77]	176	21	170	5	Fair
Benkert et al., 2000[2]	139	12	136	10	Fair
Blier et al., 2009[97]	21	0	19	1	Fair
Hong et al., 2003[31]	66	13	66	8	Fair
Leinonen et al., 1999[98]	137	5	133	4	Fair
Schatzberg et al., 2002[104]	128	19	126	33	Fair
Versiani, 2005[75]	147	4	152	4	Fair
Wheatley et al., 1998[69]	66	7	67	9	Fair
BUPROPION VS. SSRIs					
Trial	Total #	BUP # disc. AEs	Total #	SSRIs # disc. AEs	Quality Rating
Coleman et al., 2001[12]	150	13	154	6	Fair
Coleman et al., 1999[11]	122	7	118	9	Fair
Croft et al., 1999[13]	120	8	119	4	Fair
Feighner et al., 1991[24]	61	6	62	4	Fair
Kavoussi et al., 1997[99]	122	4	126	17	Fair
Weihs et al., 2000[61]	48	4	52	3	Fair
DULOXETINE VS. SSRIs					
Trial	Total #	DUL # disc. AEs	Total #	SSRIs # disc. AEs	Quality Rating
Detke et al., 2004[18]	188	7	86	3	Fair
Goldstein et al., 2002[27]	70	7	33	1	Fair

Khan et al., 2007[34]	138	17	140	3	Fair
Lee et al., 2007[35]	238	20	240	17	Fair
Nierenberg et al., 2007[44]	273	20	274	14	Fair
Perahia et al., 2006[46]	200	4	97	1	Fair
Wade et al., 2007[60]	151	26	144	13	Fair
NEFAZODONE VS. SSRIs					
Trial	Total #	NEF # disc. AEs	Total #	SSRIs # disc. AEs	Quality Rating
Baldwin et al., 1996[73]	105	15	101	13	Fair
Feiger et al., 1996[22]	78	15	82	10	Fair
Hicks et al., 2002[30]	20	4	20	1	Fair
Rush et al., 1998[101]	64	6	61	5	Fair
TRAZODONE VS. SSRIs					
Trial	Total #	TRAZ # disc. AEs	Total #	SSRIs # disc. AEs	Quality Rating
Beasley et al., 1991[102]	61	6	65	9	Fair
Kasper et al., 2005[33]	55	3	53	0	Fair
Munizza et al., 2006[41]	62	2	60	6	Fair
Perry et al., 1989[68]	19	2	21	2	Fair

Studies Included in KQ4 Meta-Analysis: Loss to Follow-up Due to Lack of Efficacy

VENLAFAXINE VS. SSRIs					
Trial	Total #	VEN # disc. lack of efficacy	Total #	SSRIs # disc. lack of efficacy	Quality Rating
Alves et al., 1999[1]	40	0	47	2	Fair
Ballus et al., 2000[80]	41	2	43	4	Fair
Clerc et al., 1994[91]	34	3	34	6	Poor
Costa e Silvia, 1998[92]	196	5	186	2	Fair
De Nayer et al., 2002[14]	73	5	73	10	Fair
Dierick et al., 1996[19]	153	9	161	14	Fair
McPartlin et al., 1998[82]	183	2	178	5	Fair
Mehtonen et al., 2000[40]	75	6	72	4	Good
Montgomery et al., 2004[76]	145	3	148	6	Fair
Nemeroff et al., 2007[42]	102	4	104	4	Fair
Rudolph and Feiger, 1999[49]	100	3	103	7	Fair
Silverstone and Ravindran, 1999[84]	128	6	121	6	Fair
Schatzberg and Roose, 2006[93]	104	2	100	6	Fair
Tylee et al., 1997[94]	171	4	170	7	Fair

MIRTAZAPINE VS. SSRIs					
Trial	Total #	MIR # disc. lack of efficacy	Total #	SSRIs # disc. lack of efficacy	Quality Rating
Benkert et al., 2000[2]	139	3	136	7	Fair
Hong et al., 2003[31]	66	0	66	2	Fair
Leinonen et al., 1999[98]	137	4	133	1	Fair
Schatzberg and Roose, 2006[93]	128	5	126	0	Fair
Versiani, 2005[75]	147	10	152	12	Fair
Wheatley et al., 1998[69]	66	3	67	5	Fair
BUPROPION VS. SSRIs					
Trial	Total #	BUP # disc. lack of efficacy	Total #	SSRIs # disc. lack of efficacy	Quality Rating
Coleman et al., 2001[12]	150	4	154	7	Fair
Coleman et al., 1999[11]	122	3	118	7	Fair
Croft et al., 1999[13]	120	2	119	2	Fair
Feighner et al., 1991[24]	61	1	62	2	Fair
Kavoussi et al., 1997[99]	122	8	126	6	Fair
DULOXETINE VS. SSRIs					
Trial	Total #	DUL # disc. lack of efficacy	Total #	SSRIs # disc. lack of efficacy	Quality Rating
Goldstein et al., 2002[27]	70	2	33	3	Fair
Khan et al., 2007[34]	138	2	140	1	Fair
Lee et al., 2007[35]	238	1	240	1	Fair
Nierenberg et al., 2007[44]	273	9	274	4	Fair
Perahia et al., 2006[46]	200	5	97	1	Fair
Wade et al., 2007[60]	151	2	144	7	Fair
NEFAZODONE VS. SSRIs					
Trial	Total #	NEF # disc. lack of efficacy	Total #	SSRIs # disc. lack of efficacy	Quality Rating
Baldwin et al., 1996[73]	105	3	101	1	Fair
Feiger et al., 1996[22]	78	0	82	2	Fair
Hicks et al., 2002[30]	20	0	20	2	Fair
TRAZODONE VS. SSRIs					
Trial	Total #	TRAZ # disc. lack of efficacy	Total #	SSRIs # disc. lack of efficacy	Quality Rating
Beasley et al., 1991[102]	61	4	65	4	Fair
Kasper et al., 2005[33]	55	1	53	0	Fair
Munizza et al., 2006[41]	62	1	60	0	Fair

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Source: *PubMed*

Appendix G. Strength of Evidence Tables

Table 1. Strength of evidence for the comparative efficacy and effectiveness for second-generation antidepressants for the treatment of major depressive disorder in adults

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Comparative efficacy 91 RCTs	Medium[1] 88 RCTs/fair 3 RCTs/good	Consistent	Some indirectness[2]	Precise	Publication bias is likely	Results from direct and indirect comparisons indicate that no substantial differences in efficacy exist among second-generation antidepressants.	Moderate
Comparative effectiveness 3 pragmatic RCTs	Medium[1] 2 RCTs/fair 1 RCT/good	Consistent	Some indirectness[3]	Precise	None	Direct evidence from three pragmatic trials and indirect evidence from efficacy trials indicate that no substantial differences in effectiveness exist among second-generation antidepressants.	Moderate
Quality of life 18 RCTs	Medium[1] 18 RCTs/fair	Consistent	Some indirectness[4]	Precise	None	Consistent results indicate that the efficacy of second-generation antidepressants with respect to quality of life does not differ among drugs	Moderate
Onset of action 7 RCTs	Medium[1] 7 RCTs/fair	Consistent	Some indirectness[4]	Precise	Publication bias is likely	Consistent results suggest that mirtazapine has a significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline (NNT for response after 1-2 weeks: 7; 95% CI 4-12) Whether this difference can be extrapolated to other second-generation antidepressants is unclear. Most other trials do not indicate a faster onset of action of one second-generation antidepressant compared with another.	Moderate

NNT: number needed to treat; RCT: randomized controlled trial

[1] Considerable attrition in most studies; lack of reporting of allocation concealment

[2] Most estimates of treatment effects are based on network meta-analyses

[3] Indirect evidence from efficacy trials

[4] Data are not available for all possible comparisons

Table 2. Strength of evidence for the comparative efficacy and effectiveness of second-generation antidepressants for the treatment of dysthymia

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Comparative efficacy; none	NA	NA	NA	NA	NA	No evidence	Insufficient
Comparative effectiveness; none	NA	NA	NA	NA	NA	No evidence	Insufficient
Quality of life; none	NA	NA	NA	NA	NA	No evidence	Insufficient
Onset of action; none	NA	NA	NA	NA	NA	No evidence	Insufficient

Table 3. Strength of evidence for the comparative efficacy and effectiveness of second-generation antidepressants for the treatment of subsyndromal depression

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Comparative efficacy; 1 RCT	High [1,2] 1 non-randomized RCT/ fair	N/A	Direct	Imprecise[3]	None	No difference between citalopram and sertraline.	Low
Comparative effectiveness; none	NA	NA	NA	NA	NA	No evidence	Insufficient
Quality of life; none	NA	NA	NA	NA	NA	No evidence	Insufficient
Onset of action; none	NA	NA	NA	NA	NA	No evidence	Insufficient

[1] lack of randomization

[2] lack of blinding

[3] confidence intervals encompass clinically relevant differences

Table 4. Strength of evidence regarding efficacy and effectiveness of previously effective versus new second-generation antidepressants for the treatment of depressive disorders

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Major depressive disorder; none	NA	NA	NA	NA	NA	No evidence	Insufficient
Dysthymia; none	NA	NA	NA	NA	NA	No evidence	Insufficient
Subsyndromal depression; none	NA	NA	NA	NA	NA	No evidence	Insufficient

Table 5. Strength of evidence for the differences in efficacy and effectiveness for second-generation antidepressants between immediate- and extended-release formulations

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Major depressive disorder; 2 RCTs	Low 2 RCTs/Good	Consistent	Direct	Imprecise[2]	None	Results indicate no differences in response to treatment between paroxetine IR and paroxetine CR. No differences in maintenance of response and remission between fluoxetine daily and fluoxetine weekly.	Moderate
	Medium[1] 1 RCT/fair	N/A	Direct	Imprecise[2]	None	One trial reported higher response rates for venlafaxine XR than venlafaxine IR.	Low
Dysthymia; none	NA	NA	NA	NA	NA	No evidence	Insufficient
Subsyndromal depression; none	NA	NA	NA	NA	NA	No evidence	Insufficient

[1] Considerable attrition; lack of reporting of allocation concealment

[2]Confidence intervals encompass differences that would be clinically irrelevant

Table 6. Strength of evidence for the comparative efficacy and effectiveness of second-generation antidepressants for maintaining response or remission (i.e., preventing relapse or recurrence) of continuing initial medications

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Comparative efficacy 7 RCTs	Medium 7 RCTs/ fair	Consistent	Direct	Precise	Duration of relapse and recurrence prevention is variable and could influence results; not all comparisons are represented	Based on results from six efficacy trials and one naturalistic study, no significant differences exist between escitalopram and desvenlafaxine, escitalopram and paroxetine, fluoxetine and sertraline, fluoxetine and venlafaxine, fluvoxamine and sertraline, and trazodone and venlafaxine for preventing relapse or recurrence.	Moderate
Comparative effectiveness; none	NA	NA	NA	NA	NA	No evidence	Insufficient

Table 7. Strength of evidence for the comparative efficacy and effectiveness of second-generation antidepressants for maintaining response or remission (i.e., preventing relapse or recurrence) of switching medications

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Comparative efficacy; none	NA	NA	NA	NA	NA	No evidence	Insufficient
Comparative effectiveness; none	NA	NA	NA	NA	NA	No evidence	Insufficient

Table 8. Strength of evidence for the comparative efficacy and effectiveness of second-generation antidepressants in managing treatment-resistant depression syndrome or treating recurrent depression

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Comparative efficacy; 4 RCTs	Medium 4 RCTs/fair	Inconsistent	Direct	Imprecise	Not all comparisons are represented	Results from four trials suggest no differences, or only modest differences, between SSRIs and venlafaxine. Numerical trends favored venlafaxine over comparator drugs in three of these trials, but differences were statistically significant in only one trial, which compared venlafaxine with paroxetine.	Low
Comparative effectiveness; 2 RCTs	Medium 1 RCT/good 1 open trial/fair	Inconsistent	Direct	Imprecise[1]	Good-rated trial assigned greater weight in conclusions due to risk of bias in fair-rated open trial; not all comparisons are represented	Results from two effectiveness studies are conflicting. Based on one trial rated good, no significant differences in effectiveness exist among bupropion SR, sertraline, and venlafaxine XR. One effectiveness trial found venlafaxine to be modestly superior to citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline.	Low

[1] data limited to two RCTs which showed differing results: one indicated a significant difference between agents and one showed no difference.

Table 9. Summary of findings with strength of evidence: Key Question 3: Comparative efficacy and effectiveness of second-generation antidepressants for treatment of depression in patients with accompanying symptom clusters

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Anxiety: Comparative efficacy for depression; 7 RCTs	Medium 7 RCTs/ fair	Consistent	Some indirectness[1]	Precise	None	Results from five head-to-head trials suggest that efficacy does not differ substantially for treatment of depression in patients with accompanying anxiety.	Moderate
Anxiety: Comparative effectiveness for depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Anxiety: Comparative efficacy for anxiety; 13 RCTs	Medium 13 RCTs/ fair	Consistent	Direct	Imprecise[2]	None	Results from eight head-to-head trials and three placebo-controlled trials suggest that no substantial differences in efficacy exist among second-generation antidepressants for treatment of accompanying anxiety symptoms	Moderate
Anxiety: Comparative effectiveness for anxiety; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Insomnia: Comparative efficacy for depression; 2 RCTs	Medium 2 RCTs/ fair	Consistent	Some indirectness[1]	Precise	None	Results from one head-to-head study are insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting insomnia.	Insufficient
Insomnia: Comparative effectiveness for depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Insomnia: Comparative efficacy for insomnia; 7 RCTs	Medium 7 RCTs/ fair	Inconsistent	Some indirectness[1]	Imprecise[2]	None	Results from five head-to-head trials suggest that no substantial differences in efficacy exist among second-generation antidepressants for treatment of accompanying insomnia. Results are limited by study design; differences in outcomes are of unknown clinical significance.	Low
Insomnia: Comparative effectiveness for insomnia; None	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Low Energy: Comparative efficacy for depression; 1 RCT	Medium 1 RCT/ fair	Consistency unknown (single study)	Indirect[3]	Imprecise[3]	None	Results from one placebo-controlled trial of bupropion XL is insufficient draw conclusions about treating depression in patients with coexisting low energy. Results from head-to-head trials are not available.	Insufficient
Low Energy: Comparative effectiveness for depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Low Energy: Comparative efficacy for low energy; 1 RCT	Medium 1 RCT/ fair	Consistency unknown (single study)	Indirect[3]	Imprecise[3]	None	Results from one placebo-controlled trial of bupropion XL are insufficient draw conclusions about treating low energy in depressed patients. Results from head-to-head trials are not available.	Insufficient
Low Energy: Comparative effectiveness for low energy; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Melancholia: Comparative efficacy for depression; none	Medium 2 RCTs/ fair	Inconsistent[4]	Some indirectness[1]	Imprecise[4]	None	Results from two head-to-head trials are insufficient to draw conclusions about treating depression in patients with coexisting melancholia. Results are inconsistent across studies.	Insufficient
Melancholia: Comparative effectiveness for depression (zero studies)	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Melancholia: Comparative efficacy for melancholia; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Melancholia: Comparative effectiveness for melancholia; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Pain: Comparative efficacy for depression; 2 RCTs	Medium 2 RCTs/ fair	Inconsistent[5]	Indirect[5]	Imprecise[5]	None	Results from two placebo-controlled trials are conflicting regarding the superiority of duloxetine over placebo. Results from head-to-head trials are not available.	Insufficient
Pain: Comparative effectiveness for depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Pain: Comparative efficacy for pain; 6 RCTs, 1 SR	Medium 1 SR, 6 RCTs/ fair	Consistent	Some indirectness[1]	Precise	None	Evidence from one systematic review, two head-to-head trials (one poor) and five placebo-controlled trials indicate no difference in efficacy between paroxetine and duloxetine.	Moderate

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Pain: Comparative effectiveness for pain; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Psychomotor change: Comparative efficacy for depression; None	Medium 1 RCT/ fair	Consistency unknown (single study)	Indirect[6]	Imprecise[6]	None	Results from one head-to-head trial is insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting psychomotor change.	Insufficient
Psychomotor change: Comparative effectiveness for depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Psychomotor change: Comparative efficacy for psychomotor change; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Psychomotor change: Comparative effectiveness for psychomotor change; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Somatization: Comparative efficacy for depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Somatization: Comparative effectiveness for depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Somatization: Comparative efficacy for somatization; 1 RCT	Medium 1 RCT/ fair	Consistency unknown (single study)	Indirect[7]	Imprecise[7]	None	Results from one head-to-head trial are insufficient to draw conclusions about the comparative efficacy for treating somatization in depressed patients. Results indicate similar improvement in somatization.	Insufficient
Somatization: Comparative effectiveness for somatization; 1 RCT	Medium 1 RCT/ fair	Consistency unknown (single study)	Indirect[7]	Imprecise[7]	None	Evidence from one open-label head-to-head trial is insufficient to draw conclusions about the comparative efficacy for treating coexisting somatization in depressed patients. Results indicate no difference in effectiveness.	Insufficient

N/A: not applicable; RCT: randomized controlled trial; SR: systematic review

[1] data are not available for all possible comparisons.

[2] some comparisons showed a statistically significant difference, but the majority did not. Therefore is precision of this result is low.

[3] data limited to the results of one placebo-controlled trial.

[4] data limited to two RCTs which showed differing results: one indicated a significant difference between agents and one showed no difference.

[5] data limited to two placebo-controlled RCTs which showed conflicting results.

[6] data limited to one RCT

[7] data limited to one trial and not all possible comparisons

Table 10. Summary of findings with strength of evidence: Key Question 4a: Comparative risk of harms (safety, adverse events), adherence, and persistence

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
General tolerability: Adverse events profiles; 140 Studies	Low 92 RCTs 48 studies of other designs/good or fair	Consistent	Direct	Precise	None	Adverse events profiles of experimental or observational studies are similar among second-generation antidepressants. The incidence of specific adverse events differs across antidepressants	High
General tolerability: Comparative risk of nausea and vomiting; 15 RCTs	Low 15 RCTs/fair	Consistent	Direct	Precise	None	Meta-analysis of 15 studies indicates that venlafaxine has a higher rate of nausea and vomiting than SSRIs as a class (RR 1.52; 1.25 to 1.84).	High
General tolerability: Comparative risk of weight change; 7 RCTs	Medium[1] 7 RCTs/fair	Consistent	Direct	Precise	None	Results indicate that mirtazapine leads to higher weight gains than citalopram, fluoxetine, paroxetine, and sertraline (range 0.8 to 3.0 kg after 6 to 8 weeks).	High
General tolerability: Comparative risk of gastrointestinal adverse events; 7 RCTs	Medium[1] 7 RCTs/fair	Consistent	Direct	Precise	None	Results indicate that sertraline has on average an 8% (3 to 11%) higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine. Results from one systematic review confirm some of these findings.	Moderate
General tolerability: Comparative risk of somnolence; 6 RCTs	Medium[1] 6 RCTs/fair	Consistent	Direct	Precise	None	Results indicate that trazodone has a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine.	Moderate
General tolerability: Comparative risk of	Low Low 1 systematic	Consistent	Some indirectness[2]	Precise	None	A good systematic review indicates that paroxetine and venlafaxine have the highest rates of discontinuation syndrome; fluoxetine has the lowest.	Moderate

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
discontinuation syndrome; 1 RCT	review/good						
General tolerability: Comparative risk of discontinuation of treatment; 3 MAs	Low 3 meta-analyses/good	Consistent	Direct	Precise	None	Meta-analyses of numerous efficacy trials indicate that overall discontinuation rates are similar. Duloxetine and venlafaxine have a higher rate of discontinuations because of adverse events than SSRIs as a class. Venlafaxine has a lower rate of discontinuations because of lack of efficacy than SSRIs as a class.	High
Severe adverse events: Comparative risk of suicidality (suicidal thoughts and behavior); 16 Studies	High 9 observational studies/fair 2observational studies/good 4 meta-analyses/good 1 systematic review/fair	Inconsistent	Indirect[3]	Imprecise[4]	Reporting and classification bias likely	Results yield conflicting information about the comparative risk of suicidality.	Insufficient
Severe adverse events: Comparative risk of sexual dysfunction; 7 RCTs	Low 7 RCTs/fair	Consistent	Direct	Precise	None	Results indicate that bupropion causes significantly less sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline.	High
Severe adverse events: Comparative risk of seizures; 3 Studies	Medium[5] 2 open-label trials/fair 1 prospective cohort study/good	Inconsistent	Direct	Imprecise[4]	None	Results yield conflicting information about the comparative risk of seizures.	Insufficient
Severe adverse events: Cardiovascular	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
events; none							
Severe adverse events: Comparative risk of hyponatremia; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Severe adverse events: Comparative risk of hepatotoxicity; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Severe adverse events: Comparative risk of serotonin syndrome; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Adherence: Comparative adherence in efficacy studies; 8 RCTs	Medium[1] 6 RCTs/fair 2 RCTs/good	Consistent	Direct	Precise	None	Efficacy studies indicate no differences in adherence.	Moderate
Adherence: Comparative adherence in effectiveness studies; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Comparative persistence; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient

[1] Considerable attrition in most studies; lack of reporting of allocation concealment

[2] Only few drugs have been assessed

[3]Few direct head-to-head comparisons

[4] Event rates too low to draw conclusions about the comparative risk

5 Lack of blinding; lack of reporting of allocation concealment

Table 11. Summary of findings with strength of evidence: Key Question 4b: Differences in harms, adherence, and persistence between immediate- and extended-release formulations

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Major depressive disorder: Comparative risk of harms; 4RCTs	Medium[1] 3 RCTs/fair	Consistent	Direct	Imprecise[2]	None	Findings from one trial each indicate that no differences in harms exist between fluoxetine daily and fluoxetine weekly or between venlafaxine IR and venlafaxine XR.	Moderate
	1 RCT/fair					One trial provides evidence that paroxetine IR leads to higher rates of nausea than paroxetine CR.	Low
Major depressive disorder: Comparative adherence; 2 RCTs	Medium[1] 1 RCT/ fair 1 open-label RCT/fair	Consistent	Direct	Imprecise[2]	None	One trial provides evidence that fluoxetine weekly has better adherence rates than fluoxetine daily. No differences in adherence could be detected for paroxetine IR and paroxetine CR.	Moderate
Major depressive disorder: Comparative persistence; 1 cohort study	High[3] Retrospective cohort study/high	Consistent	Direct	Precise	None	Evidence from one observational study indicates that prescription refills are more common with the extended- than the immediate-release formulation of bupropion.	Low
Dysthymia; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Subsyndromal depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient

[1] Considerable attrition; lack of reporting of allocation concealment

[2]Confidence intervals encompass differences that would be clinically irrelevant

[3] Selection bias likely

Table 12. Summary of findings with strength of evidence: Key Question 5: Subgroups

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Age: Comparative efficacy in MDD; 11 RCTs	Medium 10 RCTs/fair 1 RCT/good	Consistent	Direct	Some imprecision	None	Efficacy does not differ substantially among second-generation antidepressants for treating MDD in patients age 60 years or older.	Moderate
Age: Comparative efficacy in dysthymia or subsyndromal depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Age: Comparative effectiveness in MDD, dysthymia or sybsyndromal depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Age: Comparative harms in MDD 7 RCTs	Medium 6 RCTs/fair 1 RCT/good	Some inconsistency	Direct	Imprecise	None	Adverse events may differ somewhat across second-generation antidepressants in older adults.	Low
Age: Comparative harms in dysthymia or sybsyndromal depression; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Sex:	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Comparative efficacy; none							
Sex: Comparative effectiveness; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Sex: Comparative harms ;	Medium 2 RCTs/fair	Consistent	Direct	Precise	None	Two trials suggest differences between men and women in sexual side effects	Low
Race or Ethnicity: Comparative efficacy; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Race or Ethnicity: Comparative effectiveness; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Race or Ethnicity: Comparative harms; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient
Comorbidities: Comparative efficacy: 1 RCT	Low 1 RCT/fair	Unknown, 1 trial	Direct	Precise	Subgroup analysis of one RCT	Results from a subgroup analysis of one trial indicate significantly greater response with venlafaxine XR than fluoxetine in patients with MDD and comorbid generalized anxiety disorder.	Low
Comorbidities:	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient

Outcome; Number of Studies	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Other considerations	Results	Strength of Evidence
Comparative effectiveness; none							
Comorbidities: Comparative harms; none	N/A	N/A	N/A	N/A	N/A	No evidence	Insufficient

Appendix H. Review and Abstraction Forms

Previewing Only: You cannot submit data from this form

Previewing at Level 1

Refid: 1, M. C. Harlow, C. M. Davidson and J. A. Bourgeois, Psychogenic tremor in a patient with a major depressive episode, *S D Med*, 62(6), 2009, p.233, 235
State: Excluded, Level: 1

Abstract Review

Keywords:
Adult

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Abstract:
Psychogenic tremor is a variant of psychogenic movement disorder. Psychogenic tremor often starts in an abrupt manner and affects voluntary motor function, rapidly reaching maximum impairment for the patient. Patients often present with comorbid psychiatric disorders, including depression, anxiety and personality disorders. Overall prognosis is poor, with 80 to 90 percent of patients symptomatic after one year. The authors present the case of a 33-year-old woman who experienced an acute episode of psychogenic tremor. They review the literature on psychiatric and neurologic manifestations of psychogenic tremor, consider diagnostic and treatment implications and discuss overall prognosis of recovery for patients afflicted with psychogenic tremor.

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1. Original research (no review articles, editorials, letters to the editor) published in English after 1980?

- Yes
- No
- Cannot determine

Clear Selection

2. Use for background ? (If Yes, check)

- Yes

Clear Selection

3. Study was conducted in adult patients with MDD, dysthymia, or subsyndromal depressive disorders and compares at least 2 of the following pharmaceutical interventions, OR compares an immediate release with an extended release formulation of the SAME drug

- Bupropion
- Citalopram
- Desvenlafaxine
- Duloxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Mirtazapine
- Nefazadone
- Paroxetine
- Sertraline
- Trazadone
- Venlafaxine
- Placebo or Augmentation drug
- Comparison is not of interest or there is not one!
- Cannot determine

4. Addresses one or more of the following key questions:

1a. For adults with MDD, dysthymia, or subsyndromal depressive disorders, do commonly used medications for depression differ in efficacy or effectiveness in treating depressive symptoms?

1b. If a patient has responded to one agent in the past, is that agent better than current alternatives at treating depressive symptoms?

1c. Are there any differences in efficacy or effectiveness between immediate release and extended release formulations of second-generation antidepressants?

2a. For adults with a depressive syndrome, do antidepressants differ in their efficacy or effectiveness for maintaining response or remission (i.e., preventing relapse or recurrence)?

2b. For adults receiving antidepressant treatment for a depressive syndrome that either has not responded (acute phase) or has relapsed (continuation phase) or recurred (maintenance phase), do alternative antidepressants differ in their efficacy or effectiveness?

2c. If a person has responded or remitted to a second-generation antidepressant, can the response or remission be maintained if this person is switched to another second-generation antidepressant?

3a. Do medications or combinations of medications (including tricyclics in combination) used to treat depression differ in their efficacy or effectiveness for treating accompanying symptoms, such as anxiety, insomnia, and neurovegetative symptoms?

3b. Do medications differ in their efficacy and effectiveness in treating the depressive episode?

3c. Do medications differ in their efficacy and effectiveness in treating the accompanying symptoms?

4a. For adults with a depressive syndrome, do commonly used antidepressants differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to nausea, diarrhea, headache, tremor, daytime sedation, decreased libido, failure to achieve orgasm, nervousness, insomnia, and more severe events including suicide.

4b. Are there any differences in safety, adverse events, or adherence between immediate release and extended release formulations of second-generation antidepressants?

5. How do the efficacy, effectiveness, or harms of treatment with antidepressants for a depressive syndrome differ for the following subpopulations:

- elderly or very elderly patients (i.e. populations with a mean age of 60 or older);
- other demographic groups (defined by age, ethnic or racial groups, and sex);
- patients with medical comorbidities (in general, all populations where we can assume that the existence of a primary disease might be the reason for the depressive episode and might influence the response to the treatment; e.g. cancer patients, patients with HIV, stroke patients, etc.)?

check all that apply:

- ☐ KQ1
- ☐ KQ2
- ☐ KQ3
- ☐ KQ4
- ☐ KQ5
- ☐ Cannot determine by the title or abstract
- ☐ None of the above

5. Study duration

- ○ RCT 6 weeks or longer
- ○ RCT shorter than 6 weeks
- ○ Observational study 3 months or longer
- ○ Observational studies shorter than 3 months
- ○ None of the above
- ○ Cannot determine

Clear Selection

6. Study design is one of the following:

- ☐ RCT
- ☐ Meta-analysis
- ☐ Observational Study (n<100)
- ☐ Observational Study (n>100)
- ☐ Case series
- ☐ Case report
- ☐ None of the above
- ☐ Cannot determine

Save to finish later | Submit Data

Form took 0.3554688 seconds to render
Form Creation Date: Not available
Form Last Modified: Oct 12 2009 4:18PM

Previewing Only: You cannot submit data from this form

Previewing at Level 3

Refid: 1, M. C. Harlow, C. M. Davidson and J. A. Bourgeois, Psychogenic tremor in a patient with a major depressive episode, *S D Med*, 62(6), 2009, p.233, 235
State: Excluded, Level: 1

Full Abstraction

Save to finish later | Submit Data

1. First abstraction completed by:

Enlarge Shrink

2. Second abstraction completed by:

Enlarge Shrink

3. Author, Year

Enlarge Shrink

4. Country and setting:
- If more than two countries are included, call it multinational.
- Settings include: primary care, hospitals, university clinics, doctors offices, nursing homes, multicenter, etc.

Enlarge Shrink

5. Source of funding:

- ☐ Pharmaceutical company or other commercial source (please list name):
- ☐ Government or non-profit organization (please list name):
- ☐ Not reported

6. Research objective (please be concise):

Enlarge Shrink

7. Please check off ALL drugs studied and record the daily doses as well as the range (e.g., low, medium, high):

- ☐ Bupropion (100-450 mg 3 x daily):
- ☐ Bupropion (SR 150-400 mg 2 x daily):
- ☐ Bupropion XL (150-450 mg 1 x daily):
- ☐ Citalopram (20-60 mg 1 x daily):
- ☐ Desvenlafaxine (50 mg 1 x daily):
- ☐ Duloxetine (40-60 mg 1-2 x daily):
- ☐ Escitalopram (10-20 mg 1 x daily):
- ☐ Fluoxetine (10-80 mg 1-2 x daily):
- ☐ Fluoxetine (90 mg 1 x weekly):
- ☐ Fluoxetine (20 mg 1 x daily):
- ☐ Fluvoxamine (25, 50, 100 mg 1-2 x daily):
- ☐ Fluvoxamine extended release (100, 150 mg 1 x daily):
- ☐ Mirtazapine (15-45 mg 1 x daily):
- ☐ Mirtazapine orally disintegrating (15-45 mg 1 x daily):

- [ ] Nefazodone (200-600 mg 2 x daily):
- [ ] Paroxetine (10-60 mg 1 x daily):
- [ ] Paroxetine (CR 12.5-75 mg 1 x daily):
- [ ] Sertraline (25-200 mg 1 x daily):
- [ ] Trazodone (150-400 mg 3 x daily):
- [ ] Venlafaxine (75-375 mg 2-3 x daily):
- [ ] Venlafaxine XR (75-225 mg 1 x daily):
- [ ] Placebo
- [ ] Other (augmentation):

8. Fixed dose (same dose throughout) trial?

- ( ) Yes
- ( ) No

Clear Selection

9. Flexible dose (adjusted by clinician) trial?

- ( ) Yes
- ( ) No

Clear Selection

10. Are the dosages equivalent across treatment groups?

- ( ) Yes
- ( ) No

Clear Selection

11. Study design:

- ( ) Randomized Controlled Trial (RCT)
- ( ) Observational

Clear Selection

12. Overall study n =

Enlarge Shrink

13. Study duration is:

- ( ) less than 24 weeks
- ( ) 24 weeks or longer

Clear Selection

14. Type of depression (Check all that apply):

- [ ] Acute
- [ ] Chronic
- [ ] Recurrent
- [ ] Severe
- [ ] Double Depression
- [ ] Subsyndromal depressive disorder
- [ ] Major depressive disorder
- [ ] Dysthmia
- [ ] Minor depression
- [ ] Other- please explain

15. Inclusion criteria (record what was used in the studies; check off all that apply and list additional criteria)

- [ ] Adults (age range):
- [ ] Diagnosed with MDD according to DSM III or IV:
- [ ] HAM-D:
- [ ] MADRS:
- [ ] CGIS:
- [ ] Concomitant condition (e.g., alcoholism, anxiety, stroke):
- [ ] Dysthymia:
- [ ] Other:

16. Exclusion criteria (as reported in studies)

- [ ] Pregnant:
- [ ] Lactating:
- [ ] Concomitant psychotheraputic or psychotropic medications:
- [ ] Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar):
- [ ] Illicit drug and alcohol abuse:
- [ ] Clinically significant medical disease:
- [ ] Investigational drug use within the last:
- [ ] ECT within the last:
- [ ] Suicidal tendencies (acute or other):
- [ ] Other:

17. Should the article be excluded for any of the following reasons?

- [ ] Study reported only in abstract (full text is not available)
- [ ] Background article
- [ ] Wrong outcome (e.g., no pharmakinetic or other intermediate outcoimes)
- [ ] Wrong drug
- [ ] Wrong population (e.g., no pediatric or perinatal studies)
- [ ] Wrong publication type (e.g. letter or editorial)
- [ ] Wrong design (e.g., uncontrolled study- no comparision arm)
- [ ] Too short of a duration (RCT < 6 weeks, Observational <12 weeks)
- [ ] Other? (Please explain!)
- [ ] None of the above- should be included!

18. Comments

Enlarge Shrink

Population characteristics

19. Groups similar at baseline? (Reviewer's opinion)

- ( ) Yes
- ( ) No- what are differences
- ( ) Not reported
- ( ) Not applicable

Clear Selection

Drug 1 Drug 2 Drug 3 Drug 4 Drug 5

20. n=					
21. Intervention					
22. Mean age (years):					
23. Sex (% female):					
24. Race (% white)					
25. Baseline HAM-A					
26. Insomnia (%):					
27. Concomitant anergia (%)					
28. Experienced prior depressive episodes (%):					
29. Comments:					

30. **Participants are:**

- Outpatients
- Inpatients
- Both

Clear Selection

31. **At baseline, is the study population characterized by concomitant moderate to severe anxiety (mean HAM-A > 25) ?**

- Yes
- No
- Not reported or not applicable

Clear Selection

32. **Is the mean age of the study population, at baseline:**

- Less than 65 years
- Equal to or greater than 65 years

Clear Selection

33. **At baseline, was the mean HAM-D score of the study population:**

- 10 - 17 (mild to moderate)
- Greater than 17 (moderate to severe)
- Not reported

Clear Selection

OUTCOME ASSESSMENTS:

34. Outcome Measures:

- HAM-D
- MADRS
- CGI-S or CGI-I
- Quality of life scales (please name scales)
- Others? Please list:

Health Outcome Results:
- **Include *all* the health outcomes such as HAM-D, QOL, CGI, rates of response and remission.**
- **Include effect size as percentages (%), 95% confidence interval, risk ratios, odds ratios, NNT and Ps.**

35.

ITT Analysis

- Yes
- No another type of analysis was used (define)
- Not applicable (why not?)

Clear Selection

ATTRITION

36. Overall rate of attrition (%):

Enlarge Shrink

	Drug 1	Drug 2	Drug 3	Drug 4
37. Intervention				
38. Attrition rate (%):				
39. Withdrawals due to adverse events (%):				
40. Attrition due to lack of efficacy (%):				

41. Additional comments:

Enlarge Shrink

RESULTS:

42. **HAM-D:**

- Yes
- No

Clear Selection

	Drug 1	Drug 2	Drug 3	Drug 4
43. Intervention				
44. n at baseline:				
45. # of responders:				
46. # of remitters:				
47. Mean score at baseline (SD):				
48. Mean score at endpoint (SD):				
49. Mean score change (SD):				

50. Comments?

Enlarge Shrink

51. **MADRS:**

- Yes

No

Clear Selection

	Drug 1	Drug 2	Drug 3	Drug 4
52. Intervention				
53. n at baseline:				
54. # of responders:				
55. # of remitters:				
56. Mean score at baseline (SD):				
57. Mean score at endpoint (SD):				
58. Mean score change (SD):				

59. Comments?

Enlarge Shrink

60. **CGI-S:**

Yes

No

Clear Selection

	Drug 1	Drug 2	Drug 3	Drug 4
61. Intervention:				
62. n at baseline:				
63. Mean score at baseline (SD):				
64. Mean score at endpoint (SD):				
65. Mean score change (SD):				

66. Comments?

Enlarge Shrink

67. **CGI-I**

Yes

No

Clear Selection

	Drug 1	Drug 2	Drug 3	Drug 4
68. Intervention				
69. n at baseline:				
70. Mean score at endpoint (SD):				
71. Number of patients achieving a score of "1" or "2" at endpoint:				

72. Comments?

Enlarge Shrink

73. **CGI:**

Yes

No

Clear Selection

	Drug 1	Drug 2	Drug 3	Drug 4
74. Intervention				
75. n at baseline:				
76. Mean score at baseline (SD):				
77. Mean score at endpoint (SD):				
78. Mean score change (SD):				

79. Comments?

Enlarge Shrink

80. **QOL scale:**

- Yes
- No

Clear Selection

81. Which scale was used?

Enlarge Shrink

	Drug 1	Drug 2	Drug 3	Drug 4
82. Intervention				
83. n at baseline:				
84. Mean score at baseline (SD):				
85. Mean score at endpoint (SD):				
86. Mean score change (SD):				

87. Comments?

Enlarge Shrink

88. **Another QOL scale:**

- Yes
- No

Clear Selection

89. Which scale was used?

Enlarge Shrink

	Drug 1	Drug 2	Drug 3	Drug 4
90. Intervention				
91. n at baseline:				
92. Mean score at baseline (SD):				
93. Mean score at endpoint (SD):				
94. Mean score change (SD):				

95. Comments?

Enlarge Shrink

96. Is adherence reported?

- Adherence
- Not reported

Clear Selection

97. Please provide the rate of adherence or compliance that is given in the article and any differences between treatment groups?

Enlarge Shrink

98. Additional Results:

Enlarge Shrink

Adverse Events for drugs (%)

	Drug 1	Drug 2	Drug 3	Drug 4
99. Intervention				
100. Overall adverse events reported (%):				
101. Cardiovascular adverse events (%):				
102. Changes in weight - weight gain (%):				
103. Changes in weight - weight loss (%):				
104. Constipation (%):				
105. Diarrhea (%):				
106. Dizziness (%):				
107. Headache (%):				
108. Hepatotoxicity (%):				
109. Insomnia (%):				
110. Nausea (%):				
111. Vomiting (%):				
112. Sexual dysfunction (%):				
113. Somnolence (fatigue) (%):				
114. Suicidality (%):				
115. Sweating-increased (%):				

116. Additional comments

Enlarge Shrink

117. **Methods of adverse effects assessment**

- Patient reported
- Physical exam at study visits
- Lab evaluations
- Standardized scale (e.g., WHO, UKU-SES)
- Other (please specify)
- Not applicable
- Not applicable

118. **Adverse events are pre-specified and defined?**

Clear Selection

119. Serious adverse events:

- [ ] Death
- [ ] Life threatening (e.g., pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flov
- [ ] Hospitalization (initial or prolonged) (e.g., anaphylaxis; pseudomembranous colitis; or bleeding causing or prolonging hospitalization)
- [ ] Disability (e.g., cerebrovascular accident due to drug-induced hypercoagulability; toxicity; peripheral neuropathy)
- [ ] Congenital Anomaly (e.g., vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide)
- [ ] Requires Intervention to Prevent Permanent Impairment or Damage (e.g., acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylc burns from radiation equipment requiring drug therapy; breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone)

120. **Techniques for detecting adverse events are non-biased and adequately described?**

- ( ) Yes
- ( ) No
- ( ) Not applicable

Clear Selection

Quality Assessment of RCTs:

121. **Randomization adequate?**

- ( ) Yes
- ( ) No
- ( ) Not randomized
- ( ) Method not reported

Clear Selection

122. **Allocation concealment adequate?**

- ( ) Yes
- ( ) No
- ( ) Not randomized
- ( ) Method not reported

Clear Selection

123. **Groups similar at baseline?**

- ( ) Yes
- ( ) No

Clear Selection

124. **Outcome assessors masked?**

- ( ) Yes
- ( ) No
- ( ) Yes, but method not described
- ( ) Not reported

Clear Selection

125. **Care provider masked?**

- ( ) Yes
- ( ) No
- ( ) Yes, but method not described
- ( ) Not reported

Clear Selection

126. **Patient masked?**

- Yes
- No
- Yes, but method not described
- Not reported

Clear Selection

127. **Overall attrition high (≥ 20%)?**

- Yes (please state how high)
- No

Clear Selection

128. **Differential attrition high (≥ 15%)?**

- Yes (please state difference)
- No

Clear Selection

129. **Was the statistical analysis based on intention-to-treat (ITT)?**

- Yes
- No
- Cannot tell

Clear Selection

130. **Were there any post-randomization exclusions?**

- Yes (how many?)
- No
- Cannot tell

Clear Selection

131. Are primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?

- Yes
- No
- Not applicable

Clear Selection

132. **Quality rating of RCT**

- Good
- Fair
- Poor

Quality Assessment of Observational Studies:

133. Were both groups selected from the same source population?

- Yes
- No
- Yes, but method not described
- Not reported

Clear Selection

134. Did both groups have the same risk of having the outcome of interest at baseline?

- Yes
- No
- Not reported
- Not applicable

Clear Selection

135. Were subjects in both groups recruited over the same time period?

- Yes
- No
- Yes, but method not described
- Not reported
- Not applicable

Clear Selection

136. Were measurement methods adequate and equally applied to both groups?

- Yes
- No
- Not reported
- Not applicable

Clear Selection

137. Does the analysis control for baseline differences?

- Yes
- No
- Not applicable

Clear Selection

138. Were important potential confounding and modifying variables taken into account in the design and analysis (e.g., through matching, stratification, or statis

- Yes
- No
- Not applicable

Clear Selection

139. Were the statistical methods used to assess the abstracted outcomes appropriate?

- Yes
- No
- Not applicable

Clear Selection

140. Was an attempt made to blind the outcome assessors?

- Yes
- No
- Yes, but method not described
- Not reported
- Not applicable

Clear Selection

141. Was the time of follow-up equal in both groups?

- Yes
- No
- Not reported
- Not applicable

Clear Selection

142. Overall attrition high (≥ 20%)?

- Yes (please state how high)
- No

Clear Selection

143. Differential attrition high (≥ 15%)?

Yes (please state the difference)

No

Not applicable

Clear Selection

144. Have primary outcomes been pre-defined and assessed using valid and reliable measures, implemented consistently across all study participants?

Yes

No

Not applicable

Clear Selection

145. **Quality rating for observational study:**

Good

Fair

Poor

Clear Selection

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Form took 1.46875 seconds to render
Form Creation Date: Not available
Form Last Modified: Jan 4 2010 2:01PM

Previewing Only: You cannot submit data from this form

Previewing at Level 2

Reviewer Comments (Add a Comment)

Refid: 1, M. C. Harlow, C. M. Davidson and J. A. Bourgeois, Psychogenic tremor in a patient with a major depressive episode, *S D Med*, 62(6), 2009, p.233, 235
State: Excluded, Level: 1

Full Text Review

Save to finish later | Submit Data

1. Should the article be excluded for any of the following reasons?

- [ ] Study only reported in abstract form (e.g., full text is not available)
- [ ] Background article
- [ ] Wrong outcome (e.g., no pharmakinetic or other intermediate outcomes)
- [ ] Wrong drug
- [ ] Wrong population (e.g., pediatric or perinatal studies)
- [ ] Wrong publication type (e.g., letter or editorial)
- [ ] Wrong design (e.g., uncontrolled study - no comparision arm)
- [ ] Too short of a duration (e.g., RCT < 6 weeks, Observational < 12 weeks)
- [ ] Other? (Please explain!)
- [ ] None of the above - should be included!

2. Which of the following outcomes are presented in the article?

- [ ] KQ1: Efficacy or effectiveness measures in H-H and placebo controlled studies or meta-analyses
- [ ] KQ2 a: Rates of maintenance of response/remission or recurrence of depression in any type of prospective controlled study or meta-analysis
- [ ] KQ2 b: Efficacy or effectiveness in patients who have relapsed or who have not responded with initial AD treatment in any type of prospective controlled study or meta-analysis
- [ ] KQ3: Efficacy or effectiveness measures of single or combination treatments in depressed patients with accompanying symptoms in H-H and placebo controlled studies or meta-analyses
- [ ] KQ4: Safety, adverse events and adherence measures in any type of study (but no case reports)
- [ ] KQ5: Sub-population evaluations of efficacy, effectiveness, safety and adverse events in head to head and placebo controlled studies
- [ ] None of the above

3. What is the sample size?

- ( ) RCT n < 40
- ( ) RCT n >= 40
- ( ) Controlled observational study for KQ2 n < 100
- ( ) Controlled observational study for KQ2 n >= 100
- ( ) Any observational study for KQ4 (adverse events) n < 1000
- ( ) Any observational study for KQ4 (adverse events) n >= 1000
- ( ) Meta-analysis
- ( ) Not applicable (Why not?)

Clear Selection

4. Type of abstraction:

- ( ) Full Abstraction
- ( ) Abbreviated abstraction for use in our meta-analysis
- ( ) Abstraction of meta-analysis or systematic review

Clear Selection

5. Reviewer Initials:

Previewing Only: You cannot submit data from this form

Previewing at Level 4

Refid: 1, M. C. Harlow, C. M. Davidson and J. A. Bourgeois, Psychogenic tremor in a patient with a major depressive episode, *S D Med*, 62(6), 2009, p.233, 235
State: Excluded, Level: 1

Abbreviated Abstractin

Save to finish later | Submit Data

1. First abstraction completed by:

Enlarge Shrink

2. Second abstraction completed by:

Enlarge Shrink

3. Author, Year

Enlarge Shrink

4. Country and setting:

Enlarge Shrink

5. Please check off the drug(s) studied and put the daily doses used in the adjacent box:

- Bupropion
- Citalopram
- Desvenlafaxine
- Duloxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Mirtazapine
- Nefazodone
- Paroxetine
- Sertraline
- Trazodone
- Venlafaxine
- Placebo
- Other

6. Source of funding:

- Pharmaceutical company or other commercial source- please list name.
- Government or non-profit organization- please list name.
- Not reported

7. Research objective (please be concise):

Enlarge Shrink

8. Type of depression (check all that apply):

- [ ] Acute
- [ ] Chronic
- [ ] Recurrent
- [ ] Severe
- [ ] Double depression
- [ ] Subsyndromal depressive disorder
- [ ] Major depressive disorder
- [ ] Dysthmia
- [ ] Minor depression
- [ ] Other - please explain

9. Study design:

- ( ) RCT
- ( ) Observational
- ( ) Other
- ( )

Clear Selection

10. n =

Enlarge Shrink

Dose levels - include only the active drug, not the placebo!

	Drug 1	Drug 2	Drug 3	Drug 4	Dru
11. Intervention					
12. Low	[ ]	[ ]	[ ]	[ ]	[ ]
13. Medium	[ ]	[ ]	[ ]	[ ]	[ ]
14. High	[ ]	[ ]	[ ]	[ ]	[ ]

15. Study duration is :

- ( ) less than 24 weeks
- ( ) 24 weeks or longer

Clear Selection

16. **Participants are:**

- ( ) Outpatients
- ( ) Inpatients
- ( ) Both

Clear Selection

17. **At baseline, is the study population characterized by concomitant moderate to severe anxiety (mean HAM-A > 25)?**

- ( ) Yes - please record baseline values
- ( ) No - please record baseline values if available
- ( ) Not reported or not applicable

Clear Selection

18. **At baseline, is the mean age of the study population:**

- [ ] Less than 65 years
- [ ] Equal to or greater than 65 years
- [ ] Overall mean age:

- 10 - 17 (mild to moderate)
- Greater than 17 (moderate to severe)
- Not reported

Clear Selection

RESULTS:

Please include active and placebo arms!

20. **HAM-D:**

- Yes
- No

Clear Selection

	Drug 1	Drug 2	Drug 3	Drug 4	Dru
21. Intervention					
22. n at baseline:					
23. # of responders:					
24. # of remitters:					
25. Mean score at baseline (SD):					
26. Mean score at endpoint (SD):					
27. Mean score change (SD):					

28. Comments?

Enlarge Shrink

29. MADRS:

- Yes
- No

Clear Selection

	Drug 1	Drug 2	Drug 3	Drug 4	Dru
30. Intervention					
31. n at baseline:					
32. # of responders:					
33. # of remitters:					
34. Mean score at baseline (SD):					
35. Mean score at endpoint (SD):					
36. Mean score change (SD):					

37. Comments?

Enlarge Shrink

38. **CGI-S:**

Yes

No

Clear Selection

	Drug 1	Drug 2	Drug 3	Drug 4	Dru
39. Intervention:					
40. n at baseline:					
41. Mean score at baseline (SD):					
42. Mean score at endpoint (SD):					
43. Mean score change (SD):					

44. Comments?

Enlarge Shrink

45. **CGI-I**

Yes

No

Clear Selection

	Drug 1	Drug 2	Drug 3	Drug 4	Dru
46. Intervention					
47. n at baseline:					
48. Mean score at endpoint (SD):					

49. Comments?

Enlarge Shrink

50. **CGI:**

Yes

No

Clear Selection

	Drug 1	Drug 2	Drug 3	Drug 4	Dru
51. Intervention					
52. n at baseline:					
53. Mean score at baseline (SD):					
54. Mean score at endpoint (SD):					
55. Mean score change (SD):					

56. Comments?

Enlarge Shrink

57. **QOL scale:**

- Yes
- No

Clear Selection

58. Which scale was used?

Enlarge Shrink

	Drug 1	Drug 2	Drug 3	Drug 4	Dru
59. Intervention					
60. n at baseline:					
61. Mean score at baseline (SD):					
62. Mean score at endpoint (SD):					
63. Mean score change (SD):					

64. Comments?

Enlarge Shrink

65. **QOL scale:**

- Yes
- No

Clear Selection

66. Which scale was used?

Enlarge Shrink

	Drug 1	Drug 2	Drug 3	Drug 4	Dru
67. Intervention					
68. n at baseline:					
69. Mean score at baseline (SD):					
70. Mean score at endpoint (SD):					
71. Mean score change (SD):					

72. Comments?

Enlarge Shrink

73. Is adherence or compliance reported?

- Adherence
- Compliance

None reported

Clear Selection

74. Please provide the rate of adherence or compliance that is given in the article and any differences between treatment groups.

Enlarge Shrink

Adverse Events (%) (Record only the AEs for the active arm(s), do not bother with the placebo arm!)

	Drug 1	Drug 2	Drug 3	Drug 4	Dru
75. Intervention					
76. Overall adverse events reported (%):					
77. Cardiovascular adverse events (%):					
78. Changes in weight - weight gain (%):					
79. Changes in weight - weight loss (%):					
80. Constipation (%):					
81. Diarrhea (%):					
82. Dizziness (%):					
83. Headache (%):					
84. Hepatotoxicity (%):					
85. Insomnia (%):					
86. Nausea (%):					
87. Sexual dysfunction - male ejaculation (%):					
88. Somnolence (fatigue) (%):					
89. Suicidality (%):					
90. Sweating-increased (%):					

91. **Randomization adequate?**

Yes

No

Not randomized

Method not reported

Clear Selection

92. **Allocation concealment adequate?**

Yes

No

- Not randomized
- Method not reported

Clear Selection

93. **Groups similar at baseline?**

- Yes
- No

Clear Selection

94. **Outcome assessors masked?**

- Yes
- No
- Yes, but method not described
- Not reported

Clear Selection

95. **Care provider masked?**

- Yes
- No
- Yes, but method not described
- Not reported

Clear Selection

96. **Patient masked?**

- Yes
- No
- Yes, but method not described
- Not reported

Clear Selection

97. **Overall attrition high (≥20%)?**

- Yes (please state how high)
- No
- Not reported

Clear Selection

98. **Differential attrition high (≥ 15%)?**

- Yes (please state difference)
- No
- Not reported

Clear Selection

99. **Was the statistical analysis based on intention-to-treat (ITT)?**

- Yes
- No
- Cannot tell

Clear Selection

100. **Were there any post-randomization exclusions?**

- Yes (how many?)
- No
- Cannot tell

Clear Selection

101. **Quality rating for efficacy/effectiveness**

- [ ] Good
- [ ] Fair
- [ ] Poor
- [ ] Not applicable (e.g., safety study)

102. **Adverse events are pre-specified and defined?**

- ( ) Yes
- ( ) No

Clear Selection

103. **Methods of adverse effects assessment**

- [ ] Patient reported
- [ ] Physical exam at study visits
- [ ] Lab evaluations
- [ ] Standardized scale (e.g., WHO, UKU-SES)
- [ ] other (please specify)

104. **Techniques for detecting adverse events are non-biased and adequately described?**

- ( ) Yes
- ( ) No
- ( ) Not applicable

Clear Selection

105. **Quality rating:**

- ( ) Good
- ( ) Fair
- ( ) Poor
- ( ) Not applicable (e.g., efficacy only)

Clear Selection

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Previewing at Level 5

Refid: 1, M. C. Harlow, C. M. Davidson and J. A. Bourgeois, Psychogenic tremor in a patient with a major depressive episode, *S D Med*, 62(6), 2009, p.233, 235
State: Excluded, Level: 1

Meta-Analysis or Systematic Review

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1. First abstraction completed by:

Enlarge Shrink

2. Second abstraction completed by:

Enlarge Shrink

3. Author:

Enlarge Shrink

4. Year:

Enlarge Shrink

5. Country:

Enlarge Shrink

6. Funding:

Enlarge Shrink

7. Study design:

Enlarge Shrink

8. Number of patients:

Enlarge Shrink

9. Aims of review:

Enlarge Shrink

10. Studies included in analysis or review:

Enlarge Shrink

11. Characteristics of included studies:

Enlarge Shrink

12. Characteristics of included populations:

Enlarge Shrink

13. Characteristics of interventions:

Enlarge Shrink

14. Main results:

Enlarge Shrink

15. Adverse Events:

Enlarge Shrink

16. Comprehensive literature search strategy (briefly describe):

Enlarge Shrink

17. Standard method of appraisal of studies?

Enlarge Shrink

18. Publication bias assessed?

Enlarge Shrink

19. Heterogeneity assessed?

Enlarge Shrink

20. Quality rating:

Enlarge Shrink

21. Additional comments:

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