Comparative Effectiveness Review

Number 7

Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression

This report is based on research conducted by the RTI International-University of North Carolina Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0016). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

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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. 290-02-0016

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AHRQ Publication No. 07-EHC007-EF
January 2007

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

Suggested citation:
Gartlehner G, Hansen RA, Thieda P, DeVeaugh-Geiss AM, Gaynes BN, Krebs EE, Lux LJ, Morgan LC, Shumate JA, Monroe LG, Lohr KN. Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression. Comparative Effectiveness Review No. 7. (Prepared by RTI International-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) Rockville, MD: Agency for Healthcare Research and Quality. January 2007. Available at: 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 State Children's Health Insurance Program (SCHIP).

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 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 strengths 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 http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews 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 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.

Acknowledgments

This study was supported by Contract 290-02-0016 from the Agency for Healthcare Research and Quality, Task No. 7. We acknowledge the continuing support of Beth Collins-Sharp, Ph.D., R.N., and Lia Snyder, M.P.H., of AHRQ.

We extend our appreciation to the members of our Technical Expert Panel, listed below. 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 particularly acknowledge Timothy Carey, M.D., M.P.H., for insightful comments on the first draft and helpful suggestions throughout the project; Lynn Whitener, Dr.P.H., M.S.L.S., our EPC Librarian; and UNC supporting staff Stacey Williams and Jonathan Ward. We also express our gratitude to RTI staff Tammeka Swinson, Research Analyst, and both Jennifer Drolet, M.A., and Melissa Fisch, B.A., editors.

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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. 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) and serotonin and norepinephrine reuptake inhibitors (SNRIs). 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 major depressive disorder and are the focus of this review.

This report summarizes the available evidence on the comparative efficacy, effectiveness, and harms of 12 second-generation antidepressants: bupropion, citalopram, 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 for treating accompanying symptoms such as anxiety, insomnia, or neurovegetative symptoms.

We rate the strength of evidence according to a modified GRADE approach. GRADE incorporates four key elements--study design, study quality, consistency, and directness--to characterize the strength of the body of evidence to answer key questions. We used three grades: high, moderate, and low (combining the GRADE category of very low with low). The quality of individual studies is denoted as good, fair, or poor. We assessed statistically each of the 66 possible drug comparisons of second-generation antidepressants. When data were sufficient, we did four direct comparisons; the remaining 62 analyses employed indirect comparison approaches.

Specifically, we address the following key questions (KQs) in this report:

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?

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?

3. 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?

3a: Do medications differ in their efficacy and effectiveness in treating the depressive episode?

3b: Do medications differ in their efficacy and effectiveness in treating the accompanying symptoms?

4. 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.

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

4. Elderly or very elderly patients;

5. Other demographic groups (defined by age, ethnic or racial groups, and sex);

6. Patients with medical comorbidities (e.g., ischemic heart disease, cancer)?

Table A summarizes the findings on second-generation antidepressants in the treatment of adult depression.

Conclusions

Treatment of Major Depressive Disorder (KQ 1)

Efficacy and effectiveness. From a total of 2,099 citations identified, we ultimately included 293 articles in this review, which represented 187 studies of good or fair quality. Of these, 89 were head-to-head randomized controlled trials (RCTs) and 57 were placebo-controlled RCTs; the remainder were observational or other types of studies or other qualitative or quantitative systematic reviews.

Of these 187 studies, 126 were financially supported by pharmaceutical companies and 17 by government agencies or independent funds; for 44 studies, we could not determine the funding source.

Overall, 38 percent of patients did not respond during 6 to 12 weeks of treatment with second-generation antidepressants; 54 percent did not achieve remission. The evidence is insufficient to determine factors that can reliably predict response or nonresponse in individual patients.

Seventy-two head-to-head comparisons (i.e., comparisons between medications conducted within trials) provided data on 35 of the potential comparisons between the 12 second-generation antidepressants addressed in this report. Five trials directly compared any non-SSRI second-generation antidepressant with any other non-SSRI second-generation antidepressant; of these, only one comparison was 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 for four 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 vs. escitalopram (five studies; 1,545 patients): Patients on escitalopram had an additional treatment effect of a 1.25-point reduction (95-percent confidence interval [CI], 0.10-2.39) on the Montgomery-Asberg Depression Rating Scale (MADRS) compared with patients on citalopram. The relative risk (RR) of response was statistically significantly greater for escitalopram than for citalopram (RR: 1.14; 95-percent CI, 1.04-1.26). The number needed to treat (NNT) to gain one additional responder at week 8 with escitalopram was 14 (95-percent CI, 7-111). Both drugs are produced by the same manufacturer, which funded all available studies.

- Fluoxetine vs. paroxetine (seven studies; 950 patients): We did not find any statistically significant differences in effect sizes on the Hamilton Depression Rating Scale (HAM-D) or response rates between fluoxetine and paroxetine. Fluoxetine had an additional reduction of 0.55 (95-percent CI, –1.4-0.36; $P = 0.23$) points on HAM-D compared with paroxetine; paroxetine led to a higher rate of responders than fluoxetine (RR 1.09; 95-percent CI, 0.99-1.21).

- Fluoxetine vs. sertraline (four studies; 940 patients): Patients on sertraline had an additional, statistically nonsignificant treatment effect of a 0.75-point reduction (95-percent CI, –0.45-1.95) on the Hamilton Rating Scale for Depression (HAM-D) scale compared with patients on fluoxetine. The relative risk of response was statistically significantly greater for sertraline than for fluoxetine (RR: 1.11; 95-percent CI, 1.01-1.21). The NNT to gain one additional responder at 6 to 12 weeks with sertraline was 14 (95-percent CI, 8-22).

- Fluoxetine vs. venlafaxine (eight studies; 1,814 patients): Patients on venlafaxine had an additional, statistically nonsignificant treatment effect of a 1.31-point reduction (95-percent CI, 0.10-2.39) on the HAM-D scale compared with patients on fluoxetine. The relative risk of response was statistically significantly greater for venlafaxine than for fluoxetine (RR: 1.12; 95 percent CI, 1.01-1.24). The NNT to gain one additional responder at 6 to 12 weeks with venlafaxine was 12 (95-percent CI, 7-50). All studies were funded by the makers of venlafaxine.

Most trials were efficacy trials 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 generalizability 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 (i.e., comparisons of medications conducted across placebo-controlled trials rather than within a single trial) yielded no statistically significant differences in response rates. The precision of some of these estimates was low, leading to inconclusive results with wide confidence intervals. Nevertheless, point estimates of treatment effects from these analyses were consistent with those from direct evidence trials in indicating no or minimal differences in efficacy among available comparisons.

Overall, we rated the strength of the evidence as moderate for both comparative efficacy and comparative effectiveness.

Although second-generation antidepressants appear similar in average efficacy and effectiveness, the studies were not designed to test variation among individuals in their responses to individual drugs. The second-generation antidepressants cannot be considered identical drugs. Evidence of moderate strength supports some differences among individual drugs with respect to onset of action and some measures (e.g., sexual functioning) that could affect health-related quality of life. These are statistically significant but of modest magnitude; potential benefits might be offset by specific adverse events. Nonetheless, some of these differences may influence the choice of a medication for specific patients.

Quality of life. Quality of life or functional capacity was infrequently assessed, usually as a secondary outcome. Eighteen studies (4,050 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 NNT to yield one additional responder after 1 or 2 weeks of treatment is 7 (95-percent CI, 5-12); after 4 weeks of treatment, however, most response rates were similar. Again, this treatment effect was consistent across all studies, but whether this difference can be extrapolated to other second-generation antidepressants remains unclear. The strength of evidence is moderate.

Response to a second agent. The Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial is the only well-done study looking at the question of response to a second agent among those failing initial therapy. Results show that about one in four of the 727 people who participated in the switch became sym—bupropion sustained release (SR), sertraline, and venlafaxine extended release (XR).

Treatment of Dysthymia

Efficacy and effectiveness. We identified no head-to-head trial comparing different medications in a population with dysthymia. In placebo-controlled trials, significant differences in population characteristics make the evidence insufficient to identify differences between treatments.

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 showed a significantly greater improvement than those on placebo; a subgroup of patients younger than 60 years did not show any difference in effectiveness between paroxetine and placebo. The strength of evidence is low.

Treatment of Subsyndromal Depression

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.

Maintenance of Response or Remission (KQ 2a)

Efficacy and effectiveness. Three head-to-head RCTs suggest that no substantial differences exist between fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine for maintaining response or remission (i.e., preventing relapse or recurrence of MDD). The strength of the evidence is moderate. Twenty-one placebo-controlled trials support the general efficacy and effectiveness of most second-generation antidepressants for preventing relapse or recurrence. No evidence exists for duloxetine. The overall strength of this evidence is moderate.

Treatment of Treatment-Resistant Depression Syndrome or Relapse or Recurrence (KQ 2b)

Efficacy and effectiveness. One head-to-head efficacy study and two effectiveness studies provide conflicting evidence on differences among second-generation antidepressants in treatment-resistant depression. The efficacy study (fair quality) suggests that venlafaxine is modestly more effective than paroxetine. A good-quality effectiveness study suggests that no substantial differences exist among bupropion SR, sertraline, and venlafaxine XR, but a fair-quality effectiveness study suggests that venlafaxine is modestly more effective than citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline. Given the conflicting results, the overall strength of the evidence is moderate.

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 3a)

Anxiety. Evidence from six head-to-head trials and one placebo-controlled trial (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 between fluoxetine, paroxetine, and sertraline; sertraline and bupropion; and sertraline and venlafaxine. One trial found statistically significant superiority of venlafaxine over fluoxetine. The strength of evidence is moderate.

Insomnia. Three head-to-head trials that identified a specific insomnia group (all fair quality) provide limited evidence regarding comparative efficacy of medications for treating depression in patients with accompanying insomnia. One trial found statistically significant superiority for escitalopram over citalopram. The strength of evidence is low.

Melancholia. Two head-to-head trials (both fair quality), one poor-quality head-to-head trial, and one fair-quality placebo-controlled study 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 more for venlafaxine than for fluoxetine. The strength of evidence is low.

Pain. One fair-quality trial that required baseline pain for inclusion found no difference in efficacy for duloxetine compared with placebo for treating depression in patients with pain of at least mild intensity. The strength of evidence is low.

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 low.

Somatization. We identified no relevant study.

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

Anxiety. Ten 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 between fluoxetine, paroxetine, and sertraline; sertraline and bupropion; sertraline and venlafaxine; citalopram and mirtazapine; and paroxetine and nefazodone. One trial found that venlafaxine was statistically significantly superior to fluoxetine. The strength of evidence is moderate.

Insomnia. Six head-to-head trials (all fair quality) provide limited evidence about comparative effects of antidepressants on insomnia in patients with depression. The strength of evidence is low.

Melancholia. We identified no relevant study.

Pain. Two head-to-head trials (one of fair and the other of poor quality) and three placebo-controlled trials (all fair quality) provide limited evidence about effects of antidepressants on pain symptoms in depressed patients. Two trials found no substantial difference in efficacy between duloxetine and paroxetine. The strength of evidence is low.

Psychomotor changes. We identified no relevant study.

Somatization. One open-label effectiveness trial found no statistically significant difference among three SSRIs for treating somatization in patients with depression. The strength of evidence is low.

Differences in Harms (Adverse Events) (KQ 4)

We analyzed adverse events data from 72 head-to-head efficacy studies on 16,780 patients, along with data from 39 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.

Adverse events profiles. Constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence were commonly and consistently reported adverse events. On average, 61 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 10-percent (95-percent CI, 4-17 percent) higher incidence of nausea and vomiting than SSRIs as a class. In addition, pooled discontinuation rates because of adverse events in efficacy trials are statistically significantly higher for venlafaxine than for SSRIs (RR: 1.50; 95-percent CI, 1.21-1.84). The strength of evidence is high.

- In most studies, sertraline led to higher rates of diarrhea than comparator drugs (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine). The incidence was 8-percent (95-percent CI, 3-11 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 is moderate.

- Mirtazapine led to higher weight gains than comparator drugs (fluoxetine, paroxetine, venlafaxine, and trazodone). Mean weight gains compared to pretreatment ranged from 0.8 kg to 3.0 kg after 6 to 8 weeks of treatment. Paroxetine had higher weight gains than fluoxetine and sertraline. The strength of evidence 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 is moderate.

- Discontinuation syndromes (e.g., headache, dizziness, nausea) occurred in 0 to 86 percent of patients. Paroxetine and venlafaxine had the highest incidence of this problem, and fluoxetine the lowest incidence. The strength of evidence is moderate.

Discontinuation rates. Overall discontinuation rates did not differ significantly between SSRIs as a class and bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine. In the case of venlafaxine compared with SSRIs, higher discontinuation rates because of adverse events (11.5 percent vs. 8.5 percent) appear to be balanced by lower discontinuation rates because of lack of efficacy (3.5 percent vs. 4.4 percent). The strength of evidence is high.

Severe adverse events.

Sexual dysfunction. Bupropion is associated with a lower incidence of sexual dysfunction than fluoxetine, paroxetine, and sertaline. The NNT to gain one additional person with high overall satisfaction of sexual functioning is 6 (95-percent CI, 4-9). In head-to-head trials, paroxetine consistently had higher rates of sexual dysfunction than comparators (fluoxetine, fluvoxamine, nefazodone, and sertraline; 16 percent vs. 6 percent). Underreporting of absolute rates of sexual dysfunction, however, is likely in these studies. Whether these findings can be extrapolated to comparisons of bupropion and paroxetine with other second-generation antidepressants is unclear. 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 (i.e., elevated systolic and diastolic blood pressure and elevated pulse/heart rate), hyponatremia, hepatotoxicity, and serotonin syndrome, is insufficient to draw firm conclusions. The strength of evidence is low. 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. One observational study indicated that extended-release formulations might have a better adherence rate than immediate-release medications. This finding, however, is likely attributable more to differences in dosing regimens than to differences in efficacy and harms. 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. The strength of evidence is low.

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

Age. Twelve head-to-head trials (one an effectiveness study), nine placebo-controlled trials, one retrospective cohort study, and one set of meta-analyses suggest that no major differences in efficacy and effectiveness exist among second-generation antidepressants in elderly or very elderly populations. The strength of the evidence is moderate.

Harms such as hyponatremia and weight loss may differ in elderly or very elderly patients on active treatment vs. placebo, but the evidence on these two adverse events is limited to one small RCT and one observational study (both fair quality). The strength of the evidence is low.

Sex. Indirect evidence from one fair-quality pooled analysis of head-to-head RCTs suggests that efficacy among second-generation antidepressants does not differ between men and women. This conclusion is supported by observational evidence. One fair-quality observational study indicated that harms, specifically the rates of sexual dysfunction, might differ between men and women. The strength of the evidence is low.

Race or ethnicity. One poor-quality RCT suggests that the efficacy of second-generation antidepressants does not differ for patients in different race or ethnic groups. This study, however, may not have been powered to detect a difference. The strength of the evidence is low.

Comorbidities. The evidence for various comorbidities (e.g., HIV/AIDS, alcohol abuse, Alzheimer's disease or other dementia, breast cancer, cardiovascular disease, stroke, and substance abuse) is limited to one head-to head study, a small number of placebo-controlled trials, and one systematic review. They provide limited evidence on the comparative efficacy of second-generation antidepressants in subgroups with different coexisting conditions. The strength of the evidence is low.

Remaining Issues

We found no studies that identified reliable predictors of individual responses to a specific drug based on patients' clinical, demographic, or genetic characteristics. Owing to a substantial nonresponse rate to individual drugs and generally high incidence of side effects, many patients try multiple antidepressant medications before finding an effective, well-tolerated drug, but predicting which drug will be most effective or best tolerated in any given individual is not yet possible. Studies of tailoring therapy would have been eligible for this review, but we did not find any. Most of the included studies looked only at average effectiveness, excluded subjects with comorbidities, and did not examine differences in effectiveness according to broad demographic characteristics.

Effectiveness studies that would be most applicable to the broad population of depressed patients are generally lacking for most drugs. Effectiveness trials with less stringent eligibility criteria, patient-centered health outcomes, long study durations, and populations representative of patients encountered in primary care 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.

Major Depressive Disorder

Although the strength of evidence is moderate for the comparative efficacy for treating MDD during the acute phase, more 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. In efficacy trials, on average, 38 percent of patients did not achieve a treatment response, and 54 percent did not achieve remission. The STAR-D trial is the best available evidence so far, but its results are limited to bupropion SR, sertraline, and venlafaxine XR.

Given the fact 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 predict better 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.

In addition, more evidence is needed regarding the most appropriate duration of antidepressant treatment for maintaining response and 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 role of other depression treatments, such as psychotherapy, vagal nerve stimulations, light therapy, and complementary medicines, as substitutes or complements to pharmaceutical management also needs to be better understood.

More research is also needed to evaluate whether 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 more accurate measures to identify these subgroups. Likewise, future research has to clarify differences of second-generation antidepressants in subgroups based on age, race, and common comorbidities.

Dysthymia and Subsyndromal Depression

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 for treating these two conditions. If general efficacy can be established reliably, differences in subgroups based on accompanying symptoms, demographic characteristics, or comorbidities should be explored.

Addendum

As this report was going to press, a relevant study addressing sequential treatment steps among patients who did not obtain remission with initial acute-phase treatment was published. We were unable to incorporate this study fully into this report, but we found its results important in light of the general lack of high-quality evidence for treating patients who do not obtain remission with initial treatments.

The STAR-D trial–described in detail in the discussion of Key Question 2b (in the main report)–consisted of a series of RCTs examining sequential treatment steps in patients who did not obtain remission or could not tolerate previous treatments. Key Question 2b detailed the medication switch arms of the second-step treatment in which all patients in the analysis had failed initial treatment with citalopram and were randomized to second-step treatment with bupropion SR (N = 239), sertraline (N = 238), or venlafaxine XR (N = 250); this analysis found no statistically significant differences in remission rates between second-step treatments.

The more recently published study describes the acute and longer term outcomes associated with all four treatment steps. Patients not achieving remission or unable to tolerate a treatment step were encouraged to move to the next step; patients achieving acceptable benefit could enter a 12-month followup phase. All patients (N = 3,671) received citalopram in Step 1. Step 2 and Step 3 treatments were randomly assigned using an equipoise stratified randomized design. In this, 1,439 patients were randomized in Step 2, which included seven possible treatment alternatives (bupropion SR, sertraline, venlafaxine XR, cognitive therapy, citalopram plus bupropion, citalopram plus buspirone, or citalopram plus cognitive therapy). Step 3 randomized 390 patients to switch to mirtazapine or nortriptyline or to receive augmentation with lithium or triiodothyronine (T3). Step 4 used only a single randomization; 123 patients were randomized to tranylcypromine or venlafaxine XR plus mirtazapine.

Overall, 67 percent of patients achieved remission. Remission rates were 36.8 percent for Step 1, 30.6 percent for Step 2, 13.7 percent for Step 3, and 13.0 percent for Step 4. For patients achieving acceptable benefits who continued on in the 12-month followup study, relapse rates were 40.1 percent, 55.3 percent, 64.6 percent, and 71.1 percent for those achieving benefit in

Steps 1, 2, 3, and 4, respectively. In all steps, patients achieving remission (Quick Inventory of Depressive Symptomatology–Self Report [QIDS-SR-16] ≤ 5) were less likely to relapse than patients not achieving remission (acceptable benefit but QIDS-SR-16 > 5).

Table A. Summary of findings on treatment of adult depression with strength of evidence

Key question, disorder, and outcome of interest	Strength of evidence[1]	Findings[2]
Key Question 1a. Comparative efficacy and effectiveness of second-generation antidepressants		
Major depressive disorders		
Comparative efficacy	Moderate	Results from direct and indirect comparisons indicate that no substantial differences in efficacy exist among second-generation antidepressants.
Comparative effectiveness	Moderate	Direct evidence from 1 good and 2 fair effectiveness studies 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 studies, most of fair quality, 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 7 fair 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 1 second-generation antidepressant compared with another.
Dysthymia		
Comparative efficacy	Low	No head-to head evidence exists. Findings from 5 placebo-controlled trials were insufficient to draw conclusions about comparative efficacy.
Comparative effectiveness	Low	One fair effectiveness study provides mixed evidence about paroxetine vs. placebo; patients older than 60 showed greater improvement on paroxetine; those younger than 50 did not show any difference.
Quality of life	No evidence	
Onset of action	No evidence	
Subsyndromal depression		
Comparative efficacy	Low	One nonrandomized, open-label trial did not detect any difference between citalopram and sertraline. Findings from 2 placebo-controlled trials were insufficient to draw conclusions.
Comparative effectiveness	No evidence	
Quality of life	No evidence	
Onset of action	No evidence	
Key Question 1b: Greater efficacy and effectiveness with previously effective medications		
Major depressive disorder	No evidence	
Dysthymia	No evidence	
Subsyndromal depression	No evidence	

Table A. Summary of findings on treatment of adult depression with strength of evidence (continued)

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Key Question 2a: Efficacy and effectiveness of second-generation antidepressants for maintaining response or remission (i.e., preventing relapse or recurrence)		
Comparative efficacy	Moderate	Based on findings from 3 efficacy trials, no significant differences exist between fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine for preventing relapse or recurrence. Whether this finding can be extrapolated to other second-generation antidepressants is unclear.
Comparative effectiveness	No evidence	
General effectiveness/efficacy	Moderate	Based on findings from 21 placebo-controlled trials, second-generation antidepressants are effective for preventing relapse or recurrence.
Key Question 2b: Efficacy and effectiveness of second-generation antidepressants in managing treatment-resistant depression syndrome or treating recurrent depression		
Managing treatment-resistant depression		
Comparative efficacy	Low	Results from 1 fair trial support modestly better efficacy for venlafaxine compared with paroxetine.
Comparative effectiveness	Moderate	Results from 2 effectiveness studies are conflicting. Based on 1 good trial, no significant differences in effectiveness exist among bupropion SR, sertraline, and venlafaxine XR. One fair effectiveness trial found venlafaxine to be modestly superior to citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline.
General effectiveness/efficacy	Low	No placebo-controlled evidence was identified. Uncontrolled, open-label evidence supports the general efficacy of second-generation antidepressants.
Treating recurrent depression		
Comparative efficacy	No evidence	
Comparative effectiveness	No evidence	
Key Question 3a: Comparative efficacy and effectiveness of second-generation antidepressants for treatment of depression in patients with accompanying symptom clusters		
Anxiety		
Comparative efficacy	Moderate	Results from 6 head-to-head trials and 1 placebo-controlled trial (all fair quality) suggest that efficacy does not differ substantially for treatment of depression in patients with accompanying anxiety.
Comparative effectiveness	No evidence	
Insomnia		
Comparative efficacy	Low	Evidence from 3 fair head-to-head studies is insufficient to draw conclusions about treating depression in patients with coexisting insomnia. Results are limited by study design.
Comparative effectiveness	No evidence	

Table A. Summary of findings on treatment of adult depression with strength of evidence (continued)

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Melancholia		
Comparative efficacy	Low	Evidence from 2 fair head-to-head studies, 1 poor head-to-head study, and 1 fair placebo-controlled trial is insufficient to draw conclusions about treating depression in patients with coexisting insomnia. Results are inconsistent across studies.
Comparative effectiveness	No evidence	
Pain		
Comparative efficacy	Low	Evidence from 1 fair placebo-controlled study is insufficient to draw conclusions about treating depression in patients with coexisting pain. Results from head-to-head trials are not available.
Comparative effectiveness	No evidence	
Psychomotor change		
Comparative efficacy	Low	Evidence from 1 fair head-to-head trial is insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting psychomotor change. Results indicate that comparative outcomes for psychomotor retardation and psychomotor change may be different.
Comparative effectiveness	No evidence	
Somatization		
Comparative efficacy	No evidence	
Comparative effectiveness	No evidence	
Key Question 3b: Comparative efficacy and effectiveness of second-generation antidepressants for treatment of symptom clusters in patients with depression		
Anxiety		
Comparative efficacy	Moderate	Results from 10 fair head-to-head trials and 2 fair placebo-controlled trials suggest that no substantial differences in efficacy exist among second-generation antidepressants for treatment of accompanying anxiety symptoms.
Comparative effectiveness	No evidence	
Insomnia		
Comparative efficacy	Low	Evidence from 6 fair head-to-head trials is insufficient to draw conclusions about treating insomnia in depressed patients. Results are limited by study design; differences in outcomes are of unknown clinical significance.
Comparative effectiveness	No evidence	
Melancholia		
Comparative efficacy	No evidence	
Comparative effectiveness	No evidence	
Pain		
Comparative efficacy	Low	Evidence from 2 head-to-head trials (1 fair, 1 poor) and 3 placebo-controlled trials is insufficient to draw conclusions about treating coexisting pain in depressed patients. Results indicate no difference in efficacy but are limited by study design.
Comparative effectiveness	No evidence	

Table A. Summary of findings on treatment of adult depression with strength of evidence (continued)

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Psychomotor change		
Comparative efficacy	No evidence	
Comparative effectiveness	No evidence	
Somatization		
Comparative efficacy	No evidence	
Comparative effectiveness	Low	Evidence from 1 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.
Key Question 4: Comparative risk of harms		
General tolerability		
Adverse events profiles	High	Adverse events profiles are similar among second-generation antidepressants. Incidence rates of specific adverse events differ.
Nausea and vomiting	High	Meta-analysis of 15 fair studies indicates that venlafaxine has a higher rate of nausea and vomiting than SSRIs as a class.
Diarrhea	Moderate	Evidence from 15 fair studies indicates that sertraline has a higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine.
Weight change	Moderate	Seven fair trials indicate that mirtazapine leads to higher weight gains than citalopram, fluoxetine, paroxetine, and sertraline.
Somnolence	Moderate	Six fair studies provide evidence that trazodone has a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine.
Discontinuation syndrome	Moderate	A good systematic review provides evidence that paroxetine and venlafaxine have the highest rates of discontinuation syndrome; fluoxetine has the lowest.
Discontinuation rates	High	Meta-analyses of efficacy trials indicate that overall discontinuation rates are similar. Venlafaxine has a higher rate of discontinuations from adverse events and a lower rate of discontinuations from lack of efficacy than SSRIs as a class.
Severe adverse events		
Sexual dysfunction	Moderate	Evidence from 5 fair trials provides evidence that bupropion causes significantly less sexual dysfunction than fluoxetine, paroxetine, and sertraline. Among SSRIs, paroxetine has the highest rates of sexual dysfunction.
Suicidality	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of suicidality.
Seizures	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of seizures. Weak evidence indicates that bupropion may have an increased risk of seizures.
Cardiovascular events	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of cardiovascular adverse events. Weak evidence indicates that venlafaxine might have an increased risk of cardiovascular adverse events.

Table A. Summary of findings on treatment of adult depression with strength of evidence (continued)

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Hyponatremia	Low	The evidence is insufficient to draw conclusions about the comparative risk of hyponatremia.
Hepatotoxicity	Low	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.
Serotonin syndrome	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of serotonin syndrome. Observational studies indicate no differences in risk among second-generation antidepressants.
Adherence in efficacy studies	Moderate	Efficacy studies indicate no differences in adherence. One observational study suggests that extended-release formulations may have better adherence than immediate-release formulations.
Adherence in effectiveness studies	Low	Evidence from existing studies is insufficient to draw conclusions about adherence in "real-world" settings.
Key Question 5: Selected Populations		
Age		
Comparative efficacy	Moderate	Results from numerous different types of studies indicate that no substantial differences exist in efficacy among second-generation antidepressants in the elderly or the very elderly.
Comparative effectiveness	Moderate	Based on findings from 1 fair head-to-head effectiveness trial, no substantial differences exist among second-generation antidepressants in the elderly compared with other age groups. A second trial in patients with dysthymia or minor depression provides mixed evidence.
Comparative harms	Low	Results from 2 fair studies indicate that adverse events may differ somewhat across second-generation antidepressants in the elderly or very elderly.
Sex		
Comparative efficacy	Low	Results from 1 fair pooled analysis of RCTs indicates that efficacy among second-generation antidepressants may not differ substantially between men and women.
Comparative effectiveness	No evidence	
Comparative harms	Low	One fair head-to-head trial suggests that harms (headache, nausea) may differ between men and women treated with venlafaxine vs. placebo and venlafaxine vs. SSRIs or placebo. Observational evidence (1 fair study) suggests that some sexual side effects may differ between men and women.

Table A. Summary of findings on treatment of adult depression with strength of evidence (continued)

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Conclusion
Race or ethnicity		
Comparative efficacy	Low	Results from 1 poor RCT indicate that efficacy does not differ substantially among second-generation antidepressants in different racial subgroups.
Comparative effectiveness	No evidence	
Comparative harms	No evidence	
Comorbidities		
Comparative efficacy	Low	One poor head-to-head trial included patients with depression and HIV/AIDS; this study indicated that efficacy does not differ substantially among second-generation antidepressants. Findings from placebo-controlled trials were insufficient to draw conclusions about comparative efficacy.
Comparative effectiveness	No evidence	
Comparative harms	No evidence	

[1]Strength of evidence is based on a modified version of the GRADE system; see text above.
[2]Good, fair, or poor designations relate to quality grades given to each study.
Abbreviations: RCT = randomized controlled trial; SR = sustained release; SSRI = selective serotonin reuptake inhibitor; XR = extended release.

Introduction

Background

Axis I psychiatric disorders such as depressive disorder, anxiety disorder, adjustment disorder, and premenstrual dysphoric disorders can be serious disabling illnesses. Combined, they affect approximately one in five Americans.[1] Major depressive disorder (MDD) is the most prevalent, affecting more than 16 percent (lifetime) of US adults.[2] In 2000, the US economic burden of depressive disorders was estimated to be $83.1 billion.[3] More than 30 percent of these costs were attributable to direct medical expenses.

Pharmacotherapy dominates the medical management of Axis I mood and anxiety disorders. Before the late 1980s, pharmacologic treatment was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (with the exception of premenstrual dysphoric disorder, which historically was untreated). TCAs and MAOIs sometimes are referred to as traditional or first-generation antidepressants. They are often 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 hypertensive crisis if taken along with certain foods or dietary supplements containing excessive amounts of tyramine. Thus, first-generation antidepressants are no longer agents of choice in many circumstances.

Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs. The first of the second-generation drugs was introduced to the US market in 1982, when trazodone was approved for treatment of patients with MDD. In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine. Since then, five other SSRIs have been introduced: sertraline (1991), paroxetine (1992), citalopram (1999), fluvoxamine (2000), and escitalopram (2002).

Two other second-generation antidepressant drugs, trazodone and nefazodone, also function as serotonin reuptake inhibitors, but they possess additional serotonin antagonist properties. Trazodone, which was first synthesized in 1966, 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. Although approved for MDD, trazodone commonly is used as a sedative to complement newer stimulating antidepressants. In 1994, the FDA approved nefazodone, which is essentially an SSRI with additional 5-HT2 and 5-HT3 antagonist properties.

The SNRIs were first introduced to the market in 1993 with the approval of venlafaxine. Mirtazapine, a drug that acts centrally on adrenergic autoreceptors, was added to the therapeutic arsenal in 1996.[4] Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), was approved for the treatment of MDD and diabetic peripheral neuropathic pain in 2004.

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. 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. The 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 SNRIs (venlafaxine) are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Mirtazapine, sometimes characterized as an SNRI, is believed to enhance central noradrenergic and serotonergic activity as a 5-HT2 and 5-HT3 receptor antagonist. Trazodone inhibits neuronal uptake of serotonin. At low doses, it appears to act as a serotonin antagonist and at higher doses as an agonist.[5,6] Nefazodone is believed to inhibit neuronal uptake of serotonin and norepinephrine. Preclinical studies of duloxetine suggest that it is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake.

Except for fluvoxamine, which is approved only for the treatment of obsessive-compulsive disorder (OCD), all second-generation antidepressants are approved for the treatment of MDD. Table 1 summarizes the newer products that are available in the United States by mechanism of action; it shows names, all dosage forms, therapeutic class, and FDA-approved (labeled) uses. The second-generation antidepressants have established a prominent role in the US pharmaceutical market. In 2003, the antidepressant class, including SSRIs and SNRIs, ranked third in US prescription sales among all drug therapy classes.[7] The serotonergic class dominates this market, accounting for 57.6 percent of market share in 2002.[7] Prescription drug spending for these products is not anticipated to decline until 2009, when the patents for leading brands will expire.

Compared with the first-generation antidepressants, the SSRIs and other second-generation antidepressant have comparable efficacy and comparable or better side effect profiles.[8,9] However, comparative differences in efficacy, tolerability, and safety are not well defined among the second-generation drugs. The tremendous volume and large variability in the quality of evidence to support use of these products makes it difficult for clinicians, patients, and others to make evidence-based decisions.

Purpose of this Report

The purpose of this review is to help policymakers and clinicians make informed choices about the use of SSRIs and newer 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 newer antidepressants: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, trazodone, nefazodone, and venlafaxine. We examine the role of these agents in treating patients with depressive syndrome, including MDD, dysthymic disorder, and subsyndromal depressive disorders. We focus this review on these disorders in adult populations.

This report extends prior analyses by addressing two areas that are relevant for clinicians and policymakers but that previous reports have not covered. First, we consider treatment in the continuation and maintenance phases of depression, not simply the acute phase of treatment (see

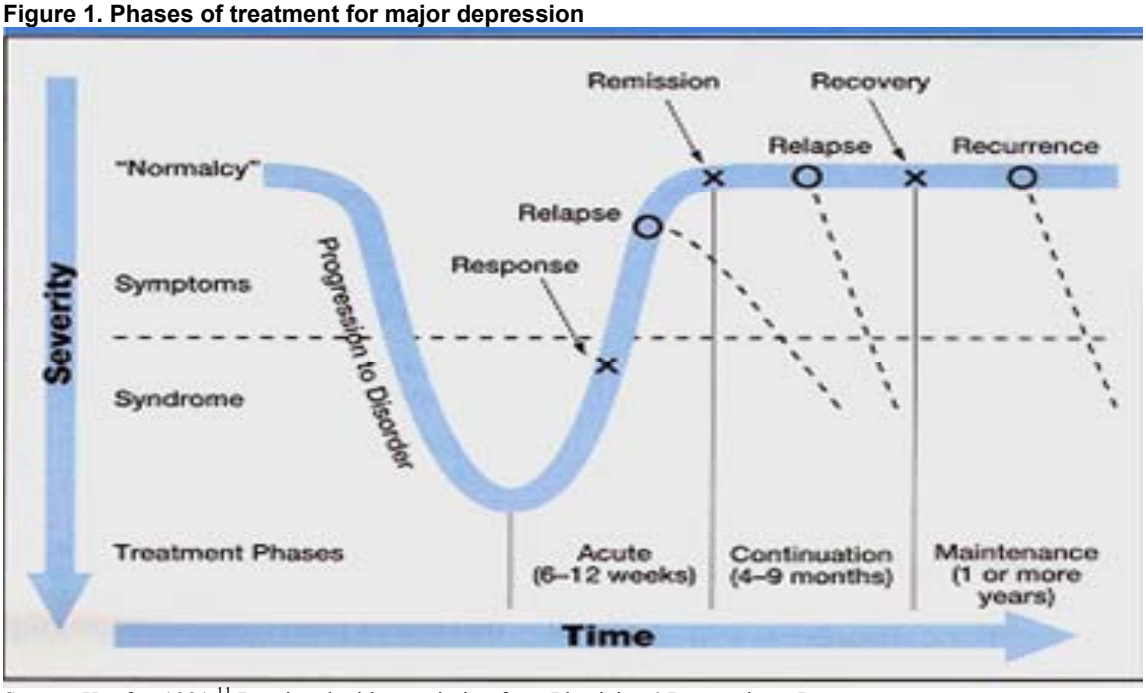
Figure 1). Previous estimates suggest that continuing treatment beyond the acute phase can reduce the odds of relapse by 70 percent.[10] However, most reports have been limited to outcomes in the acute phase of management, i.e., the initial part of treatment during which the treatment goal is eradication of the depressive symptoms to achieve remission.

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

Generic Name	US Trade Name*	Dosage Forms	Therapeutic Classification	Labeled Uses†
Bupropion‡	Wellbutrin®; Wellbutrin SR®; Wellbutrin XL®; Zyban®	75, 100 mg tabs; 50, 100, 150, 200 mg SR tabs 150, 300 mg XL tabs	Other	MDD
Citalopram‡	Celexa®	10, 20, 40 mg tabs; 1, 2 mg/ml solution	SSRI	MDD
Duloxetine	Cymbalta®	20, 30, 60 mg caps	Other	MDD; Neuropathic pain
Escitalopram	Lexapro®§	10, 20 mg tabs 1 mg/ml solution	SSRI	MDD; GAD
Fluoxetine‡	Prozac®; Prozac Weekly®; Sarafem®	10, 20, 40 mg caps; 10 mg tabs; 4 mg/ml solution; 90 mg pellets (weekly)	SSRI	MDD; OCD; PMDD; Panic disorder
Fluvoxamine‡	Luvox®‖	25, 50, 100 mg tabs	SSRI	OCD
Mirtazapine‡	Remeron®	15, 30, 45 mg tabs; 15, 30, 45 mg orally disintegrating tabs	Other	MDD
Nefazodone‡	Serzone®‖	50, 100, 150, 200, 250 mg tabs	Other	MDD
Paroxetine‡	Paxil®; Paxil CR®	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¶
Sertraline‡	Zoloft®	25, 50, 100 mg tabs; 20 mg/ml solution	SSRI	MDD; OCD; Panic disorder; PTSD; PMDD; Social anxiety disorder
Trazodone‡	Desyrel®	50, 100, 150, 300 mg tabs	Other	MDD
Venlafaxine	Effexor®; Effexor XR®	25, 37.5, 50, 75, 100 mg tabs; 37.5, 75, 150 mg XR caps	SNRI	MDD; GAD;** Social anxiety disorder**

* CR, SR, XL, and XR are registered trademarks referring to controlled, sustained, or extended-release dosage forms.
† GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PMDD, premenstrual dysphoric disorder; PTSD, post-traumatic stress disorder.
‡ Generic available for some dosage forms.
§ Lexapro was denied approval for social anxiety disorder March 30, 2005.
‖ Brand-name product no longer available in the US.
¶ Only Paxil CR® (not Paxil®) is approved for the treatment of PMDD.
** Only Effexor XR® (not Effexor®) is approved for the treatment of GAD and social anxiety disorder.

Figure 1. Phases of treatment for major depression



Source: Kupfer, 1991.[11] Reprinted with permission from Physicians' Postgraduate Press.

We consider all three phases of depression management:

- acute phase, usually 6 to 12 weeks in length;
- continuation phase, during which the treatment goal is continued absence of depressive symptoms for an additional 4 to 9 months such that the patient's episode can be considered completely resolved; and
- maintenance phase, the frequently multi-year period during which the treatment goal is preventing the recurrence of a new, distinct episode.

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 the long-term treatment plan. 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.[12,13] 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 time period of much greater duration than the first one.

Second, 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 more successfully treat such a depression 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.

Table 1 (above) and Table 2 provide detailed information on second-generation agents approved for use in the United States. Table 2 shows trade names, usual (recommended) daily doses, and frequency.

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

Generic Name	US Trade Name*	Usual Daily Dosing Range	Frequency
Bupropion	Wellbutrin®	100-450 mg	Three times daily
	Wellbutrin SR®	150-400 mg	Twice daily
	Wellbutrin XL®	150-450 mg	Once daily
Citalopram	Celexa®	20-60 mg	Once daily
Duloxetine	Cymbalta®	40-60 mg	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
	Sarafem®	20 mg	Once daily†
Fluvoxamine	Luvox®§	50-300 mg	Once or twice daily
Mirtazapine	Remeron®	15-45 mg	Once daily
Nefazodone‡	Serzone®§	200-600 mg	Twice daily
Paroxetine	Paxil®	10-60 mg	Once daily
	Paxil CR®	12.5-75 mg	Once daily
Sertraline	Zoloft®	25-200 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

* CR, SR, XL, and XR are registered trademarks referring to controlled-, sustained-, or extended-release dosage forms.
† Sarafem is marketed for the treatment of premenstrual dysphoric disorder (PMDD); dosing may be continuous or intermittent.
‡Branded product withdrawn from the US market effective June 14, 2004.
§ Brand-name product no longer available in the US.

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?

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 for treatment-resistant or recurrent depression?

3. 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? This question focuses on accompanying neurovegetative (physical) symptoms of depression (such as disturbances in sleep, appetite, or motor activity; or symptoms of fatigue or pain). These symptom clusters are in contrast to psychological or cognitive symptoms, such as worthlessness, hopelessness, excessive guilt, and suicidal ideation. For patients presenting with these accompanying symptom clusters, two treatment outcomes are relevant: the effect on the depressive disorder overall, and the effect on the particular accompanying symptoms. Consequently, we further divide this question into two subquestions:

    3a: Do medications differ in their efficacy and effectiveness in treating the depressive episode?

    3b: Do medications differ in their efficacy and effectiveness in treating the accompanying symptoms?

4. 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.

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); and
    - 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 followup periods than most *efficacy* studies.[14] We deemed studies that met at least six of seven predefined criteria as effectiveness studies (Table 3). Their results are more applicable to the average patient than 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	$\geq$ 8 weeks study duration; flexible dose design; physician-based diagnosis
Assessment of adverse events	Always
Adequate sample size to assess a minimally important difference from a patient perspective	N $\geq$ 150
Intention-to-treat analysis	Always

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. When sufficient head-to-head evidence was unavailable, we evaluated placebo-controlled 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** • 6 weeks **Study population** • Adult inpatients and outpatients with major depressive disorder, dysthymia, or subsyndromal depression **Sample size** • For quantitative analysis: no limit • For qualitative analysis: n ≥ 40
Key Question 2a: Maintenance of remission	**Study design** • Head-to-head, double-blind, RCTs • High-quality meta-analyses • High-quality, controlled observational studies **Minimum study duration** • For all studies: 3 months **Study population** • Adult inpatients and outpatients with a history of depressive illnesses currently in remission **Sample size** • For RCTs: no limit • For observational studies: n ≥ 100

RCT, randomized controlled trial.

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

Key Question Outcomes of Interest and Specific Measures	Study Eligibility Criteria
Key Question 2b: **Response and remission for recurrent depression**	**Study design** • Head-to-head, double-blind, RCTs • High-quality meta-analyses • 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: 1. For quantitative analysis: no limit 2. 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: 3. hyponatremia 4. seizures 5. suicide 6. hepatoxicity 7. weight gain 8. gastrointestinal symptoms 9. sexual side effects **10.** others	**Study design** • Head-to-head, double-blind, RCTs • High-quality meta-analyses • Observational studies (cohort studies, case-control studies, large database reviews) **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: 11. For quantitative analysis: no limit 12. For qualitative analysis: n ≥ 40 • For observational studies: n ≥ 100

Appendix A lists our peer reviewers. Appendices B-I pertain to aspects of our results.

Methods

Topic Development

The topic of this report and preliminary key questions arose through a public process involving the public, the Scientific Resource Center (www.effectivehealthcare.ahrq.gov/aboutUs/contact.cfm) for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ) (www.effectivehealthcare.ahrq.gov), and various stakeholder groups (www.effectivehealthcare.ahrq.gov/aboutUs/stakeholder.cfm). Investigators from the RTI International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) then refined the questions in consultation with AHRQ, the Scientific Resource Center, and a Technical Expert Panel (TEP).

Literature Search

To identify articles relevant to each key question (Appendix B), we searched MEDLINE®, Embase, The Cochrane Library, PsychLit, and the International Pharmaceutical Abstracts. We used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (major depressive disorder [MDD], dysthymia, minor depression, subsyndromal depressive disorder), drug interactions, and adverse events with a list of 12 specific second-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine). We limited the electronic searches to "human" and "English language." Sources were searched from 1980 to 2006 (February) 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. We also manually searched reference lists of pertinent review articles and letters to the editor. We imported all citations into an electronic database (EndNote 9.0). Additionally, we handsearched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the US Food and Drug Administration (FDA).

The Scientific Resource Center contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations. We received dossiers from three pharmaceutical companies (Eli Lilly, GlaxoSmithKline, and Wyeth).

Our searches found 1,967 citations, unduplicated across databases. Additionally, we detected 129 articles from manually reviewing the reference lists of pertinent review articles. Three other studies came from pharmaceutical dossiers. The total number of citations in our database was 2,099.

Study Selection

We developed eligibility criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons to antidepressant medications outside our scope of interest, as described in Table 4 (in the introduction). Two persons 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 an adult study population with a sample size of at least 40 participants were eligible for inclusion.

We did not examine placebo-controlled trials in detail if head-to-head trials were available. If no head-to-head evidence was published, we reviewed placebo-controlled trials to provide an overview of efficacy. 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 with large sample sizes ($\geq$100 patients), lasting at least 3 months, that reported an outcome of interest.

Initially, we reviewed studies with health outcomes as primary outcome measures. Outcomes for efficacy or effectiveness, for example, were quality of life, relapse, functional capacity, and hospitalization. If no study measuring health outcomes was available for a particular indication or population subgroup, we included intermediate outcomes (e.g., changes in depression scores). We reviewed response and remission when based on changes in depression scores as proxies for health outcomes (e.g., 50 percent improvement of depression scores for response). For harms (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), 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), withdrawals attributable to adverse events, and drug interactions.

We included meta-analyses in our evidence report if we found them to be relevant for a key question and of good or fair methodological quality (based on the QUORUM statement[15]). We did not review individual studies if they were 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 abstracted data from each study and assigned an initial quality

rating. A senior reviewer read each abstracted article, evaluated the completeness of the data abstraction, and confirmed the quality rating.

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) if available. All data abstraction employed SRS 3.0, TrialStat™ Corporation.

Quality Assessment

To assess the quality (internal validity) of trials, we used predefined criteria based on those developed by the US Preventive Services Task Force (ratings: good, fair, poor)[16] and the National Health Service Centre for Reviews and Dissemination.[17] Elements of quality assessment included, among others, randomization and allocation concealment, similarity of compared groups at baseline, use of ITT analysis (i.e., all patients are analyzed as randomized with missing values imputed), and overall and differential loss to followup.

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 assess the quality of observational studies, we used criteria outlined by Deeks et al.[18] Items assessed included selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of followup, and statistical analysis.

Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting a third, independent party.

Studies that met all criteria were rated good quality. The majority of studies received a quality rating of fair. This category includes studies that presumably fulfilled all quality criteria but did not report their methods to an extent that answered all our questions. Time constraints precluded our contacting study authors for clarification of methodological questions. Thus, the fair quality category includes studies with quite different strengths and weaknesses. Studies that had a fatal flaw in one or more categories were rated poor quality and, generally, excluded from our analyses. If no other evidence on an outcome of interest was available, we comment on findings from poor studies.

In addition to internal and external validity, we assessed the comparability of dosages. Because we could not find any clear definitions about equivalence of dosages among second-generation antidepressants in the published literature, we developed a roster of low, medium, and high dosages for each drug, which is outlined in Table 5. This classification, based on the interquartile dosing range, does not indicate dosing equivalence. We used this roster to detect gross inequalities in dosing that could affect comparative efficacy and effectiveness.

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 that 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.[19] 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.

Table 5. Dosing classification based on lower and upper dosing range quartiles

Drug	Range	Low	Medium	High
Bupropion	300-450 mg/d	< 337.5	337.5-412.5	> 412.5
Citalopram	20-60 mg/d	< 30	30-50	> 50
Duloxetine	60-100 mg/d	< 70	70-90	> 90
Escitalopram	10-30 mg/d	< 15	15-25	> 25
Fluoxetine	20-60 mg/d	< 30	30-50	> 50
Fluvoxamine	50-150 mg/d	< 75	75-125	> 125
Mirtazapine	15-45 mg/d	< 22.5	22.5-37.5	> 37.5
Nefazodone	300-600 mg/d	< 375	375-525	> 525
Paroxetine	20-60 mg/d	< 30	30-50	> 50
Sertraline	50-150 mg/d	< 75	75-125	> 125
Trazodone	300-600 mg/d	< 375	375-525	> 525
Venlafaxine	125-250 mg/d	< 156.25	156.25-218.75	> 218.75

Rating Strength of a Body of Evidence

We rated the strength of the available evidence in a three-part hierarchy based on an approach devised by the GRADE working group.[20] Developed to grade the quality of evidence and the strength of recommendations, this approach incorporates four key elements: study design, study quality, consistency, and directness. As shown in Table 6, we used three grades: high, moderate, and low (combining the GRADE category of very low with low).[21] Gradings reflect the strength of the body of evidence to answer key questions on the comparative efficacy, effectiveness, and harms of second-generation antidepressants. Gradings do not refer to the general efficacy or effectiveness.

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

High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.

Source: Adapted from the GRADE working group.[20]

This approach does not incorporate other factors that might be relevant to assess reliably the comparative efficacy, effectiveness, and harms, such as funding sources and comparable dosing. We have assessed these additional factors and highlighted inequalities that could potentially bias our assessments (e.g., all studies funded by the same manufacturer).

Data Synthesis

Throughout this report we synthesized the literature qualitatively. If 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 relative risk (RR) 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 statistic) and applied both a random and a fixed effects model. We report the results from random effects models because, in all meta-analyses, the results from random and fixed effects models were very similar. If the RR was statistically significant, we then conducted a meta-analysis of the risk differences to calculate the number needed to treat (NNT) on the pooled risk difference.

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.

If fewer than three head-to-head trials were available for any drug comparison, we computed indirect comparisons. 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.[22]

For indirect comparisons we employed two statistical approaches:

1. We conducted meta-regressions of good or fair placebo-controlled trials using individual drugs as covariates. We also attempted to assess the influence of disease

severity, concomitant anxiety, and dosing on our findings. Data, however, were insufficient to use these factors as covariates in the meta-regression models.

2. When the number of placebo-controlled trials was insufficient to conduct meta-regressions, we used network meta-analyses.[23] Network meta-analyses allow the use of studies with multiple common comparators. Therefore, we could include both placebo-controlled and active-controlled studies, increasing the precision of results. All statistical analyses used StatsDirect Ltd. version 2.4.5, and STATA 9.1.

Results

Overview of All Key Questions

We identified 2,099 citations from searches and reviews of reference lists. Figure 2 documents the disposition of the 293 articles in this review, working from 884 articles retrieved for full review, 66 included for background, and 525 excluded at this stage (Appendix C). One study of interest could not be retrieved after multiple attempts. We included 293 published articles reporting on 187 studies of good or fair quality: 89 head-to-head randomized controlled trials (RCTs) (94 articles), 57 placebo-controlled RCTs (63 articles), 7 articles on meta-analyses or systematic reviews (7 articles), 20 observational studies (27 articles), and 14 studies of other design (16 articles). We incorporated data from 24 additional placebo-controlled studies for meta-regression only. Evidence tables for included studies, by key question, can be found in Appendix D.

Reasons for exclusion were based on eligibility criteria or methodological criteria. We excluded 62 studies that originally met eligibility criteria but were later rated as poor quality for internal validity (Appendix E). The two main reasons for rating as poor of RCTs were high loss to followup (more than 40 percent) 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.

Most efficacy trials were not powered to establish a greater efficacy of a particular drug over another. Therefore, we report differences in effect sizes for individual studies, even if they are not statistically significant.

Of 187 included studies, 126 (67.4 percent) were financially supported by pharmaceutical companies; 17 (9.2 percent) were funded by governmental agencies or independent funds. For 44 (23.5 percent) of included studies, we could not determine the funding source.

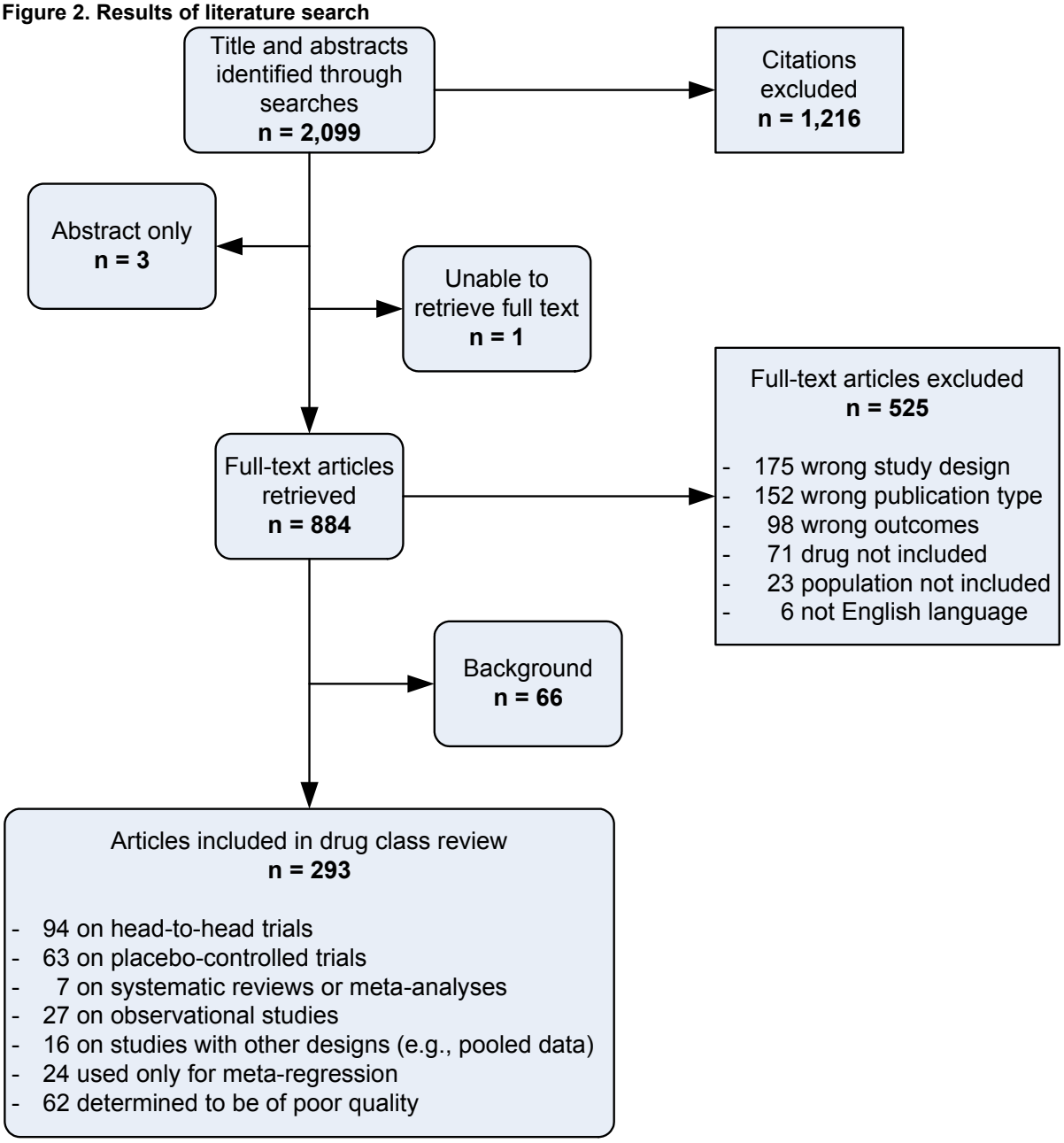
Studies reviewed for this report employed a notable array of diagnostic scales and health status or quality of life instruments. Most were pertinent to depressive and other disorders considered in this report, but some are considered more generic instruments that assess, e.g., health-related quality of life. Table 7 lists abbreviations of diagnostic scales and health status or quality of life instruments encountered in this literature.

Key Question 1: Efficacy or effectiveness in treating depressive disorders and symptoms

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

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

Figure 2. Results of literature search



Major Depressive Disorder (MDD): Overview

The following second-generation antidepressants are currently approved by the US Food and Drug Administration (FDA) for the treatment of depressive disorders in adults: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline,

trazodone, and venlafaxine. Fluvoxamine has not been approved for the treatment of MDD but was included on the list of medications of interest that Agency for Healthcare Research and Quality (AHRQ) provided to us for this review.

Table 7. Abbreviations and full names of diagnostic scales and other instruments

Abbreviation	Full Name of Instrument
BDI	Beck Depression Inventory
Beck's SSI	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
BSI	Brief Symptom Inventory of Depression
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
CLAS	Clifton Assessment Schedule
DESS	Discontinuation Emergent Signs and Symptoms Checklist
FSCL	Fatigue Symptoms Checklist
FSQ	Functional Status Questionnaire
GAF-S	Global Assessment of Functioning Scale
HAD-A	Hospital Anxiety and Depression Rating Scale
HAM–A	Hamilton Rating Scale for Anxiety
HAM–D	Hamilton Rating Scale for Depression
HADRS	Hamilton Depression Rating Scale
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
MAF	Multidimensional Assessment of Fatigue
MMSE	Mini Mental State Examination
PGI-I	Patient Global Impression of Improvement
POMS-FI	Profile of Mood States Fatigue/Inertia Subscale
PRSexDQ	Psychotropic-Related Sexual Dysfunction Questionnaire
QLDS	Quality of Life in Depression Scale
Q-LES-Q, QLSQ	Quality of Life Enjoyment and Satisfaction Questionnaire
SCL 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

In all, 72 RCTs (reported in 74 articles) compared the efficacy or effectiveness of one second-generation antidepressant with another for treating patients with MDD. Details can be found in Evidence Table 1, Appendix D.

Table 8 provides selected information on all these studies; they are grouped according to the main classes compared—selective serotonin reuptake inhibitors (SSRI) vs. SSRI, SSRI vs. selective serotonin and norepinephrine reuptake inhibitor (SSNRI) and SNRI; SSRI vs. other second-generation antidepressants—and then listed alphabetically by the specific drugs compared. Most subjects were younger than 60 years; 10 trials were conducted in populations of 60 years or older. 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 66 possible comparisons of included second-generation antidepressants (51 involving SSRIs, 15 more involving non-SSRI agents), we found direct head-to-head evidence for only 35 comparisons (30 and 5, respectively). Tables 9 and 10 depict possible comparisons and the numbers of available head-to-head trials for each comparison (shown in italics). For those with fewer than three head-to-head trials, we conducted indirect comparisons. Appendix E presents placebo-controlled studies included for indirect comparisons; Appendix F lists studies excluded from indirect comparisons because of poor internal validity.

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 (e.g., 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]). All studies used physician-rated scales to assess the main outcome measures.

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), could be seen as proxies to health outcomes. Therefore, we focused on differences in response or remission rates rather than differences in changes of scores.

Most studies received a fair rating for internal validity. The applicability of the results was hard to determine and might often be limited. Most trials (70 percent) were of short (6 weeks to 8 weeks) or medium (9 weeks to 11 weeks) duration; 30 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 2 decades. Therefore, study populations might vary 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 of the drop out of patients at different time points) were a frequent approach to

Table 8. Study characteristics, response and remission rates, and quality ratings of studies in adults with major depressive disorder

Study	N	Duration	Comparison and Dose (mg/d)	Response (%) and Significance Level	Remission (%) and Significance Level	Quality Rating
SSRIs vs. SSRIs						
Burke et al., 2002[24]	491	8 weeks	Citalopram 40 Escitalopram 20	45.6 vs. 51.2 *P* = NR (ns)	NR	Fair
		8 weeks	Citalopram 40 Escitalopram 10	45.6 vs. 50 *P* = NR (ns)	NR	
Colonna et al., 2005[25]	357	8 weeks	Citalopram 20 Escitalopram 10	55 vs. 63 *P* < 0.05	45 vs. 55 *P* = NR	Fair
		24 weeks	Citalopram 20 Escitalopram 10	78 vs. 80 *P* = NR (ns)	71 vs. 76 *P* = NR	
Lepola et al., 2003[26]	471	8 weeks	Citalopram 20-40 Escitalopram 10-20	52.6 vs. 63.7 *P* = 0.021	42.8 vs. 52.1 *P* = 0.036	Fair
Moore et al., 2005[27]	280	8 weeks	Citalopram 40 Escitalopram 20	61.3 vs. 76.1 *P* = 0.008	43.6 vs. 56.1 *P* = 0.04	Fair
Patris et al., 1996[28]	357	8 weeks	Citalopram 20 Fluoxetine 20	78 vs. 76 *P* = NR (ns)	75 vs. 68 *P* = 0.26	Fair
Haffmans et al., 1996[29]	217	6 weeks	Citalopram 20-40 Fluvoxamine 100-200	30.5 vs. 28.4 *P* = NR	14 vs. 8 *P* = NR (ns)	Fair
Ekselius et al., 1997[30]	400	24 weeks	Citalopram 20-60 Sertraline 50-150	81 vs. 75.5 *P* = NR (ns)	NR	Good
Kasper et al., 2005[31]	518	8 weeks	Escitalopram 10 Fluoxetine 20	46 vs. 37 *P* = NR (ns)	40 vs. 30 *P* = NR (ns)	Fair
Dalery and Honig, 2003[32]	184	6 weeks	Fluoxetine 20 Fluvoxamine 100	60 vs. 60 *P* = NR (ns)	NR	Fair
Rapaport et al., 1996[33]	100	7 weeks	Fluoxetine 20-80 Fluvoxamine 100-150	NR	NR	Fair
Cassano et al., 2002[34]	242	52 weeks	Fluoxetine 20-60 Paroxetine 20-40	NR	NR	Fair
Chouinard et al., 1999[35]	203	12 weeks	Fluoxetine 20-80 Paroxetine 20-50	68.4 vs. 67 *P* = 0.93	59.2 vs. 58 *P* = 0.84	Fair
De Wilde et al., 1993[36]	100	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	62 vs. 67 *P* = NR	NR	Fair
Fava et al., 1998[37]	128	12 weeks	Fluoxetine 20-80 Paroxetine 20-50	NR	NR	Fair
Gagiano et al., 1993[38]	90	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	63 vs. 70 *P* = NR	NR	Fair
Schöne and Ludwig, 1993[39]	108	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	37.5 vs. 16 *P* = 0.03	NR	Fair
Tignol, 1993[40]	178	6 weeks	Fluoxetine 20 Paroxetine 20	78 vs. 75 *P* = NR (ns)	NR	Fair
Fava et al., 2002[41]	284	10-16 weeks	Fluoxetine 20-60 Paroxetine 20-60 Sertraline 50-200	64.8 vs. 68.8 vs. 72.9 *P* = NR	54.4 vs. 57.0 vs. 59.4 *P* = NR	Fair

NR, not reported; ns, not significant.

Table 8. 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/d)	Response (%) and Significance Level	Remission (%) and Significance Level	Quality Rating
Bennie et al., 1995[42]	286	6 weeks	Fluoxetine 20-40 Sertraline 50-100	51 vs. 59 *P* = NR	NR	Fair
Boyer et al., 1998[43]	242	≈ 26 weeks	Fluoxetine 50-150 Sertraline 20-60	42.6 vs. 47.4 *P* = NR	NR	Fair
Newhouse et al., 2000[44,45]	236	12 weeks	Fluoxetine 20-40 Sertraline 50-100	71 vs. 73 *P* = NR	46 vs. 45 *P* = NR	Fair
Sechter et al., 1999[46]	234	24 weeks	Fluoxetine 20-60 Sertraline 50-150	64 vs. 74 *P* = NR	NR	Fair
Van Moffaert et al., 1995[47]	165	8 weeks	Fluoxetine 20 Sertraline 50	Data NR *P* = NR (ns)	NR	Fair
Fava et al., 2000[48]	284	26-32 weeks	Fluoxetine 20-60 Sertraline 50-200 Paroxetine 20-60	NR	NR	Fair
Kroenke et al., 2001[49]	601	36 weeks	Fluoxetine 20 Sertraline 50 Paroxetine 20	NR	NR	Fair
Kiev and Fieger, 1997[50]	60	7 weeks	Fluvoxamine 50-150 Paroxetine 20-50	Data NR *P* = NR (ns)	NR	Fair
Nemeroff et al., 1995[51]	95	7 weeks	Fluvoxamine 50-150 Sertraline 50-200	Data NR *P* = NR (ns)	NR	Fair
Rossini et al., 2005[52]	93	7 weeks	Fluvoxamine 150 Sertraline 200	Data NR *P* = NR (ns)	NR	Fair
Aberg-Wistedt et al., 2000[53]	353	8 weeks	Paroxetine 20-40 Sertraline 50-150	63 vs. 63 *P* = NR (ns)	57.3 vs. 51.6 *P* = NR (ns)	Fair
	353	24 weeks	Paroxetine 20-40 Sertraline 50-150	69 vs. 72 *P* = NR (ns)	73.7 vs. 80.2 *P* = NR (ns)	
SSRIs vs. SSNRIs and SNRIs						
Leinonen et al., 1999[54]	270	8 weeks	Citalopram 20-60 Mirtazapine 15-60	88 vs. 85 *P* = 0.54 Faster onset of mirtazapine	NR	Fair
Allard et al., 2004[55]	150	22 weeks	Citalopram 10-30 Venlafaxine XR 75-150	93 vs. 93 *P* = NR (ns)	23 vs. 19 *P* = NR (ns)	Fair
Bielski et al., 2004[56]	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[57]	293	8 weeks	Escitalopram 10-20 Venlafaxine XR 75-150	77 vs. 80 *P* = NR (ns)	70 vs. 70 *P* = NR (ns)	Fair
Goldstein et al., 2002[58]	173	8 weeks	Fluoxetine 20 Duloxetine 40-120	45 vs. 49 *P* = 0.39	30 vs. 43 *P* = 0.82	Fair
Hong et al., 2003[59]	133	6 weeks	Fluoxetine 20-40 Mirtazapine 15-45	51 vs. 58 *P* = NR (ns) Faster onset of mirtazapine	27 vs. 35 *P* = NR (ns)	Fair
Versiani et al., 2005[60]	297	8 weeks	Fluoxetine 20-40 Mirtazapine 15-60	Data NR *P* = NR (ns) Faster onset of mirtazapine	41.4 vs. 40.1 *P* = NR (ns)	Fair

Table 8. 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/d)	Response (%) and Significance Level	Remission (%) and Significance Level	Quality Rating
Wheatley et al., 1998[61]	133	6 weeks	Fluoxetine 20-40 Mirtazapine 15-60	Data NR *P* = NR (ns) Faster onset of mirtazapine	25.4 vs. 23.3 *P* = NR (ns)	Fair
Alves et al., 1999[62]	87	12 weeks	Fluoxetine 20-40 Venlafaxine 75-150	74 vs. 87 *P* = NR	41 vs. 51 *P* = NR	Fair
Costa e Silva, 1998[63]	382	8 weeks	Fluoxetine 20-40 Venlafaxine 75-225	82 vs. 86.8 *P* = 0.074	60.2 vs. 60.2 *P* = NR	Fair
De Nayer et al., 2002[64]	146	12 weeks	Fluoxetine 20-40 Venlafaxine 75-150	49.3 vs. 75 *P* = 0.001	40.3 vs. 59.4 *P* = 0.028	Fair
Dierick et al., 1996[65]	314	8 weeks	Fluoxetine 20 Venlafaxine 75-150	60 vs. 72 *P* = 0.023 (at week 6)	NR	Fair
Nemeroff and Thase, 2005[66]	308	6 weeks	Fluoxetine 20-60 Venlafaxine 75-225	45 vs. 53 *P* = 0.034	28 vs. 32 *P* = 0.250	Fair
Rudolph and Feiger, 1999[67]	301	8 weeks	Fluoxetine 20-60 Venlafaxine XR 75-225	50 vs. 57 *P* = 0.07	22 vs. 37 *P* < 0.05	Fair
Silverstone and Ravindran, 1999[68]	368	12 weeks	Fluoxetine 20-60 Venlafaxine XR 75-225	62 vs. 67 *P* < 0.05	NR	Fair
Tzanakaki et al., 2000[69]	109	6 weeks	Fluoxetine 60 Venlafaxine 225	66 vs. 70 *P* = NR	36 vs. 41 *P* = NR	Fair
Tylee et al., 1997[70]	341	12 weeks	Fluoxetine 20 Venlafaxine 75	62.8 vs. 55.1 *P* = NR	34.1 vs. 35.4 *P* = NR (ns)	Fair
Detke et al., 2004[71]	367	8 weeks	Paroxetine 20 Duloxetine 80 Duloxetine 120	74 vs. 65 vs. 71 *P* = NR (ns)	44 vs. 46 vs. 52 *P* = NR (ns)	Fair
Benkert et al., 2000[72]	275	6 weeks	Paroxetine 20-40 Mirtazapine 15-45	53.7 vs. 58.3 *P* = NR (ns) Faster onset of mirtazapine	34.1 vs. 40.9 *P* = NR (ns)	Fair
Schatzberg et al., 2002[73]	255	8 weeks	Paroxetine 20-40 Mirtazapine 15-45	56.7 vs. 64.0 *P* = NR (ns) Faster onset of mirtazapine	NR	Fair
Ballus et al., 2000[74]	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	49 vs. 59 *P* = NR (ns)	NR *P* = NR (ns)	
McPartlin et al., 1998[75]	361	12 weeks	Paroxetine 20 Venlafaxine XR 75	76 vs. 76 *P* = NR (ns)	46 vs. 48 *P* = NR (ns)	Fair
Behnke et al., 2003[76]	345	8 weeks	Sertraline 50-150 Mirtazapine 30-45	NR *P* = NR (ns) Faster onset of mirtazapine	NR	Fair
Mehtonen et al., 2000[77]	147	8 weeks	Sertraline 50-100 Venlafaxine 75-150	68 vs. 83 *P* = 0.05	45 vs. 68 *P* = 0.008	Good
Sir et al., 2005[78]	163	8 weeks	Sertraline 50-150 Venlafaxine XR 75-225	70.9 vs. 70.9 *P* = 0.95	59.5 vs. 54.4 *P* = 0.47	Good

Table 8. 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/d)	Response (%) and Significance Level	Remission (%) and Significance Level	Quality Rating

SSRIs vs. other second-generation antidepressants						
Coleman et al., 2001[79]	456	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[80]	123	6 weeks	Fluoxetine 20-80 Bupropion 225-450	58 vs. 63 *P* = NR (ns)	NR	Fair
Rush et al., 1998[81]	85	8 weeks	Fluoxetine 20-40 Nefazodone 200-500	45 vs. 47 *P* = NR (ns)	NR	Fair
Beasley et al., 1991[82]	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[83]	40	6 weeks	Fluoxetine 20-60 Trazodone 50-400	NR	NR	Fair
Weihs et al., 2000[84]	100	6 weeks	Paroxetine 10-40 Bupropion SR 100-300	77 vs. 71 *P* = NR (ns)	NR	Fair
Baldwin et al., 1996[85]	206	8 weeks	Paroxetine 20-40 Nefazodone 200-600	60 vs. 58 *P* = NR (ns)	NR	Fair
Hicks et al., 2002[86]	40	8 weeks	Paroxetine 20-40 Nefazodone 400-600	*P* = NR (ns)	NR	Fair
Kasper et al., 2005[87]	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[88]	364	8 weeks	Sertraline 50-200 Bupropion SR 150-400	61 vs. 66 *P* = NR (ns)	NR	Fair
Croft et al., 1999[89]	360	8 weeks	Sertraline 50-200 Bupropion SR 150-400	68 vs. 66 *P* = NR (ns)	NR	Fair
Kavoussi et al., 1997[90] Rush et al., 2001[91]	248	16 weeks	Sertraline 50-200 Bupropion SR 100-300	NR	NR	Fair
Feiger et al., 1996[92]	160	6 weeks	Sertraline 50-200 Nefazodone 100-600	57 vs. 59 *P* = NR (ns)	NR	Fair
SSNRIs and SNRIs vs. SNRIs						
Guelfi et al., 2001[93]	157	8 weeks	Mirtazapine 45-60 Venlafaxine 225-375	62 vs. 52 *P* = NR (ns)	NR	Fair
SNRIs vs. other second-generation antidepressants						
Halikas, 1995[94]	150	6 weeks	Mirtazapine 5-35 Trazodone 40-280	51 vs. 41 *P* = NR (ns)	NR	Fair
van Moffaert et al., 1995[95]	200	6 weeks	Mirtazapine 24-72 Trazodone 150-450	61 vs. 51 *P* = NR	NR	Fair
Cunningham et al., 1994[96]	225	6 weeks	Venlafaxine 75-200 Trazodone 150-400	72 vs. 60 *P* = NR (ns)	NR	Fair
Other second-generation antidepressants vs. other second-generation antidepressants						
Weisler et al., 1994[97]	124	6 weeks	Bupropion 225-450 Trazodone 150-400	55.9 vs. 40.4 *P* = NR	46 vs. 31 *P* = NR	Fair

Note: Venlafaxine not otherwise specified refers to the immediate-release formulation (given twice a day), venlafaxine XR is the extended-release formulation.

Table 9. Possible comparisons of second-generation antidepressants involving SSRIs and number of included head-to-head trials

Comparison	Number of Studies	Comparison	Number of Studies
SSRIs vs. SSRIs		**SSRIs vs. Other Second-Generation Antidepressants**	
Citalopram vs. Escitalopram	4	Citalopram vs. Bupropion	0
Citalopram vs. Fluoxetine	1	Citalopram vs. Nefazodone	0
Citalopram vs. Fluvoxamine	1	Citalopram vs. Trazodone	0
Citalopram vs. Paroxetine	0	Escitalopram vs. Bupropion	0
Citalopram vs. Sertraline	1	Escitalopram vs. Nefazodone	0
Escitalopram vs. Fluoxetine	1	Escitalopram vs. Trazodone	0
Escitalopram vs. Fluvoxamine	0	*Fluoxetine vs. Bupropion*	2
Escitalopram vs. Paroxetine	0	*Fluoxetine vs. Nefazodone*	1
Escitalopram vs. Sertraline	0	*Fluoxetine vs. Trazodone*	2
Fluoxetine vs. Fluvoxamine	2	Fluvoxamine vs. Bupropion	0
Fluoxetine vs. Paroxetine	10	Fluvoxamine vs. Nefazodone	0
Fluoxetine vs. Sertraline	8	Fluvoxamine vs. Trazodone	0
Fluvoxamine vs. Paroxetine	1	*Paroxetine vs. Bupropion*	1
Fluvoxamine vs. Sertraline	2	*Paroxetine vs. Nefazodone*	2
Paroxetine vs. Sertraline	4	*Paroxetine vs. Trazodone*	1
SSRIs vs. SSNRIs		*Sertraline vs. Bupropion*	3
Citalopram vs. Duloxetine	0	*Sertraline vs. Nefazodone*	1
Escitalopram vs. Duloxetine	0	Sertraline vs. Trazodone	0
Fluoxetine vs. Duloxetine	1		
Fluvoxamine vs. Duloxetine	0		
Paroxetine vs. Duloxetine	1		
Sertraline vs. Duloxetine	0		
SSRIs vs. SNRIs			
Citalopram vs. Mirtazapine	1		
Citalopram vs. Venlafaxine	1		
Escitalopram vs. Mirtazapine	0		
Escitalopram vs. Venlafaxine	2		
Fluoxetine vs. Mirtazapine	3		
Fluoxetine vs. Venlafaxine	9		
Fluvoxamine vs. Mirtazapine	0		
Fluvoxamine vs. Venlafaxine	0		
Paroxetine vs. Mirtazapine	2		
Paroxetine vs. Venlafaxine	2		
Sertraline vs. Mirtazapine	1		
Sertraline vs. Venlafaxine	2		

Table 10. Possible comparisons of second-generation antidepressants involving SSNRIs, SNRIs, and other antidepressants and number of included head-to-head trials

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

ITT analysis. Few authors, however, reported the overall number of patients lost to followup from randomization to the end of the trial. In addition, many studies did not report the ethnic backgrounds of participants.

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. Only 14 trials (17.5 percent) reported a loss to followup of less than 20 percent. The high drop-out rates 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 class.

Major Depressive Disorders: Key Points

Seventy-two head-to-head comparisons (Table 9) were available for a total of 35 potential comparisons between the 12 second-generation antidepressants addressed in this report. Of these, only five trials[93-97] directly compared any non-SSRI second-generation antidepressant to any other non-SSRI agent (Table 10); of these, only one comparison was evaluated in more than one trial. The strength of evidence, overall for comparative efficacy and effectiveness, was rated moderate. Overall, 38 percent of patients did not achieve a treatment response during 6 weeks to 12 weeks of treatment with second-generation antidepressants; 54 percent did not achieve remission.

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

- Citalopram vs. escitalopram (four published studies[24-27] and one FDA review;[98] 1,545 patients): Patients on escitalopram had an additional treatment effect of a 1.25 point reduction (95% CI, 0.10-2.39; *P* = 0.02) on the MADRS compared with patients on citalopram. The relative risk of response was statistically significantly greater for escitalopram than for citalopram (RR, 1.14; 95% CI, 1.04-1.26). The number needed to treat (NNT) to gain one additional responder at week 8 with escitalopram was 14 (95% CI, 7-111). Both drugs are produced by the same manufacturer, which funded all available studies.

- Fluoxetine vs. paroxetine (seven studies;[35-41] 950 patients): We did not find any statistically significant differences in either effect sizes on HAM-D or response rates between fluoxetine and paroxetine. Fluoxetine had an additional reduction of 0.55 (95% CI, -1.4-0.36; *P* = 0.23) points on HAM-D compared with paroxetine; paroxetine led to a higher rate of responders than fluoxetine (RR, 1.09; 95% CI, 0.99-1.21).

- Fluoxetine vs. sertraline (four studies;[41,42,44,46] 940 patients): Patients on sertraline had an additional, statistically nonsignificant treatment effect of a 0.75 point reduction (95% CI, -0.45-1.95) on the HAM-D scale compared with patients on fluoxetine. The relative risk of response was statistically significantly greater for sertraline than for fluoxetine (RR, 1.11; 95% CI, 1.01-1.21). The NNT to gain one additional responder at 6 to 12 weeks with sertraline was 14 (95% CI, 8-22).

- Fluoxetine vs. venlafaxine (eight studies;[62-67,69,70] 1,814 patients): Patients on venlafaxine had an additional, statistically nonsignificant treatment effect of a 1.31 point reduction (95% CI, 0.10-2.39; *P* = 0.13) on the HAM-D scale compared with patients on fluoxetine. The relative risk of response was statistically significantly greater for venlafaxine than for fluoxetine (RR, 1.12; 95% CI, 1.01-1.24). The NNT to gain one additional responder at 6 to 12 weeks with venlafaxine was 12 (95% CI, 7-50). All studies were funded by the makers of venlafaxine.

Very few comparative effectiveness trials were available; their findings were generally consistent with efficacy trials.[30,46,49]

Findings from indirect comparisons yielded no statistically significant differences in response rates among other potential comparisons. Although the precision of some estimates was low, leading to inconclusive results, treatment effects are similar across all comparisons.

Eighteen studies (N = 4,050) comparing one second-generation antidepressant with another indicated no differences in health-related quality of life.[24,43,45,46,53,54,56,60,61,66,75,78,82,84,93,99-101] 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 significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline (Table 11).[54,59-61,72,73,76] The NNT to yield one additional responder after 1 or 2 weeks of treatment is 7 (95% CI, 5-12). This treatment effect was consistent across all studies. The strength of evidence is moderate.

Five trials provide evidence that bupropion leads to greater satisfaction with sexual activity than sertraline[88-90] and fluoxetine (Table 12).[79,80] The NNT to yield one additional person with a

high overall satisfaction of sexual functioning is 7. This treatment effect was consistent across all studies.

We did not find any efficacy evidence addressing Key Question 1b.

Table 11. Characteristics of trials comparing mirtazapine to SSRIs on onset of action (response rate)

Study	Sample Size	Comparison	Effect Size	*P*-value	Comments
Leinonen et al., 1999[54]	270	Citalopram	Significantly greater reduction of HAM-D scores with mirtazapine at day 14 (difference: -2.3)	*P* = 0.002	No statistically significant differences in response and remission rates at endpoint
Hong et al., 2003[59]	133	Fluoxetine	At day 28 significantly more responders with mirtazapine (53.3% vs. 39.0%) RRR, 0.23 RD: 0.14 NNT: 7	*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[60]	297	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 42)
Wheatley et al., 1998[61]	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 56)
Benkert et al., 2000[72]	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 0.07 RD: 0.14 0.07 NNT: 8 15	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: 58.3% vs. 53.7%; remission: 40.9% vs. 34.8%)
Schatzberg et al., 2002[73]	255	Paroxetine	Significantly more responders at day 14 with mirtazapine (27.8% vs. 13.3%) RRR, 0.17 RD: 0.14 NNT: 7 Significantly greater decrease of HAM-D scores from day 7 to day 21 with mirtazapine Median time to response: Mirtazapine: 26 days Paroxetine: 40 days	*P* = 0.005 *P* < 0.01 (day 7, 14) *P* = 0.024 (day 21) Kaplan-Mayer: *P* = 0.016	No statistically significant differences in overall response rate at week 8; more responders in the mirtazapine group (51% vs. 8%) at endpoint

Behnke et al., 2003[76]	346	Sertraline	Significantly higher response rates at days 7, 10, and 14 with mirtazapine (data NR)	day 7: $P < 0.05$ day 10: $P < 0.01$ day 14: $P < 0.05$	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.

Table 12. Characteristics of trials comparing bupropion to SSRIs on sexual functioning and satisfaction

Study	Sample Size	Comparison	Effect Size	*P*-value	Comments
Feighner et al., 1991[80]	61	Fluoxetine	Higher rates for fluoxetine of impotence (4.7% vs. 0%) anorgasmia (1.7% vs. 0%) libido decrease (1.7% vs. 0%)	NR	Self-reporting of sexual adverse events
Coleman et al., 2001[79]	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)
Coleman et al., 1999[88]	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[89]	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)
Kavoussi et al., 1997[90,102]	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)

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.

Major Depressive Disorder: Detailed Analysis

Head-to-head evidence: SSRIs vs. SSRIs. *Citalopram vs. escitalopram.* Four published trials[24-27] and one unpublished[98] trial compared the efficacy of citalopram and escitalopram. Four studies were conducted over 8 weeks[24,26,27,98] and one over 24 weeks.[25] One study was a flexible dose trial.[26] Table 13 summarizes study characteristics and differences in effect sizes of studies comparing citalopram with escitalopram.

Table 13. Characteristics and effect sizes of studies comparing citalopram with escitalopram

Study	N	Duration	Dosage Cit. - Esc. mg/d	Response (%)	Remission (%)	Quality Rating
Burke et al., 2002[24]	491	8 weeks	40 vs. 20	45.6 vs. 51.2 *P* = NR (ns)	NR	Fair
			40 vs. 10	45.6 vs. 50 *P* = NR (ns)	NR	
Colonna et al., 2005[25]	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[26]	471	8 weeks	20-40 vs. 10-20	52.6 vs. 63.7 *P* = 0.021	42.8 vs. 52.1 *P* = 0.036	Fair
Moore et al., 2005[27]	280	8 weeks	40 vs. 20	61.5 vs. 76.1 *P* = 0.009	43.6 vs. 56.1 *P* = 0.04	Fair
Unpublished Study SCT MD-02[98]	375	8 weeks	20-40 vs. 10-20	51 vs. 46 *P* = NR	NR	Fair

NR, not reported; ns, not significant.

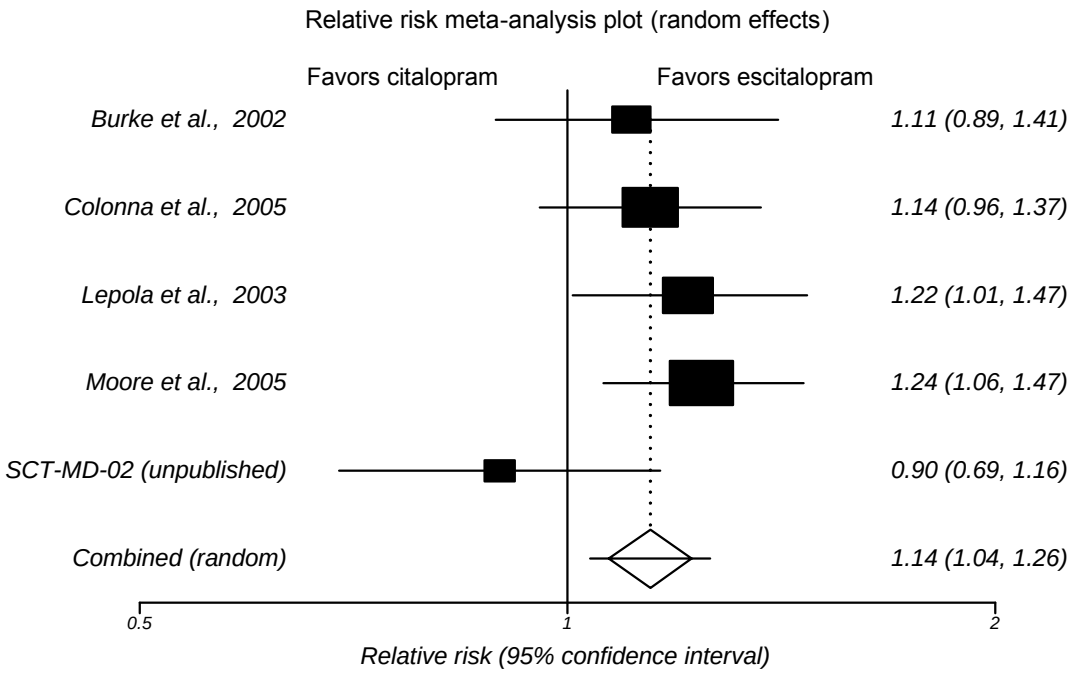
Overall, results of individual studies favored escitalopram over citalopram. In three studies, differences in response rates reached statistical significance at 8 weeks.[25-27] The flexible dose trial was a European-Canadian study that compared efficacy and harms of citalopram (20-40 mg/day), escitalopram (10-20 mg/day), and placebo in 471 depressed outpatients attending primary care centers.[26] 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.[25] 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 week 8. The outcome of the first meta-analysis was the relative risk of being a responder on the MADRS scale at week 8 (Figure 3). In addition to

the four published trials, we included data from one unpublished study from the FDA Center for Drug Evaluation and Research (CDER) database.[98] A "response" was defined as an improvement of 50 percent or more on the MADRS. Pooled results included 1,545 patients and yielded a statistically significant additional treatment effect for escitalopram. The relative risk that a patient would respond was 1.14 (95% CI, 1.04-1.26) for escitalopram relative to citalopram. 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 is 14 (95% CI, 7-111).

Figure 3. Relative risk meta-analysis of MADRS response rates comparing citalopram with escitalopram



The second meta-analysis was an effect size meta-analysis of all five studies assessing the pooled difference of points on the MADRS (Figure 4). Overall, this analysis included data on 1,545 patients. The weighted mean difference (WMD) presented an additional treatment effect of a 1.13 point reduction (95% CI, 0.18-2.09; $P = 0.02$) for escitalopram compared with citalopram. Although the difference was statistically significant, the clinical implications remain to be clarified. A 1.13 point change on the MADRS represents about one-fifth to one-quarter of a standard deviation. A recent methods study concluded that, in general, a change of about one-half of a standard deviation on a health-related scale reflects a minimally important difference for a patient.[103]

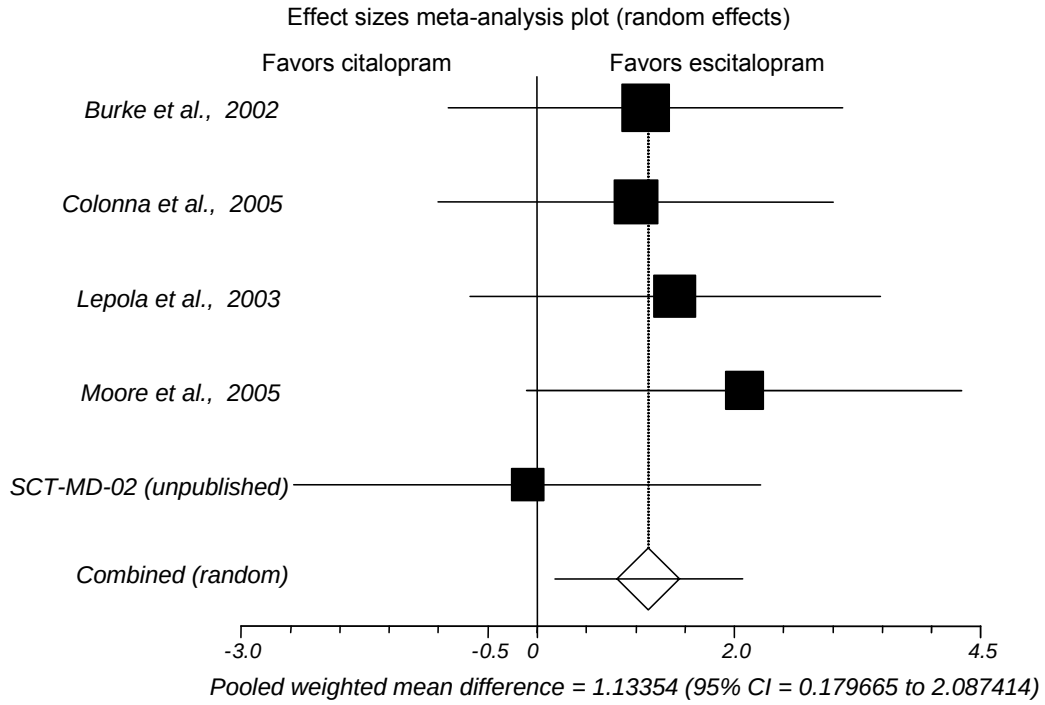
Both citalopram and escitalopram are produced by the same manufacturer, which funded all available studies. Generic brands of citalopram are available in the United States; escitalopram is still under patent protection.

Citalopram vs. fluoxetine. In a French trial, 397 outpatients with MDD attending general practices were randomly assigned to citalopram (20 mg/day) or fluoxetine (20 mg/day) over 8

weeks.[28] 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).

Citalopram vs. 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).[29] Remission rates did not differ significantly between citalopram and fluvoxamine treatments (14 percent vs. 8 percent; P = NR).

Figure 4. Effect size meta-analysis comparing citalopram with escitalopram on the MADRS



Citalopram vs. 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.[30] The majority of patients suffered recurrent depression (sertraline, 56 percent; citalopram, 65 percent) and used other medications for medical illnesses (sertraline, 55 percent; citalopram, 44.5 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, in a subgroup analysis of patients with recurrent depression and single episode depression, they did not report any differences in effectiveness between drugs. Response rates 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 vs. fluoxetine. A multinational RCT enrolled patients older than 65 years (n = 518) in general-practice and psychiatric-specialist settings to assess the comparative efficacy of escitalopram (10 mg/day) and fluoxetine (20 mg/day).[31] Both treatment groups had no greater efficacy than the placebo control group after 8 weeks of treatment. Response and remission rates did not differ significantly between the active treatment groups.

Fluoxetine vs. fluvoxamine. Two studies evaluated the comparative efficacy and safety of fluoxetine and fluvoxamine in 284 outpatients with MDD.[32,33] 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]).[33] 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,[32] 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 vs. paroxetine. Ten studies compared fluoxetine to paroxetine.[34-41,48,49] 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.[35] 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.[40] Results were consistent with findings of the other studies.

We conducted a meta-analysis of these seven studies (excluding three that did not report data[34,48,49]) using HAM-D scores at the end of followup.[35-41] We defined "response" as an improvement of 50 percent or more on the HAM-D. The statistical analysis included 950 patients. The pooled estimate of the random effects model, presented in Figure 5, indicates that fluoxetine and paroxetine do not differ significantly in efficacy (RR, 1.09; 95% CI, 0.99-1.21). Removing the study conducted in an inpatient population[40] from the analysis did not change the point estimate. An effect size meta-analysis (Figure 6) also did not detect a statistically significant difference between fluoxetine and paroxetine (-0.55; 95% CI, -1.46-0.36).

Figure 5. Relative risk meta-analysis of response rates comparing fluoxetine with paroxetine on the HAM-D

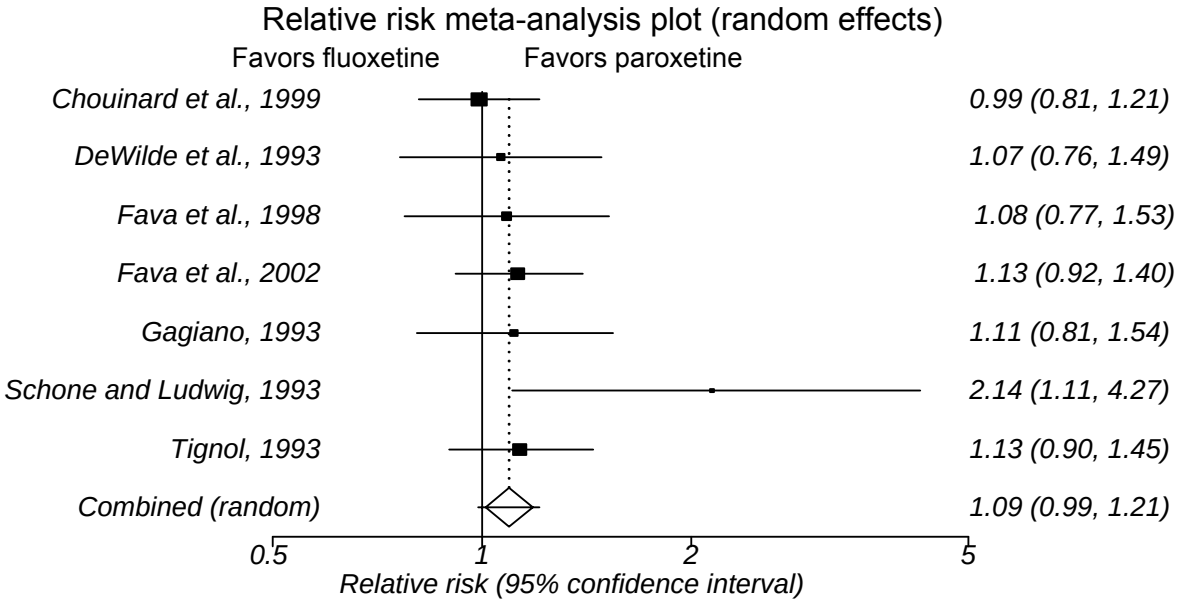
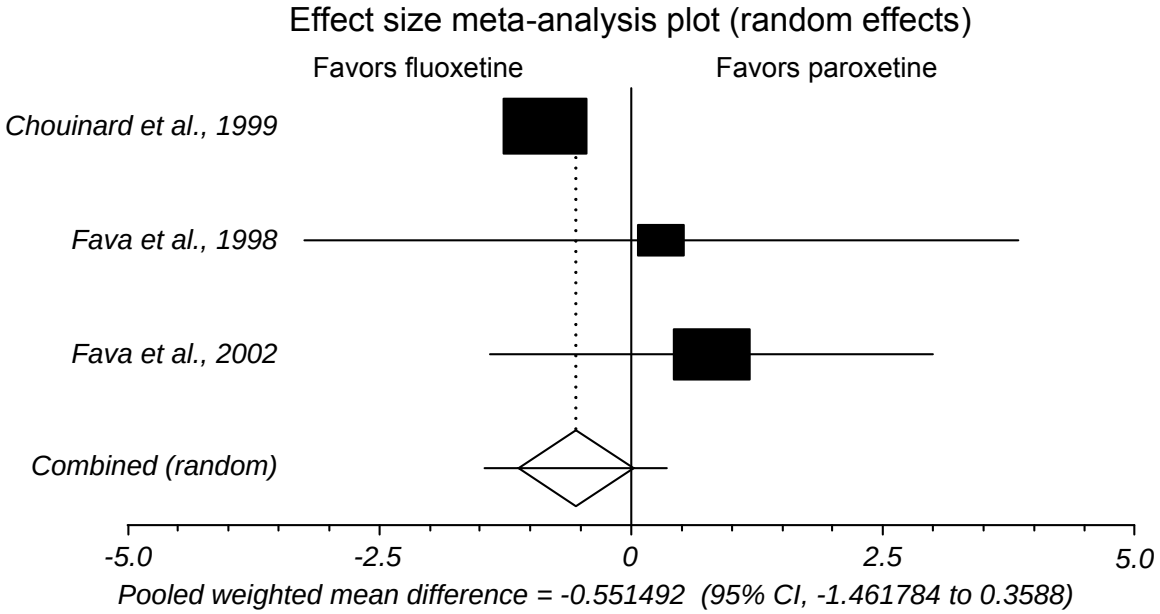


Figure 6. Effect size meta-analysis comparing fluoxetine with paroxetine on the HAM-D



Two RCTs were conducted in a population older then 60 years.[34,39] An Italian study lasting 1 year 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 persons (65 years or older).[34]

In both trials, paroxetine-treated patients achieved higher response rates than patients in the fluoxetine group. In one study, differences in response rates reached statistical significance (37.5

percent vs. 17.5 percent; $P = 0.04$).[39] In the long-term Italian study, treatment groups did not differ significantly at study endpoint on CGI scores or most cognitive scales (Blessed Information and Memory Test [BIMT], Mini-Mental State Examination [MMSE], Clifton Assessment Schedule [CLAS]).[34]

Five studies did not detect differences between fluoxetine and paroxetine in improvement of anxiety in patients with depression (HAM-A, Covi Anxiety Scale).[34,35,37,38,41]

Fluoxetine vs. sertraline. Eight studies compared fluoxetine with sertraline.[41-49] The best evidence consisted of two effectiveness trials[46,49] and one efficacy trial[43] 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]).[43,46] The psychiatrist study[46] randomized 238 patients for 24 weeks; the GP study[43] 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.[49] This study did not meet our eligibility criteria because it was an open-label trial; 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.[49] 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).[41,42,44,45,47] Studies lasted from 6 weeks to 16 weeks. One study was conducted in 236 participants older than 60 years.[44,45] 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. A subgroup analysis of 75 patients 70 years of age or older showed a greater response rate for sertraline than fluoxetine (59 percent vs. 42 percent; $P = 0.027$).[45]

We conducted two meta-analyses of four studies[41,42,44,46] comparing the effects of fluoxetine and sertraline at study endpoint. The outcome of the first meta-analysis was the relative risk (benefit) of being a responder on the HAM-D (improvement of 50 percent or more) at study endpoint (Figure 7).

Pooled results included 940 patients and yielded a statistically significant additional treatment effect for sertraline. The relative risk of being a responder was 1.11 (95% CI, 1.01-1.21) for sertraline relative to fluoxetine. 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 is 14 (95% CI, 8-22).

The second meta-analysis was an effect size meta-analysis assessing the pooled difference of points on the HAM-D scale (Figure 8). Because of lack of reported data, we limited the analysis to three studies.[41,44,46] 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 0.75 point reduction in HAM-D (95% CI, -0.45-1.95).

Fluvoxamine vs. paroxetine. One 7-week RCT compared the efficacy and safety of fluvoxamine (50-150 mg/day) and paroxetine (20-50 mg/day) in 60 outpatients with MDD.[50] Results presented no statistically significant differences on HAM-D, HAM-A, CGI, and SCL-56 (Hopkins Symptom Checklist - 56 item). This study did not assess response and remission rates.

Fluvoxamine vs. sertraline. Two 7-week studies compared the depression scores and harms of fluvoxamine (50-150 mg/day) and sertraline (50-200 mg/day).[51,52] One trial was conducted in a mixed (84 percent unipolar, 16 percent bipolar depression) inpatient population.[52]

Figure 7. Relative risk meta-analysis of response rates comparing fluoxetine with sertraline on the HAM-D

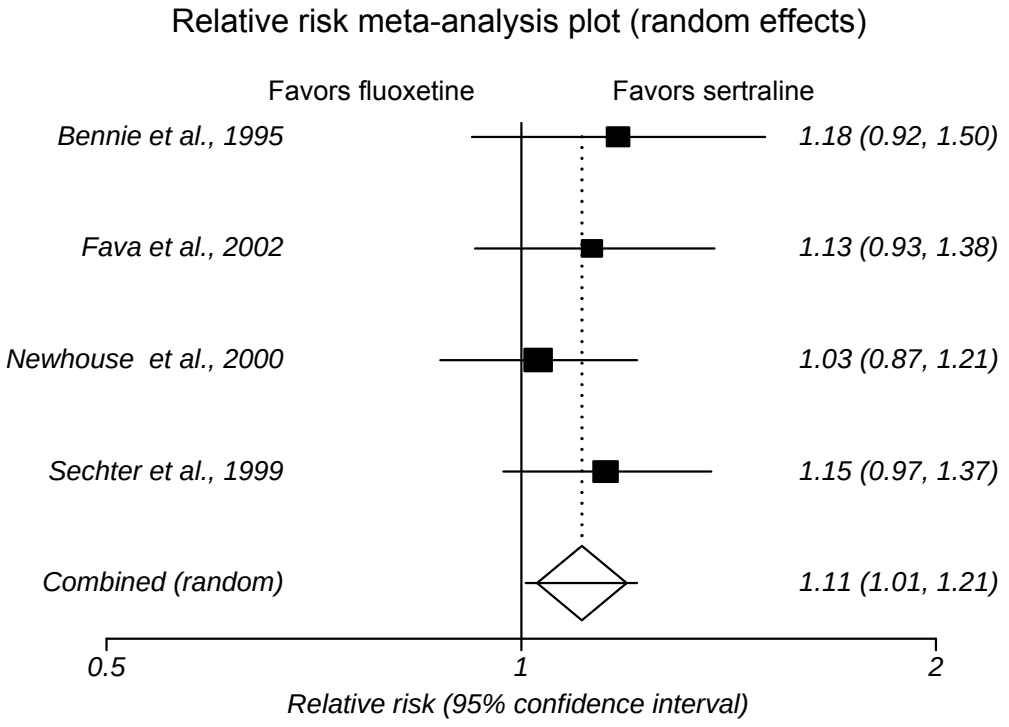
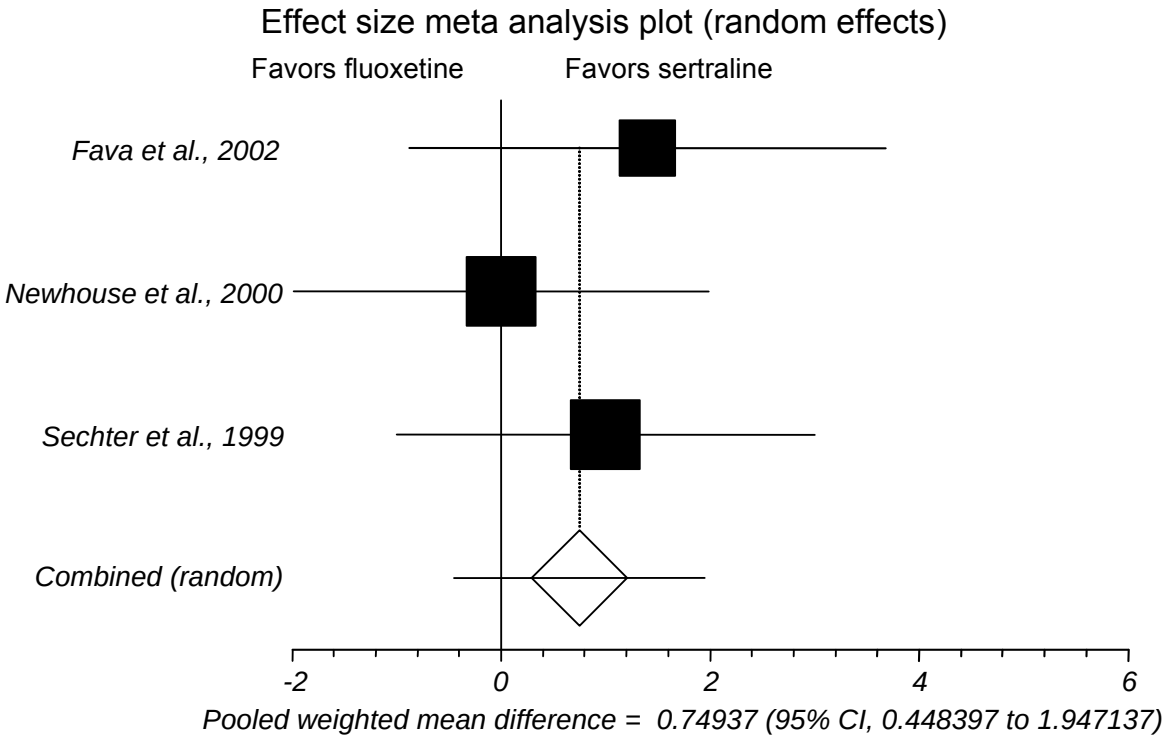


Figure 8. Effect size meta-analysis comparing fluoxetine with sertraline on the HAM-D



In both studies, efficacy did not differ significantly between treatment groups. Both regimens led to significant improvements in depression scores from baseline (HAM-D, CGI). In one study, significantly more patients withdrew because of adverse events in the fluvoxamine group (19 percent) than in the sertraline group (2 percent; $P = 0.016$).[51] Sertraline-treated patients reported a significantly greater rate of sexual dysfunction than patients on fluvoxamine (28 percent vs. 10 percent; $P = 0.047$).

Paroxetine vs. sertraline. A Swedish RCT compared paroxetine (20-40 mg/day) with sertraline (50-150 mg/day) in a 24-week study involving 353 patients.[53] 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. Diarrhea was more frequent in the sertraline group (35.2 percent vs. 15.2 percent; $P < 0.01$). By contrast, patients in the paroxetine group had higher rates of fatigue (45.8 percent vs. 21.0 percent; $P < 0.01$), decreased libido in females (8.8 percent vs. 1.8 percent; $P < 0.05$), micturition problems (6.2 percent vs. 0.6 percent; $P < 0.05$), and constipation (16.4 percent vs. 5.7 percent; $P < 0.01$).

Head-to-head evidence: SSRIs vs. SSNRIs and SNRIs. ***Citalopram vs. mirtazapine.*** A 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.[54] 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. Mirtazapine led to weight gain in significantly more patients than citalopram (15.3 vs. 4.5 percent; $P < 0.05$); citalopram had a significantly higher rate of nausea than mirtazapine (20 percent vs. 10.2 percent; $P < 0.05$) Overall discontinuation rates because of adverse events did not differ significantly between the two groups.

Citalopram vs. 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).[55] No statistical differences in any outcome measures (MADRS, CGI-S, CGI-I) could be detected at study endpoint. The remission rates were 19 percent for venlafaxine and 23 percent for citalopram (P = NR). Both treatment groups reached a 93 percent response rate.

Escitalopram vs. venlafaxine. Two 8-week studies assessed the comparative effectiveness of escitalopram and venlafaxine XR.[56,57] One study assigned 293 patients to escitalopram (10-20 mg/day) or venlafaxine XR (75-150 mg/day).[57] 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 ($P < 0.01$). Significantly fewer patients on escitalopram than on venlafaxine XR reported nausea (17 percent vs. 26 percent; $P < 0.05$), sweating (6 percent vs. 12.5 percent; $P < 0.05$), and constipation (2 percent vs. 6 percent; $P < 0.05$).

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.[56] Significantly fewer patients in the escitalopram group withdrew because of adverse events (4 percent vs. 16 percent; $P < 0.01$) or reported nausea (24 percent vs. 6 percent; $P < 0.05$). This study, however, compared a medium dose of escitalopram to a high dose of venlafaxine XR. Some differences in adverse events might be attributable to the high, fixed-dose regimen of venlafaxine XR.

Fluoxetine vs. duloxetine. A 8-week RCT assigned 173 patients to duloxetine (40-120 mg/day), fluoxetine (20 mg/day), or placebo.[58] 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 vs. mirtazapine. Three trials compared the efficacy of fluoxetine and mirtazapine.[59-61] Two studies enrolled either exclusively[60] or a large percentage[61] 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.[59]

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.[60,61] 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.[60]

Fluoxetine vs. venlafaxine. Nine studies compared the efficacy of fluoxetine to venlafaxine.[62-70] One study was conducted in inpatient populations.[69] One trial was conducted in outpatients with concomitant anxiety (minimum score of 8 on Covi Anxiety Scale).[64] The studies lasted from 6 weeks to 12 weeks. Except in one study,[70] results consistently presented greater efficacy of venlafaxine than fluoxetine; in three studies, this difference reached statistical significance.[62,64,65]

We conducted a meta-analysis of eight studies comparing fluoxetine to venlafaxine.[62-67,69,70] All studies were financially supported by the manufacturer of venlafaxine. We excluded one study because of missing data.[68] The main outcome measure was the relative risk (benefit) of being a responder on the HAM-D scale at study endpoint.

Results (Figure 9), based on 1,814 patients, present a modest additional treatment effect for venlafaxine, just reaching statistical significance (RR, 1.12; 95% CI, 1.01-1.24). The NNT to achieve one additional responder was 12 (95% CI, 7-50) for the random effects model; the fixed effects model yielded similar significant results. An effect size meta-analysis (Figure 10) yielded a statistically nonsignificant additional reduction of 1.31 points (95% CI, -0.28-2.91) for venlafaxine compared with fluoxetine on the HAM-D scale. The clinical significance of this difference is questionable.

In a sensitivity analysis, we limited studies to those with outpatients only. Results did not differ substantially from findings of analyses that combined inpatient and outpatient subjects. Patients in the venlafaxine group had statistically significantly higher response rates than did patients in the fluoxetine group (RR, 1.12; 95% CI, 1.00-1.25). Again, the additional effect size is modest, just reaching statistical significance.

Figure 9. Relative risk meta-analysis of response rates comparing fluoxetine with venlafaxine on the HAM-D

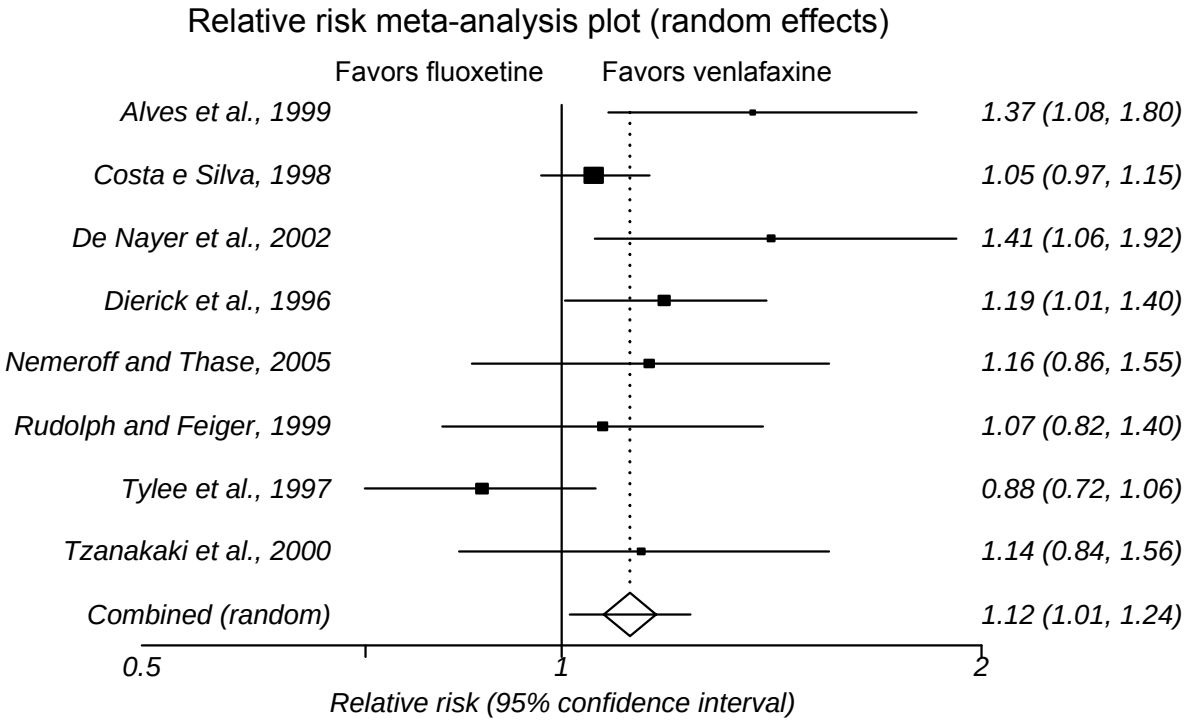
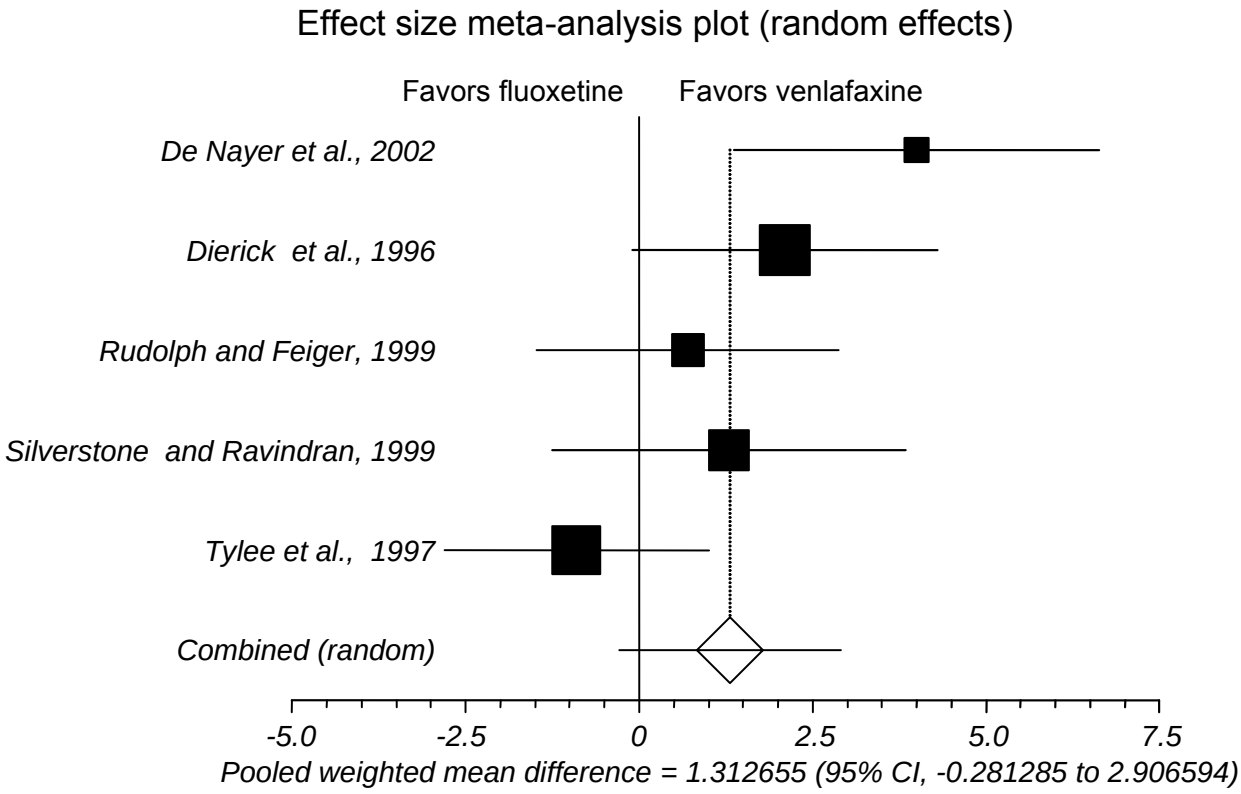


Figure 10. Effect size meta-analysis comparing fluoxetine with venlafaxine on the HAM-D



These findings are consistent with results of a meta-analysis reported by Smith et al.[104] Compared with fluoxetine, venlafaxine yielded a modest but statistically significantly greater standardized effect size (-0.14; 95% CI, -0.22 - -0.06) and a significantly greater odds ratio (OR) for remission (OR, 1.42; 95% CI, 1.17-1.73). The OR for response was numerically greater for venlafaxine but not significant (OR, 1.17; 95% CI, 0.99-1.38).

Paroxetine vs. duloxetine. An 8-week, fixed-dose trial assessed the comparative efficacy of paroxetine (20 mg/day), duloxetine (80 mg/day), duloxetine (120 mg/day), and placebo.[71] These are comparisons between a low-to-medium dose of paroxetine (20 mg) and a medium dose (80 mg) and high dose (120 mg) of duloxetine. Patients in the three active drug groups did not differ significantly in either response (74 percent; 65 percent; 71 percent; P = NR) or remission (44 percent; 46 percent; 52 percent; P = NR). The Patient Global Impression of Improvement (PGI-I) score was significantly better in patients on paroxetine than on 80 mg/day duloxetine.

Paroxetine vs. mirtazapine. Two trials, one conducted in Germany[72] and one in the United States,[73] assessed the efficacy of paroxetine (20-40 mg/day) and mirtazapine (15-45 mg/day). The US study was conducted in depressed patients 65 years or older.[73] In both trials, paroxetine and mirtazapine were equally effective in reducing HAM-D scores at the endpoint. Mirtazapine led to a faster response in both trials. In the 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). A Kaplan-Meier analysis in one trial showed a significantly faster time to response for mirtazapine than for paroxetine (mean 26 days vs. mean 40 days; $P = 0.016$).[73] No significant difference in response rates on the CGI scale was noted. Both trials reported weight gain in significantly more patients treated with mirtazapine than with paroxetine ($P < 0.05$). Paroxetine-treated patients in the US study reported significantly higher rates of nausea, tremor, and flatulence ($P < 0.05$). The NNT to yield one additional patient responding with mirtazapine at weeks 1 or 2 is 7.

Paroxetine vs. venlafaxine. Two studies compared paroxetine with venlafaxine.[74,75] 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.[74] 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).[75] Study groups did not differ significantly in efficacy measures, quality of life scores, or adverse events.

Sertraline vs. 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.[76] 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 vs. venlafaxine. Two 8-week trials, both rated good quality, compared the efficacy of sertraline to venlafaxine; they yield mixed results regarding differences in efficacy.[77,78] In a Scandinavian study (N = 147), venlafaxine (75-150 mg/day) was significantly more efficacious than sertraline (50-100 mg/day) on the HAM-D (response: 83 percent vs. 68 percent; $P = 0.05$, remission: 68 percent vs. 45 percent; $P = 0.008$).[77] The other study (N = 163) assessed quality of life as the primary outcome measure (Q-LES-Q).[78] LOCF results at 8 weeks did not detect significant differences in quality of life and response and remission rates between treatment groups. Subgroup analyses in this trial, focused on patients with anxious or severe depression, indicated that response and remission rates did not differ significantly between sertraline (50-150 mg/day) and venlafaxine XR (75-225 mg/day).

Head-to-head evidence: SSRIs vs. other second-generation antidepressants. ***Fluoxetine vs. bupropion***. Two trials compared the efficacy and harms of fluoxetine and bupropion.[79,80] Both studies 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).[79] 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 vs. nefazodone. Two studies with identical protocols examined the effects of antidepressive treatments with either fluoxetine or nefazodone in outpatients with MDD and insomnia.[105,106] Data from these trials and an unpublished study also employing the same protocol were pooled into one analysis.[81]

A total of 125 patients with MDD and sleep disturbance were enrolled for 8 weeks. Effects on sleep were measured by the HAM-D Sleep Disturbance subscale, Inventory for Depressive Symptomatology-Clinician Rated (IDS-C), Inventory for Depressive Symptomatology-Self Rated (IDS-SR), and electroencephalogram measurements. Fluoxetine and nefazodone were similarly efficacious in producing response on the HAM-D scale (45 percent vs. 47 percent; P = NR). Nefazodone led to significantly greater improvements of sleep quality than fluoxetine as assessed by clinician ratings and self-reported evaluations ($P < 0.01$).

Fluoxetine vs. trazodone. Two 6-week trials compared the efficacy and harms of fluoxetine (20-60 mg/day) and trazodone (50-400 mg/day).[82,83] 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).[82] 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 vs. bupropion. One 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.[84] 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). Both treatment groups improved significantly in quality of life scales (Quality of life in Depression Scale [QLDS], SF-36) between baseline and endpoint (*P* < 0.0001); again, the treatment groups did not differ significantly.[107]

Paroxetine vs. nefazodone. Two studies determined the comparative efficacy of paroxetine and nefazodone on depression and sleep improvement.[85,86] 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).[85] 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 consistent results for the comparative antidepressive efficacy.[86] Nefazodone, however, led to significantly greater improvements than paroxetine in objective sleep measures.

Paroxetine vs. trazodone. A European study compared paroxetine (20-40 mg/day) with trazodone (150-400 mg/day) in 108 outpatients with MDD.[87] 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 vs. bupropion. Three studies compared the efficacy and harms of sertraline and bupropion.[88-90,108] 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).[88]

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.[88,89] 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).[90] 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 vs. 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.[92] 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.

Head-to-head evidence: SNRIs vs. SNRIs. *Mirtazapine vs. venlafaxine.* An 8-week European trial evaluated efficacy and harms in hospitalized, severely depressed patients (mean HAM-D 29.3) with melancholic features.[93] 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; $P \leq 0.05$) than venlafaxine.

Head-to-head evidence: SNRIs vs. other second-generation antidepressants. *Mirtazapine vs. trazodone.* Two studies compared mirtazapine with trazodone in patients with MDD.[94,95] One trial was conducted in depressed patients 55 years of age and older;[94] the other was done in hospitalized patients with MDD.[95] 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).[95]

Venlafaxine vs. 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.[96] 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 vs. other second-generation antidepressants. *Bupropion vs. trazodone.* In a two-center study, 124 outpatients were randomly assigned to bupropion (225-450 mg/day) or trazodone (150-450 mg/day).[97] 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. A postrandomization exclusion rate of 10 percent and an overall loss to followup of 40 percent might compromise the internal validity of this study.

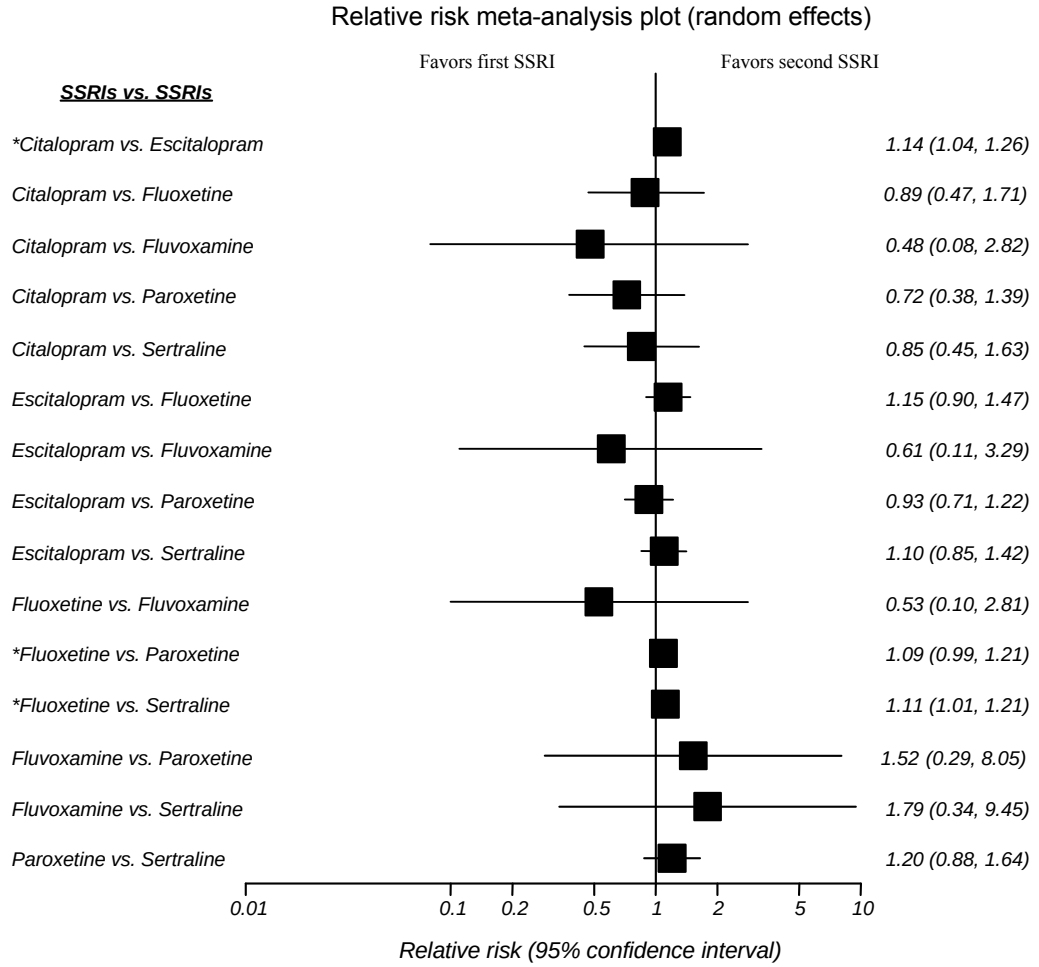
Indirect comparisons. Of 66 possible comparisons, the evidence was sufficient to pool data in meta-analyses for only four comparisons for MDD (those documented in Figures 3 through Figure 10). For the remaining 62 MDD comparisons, we conducted indirect comparisons,

through meta-regression, as outlined in the Methods section. Studies in these meta-regressions can be found in Appendix F; those excluded are listed in Appendix G.

We assessed the relative risk of response to treatment on the HAM-D scale. None of the results of indirect comparisons suggests a statistically significant difference in efficacy between any drugs. However, confidence intervals are often wide and findings do not conclusively demonstrate noninferiority.[109]

In general, findings from indirect comparisons were consistent with available head-to-head studies. Results of direct (denoted by an asterisk) and indirect comparisons are depicted in Figures 11, 12, and 13.

Figure 11. Relative risks of response rates comparing SSRIs with SSRIs on the HAM-D



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

Figure 12. Relative risks of response rates comparing SSRIs, SNRIs, SSNRIs, and other second-generation antidepressants with other second-generation antidepressants on the HAM-D

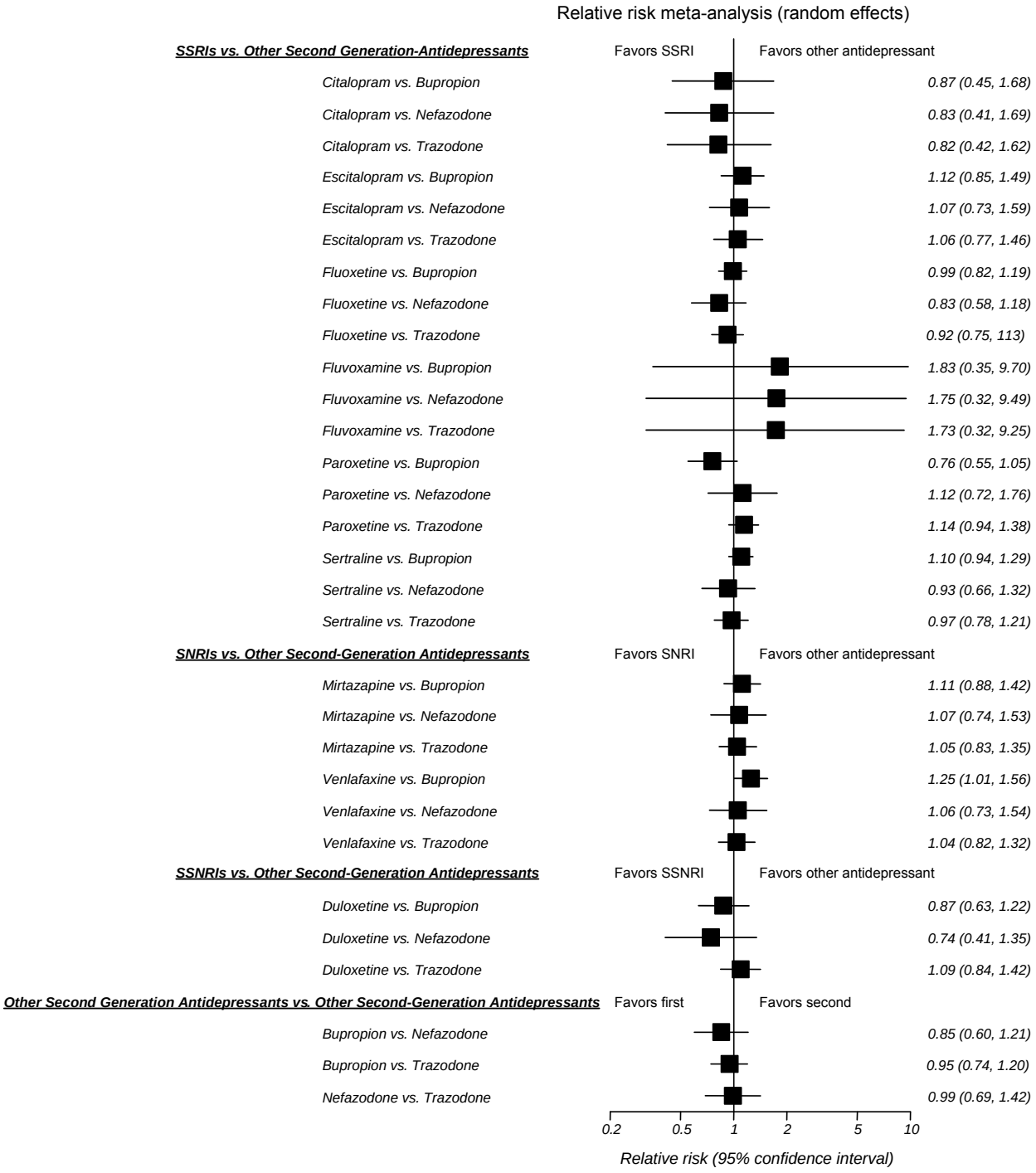
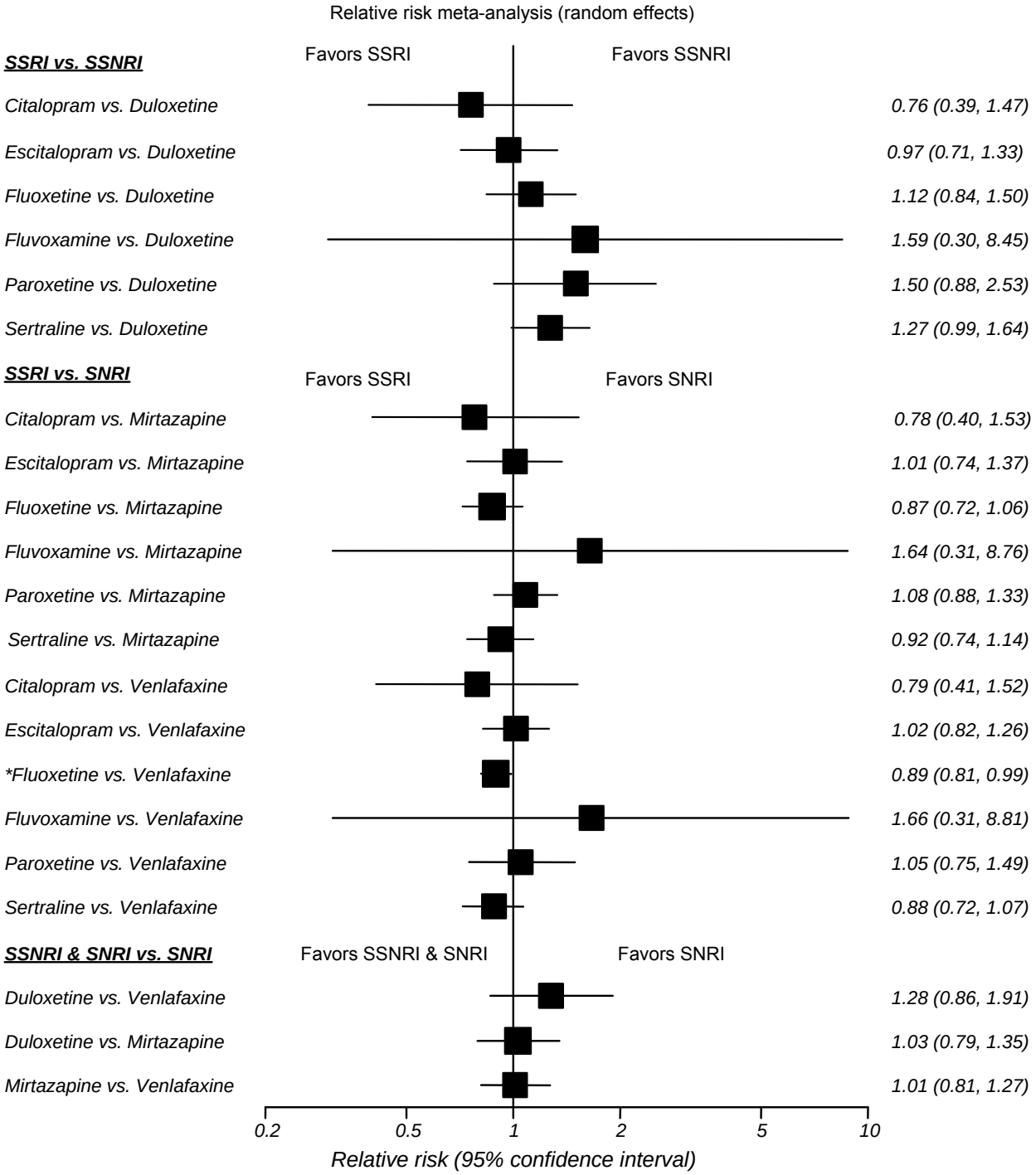


Figure 13. Relative risks of response rates comparing SSRIs with SSNRIs and SSRIs with SNRIs on the HAM-D



*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 studies (Table 14) assessed effectiveness, efficacy, and harms of fluoxetine, paroxetine, and sertraline in populations with dysthymia.[99-101,110-113] Four studies were of fair quality; the fifth was of good quality. Details can be found in Evidence Table 1 in Appendix D.

Table 14. Interventions, numbers of patients, results, and quality ratings of studies in adults with dysthymia

Study	Interventions	N	Results	Quality Rating
Devanand et al., 2005[100]	Fluoxetine vs. placebo	90	No difference in response rates and quality of life	Good
Vanelle et al., 1997[101]	Fluoxetine vs. placebo	111	Significantly more responders for fluoxetine	Fair
Barrett et al., 2001[113] Williams et al., 2000[112]	Paroxetine vs. placebo vs. behavioral therapy	656	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[111] Kocsis et al., 1997[110]	Sertraline vs. imipramine vs. placebo	412	Significantly more responders for sertraline than placebo	Fair
Ravindran et al., 2000[99]	Sertraline vs. placebo	310	Significantly more responders and remitters for sertraline	Fair

Dysthymia: Key Points

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

Five placebo-controlled trials (eight articles) provide mixed evidence on the general efficacy and effectiveness of fluoxetine, paroxetine, and sertraline for the treatment of dysthymia.[99-101,110-113] Specifically:

- Two studies provide mixed evidence about the general efficacy of fluoxetine for the treatment of dysthymia.[100,101]

- One effectiveness study provides mixed evidence on the effectiveness of paroxetine compared with placebo.[112,113] A subgroup of patients older than 60 years showed a significantly greater improvement than those on placebo; a subgroup of patients younger than 60 years did not show any difference in effectiveness between paroxetine and placebo.

- Two studies indicate that sertraline has a significantly greater efficacy in the treatment of dysthymia than placebo.[99,110,111]

Dysthymia: Detailed Analysis

Head-to-head evidence. We identified no head-to head trials.

Placebo-controlled evidence. *Fluoxetine vs. placebo.* Two studies evaluated the efficacy of fluoxetine for treating patients with dysthymia over 12 weeks; the studies provide mixed results.[100,101] An RCT of good quality examined the efficacy and safety of fluoxetine (20-60 mg/day) in patients 60 years of age and older.[100] 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 study was conducted in patients 18 years of age and older (mean 43 years).[101] Significantly more patients on fluoxetine than on placebo were rated as responders (58.3 percent vs. 35.9 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 vs. placebo vs. 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.[112,113] 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.

In the 60 or older subgroup, paroxetine-treated patients showed a greater change in HSCL-D-20 scores than placebo-treated patients ($P = 0.004$).[112] 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.[113] 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 vs. placebo. Two RCTs assessed the efficacy of sertraline (50-200 mg/day) for the treatment of dysthymia over 12 weeks.[99,110,111] 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. In both studies, patients on sertraline had significantly greater antidepressant responses than those on placebo (64 percent vs. 44 percent; $P < 0.001$[111] and 51.9 percent vs. 33.8 percent; $P = 0.001$[99]). Likewise, in both studies, 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.[114] Because of the lack of head-to-head evidence, we briefly summarize this study (Table 15), although it did not meet eligibility criteria. In addition, two placebo-controlled studies, both rated fair quality, assessed the efficacy and tolerability of fluoxetine[115] and paroxetine[112,113] in patients with dysthymia (Table 15). Details can be found in Evidence Table 1 in Appendix D.

Table 15. Interventions, numbers of patients, results, and quality ratings of studies in adults with subsyndromal depressive disorders

Study	Interventions	N	Results	Quality Rating
Rocca et al., 2005[114]	Citalopram vs. sertraline	138	No difference	NA
Judd et al., 2004[115]	Fluoxetine vs. placebo	162	Greater improvements on depression scales for fluoxetine than for placebo; no difference in psychosocial outcomes	Fair
Barrett et al., 2001[113] Williams et al., 2000[112]	Paroxetine vs. placebo vs. behavioral therapy	656	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

NA, not applicable.

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.[114]

In placebo-controlled trials, significant differences in population characteristics make the evidence insufficient to identify differences between treatments.[112,113,115] In one effectiveness study, effectiveness did not differ significantly between paroxetine and placebo for the treatment of minor depression.[112,113] The strength of evidence is low.

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.[114] Overall, both treatments improved depressive symptoms. No significant differences in efficacy could be detected 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 vs. placebo. A 12-week trial (N = 162) evaluated the efficacy of fluoxetine in patients with minor depression.[115] 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 vs. 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.[112,113] 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 ($P = 0.17$).[112] 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.[113]

Key Question 2: Efficacy or effectiveness for maintaining remission or for treating patients with unresponsive or recurrent disease

This section deals with two issues on efficacy or effectiveness of medications:

2a. For adults with a depressive syndrome, do antidepressants differ in their efficacy or effectiveness for maintaining response/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 for treating those with treatment-resistant or recurrent depression?

Overview

In all, we had 27 studies relating to these two questions (Table 16). Three head-to-head RCTs compared the efficacy of one second-generation antidepressant with another for preventing relapse or recurrence.[47,96,116,117] Comparisons included fluoxetine vs. sertraline,[47] fluvoxamine vs. sertraline,[116,117] and trazodone vs. venlafaxine (shown in italics in Table 16).[96] Another 21 RCTs[118-138] provide additional placebo-controlled evidence to support the general efficacy of bupropion, citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone,

paroxetine, sertraline, trazodone, and venlafaxine for maintaining remission in patients with depressive disorders (Table 16). No trial assessed the efficacy of duloxetine for preventing relapse or recurrence. Two effectiveness studies[139,140] and one efficacy trial[141] compared one second-generation antidepressant with another for treating patients who had not responded or could not tolerate at least one previous treatment.

Using the management framework depicted in the introduction (Figure 1), 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.

Table 16. Number of head-to-head comparisons and placebo-controlled studies for assessment of relapse and recurrence

Relapse Prevention (Continuation Treatment ≤ 9 months)		Recurrence Prevention (Maintenance Treatment)	
Comparison	**Number of Studies**	**Comparison**	**Number of Studies**
Head-to-Head Trials			
Fluoxetine vs. sertraline	1	*Fluvoxamine vs. sertraline*	1
		Trazodone vs. venlafaxine	1
Placebo-Controlled Trials			
Bupropion vs. placebo	1	Bupropion vs. placebo	0
Citalopram vs. placebo	2	*Citalopram vs. placebo*	2
Duloxetine vs. placebo	0	Duloxetine vs. placebo	0
Escitalopram vs. placebo	1	Escitalopram vs. placebo	0
Fluoxetine vs. placebo	2	*Fluoxetine vs. placebo*	1
Fluvoxamine vs. placebo	0	*Fluvoxamine vs. placebo*	1
Mirtazapine vs. placebo	1	Mirtazapine vs. placebo	0
Nefazodone vs. placebo	1	*Nefazodone vs. placebo*	1
Paroxetine vs. placebo	1*	*Paroxetine vs. placebo*	2*
Sertraline vs. placebo	1	*Sertraline vs. placebo*	3
Trazodone vs. placebo	0	*Trazodone vs. placebo*	1†
Venlafaxine vs. placebo	1	*Venlafaxine vs. placebo*	2†

* One trial reported continuation-phase and maintenance-phase results.

† Includes placebo comparison from a head-to-head trial of trazodone and venlafaxine.

Studies that compared one second-generation antidepressant with another in treating resistant depressive disorders varied in design, although all studies randomized patients with MDD, dysthymia, or minor depression to an alternative treatment after they had either failed or could

not tolerate a previous treatment. We characterized patients with treatment-resistant depressive disorder as those who had failed initial acute-phase treatment. We searched for studies specifically assessing treatment of relapse (i.e., loss of response during continuation treatment) and recurrence (i.e., a new distinct episode), but studies addressing this population included relapsing patients and/or those with recurrent depression among those studied in acute-phase treatment trials (i.e., KQ 1).

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 studies 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). Other studies 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.

Because most studies received a fair rating for quality (internal validity), we denote quality in this section only for those rated good or poor. Trial reporting was often incomplete. Most articles did not report their methods of randomization or allocation concealment. Even though investigators frequently used ITT analysis, few authors reported the overall number of patients lost to followup from randomization to the end of the trial. Because some studies defined reasons for attrition such as withdrawals because of lack of efficacy or adverse events as endpoints, we did not use loss to followup as an exclusion criteria for these studies.

Data were insufficient to use placebo-controlled trials for making indirect comparisons between drugs.

Detailed information on all studies reviewed for KQs 2a and 2b can be found in Evidence Table 2 in Appendix D.

Maintaining Remission: Key Points

In three head-to-head trials,[47,96,116,117] the overall efficacy for maintaining remission does not differ between fluoxetine and sertraline,[47] fluvoxamine and sertraline,[116,117] and trazodone and venlafaxine.[96] We rated the strength of head-to-head evidence as moderate.

Ten placebo-controlled relapse prevention trials provide consistent efficacy evidence in favor of active treatment over placebo.[118-127,142] Eleven placebo-controlled recurrence prevention trials provide consistent evidence in favor of active treatment over placebo.[119,128-138] Effect sizes generally were consistent across drugs in placebo-controlled efficacy trials. One placebo-controlled recurrence prevention study[136] rated good quality provides general evidence of the effectiveness of sertraline for maintaining remission in patients with recurrent major depression.

Maintaining Remission: Detailed Analysis

Head-to-head evidence. Three head-to-head trials compared one second-generation antidepressant with another for maintaining remission (Table 17).[47,96,116,117]

Table 17. Head-to-head studies of relapse prevention and recurrence prevention

Study	Phase	Duration (Weeks)	N	Comparison and Dose (mg/d)	Relapse or Recurrence N (%)		Quality Rating
Van Moffaert et al., 1995[47]	Acute	8	82	Fluoxetine 20-40	NA		Fair
			83	Sertraline 50-100	NA		
	Continuation	24	56	Fluoxetine 20-40	7 (13)	*P* = NR (ns)	
			49	Sertraline 50-100	5 (10)		
Franchini et al., 1997[116]	Acute	NR	NR	NR	NA		Fair
	Continuation	16	NR	NR	NA		
Franchini et al., 2000[117]	Maintenance (2 years)[116]	104	32	Fluvoxamine 200	6 (19)	*P* = 0.88	
			32	Sertraline 100	7 (22)		
	Maintenance (4 years)[117]	208	25	Fluvoxamine 200	5 (20)	*P* = 0.92	
			22	Sertraline 100	3 (14)		
Cunningham et al., 1994[96]	Acute	6	77	Trazodone 150-400	NA		Fair
			72	Venlafaxine 75-200	NA		
			76	Placebo	NA		
	Continuation/ Maintenance	52	30	Trazodone 150-400	4 (13)	*P* = NR (ns)	
			37	Venlafaxine 75-200	3 (8)		
			29	Placebo	4 (14)		

NA, not applicable; NR, not reported; ns, not statistically significant.

Fluoxetine vs. sertraline. One trial compared the efficacy of fluoxetine and sertraline for preventing relapse during a 24-week continuation phase.[47] 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), but this design may be prone to bias and confounding because patients had not been rerandomized at the start of the continuation phase.

Fluvoxamine vs. sertraline. One trial compared the efficacy of fluvoxamine and sertraline for maintaining remission over 2 years[116] and 4 years.[117] This relatively small Italian study included 64 patients with recurrent depression. 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 mg/day or sertraline 100 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).

Trazodone vs. venlafaxine. One randomized trial compared the efficacy and safety of trazodone and venlafaxine over a 1-year continuation/maintenance phase.[96] A total of 225 patients with major depression received acute treatment with trazodone 150-400 mg/day (N = 77), venlafaxine 75-200 mg/day (N = 72), or placebo (N = 76). After 6 weeks, 30 responders in the trazodone group and 37 in the venlafaxine 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 (13 percent, 8 percent, and 14 percent, respectively; *P* = NR). Fewer patients treated with venlafaxine than with

either trazodone ($P \leq 0.05$) or placebo (P = NR) withdrew from treatment for any reason; this difference reached statistical significance during the long-term phase.

Placebo-controlled evidence. Ten placebo-controlled trials (11 publications) assessed relapse prevention[118-127,142] and 11 trials (12 publications) assessed recurrence prevention.[119,128-138] 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 18) can be categorized as addressing both relapse and recurrence prevention.

Bupropion vs. placebo. One trial assessed relapse prevention with bupropion.[118] 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.

Citalopram vs. placebo. Two trials assessed relapse prevention[120,143] and two other trials assessed recurrence prevention.[128,129] Both relapse prevention trials randomized patients who responded in the acute phase (MADRS ≤ 12) to placebo or continuation treatment with citalopram. 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).[128,129] 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; $P < 0.001$,[128] and 32 percent vs. 67 percent, respectively; P = NR[129]).

Escitalopram vs. placebo. One trial treated MDD patients (N = 502) openly with escitalopram 10-20 mg/day for 8 weeks.[121] 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).

Fluoxetine vs. placebo. Two trials (three publications) assessed relapse prevention,[122,123,142] and one trial assessed recurrence prevention.[130] 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.[122] 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 second trial openly treated 932 patients with MDD for 13 weeks with fluoxetine.[123,142] 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).

The 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 mg/day (N = 70) or placebo (N = 70).[130] Recurrence rates were statistically significantly lower for fluoxetine-treated patients than for placebo-treated patients (20 percent vs. 40 percent, respectively; $P = 0.01$).

Fluvoxamine vs. placebo. One trial assessed recurrence prevention with fluvoxamine 100 mg/day.[131] 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. 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; $P < 0.001$).

Mirtazapine vs. 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.[124] 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; $P = 0.001$).

Table 18. Placebo-controlled studies of relapse prevention and recurrence prevention

Study	Phase	Duration (Weeks)	N	Comparison and Dose (mg/d)	Relapse or Recurrence N (%)		Quality Rating
Weihs et al., 2002[118]	Acute	8	816	Bupropion SR 300	NA		Fair
	Continuation	44	210	Bupropion SR 300	78 (37)	$P = 0.004$	
			213	Placebo	111 (52)		
Hochstrasser et al., 2001[128]	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[129]	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[144]	Acute	6	NR	Citalopram 20-40	NA		Fair
	Continuation	24	48	Citalopram 20	4 (8)	$P < 0.02$*	
			57	Citalopram 40	7 (12)		
			42	Placebo	13 (31)		
Robert and Montgomery, 1995[120]	Acute	8	391	Citalopram 20-60	NA		Fair
	Continuation	24	152	Citalopram 20-60	21 (14)	$P = 0.04$	
			74	Placebo	18 (24)		
Rapaport et al., 2004[121]	Acute	8	502	Escitalopram 10-20	NA		Fair
	Continuation	36	181	Escitalopram 10-20	47 (26)	$P = 0.01$	
			93	Placebo	37 (40)		
Gilaberte et al., 2001[130]	Acute	8	253	Fluoxetine 20-40	NA		Fair
	Continuation	24	179	Fluoxetine 20-40	NA		
	Maintenance	52	70	Fluoxetine 20	14 (20)	$P = 0.01$	
			70	Placebo	28 (40)		
Schmidt et al., 2000[123] Dinan, 2001[142]	Acute	13	932	Fluoxetine 20	NA		Fair
	Continuation	25	189	Fluoxetine 20	49 (26)	$P < 0.01$*	
			190	Fluoxetine 90/week	70 (37)		
			122	Placebo	61 (50)		
Reimherr et al., 1998[122] Michelson et al., 1999[145]	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)		
Terra and Montgomery, 1998[131]	Acute	6	436	Fluvoxamine 100	NA		Fair
	Continuation	18	283	Fluvoxamine 100	NA		
	Maintenance	52	110	Fluvoxamine 100	14 (13)	$P < 0.001$	
			94	Placebo	33 (35)		
Thase et al., 2001[124]	Acute	8-12	410	Mirtazapine 15-45	NA		Fair
	Continuation	40	76	Mirtazapine 15-45	15 (20)	$P = 0.001$	
			80	Placebo	35 (44)		
Gelenberg et al., 2003[132]	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[125]	Acute	16	467	Nefazodone 400-600	NA		Fair
	Continuation	36	65	Nefazodone 400-600	1 (2)	$P = 0.009$	
			66	Placebo	12 (18)		
Claghorn and Feighner, 1993[133]	Acute	6	240	Paroxetine 10-50	NA		Fair
			237	Imipramine 65-275	NA		
			240	Placebo	NA		
	Continuation	52	94	Paroxetine 10-50	11 (12)	P = NR	
			79	Imipramine 65-275	3 (4)		
			46	Placebo	10 (22)		

Montgomery and Dunbar, 1993[119]	Acute	8	172	Paroxetine 20-30	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)		
Lepine et al., 2004[136]	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[126]	Acute	8	480	Sertraline 50-200	NA		Fair
	Continuation	44	185	Sertraline 50-200	24 (13)	*P* < 0.001	
			110	Placebo	48 (46)		
Keller et al., 1998[134] Kocsis et al., 2002[135]	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)		
Wilson et al., 2003[137]	Acute	8	318	Sertraline 50-200	NA		Fair
	Continuation	16-20	254	Sertraline 50-200	NA		
	Maintenance	100	56	Sertraline 50-100	25 (45)	*P* = 0.21	
			57	Placebo	31 (54)		
Montgomery et al., 2004[138]	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[127]	Acute	8	490	Venlafaxine 75-225	NA		Fair
	Continuation	26	161	Venlafaxine XR 75-225	45 (28)	*P* < 0.001	
			157	Placebo	82 (52)		

NA, not applicable; SR, slow release.
* Active treatment vs. placebo.

Nefazodone vs. placebo. Two trials, both rated fair, evaluated nefazodone.[125,132] 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).[125] 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.[132] 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; $P = 0.043$).

Paroxetine vs. placebo. One UK trial[119] and one US trial[133] 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 UK study assessed relapse prevention after 16 weeks of double-blind treatment and recurrence prevention after an additional 36 weeks of continued double-blind treatment.[119] 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 US study was an extension of a 6-week acute-phase trial that compared paroxetine, imipramine, and placebo.[133] 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"[133, page 25S] (n = 10; 22 percent) than did patients treated with either paroxetine (n = 11; 12 percent) or imipramine (n = 3; 4 percent).

Sertraline vs. placebo. One study assessed relapse prevention;[126] three other studies assessed recurrence prevention.[134,136,137] In the 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).[126] Statistically significantly fewer sertraline-treated patients than placebo-treated patients experienced a relapse (13 percent vs. 46 percent, respectively; $P < 0.001$).

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.[136] Treatment was substituted 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; $P = 0.002$).

Similarly, the other two recurrence prevention studies found that patients treated with sertraline had fewer recurrences than did those on placebo.[134,137] In a 76-week maintenance phase, 6 percent of sertraline-treated and 23 percent of placebo-treated patients had a recurrent depressive episode ($P = 0.002$).[134] 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 ($P = 0.21$).[137]

Venlafaxine vs. placebo. Two trials studied venlafaxine.[127,138] The relapse prevention study openly treated 490 patients with major depression with venlafaxine XR 75-225 mg/day for 8 weeks.[127] 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.[138] 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; $P < 0.001$).

Treating Treatment-Resistant Depression or Relapse or Recurrence: Key Points

One head-to-head trial indicated that venlafaxine and paroxetine differ in their efficacy for treating major depression that has not responded to previous antidepressants.[141] This trial followed patients who were resistant to at least two previous antidepressant treatments; it found statistically significantly higher response and remission rates with venlafaxine than with paroxetine. Two studies yielded evidence of the effectiveness of one second-generation antidepressant compared with another for the treatment of depressive disorders in patients who had not responded to initial treatment.[140 146] One trial of good quality indicates that the compared treatments do not differ in their effectiveness as second-line agents.[146] An open-label Spanish study contradicts this finding; it reported statistically significant differences in effectiveness between compared treatments.[140] The contradictions between the one good-quality study and the two fair-quality studies led us to rate the overall strength of this evidence as moderate.

Treating Treatment-Resistant Depression or Relapse or Recurrence: Detailed Analysis

Head-to-head evidence. Three studies assessed differences among alternative antidepressants in patients who had either not responded or could not tolerate an acute-phase treatment (Table 19).[140,141,146] They covered a range of antidepressants; the common element was venlafaxine.

Bupropion SR vs. sertraline vs. venlafaxine XR. One effectiveness trial rated good quality 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.[146] 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. Of the 727 patients randomized to a second-generation antidepressant, 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. Doses were adjusted based on clinical judgment and side effect rating scales. Second-step treatment was continued for up to 14 weeks.

Table 19. Head-to-head studies of treatment-resistant and recurrent depression

Study	Duration (Weeks)	N	Comparison and Dose (mg/d)	Response N (%)		Remission N (%)		Quality Rating
Baldomero et al., 2005[140]	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* = 0.02	
		248	Fluoxetine 20-40	174 (70)	*P* = 0.012	128 (52)	*P* = 0.03	
		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* = 0.04	
		1,632	Venlafaxine 75-225	1,262 (78)		963 (59)		
Poirier and Boyer, 1999[141]	4	62	Paroxetine 30-40	18 (36)	*P* = 0.07	11 (18)	*P* = 0.02	Fair
		61	Venlafaxine 200-300	27 (45)		22 (37)		
Rush et al., 2006[146]	14	239	Bupropion 150-400	62 (26)	*P* = NR (ns)	51 (21)	*P* = 0.16	Good
		238	Sertraline 50-200	63 (27)		42 (18)		
		250	Venlafaxine 37.5-375	62 (25)		62 (25)		

NR, not reported; ns, not statistically significant.

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* = NR [ns]); 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.

Although several comparative studies included patients who had relapsed or who were experiencing a recurrent depressive episode in acute-phase management studies, no study *specifically* randomized patients to one second-generation antidepressant or another upon relapse or recurrence. The good-quality trial provides the most direct evidence relative to the second part of KQ 2; 75 percent of patients in this trial had failed acute treatment of a recurrent depressive episode. Among all patients in this trial, the investigators found no differences among bupropion SR, sertraline, and venlafaxine XR as an alternative treatment.

Venlafaxine vs. paroxetine or numerous other antidepressants. One 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.[140] 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 rates 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 each of the individual drugs characterized as conventional therapy, except for paroxetine.

The response and remission rates in this study were much higher than in the good-quality effectiveness trial just described.[146] 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 ≤ 7 to classify persons in remission.

One efficacy trial assessed differences between paroxetine and venlafaxine in patients with major depression who either had not responded or could not tolerate at least two previous treatments for their current depressive episode.[141] 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; $P = 0.02$). The incidence of adverse events was comparable between treatment groups.

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 six symptom clusters: anxiety, insomnia, 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 fatigue, loss of energy, or appetite change—some of the more common accompanying symptoms reported by depressed patients.[147]

For each symptom cluster, we arrange our summary by how the data address two subquestions:

3a. Do medications differ in their efficacy and effectiveness in treating the depressive episode?

3b. Do medications differ in their efficacy and effectiveness in treating the accompanying symptoms?

We identified 28 relevant trials (29 articles) (Tables 19-23); one trial was reported in two separate articles.[91,148] Twenty-two studies were head-to-head trials; one assessed three symptom subgroups.[149] We identified 11 head-to-head trials (12 articles) on anxiety,[35,37,38,54,64,78,85,91,108,148-150] six on insomnia,[41,60,81,82,96,151] three on melancholia,[69,149,152] two on pain,[71,153] and one each on psychomotor changes[149] and somatization.[49] One trial addressing somatization was an open-label effectiveness trial.[49] It did not meet our eligibility criteria because of the lack of double-blinding; however, we report on its results because it was a well-conducted randomized controlled effectiveness trial and comprises the only evidence for somatization in depressed patients. The

remaining six studies were placebo-controlled trials. Three addressed pain,[154-156] two addressed anxiety,[157,158] and one addressed melancholia.[159]

All but two studies[38,64] either were funded by or involved authors funded by pharmaceutical companies.

We rated all studies as fair quality with three exceptions (noted below). 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 26 percent of trials.[149,150,154,155,157-159]

We rated the quality of the one effectiveness trial as not applicable as it did not meet our initial selection criteria.[49] In addition, we have two poor-quality studies, one on melancholia[152]and the other on pain.[153] Both of the poor studies had high attrition; one had high differential attrition between treatment groups,[152] and the other had high overall attrition.[153] We comment on data from these two studies because the evidence base for pain and melancholia is otherwise very weak. Poor studies were included 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 studies can be found in Evidence Table 3 in Appendix D. Evidence Table 4 provides information on systematic reviews and meta-analyses related to treating depression and accompanying symptoms.

Anxiety: Key Points

For KQ 3a, on the treatment of depression in patients with accompanying anxiety symptoms, we identified six head-to-head trials[64,78,91,108,148-150] and one placebo-controlled trial.[157] For KQ 3b, treatment of accompanying anxiety symptoms in patients with MDD, we included 10 head-to-head trials[35,37,38,54,64,78,85,108,148,150] and two placebo-controlled trials.[157,158] Six of these trials, in seven articles, addressed both key questions.[64,78,91,108,148,150,157] Of these 13 trials, five compared various SSRIs with each other or placebo, six compared an SSRI with an SNRI or another second-generation drug, and one each compared an SSRI or another second-generation drug only with placebo (Table 20). We rated the strength of evidence for both of these questions as moderate.

Table 20. Studies of adults with major depressive disorders and accompanying anxiety

Study	Interventions	N	Results	Quality Rating
SSRIs vs. SSRIs				
Chouinard et al., 1999[35]	Fluoxetine Paroxetine	203	KQ 3b. Improvement in anxiety scores was similar for both treatment groups (*P* = NR)	Fair
Fava et al., 1998[37]	Fluoxetine Paroxetine Placebo	128	KQ 3b. Improvement in anxiety scores was similar for both treatment groups and placebo (*P* = NR)	Fair
Fava et al., 2000[150]	Fluoxetine Paroxetine Sertraline	128 (all with anxiety)	KQ 3a. Improvement in depression scores (*P* = 0.323), depression response rates (*P* = 0.405) and remission rates were similar for all groups (*P* = 0.588) KQ 3b. Improvement in anxiety scores were similar for all 3 treatment groups (*P* = 0.199)	Fair

Flament et al., 1999[149]	Fluoxetine Sertraline	286 overall; 131 with anxiety	KQ 3a. Improvement in depression scores and depression response rates were similar for both treatment groups (*P* = NR)	Fair
Gagiano, 1993[38]	Fluoxetine Paroxetine	90	KQ 3b. Improvement in anxiety scores was similar for both treatment groups (*P* = NR)	Fair
SSRI vs. SNRI or other second-generation antidepressant				
Baldwin et al.,1996[85]	Paroxetine Nefazodone	206	KQ 3b. Improvement in anxiety scores was similar for both treatment groups (95% CI for difference, -0.7-3.8)	Fair
DeNayer et al., 2002[64]	Fluoxetine Venlafaxine	146 (all with anxiety)	KQ 3a. Improvement in depression scores was greater and response rates were higher for venlafaxine compared with fluoxetine (*P* < 0.05) KQ 3b. Improvement in anxiety scores was greater for venlafaxine compared with fluoxetine (*P* = 0.0004)	Fair
Leinonen et al., 1999[54]	Citalopram Mirtazapine	270	KQ 3b. Improvement in anxiety scores was similar for both treatment groups (*P* = 0.75)	Fair
Rush et al., 2001[108]	Sertraline Bupropion SR	248 overall; top quartile of HAM-A score with anxiety (number not provided)	KQ 3a. Depression response and remission rates were similar for both treatment groups (*P* = NR) KQ 3b. Improvement in anxiety scores was similar for both treatment groups (*P* = NR)	Fair
Sir et al., 2005[78]	Sertraline Venlafaxine XR	163 overall; 120 with anxiety	KQ 3a. Improvement in depression scores (*P* = 0.70), depression response rates (*P* = 0.26), and remission rates (*P* = 0.44) were similar for both groups KQ 3b. Improvement in anxiety scores was similar for both treatment groups (*P* = 0.32)	Fair
Trivedi et al., 2001[148] and Rush et al., 2001[91]	Sertraline Bupropion SR Placebo	724 overall; top quartile of HAM-A score with anxiety (number not provided)	KQ 3a. Depression response and remission rates were similar for both active groups and placebo (*P* = NR) KQ 3b. Improvement in anxiety scores was similar for treatment groups (*P* > 0.41)	Fair
SSRI or SNRI vs. Placebo				
Joliat et al., 2004[157]	Fluoxetine (weekly vs. daily) Placebo	799 overall; 374 with anxiety	KQ 3a. Depression relapse rates were similar for both medication groups and appeared better than those for placebo, but no statistical comparisons were reported (*P* = NR) KQ 3b. Worsening of anxiety scores appeared better for medication groups than for placebo, but there were no statistical comparisons (*P* = NR)	Fair
Khan et al., 1998[158]	Venlafaxine (3 doses) Placebo	403 overall; 346 with anxiety	KQ 3b. Improvement in anxiety scores for all 3 venlafaxine groups was superior to placebo group (*P* < 0.05); improvement was similar for the 3 venlafaxine dose groups	Fair

NR, not reported; SR, slow release.

Efficacy: KQ 3a: Depressive episode in patients with anxiety. Overall, six head-to-head studies and one fair placebo-controlled study indicated that antidepressant medications do not differ in treatment efficacy for depressed patients with accompanying anxiety symptoms. All

seven trials analyzed a subgroup with identified high anxiety. However, only three used the same definition criteria (a HAM-D anxiety-somatization factor of 7 or more).[78,150,157]

The head-to-head trials compared SSRIs with each other,[149,150] with bupropion SR,[91,108,148] and with SNRIs.[64,78] Studies appeared to compare similar doses of antidepressant medications. Two studies comparing SSRIs (including fluoxetine, paroxetine, and sertraline) found no statistically significant differences in depressive improvement, response rates, or remission rates.[149,150] Two studies comparing bupropion SR and sertraline found no significant differences in response or remission rates.[91,148] Two 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,[64] and one found no statistically significant difference in depressive severity change, response rates, or remission rates between venlafaxine XR and sertraline.[78]

One placebo-controlled trial of patients whose MDD had already responded to treatment tested the efficacy of fluoxetine against placebo in preventing a relapse of depression during continuation-phase treatment.[157] Fluoxetine appeared to be more efficacious than placebo in preventing a relapse of a depressive episode, but statitistical comparsions were not reported.

Efficacy: KQ 3b: Anxiety in depressed patients. Overall, results from 10 head-to-head studies and two placebo-controlled studies suggested that antidepressant medications do not differ in treatment efficacy for treating anxiety associated with MDD. Seven of these 12 trials analyzed a subgroup with high anxiety.[64,78,108,148,150,157,158] Only three used identical definitions to identify the high anxiety group.[78,150,157] 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 fluoxetine, sertraline, and paroxetine) found no statistically significant differences for treatment of patients' anxiety symptoms.[35,37,38,150] Two studies comparing sertraline and bupropion SR found no difference in anxiety reduction.[108,148] Two studies comparing an SSRI (fluoxetine, sertraline) with venlafaxine found mixed results; venlafaxine produced a greater decrease in anxiety severity than fluoxetine in one study,[64] whereas the other study reported similar anxiety reduction for venlafaxine XR and sertraline.[78] One study comparing paroxetine and nefazodone found no difference in anxiety reduction.[85] A final head-to-head study comparing citalopram to mirtazapine found no difference in anxiety reduction.[54]

One placebo-controlled study comparing fluoxetine with placebo during continuation-phase treatment reported that anxiety worsened to a lesser degree with fluoxetine treatment, but the authors gave no statistical information.[157] A second placebo-controlled trial reported that venlafaxine treatment produced a statistically greater reduction in anxiety scores than placebo.[158]

Effectiveness: KQ 3a and KQ 3b. We identified no effectiveness trial relating to treatment of depression with accompanying anxiety symptoms. We expect, however, that if any such study were to be done, it would be less likely than the efficacy trials to show any differences between medications for this population.

Anxiety: Detailed Analysis

Head-to-head evidence. We identified 11 head-to head trials comparing the efficacy of specific medications treating depressed patients with coexisting anxiety symptoms. One study addressed only improvement in depression as an outcome (i.e., KQ 3a).[149] Five studies addressed only improvement in anxiety as an outcome (i.e., KQ 3b).[35,37,38,54,85] The remaining six articles addressed both questions.

Fluoxetine vs. paroxetine. Two studies compared the efficacy of low-to-high doses of fluoxetine with similar doses of paroxetine for treatment of anxiety.[35,38] 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.[35] Improvements on multiple measures of anxiety did not substantially differ between the two treatment groups.

A second study compared fluoxetine (20-60 mg/day) and paroxetine (20-40 mg/day) over 6 weeks in 90 patients with severe MDD.[38] Mean baseline anxiety severity was comparable, with each group having a moderate to severe degree of anxiety. Improvements in HAM-A scores were similar between the two groups.

Fluoxetine vs. paroxetine vs. placebo. One study compared low-to-high doses of fluoxetine, low-to-medium doses of paroxetine, and placebo in a pooled analysis of two multicenter trials, which were each 12 weeks in duration.[37] Patients had MDD of at least moderate severity. The analysis pooled data from five sites (not all) in the two trials; no explanation was provided for the limited inclusion. The outcome addressed was the effect of medications on co-occurring anxiety symptoms. Inclusion in the analysis did not require a high anxiety score; baseline mean Covi Anxiety Scale scores were similar (< 7) in all groups, consistent with patients not being anxious. Improvement in anxiety symptoms on the Covi Anxiety Scale did not differ among the three groups.

Fluoxetine vs. paroxetine vs. 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 scale ≥ 7 [range 0-18]).[150] 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. Depressive outcomes between the three medications were similar, as measured by improvement in HAM-D total scores, by response rates (≥ 50 percent reduction in HAM-D score; fluoxetine, 73 percent, paroxetine, 77 percent; and sertraline, 86 percent, $P = 0.405$), and by remission rates (HAM-D endpoint ≤ 7; fluoxetine, 53 percent; paroxetine, 50 percent; and sertraline, 62 percent; $P = 0.588$). Likewise, authors reported no difference between the three groups with respect to anxiety outcomes (measured by overall change on HAM-D anxiety-somatization score).

Fluoxetine vs. sertraline. One study 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 Scale score ≥ 7.[149] 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 vs. mirtazapine. One study 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.[54] 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 vs. venlafaxine. 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 ≥ 8 (consistent with clinically relevant anxiety).[64] Both depression and anxiety outcomes were reported. 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, $P = 0.0048$). Similarly, the mean reduction on the Covi Anxiety Scale was greater for venlafaxine than for fluoxetine (-5.7 points vs. -3.9 points, $P = 0.0004$).

Sertraline vs. bupropion SR. One efficacy trial compared low-to-high dose sertraline with low-dose Bupropion SR over 16 weeks in 248 patients with MDD of moderate severity.[108] 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-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 vs. bupropion SR vs. placebo. One pooled analysis of two 8-week RCTs compared the efficacy of low-to-high dose sertraline (50-200 mg/day), low-to-high dose Bupropion SR (150 mg-400 mg/day), and placebo in 724 patients with MDD of at least moderate severity.[91,148] One set of investigators reported on depressive outcomes;[91] the other set reported on anxiety outcomes.[148]

The two sets of investigators defined high anxiety in slightly different ways. In the study on depressive outcomes,[91] the high anxiety subgroup comprised patients with a HAM-A score in the top quartile of enrolled patients (HAM-A ≥ 25). For this subgroup, rates of depression response (defined as HAM-D-21 reduction of ≥ 50 percent; estimated by us from the figure in the article to be approximately 60 percent to 70 percent for each of three arms) and of remission (HAM-D-21 ≤ 8; estimated to be 25 percent to 35 percent for each arm) did not differ by treatment group. Furthermore, the authors did not report any significant relationship between quartile of baseline anxiety and antidepressant response for any of the three treatment arms.

In the study on anxiety outcomes,[148] investigators defined baseline anxiety as minimal (HAM-A ≤ 14), moderate (HAM-A 15-19), or severe (HAM-A ≥ 20). They reported no

differences in mean HAM-A reduction between patients treated with bupropion SR and those treated with sertraline for any of the anxiety severity subgroups (severe, bupropion SR ~ -15 points vs. sertraline ~ -13 points; moderate, bupropion SR ~ -8 vs. sertraline ~ -9; minimal, bupropion SR ~ -6 vs. sertraline ~ -5; all data estimated from figures in the paper).

Sertraline vs. venlafaxine XR. One efficacy study 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.[78] Outcomes included both depressive (HAM-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, 79.6 percent for sertraline vs. 68.9 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 vs. 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.[85] 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 vs. -6.5 for nefazodone, P = NS, 95% CI for difference between groups, -0.7-3.8).

Placebo-controlled evidence. Two trials compared efficacy of a second-generation antidepressant only against placebo. One involved an SSRI (for both KQ 3a and 3b), the other examined an SNRI (for only KQ 3b).

Fluoxetine vs. placebo. One study compared the efficacy of two different preparations of fluoxetine and placebo in preventing depression relapse in patients whose depression had been successfully treated.[157] The study involved continuation-phase treatment, where the clinical goal was to prevent relapse of a successfully treated depressive episode.

The authors pooled data from two 25-week RCTs. Patients who were in remission (from study 1) or who responded (from study 2) to approximately 3 months of open-label fluoxetine treatment were randomly assigned to placebo, continued treatment with 20 mg/day fluoxetine, or (in study 2 only) 90 mg/week delayed-release fluoxetine. High anxiety patients were defined as those with a HAM-D-17 anxiety-somatization subscale score of ≥ 7 at baseline.

In the high anxiety subgroup (n = 374), depression relapse rates appeared to be lower in the fluoxetine daily and fluoxetine weekly groups (27.8 percent and 28.5 percent, respectively) than in the placebo group (53.3 percent); the authors did not provide statistical information.

Anxiety levels increased (worsened) for all treatment arms in the high anxiety subgroup. This increase appeared less in the fluoxetine daily and weekly groups (1.92 and 1.93) than in the placebo group (3.12), but again statistical significance was not reported.

Venlafaxine vs. placebo. One 12-week study randomly assigned patients with severe MDD to one of three doses of immediate-release venlafaxine—75 mg/day (low), 150 mg/day (low), or 200 mg/day (medium)—or to placebo.[158] 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-17 anxiety-psychic 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-psychic and anxiety-somatization scores compared with the placebo group. The three venlafaxine groups did not differ from each other in anxiety outcomes.

Insomnia: Key Points

We identified six head-to-head studies that compared the effects of medications on treatment of depression and accompanying insomnia (Table 21).[41,60,81,82,96,151] Three of these trials required insomnia for inclusion in the analysis, although the definitions used varied by study and consisted of brief 1- or 3-item measures.[41,81,151] Three other trials did not require insomnia for inclusion but rather assessed sleep for all subjects.[60,82,96] The three studies that identified an insomnia group provided data addressing both KQ 3a (effects on depressive symptoms) and KQ 3b (effects on insomnia).[41,81,151] The other studies provided information solely on insomnia outcomes. We rated the strength of evidence for both depression outcomes in patients with accompanying insomnia (KQ 3a) and insomnia outcomes in patients with depression (KQ 3b) as low. All studies were of fair quality.

Table 21. Studies of adults with major depressive disorders and accompanying insomnia

Study	Interventions	N	Results	Quality Rating
Fava et al., 2002[41]	Fluoxetine Paroxetine Sertraline	284 overall; 125 with insomnia	KQ 3a. Improvement in depression scores was similar for all groups (P = 0.853) KQ 3b. Improvement in sleep was similar for all groups (P = 0.852)	Fair
Lader et al., 2005[151]	Citalopram Escitalopram Placebo	1,321 overall; 638 with insomnia	KQ 3a. Improvement in depression scores for escitalopram was superior to citalopram and placebo (P < 0.05) KQ 3b. Improvement in sleep for escitalopram was superior to citalopram and placebo (P < 0.01)	Fair
Rush et al., 1998[81]	Fluoxetine Nefazodone	125 (all with insomnia)	KQ 3a. Improvement in depression scores (95% CI for difference between groups, -1.7-2.8) and depression response rates (P = NR) were similar for both groups KQ 3b. Improvement in sleep for nefazodone was superior to fluoxetine (P < 0.05)	Fair
Beasley et al., 1991[82]	Fluoxetine Trazodone	126	KQ 3b. Improvement in sleep scores was greater for trazodone than for fluoxetine (P = 0.001)	Fair
Cunningham et al., 1994[96]	Venlafaxine Trazodone	227	KQ 3b. Improvement in sleep scores was greater for trazodone than venlafaxine (P < 0.05)	Fair
Versiani et al., 2005[60]	Fluoxetine Mirtazapine	299	KQ 3b. Sleep quality improved similarly for both groups (overall score not reported)	Fair

Efficacy: KQ 3a: Depressive episode in patients with insomnia. Three head-to-head studies provide mixed evidence regarding comparative efficacy of medications for treatment of depression in patients with accompanying insomnia.[41,81,151] One study found a slightly greater reduction in depressive severity for escitalopram than for citalopram or placebo.[151] The other two studies showed no statistically significant differences in depressive outcomes for fluoxetine compared with paroxetine and sertraline[41] and for fluoxetine compared with nefazodone.[81]

Efficacy: KQ 3b: Insomnia in depressed patients. Six head-to-head studies provided mixed evidence about the effects of antidepressants on insomnia in patients with depression. Two studies reported greater improvement in sleep scores for trazodone than for fluoxetine[82] and venlafaxine.[96] However, neither of these trials analyzed a subgroup of patients with insomnia. One study each reported better sleep outcomes for escitalopram than for citalopram[151] and for nefazodone than for fluoxetine.[81] The clinical meaning of the small sleep outcome differences reported in these studies is unclear. One study each found no statistically significant differences between fluoxetine, paroxetine, and sertaline[41] and between fluoxetine and mirtazapine.[60]

Effectiveness. We identified no effectiveness studies concerning depression and insomnia.

Insomnia: Detailed Analysis

Head-to-head evidence. Six head-to-head trials addressed this issue.

Citalopram vs. escitalopram vs. placebo. One study compared low-to-medium dose citalopram (20-40 mg/day) with low-to-medium dose escitalopram (10-20 mg/day) in a pooled secondary analysis of three 8-week RCTs of patients with MDD of at least moderate severity as measured by the MADRS (10 items, individual score range 0-6, total score range 0-60).[151] Insomnia was defined as a score of 4 or greater on the single MADRS sleep item (range 0-6). Among 638 patients meeting insomnia criteria, depressive symptoms improved (i.e., MADRS scores declined) for all three treatment arms. Improvement was greater for escitalopram than for citalopram and placebo (escitalopram, -16.47; citalopram, -14.02; placebo, -12.2; $P < 0.01$ for escitalopram vs. citalopram, $P < 0.001$ for escitalopram vs. placebo; P = NR, not significant for citalopram vs. placebo).

Insomnia results also favored escitalopram. Mean improvement on the MADRS sleep item was better in the escitalopram group than in the citalopram and placebo groups (escitalopram, -1.65; citalopram, -1.31; placebo, -1.26; $P < 0.01$ for escitalopram vs. citalopram, $P < 0.01$ for escitalopram vs. placebo, P = NS for citalopram vs. placebo). Escitalopram-treated patients were more likely than others to achieve improvement in insomnia, defined as a score of 0 or 1 on the MADRS sleep item at week 8 (43.6 percent for escitalopram, 28.4 percent for citalopram, 24.4 percent for placebo, overall $P < 0.001$).

Fluoxetine vs. paroxetine vs. sertraline.One study compared low-to-high doses of fluoxetine (20-60 mg/day), paroxetine (20-60 mg/day), and sertraline (50-200 mg/day) in a study of MDD patients with at least a moderate degree of depression that lasted between 10 and 16 weeks.[41] 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 study 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 vs. trazodone. One study 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.[82] 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 vs. nefazodone. One study compared low-to-moderate dose fluoxetine (20-40 mg/day) and nefazodone (200-500 mg/day) in a pooled analysis of three 8-week RCTs of patients with MDD of at least moderate severity, as measured by HAM-D-17.[81] The analysis was conducted on a subgroup of 122 patients with insomnia, defined by patient self-report at study entry of difficulty falling asleep each night, waking up during the night, or being unable to fall asleep again after getting out of bed. Depressive outcomes did not differ between treatment groups. The mean improvement in HAM-D was 12.2 points for fluoxetine and 11.4 for nefazodone (95% CI for difference, -1.7-2.8). Response rates, defined as HAM-D < 10, were essentially identical (45 percent for fluoxetine, 47 percent for nefazodone).

Sleep outcomes from the same study favored nefazodone. Patients receiving nefazodone had a mean improvement of -2.3 points on the HAM-D sleep disturbance items (range 0-6); the improvement for patients receiving fluoxetine was -1.6 ($P < 0.05$). Nefazodone-treated patients also had greater improvement on a secondary sleep measure, the Inventory for Depressive Symptomatology sleep items relating to early, middle, and late insomnia and hypersomnia (range 0-12, scored such that higher scores are better); patients receiving nefazodone improved by 2.4 points on this measure, compared with 1.7 points for patients treated with fluoxetine ($P < 0.01$).

Fluoxetine vs. mirtazapine. One study compared low-to-medium doses of fluoxetine (20-40 mg/day) with low-to-high doses of mirtazapine in an 8-week study of patients with severe MDD.[60] 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 vs. trazodone vs. placebo. One study 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.[96] 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).

Placebo-controlled evidence. We identified no placebo-controlled trials for depression and insomnia.

Melancholia: Key Points

We identified three head-to-head studies[69,149,152] and one placebo-controlled study[159] (Table 22). All addressed KQ 3a: whether, for patients with melancholia, medications differed in their effect on depressive symptoms. All but one study was rated fair quality; one was rated poor. We rated the strength of evidence for the comparative efficacy and effectiveness of second-generation antidepressants for treating depression in patients with melancholia as low.

Table 22. Studies of adults with major depressive disorders and accompanying melancholia

Study	Interventions	N	Results	Quality Rating
Flament et al., 1999[149]	Fluoxetine Sertraline	286 overall; 197 with melancholia	KQ 3a. Depression response rates for sertraline were superior to fluoxetine ($P < 0.05$); improvement in depression scores was similar for both groups (P = NR)	Fair
Clerc et al., 1994[152]	Fluoxetine Venlafaxine	68 (all with melancholia)	KQ 3a. Improvement in depression scores was better for venlafaxine than fluoxetine ($P = 0.027$); response rates did not differ ($P = 0.08$)	Poor
Tzanakaki et al., 2000[69]	Fluoxetine Venlafaxine	109 (all with melancholia)	KQ 3a. Depression response and remission rates were similar for both groups (P = NR)	Fair
Mallinckrodt et al., 2005[159]	Duloxetine Placebo	2,342 overall; 1,572 with melancholia	KQ 3a. Improvement in depression scores was better for duloxetine than placebo ($P < 0.001$)	Fair

NR, not reported.

We found no evidence addressing the comparative efficacy and effectiveness of second-generation antidepressants for the treatment of accompanying melancholic symptoms (KQ 3b).

Efficacy: KQ 3a: Depressive episode in patients with melancholia. Three head-to-head studies compared fluoxetine with sertraline[149] or venlafaxine.[69,152] One study found a greater response rate in patients receiving sertraline than fluoxetine.[149] Another found no difference between the fluoxetine and venlafaxine groups in response and remission rates.[69] One poor-quality study found a greater decrease in depressive severity for venlafaxine than for fluoxetine but only a nonsignificant tendency toward a greater rate of response (a more robust outcome).[152]

One placebo-controlled study, a pooled data analysis of duloxetine trials, found a greater decrease in depressive severity for duloxetine than for placebo.[159]

Efficacy: KQ 3b: Melancholia in depressed patients. We identified no efficacy trials addressing treatment of melancholic symptoms.

Effectiveness: KQ 3a and KQ 3b. We identified no effectiveness trials for depressed patients with accompanying melancholia.

Melancholia: Detailed Analysis

Head-to-head evidence. We identified two fair-quality studies[69,149] and one poor-quality study,[152] all 6 weeks in length.

Fluoxetine vs. sertraline. One study 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.[149] In the subgroup with melancholia by DSM-III-R criteria, depression response rates (≥ 50 percent decrease in HAM-D-17) were significantly better for sertraline than for fluoxetine (59 percent vs. 44 percent, $P < 0.05$).

Fluoxetine vs. venlafaxine. Two studies provided mixed results on the relative efficacy of moderate-to-high doses of fluoxetine and venlafaxine. One trial involved severely depressed hospitalized patients or outpatients with MDD and melancholia per DSM-IV criteria; patients were randomized to either 60 mg/day of fluoxetine or 225 mg/day of venlafaxine.[69] 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-21 score < 7) did not differ significantly (fluoxetine, 35.8 percent; venlafaxine, 40.7 percent).

The other study (rated poor) involved severely depressed hospitalized patients with MDD and melancholia per DSM-III-R criteria; investigators randomized patients to either 200 mg/day of venlafaxine or 40 mg/day of fluoxetine.[152] Using ITT approaches, the investigators determined that the improvement in depressive severity (mean decrease in HAM-D-21 score) was significantly greater in the venlafaxine group than in the fluoxetine group (-18 points vs. -12.4 points, $P = 0.027$). Response rates (≥ 50 percent decrease in HAM-D severity) did not differ significantly between groups (73 percent venlafaxine vs. 50 percent fluoxetine; $P = 0.08$).

Placebo-controlled evidence. ***Duloxetine vs. placebo.*** One study compared low-to-high doses of duloxetine (40-120 mg/day) with placebo for MDD patients with at least moderate depressive severity.[159] The authors pooled results of eight RCTs of 9 weeks' duration (all part of the New Drug Application to the FDA for duloxetine) and identified a subgroup of patients (n = 1,572) with melancholia, per DSM-IV criteria, on whom to conduct this secondary analysis. Accordingly, the randomization was not stratified by a melancholic designation. Mean reductions in HAM-D-17 score were 8.97 for patients receiving duloxetine and 6.57 for those receiving placebo ($P < 0.001$), suggesting a benefit for duloxetine, on average, of slightly more than 2 points.

Pain: Key Points

We included two head-to-head trials[71,153] and three placebo-controlled trials[154-156] that assessed the efficacy of antidepressants for treatment of depression and accompanying pain symptoms (Table 23). One placebo-controlled trial required baseline pain for inclusion; this study provided data addressing both KQ 3a (depression outcomes in patients with accompanying pain) and KQ 3b (pain outcomes in MDD patients).[154] The other four trials did not require pain for inclusion, but rather assessed pain symptoms for all subjects; these trials provided

information for KQ 3b (pain outcomes) only.[71,153,155,156] All but one study was rated fair quality; one was rated poor. We rated the strength of evidence for both questions as low.

Table 23. Studies of adults with major depressive disorders and accompanying pain

Study	Interventions	N	Results	Quality Rating
Brannan et al., 2005[154]	Duloxetine Placebo	282	KQ 3a. Improvement in depression scores (*P* = 0.544), depression response rates (*P* = 0.901), and remission rates (*P* = 0.887) was similar KQ 3b. Improvement in pain scores was similar (*P* = 0.066)	Fair
Goldstein et al., 2004[153]	Duloxetine Paroxetine Placebo	353	KQ 3b. Improvement in pain scores was similar between active medications (*P* = NR), between paroxetine and placebo (*P* = 0.088), and between duloxetine 40 mg and placebo (*P* = 0.172); improvement in pain for duloxetine 80 mg was superior to placebo (*P* = 0.005).	Poor
Detke et al., 2002[155]	Duloxetine Placebo	245	KQ 3b. Pain score improvement was slightly greater for duloxetine than placebo (*P* = 0.019)	Fair
Detke et al., 2002[156]	Duloxetine Placebo	267	KQ 3b. Pain score improvement was slightly greater for duloxetine than placebo (*P* = 0.037)	Fair
Detke et al., 2004[71]	Duloxetine Paroxetine Placebo	367	KQ 3b. Improvement in pain scores was similar between duloxetine 80 mg and placebo (*P* = 0.063), and between duloxetine 120 mg and placebo (*P* = 0.086); improvement in pain for paroxetine was superior to placebo (*P* = 0.035)	Fair

NR, not reported.

Efficacy: KQ 3a: Depressive episode in patients with pain. One study found no difference in efficacy between duloxetine and placebo for treatment of depression in patients with mild to moderate pain.[154]

Efficacy: KQ 3b: Pain in depressed patients. One fair-quality trial and one poor-quality trial reported similar efficacy for duloxetine and paroxetine for treating pain symptoms in MDD patients.[71,153] Five placebo-controlled studies provided mixed evidence for efficacy of active drugs compared to placebo for treatment of accompanying pain. Five trials compared duloxetine with placebo;[71,153-156] three of these reported statistically greater pain improvement in at least one duloxetine treatment arm.[153,155,156] Two studies compared paroxetine with placebo;[71,153] one found a statistically greater improvement for paroxetine.[71] Overall, mean differences in pain scores between groups were small and may not be clinically meaningful.

No studies evaluated the efficacy of antidepressants in a subgroup of patients with moderate to severe pain. For outcome measures, all five studies used a visual analog scale (VAS) for overall pain (0 mm to 100 mm scale, where higher scores indicate worse pain); one trial also used the Brief Pain Inventory (BPI) severity scale (0 to 10 scale, where higher scores indicate worse pain).[154] No study reported percentages of patients with clinically important improvement in pain. All studies were funded by the maker of duloxetine.

Effectiveness: KQ 3a: Depressive episode and KQ 3b: Accompanying symptoms. We identified no effectiveness trials for treatment of patients with depression and accompanying pain.

Pain: Detailed Analysis

Head-to-head evidence. ***Duloxetine vs. paroxetine vs. placebo.*** Two multicenter trials compared the efficacy of duloxetine, paroxetine, and placebo. Pain symptoms were not required for inclusion in either study. Moreover, baseline pain severity was mild in both trials.

One trial compared two high doses of duloxetine (80 mg/day and 120 mg/day) to low-dose paroxetine (20 mg/day) and placebo.[71] 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).

One multicenter trial (rated poor quality) compared the efficacy of low-dose duloxetine (40 mg/day), high-dose duloxetine (80 mg/day), and low-dose paroxetine (20 mg/day) for treatment of accompanying pain in patients with MDD over 8 weeks.[153] Statistical comparisons between active treatment groups were not reported, but median change from baseline to endpoint in VAS overall pain was minimal and similar for all groups (-4 mm for duloxetine 40 mg, -7.5 mm for duloxetine 80 mg, -3.0 mm for paroxetine, 0 mm for placebo). Pain improvement in the duloxetine 80 mg group was small but statistically significantly better than placebo ($P = 0.005$). Median improvement in pain scores did not differ between duloxetine 40 mg and placebo ($P = 0.172$) or between paroxetine and placebo ($P = 0.088$).

Placebo-controlled evidence. ***Duloxetine vs. placebo*****.** One multicenter trial compared high-dose duloxetine (60 mg/day) with placebo over 7 weeks for treating patients with MDD and pain symptoms.[154] 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).

Two trials compared the efficacy of high-dose duloxetine (60 mg/day) to placebo over 9 weeks for treatment of pain in patients with depression.[155,156] Inclusion criteria were similar in both studies: participants met DSM-IV criteria for MDD but were not required to have pain symptoms. Mean baseline pain severity was mild (VAS for overall pain: 29.0 and 25.4 for duloxetine, 28.2 and 26.2 for placebo). Both studies reported small but statistically significant differences in VAS overall pain improvement favoring duloxetine over placebo: -8.5 mm vs. -1.3 mm ($P = 0.019$)[155] and -11.0 mm vs. -6.4 mm ($P = 0.037$).[156]

Psychomotor Change: Key Points

One head-to-head trial addressed KQ 3a on depression response in subgroups with psychomotor retardation or psychomotor agitation (Table 24).[149] We rated the strength of evidence for this issue as low. We found no evidence for the comparative efficacy and effectiveness of second-generation antidepressants for the treatment of accompanying psychomotor symptoms (KQ 3b).

Table 24. Studies of adults with major depressive disorders and accompanying psychomotor change

Study	Interventions	N	Results	Quality Rating
Flament et al., 1999[149]	Fluoxetine Sertraline	286	KQ 3a. In patients with psychomotor retardation, depression scores and response rates were 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.

Efficacy: KQ 3a: Depressive episode in patients with psychomotor changes. One study provided evidence that fluoxetine and sertraline have similar efficacy for treatment of depression in patients with psychomotor retardation. The same study reported that sertraline was more efficacious than fluoxetine for treatment of depression in patients with psychomotor agitation.[149]

Efficacy: KQ 3b: Psychomotor changes in depressed patients. We identified no efficacy trials addressing treatment of psychomotor change symptoms.

Effectiveness: KQ 3a: Depressive episode and KQ 3b: Accompanying symptoms. We found no effectiveness trials concerning patients with depression and accompanying psychomotor problems.

Psychomotor Change: Detailed Analysis

Head-to-head evidence. ***Fluoxetine vs. 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.[149] 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).

Placebo-controlled evidence. We identified no placebo-controlled trials involving this patient population.

Somatization: Key Points

We identified one open-label, head-to-head effectiveness trial that compared effects of medications on accompanying somatization in depressed primary-care patients (KQ 3b) (Table 25).[49] The grade of evidence for the comparative efficacy and effectiveness of medications for the treatment of accompanying somatization (KQ 3b) is low.

Table 25. Studies of adults with major depressive disorders and accompanying somatization

Study	Interventions	N	Results	Quality Rating
Kroenke et al., 2001[49]	Fluoxetine Paroxetine Sertraline	601	KQ 3b. Improvement in somatization scores was similar in all groups (*P* = NR)	Fair

NR, not reported.

Efficacy: KQ 3a: Depressive episode and KQ 3b: Accompanying symptoms. We identified no efficacy trials that addressed either of these questions in patients with depression and somatization.

Effectiveness: KQ 3a: Depressive episode in patients with somatization. We identified no trials addressing treatment of depression in subgroups of patients with somatization.

Effectiveness: KQ 3b: Somatization in depressed patients. One open-label study provided evidence for the comparative effectiveness of SSRIs for treatment of accompanying somatization in patients with depression.[49] This trial found no difference in effectiveness among paroxetine, fluoxetine, and sertraline on a somatization severity scale measure.

Somatization: Detailed Analysis

Head-to-head evidence. ***Fluoxetine vs. paroxetine vs. 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.[49] 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).

Placebo-controlled evidence. We identified no placebo-controlled trials addressing efficacy or effectiveness of treating patients with depression and somatization.

Key Question 4: Comparative harms and adherence for second-generation antidepressants

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 were adverse events prespecified and defined. Short study durations and small sample sizes also limited the validity of adverse events assessment in many trials.

Few RCTs were designed to assess adverse events as primary outcomes. Most published studies were post hoc analyses or retrospective reviews of databases. We included observational studies if the sample size was larger than 100 and the study duration was at least 3 months.

Detailed information on included studies can be found in Evidence Table 5 in Appendix D; information on systematic reviews and meta-analyses on this topic appears in Evidence Table 6. Most studies were rated fair quality; for three studies, a quality grade was not applicable because of the nature of the study design. Studies rated other than fair are noted in text.

Adverse Events and Discontinuation Rates: Key Points

We analyzed adverse events data of 72 head-to-head efficacy studies of 16,780 patients and 39 additional studies of both experimental and observational design. Of these, only five were designed primarily to detect differences in adverse events. The method 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.

In efficacy trials, on average, 61 percent of patients experienced at least one adverse event during treatment. Nausea, headache, diarrhea, fatigue, dizziness, sweating, sexual dysfunction, tremor, dry mouth, and weight gain were the commonly reported adverse events. Overall, second-generation antidepressants led to similar adverse events.

However, results from multiple head-to-head RCTs document that the frequencies of *specific* adverse events can differ among drugs. These findings are generally consistent with results from observational studies. Specifically:

- Venlafaxine was associated with an approximately 10 percent (95% CI, 4-17 percent) higher incidence of nausea and vomiting than SSRIs as a class. In addition, pooled discontinuation rates because of adverse events in efficacy trials were statistically significantly higher for venlafaxine than for SSRIs (RR, 1.50; 95% CI, 1.21-1.84).

- In most studies, sertraline led to higher rates of diarrhea than comparator drugs (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine).[30,42,44-46,51,53,76,77,90,92,108,110,111,150] Incidence was 8 percent (95% CI, 3-11

percent) higher than with comparator drugs. Whether this finding can be extrapolated to comparisons of sertraline with other second-generation antidepressants remains unclear.

- Mirtazapine led to higher weight gains than comparator drugs.[59-61,72,73,93,94] Mean weight gains relative to pretreatment weights ranged from 0.8 kg to 3.0 kg after 6 weeks to 8 weeks of treatment. Paroxetine had higher weight gains than fluoxetine and sertraline.[41,48]

- 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).[82,83,87,94,96,97] Whether this finding can be extrapolated to comparisons of trazodone with other second-generation antidepressants remains unclear.

Discontinuation syndromes (e.g., headache, dizziness, nausea) occurred in 0 percent to 86 percent of patients. Paroxetine and venlafaxine had the highest incidence of this problem, and fluoxetine had the lowest incidence.

Pooled estimates from efficacy trials suggest that these differences do not lead to any statistically significant differences in overall discontinuation rates among SSRIs as a class and other second-generation antidepressants.

Adverse Events and Discontinuation Rates: Detailed Analysis

Table 26 presents 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), weight change, and discontinuation syndrome. 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 27 depicts, by specific drug, the mean incidence and 95 percent confidence interval for specific adverse events commonly reported in trials. Statistics are descriptive only. Comparisons across different drugs should be made with caution given differences in assessment and reporting of adverse events across trials.

General tolerability. Nausea, headache, diarrhea, fatigue, dizziness, sweating, tremor, dry mouth, and weight gain were commonly reported adverse events. In efficacy trials, on average, 61 percent of patients experienced at least one adverse event during the course of a given study.

Two large observational studies (three articles) examined the comparative rates of adverse events among SSRIs.[160-162] Overall, no substantial differences among examined drugs were apparent. However, not all currently approved SSRIs were investigated in these studies.

A British study pooled data from a cross-sectional study of a prescription-event monitoring study of general practitioners 6 months to 1 year after they had issued prescriptions.[160,161] Included drugs were fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, and nefazodone. The final cohort exceeded 10,000 patients for each drug. Demographics and

Table 26. Studies assessing adverse events and discontinuation rates

Study	Design Interventions	N	Results	Quality Rating
General Tolerability and Discontinuation				
Brambilla et al., 2005[163]	Systematic review, Fluoxetine vs. SSRIs	NR	No difference in discontinuation rates because of adverse events	Good
Greist et al., 2004[164]	Pooled analysis Duloxetine vs. paroxetine vs. fluoxetine	2,345	No differences in nausea between duloxetine and paroxetine or duloxetine and fluoxetine	NA
Haffmans et al., 1996[29]	RCT Fluvoxamine vs. paroxetine	217	Significantly more diarrhea and nausea with fluvoxamine	Fair
Mackay et al., 1997,[160] 1999[161,165]	Prescription event monitoring Fluoxetine, fluvoxamine, nefazodone, paroxetine, venlafaxine	> 60,000	Venlafaxine had highest rate of nausea and vomiting; fluvoxamine had the most overall adverse events	NA
Meijer et al., 2002[162]	Observational study Sertraline vs. SSRIs	1,251	Significantly more diarrhea with sertraline	Fair
Rapaport et al., 1996[33]	RCT Fluoxetine vs. fluvoxamine	100	Significantly more nausea with fluoxetine	Fair
Changes in Weight				
Benkert et al., 2000[72]	RCT Paroxetine vs. mirtazapine	275	Higher weight gain with mirtazapine	Fair
Croft et al., 2002[166]	RCT Bupropion vs. placebo	423	Small weight loss with bupropion over 44 weeks	Fair
Fava et al., 2000;[48] Fava et al., 2002[41]	RCT Fluoxetine vs. paroxetine vs. sertraline	284	Highest weight gain with paroxetine	Fair
Goldstein et al.,1997[167]	RCT Fluoxetine vs. placebo	671	Higher weight loss with fluoxetine in older patients	Fair
Guelfi et al., 2001[93]	RCT Venlafaxine vs. mirtazapine	157	Higher weight increase with mirtazapine	Fair
Halikas et al., 1995[94]	RCT Trazodone vs. Mirtazapine	150	More weight gain with mirtazapine	Fair
Harto et al., 1988[168]	RCT Fluoxetine vs. placebo	35	Higher weight loss with fluoxetine	Fair
Hong et al., 2003[59]	RCT Fluoxetine vs. mirtazapine	133	Higher weight gain with mirtazapine	Fair
Michelson et al., 1999[145] Reimherr et al., 1998[122]	RCT Fluoxetine vs. placebo	395	Fluoxetine and placebo showed a weight gain	Fair
Schatzberg et al., 2002[73]	RCT Paroxetine vs. mirtazapine	255	Higher weight gain with mirtazapine	Fair

NA, not applicable; NR, not reported; RCT, randomized controlled trial.

Table 26. Studies assessing adverse events and discontinuation rates (continued)

Study	Design Interventions	N	Results	Quality Rating
Versiani et al., 2005 [60]	RCT Fluoxetine vs. mirtazapine	297	Higher weight gain with mirtazapine	Fair
Wheatley et al., 1998[61]	RCT Fluoxetine vs. mirtazapine	133	Significantly higher weight gain with mirtazapine	Fair
Discontinuation Syndrome				
CSM Expert Working Group, 2004[169]	Systematic review and meta-analysis Second-generation antidepressants	NR	No differences in risk among second-generation antidepressants	Good
Judge et al., 2002[170]	Open-label trial Fluoxetine and paroxetine	150	Significantly fewer symptoms in the fluoxetine group than the paroxetine group	Fair
Perahia et al., 2005[171]	Pooled analysis Duloxetine vs. placebo	3,624	Significantly higher rate of discontinuation syndrome with duloxetine than with placebo (44% vs. 23%)	Fair
Zajecka et al., 1998[172]	RCT Fluoxetine vs. placebo	395	Dizziness significantly less frequent in fluoxetine patients at 4 and 6 weeks	Fair

Table 27. Mean incidence of specific adverse events across comparative trials

Drug	Diarrhea	Dizziness	Headache	Insomnia	Nausea	Somnolence
Mean Percentage* (95% confidence interval)						
Bupropion	10.2% (3.1%-17.2%)	11.6% (2.2%-21.1%)	28.6% (23.2%-34.1%)	15.7% (10.9%-20.6%)	14.5% (8.9%-20%)	6.7% (0%-14.2%)
Citalopram	7.5% (4%-11%)	9.1% (3.7%-14.4%)	14.3% (7.8%-20.7%)	6.9% (1.4%-12.5%)	14.3% (9.6%-19.1%)	12.6% (5.4%-19.9%)
Duloxetine	16.1% (9.5%-22.8%)	41.5% (-8.1%-91%)	15.8% (3.9%-27.7%)	16.6% (14.1%-19.1%)	42.6% (7.2%-78%)	36.8% (8.4%-65.2%)
Escitalopram	7.6% (0%-16%)	1.3% (0%-14.3%)	7.4% (3.3%-11.5%)	6.9% (1.3%-10.8%)	11.5% (7.2%-15.7%)	4.2% (0%-12.2%)
Fluoxetine	10.4% (7.5%-13.3%)	7.6% (6.2%-9%)	21.3% (16.3%-26.3%)	13.8% (11.4%-16.2%)	18.4% (15.9%-20.9%)	7.8% (5.3%-10.3%)
Fluvoxamine	19.2% (0%-53.5%)	18.3% (0%-62.4%	20.1% (3.3%-36.8%)	24.2% (0.3%-48%)	26% (14.4%-37.6%)	8.8% (0%-32.2%)
Mirtazapine	3.7% (0%-8.1%)	8.4% (4.6%-12.1%)	12.1% (10%-14.3%)	8% (1.8%-14.3%)	6.3% (3.8%-8.7%)	18.7% (10.3%-27.1%)
Nefazadone	12% (7.3%-16.8%)	21.3% (15.6%-27%)	32.4% (21.6%-43.2%)	13.3% (7%-19.5%)	21.6% (12.2%-30.9%)	25.3% (11.4%-39.1%)
Paroxetine	15% (11.1%-18.9%)	0.8% (0%-2.9%)	3.2% (0%-8.1%)	12.7% (9.9%-15.4%)	21.4% (17.1%-25.7%)	18.2% (13.7%-22.7%)
Sertraline	11.3% (7.6%-15%)	8.5% (5.9%-11.2%)	19.8% (14.9%-24.7%)	9.8% (6.1%-13.6%)	17.3% (13.7%-20.8%)	13.3% (9.8%-16.8%)
Trazodone	4.3% (0%-13.8%)	24.1% (11.8%-36.5%)	22.1% (11.7%-32.5%)	4.8% (1.8%-7.8%)	14.4% (4.6%-24.1%	42.4% (19.5%-65.2%)
Venlafaxine	6.4% (2.9%-10%)	14.3% (8.9%-19.7%)	19.3% (13.9%-24.7%)	17.8% (12.2%-23.2%)	29.3% (24.8%-33.8%)	14.5% (9.5%-19.4%)

*Weighted mean incidence calculated from RCTs. Method and extent of adverse event assessment varied among studies. Comparisons across drugs must be made cautiously.

indications were similar among study groups. Overall, the mean incidence 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.

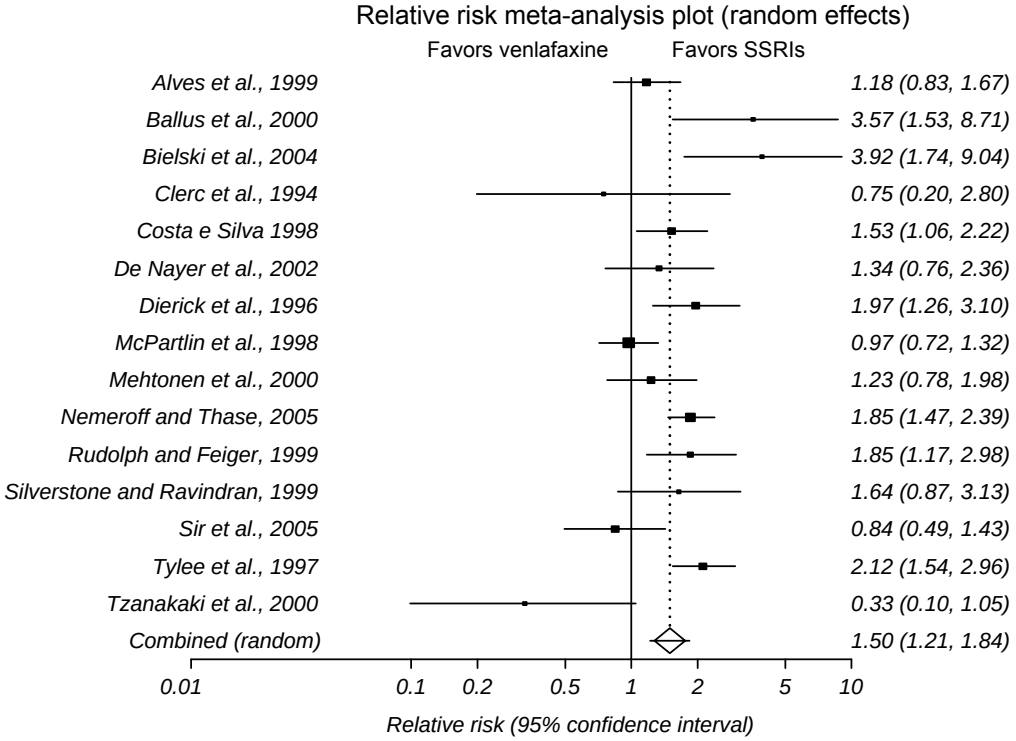
A Dutch prospective observational study followed 1,251 patients for up to 12 months to assess adverse events of sertraline (n = 659) and other SSRIs (fluoxetine, fluvoxamine, paroxetine).[162] No exclusion criteria were applied. Psychiatrists recorded adverse events at each patient visit; the investigators used the WHO adverse reaction terminology for outcome assessment. Significantly more sertraline patients than patients on other drugs had a diagnosis of depressive disorder at baseline ($P < 0.001$). Overall, 74.1 percent of patients reported at least one adverse event.

Nausea and vomiting. In efficacy trials, venlafaxine (an SNRI) had a consistently higher rate of nausea and vomiting than SSRIs. In six studies, the difference reached statistical significance.[56,57,65,67,70,74] 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.[160,161] Nausea and vomiting were the two most frequent clinical reasons for withdrawal in the first month of treatment for all drugs. Venlafaxine had the highest rate of nausea and vomiting per 1,000 patient-months.

Using data from efficacy trials, we compared the pooled relative risk of nausea and vomiting for venlafaxine with that for SSRIs as a class (Figure 14). The RR was 1.50 (95% CI, 1.21-1.84). The corresponding number needed to harm (NNH) was 9 (95% CI, 6-23).

Figure 14. Relative risk of nausea and vomiting of venlafaxine compared with 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).[164]

Changes in weight. Consistently, studies comparing mirtazapine with other second-generation antidepressants reported higher weight gains for mirtazapine than for the comparator groups.[59-61,72,73,93,94] In two RCTs, these differences reached statistical significance.[72,73] 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.

Three placebo-controlled RCTs specifically assessed weight changes with fluoxetine treatment.[122,145,167,168] Findings were mixed. Two studies, one conducted in 671 patients older than 60 years,[167] recorded a statistically significant weight loss for fluoxetine compared with placebo.[167,168] The third study reported a weight gain.[122,145]

A 32-week acute- and continuation-phase trial assessed differences in weight changes among patients treated with fluoxetine, paroxetine, and sertraline.[41,48] 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 double-blinded, placebo-controlled, 52-week acute- and continuation-phase trial assessed weight changes during bupropion treatment.[166] 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.

Gastrointestinal adverse events. Two RCTs were designed primarily to detect differences in harms between fluvoxamine and citalopram[29] and fluvoxamine and fluoxetine.[33] A Dutch multicenter trial assessed gastrointestinal side effects from citalopram (20-40 mg/day) and fluvoxamine (100-200 mg/day).[29] 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.[33] 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 ($P < 0.05$).[162] 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).[30,42,44-46,51,53,76,77,90,92,108,110,111,150] Incidence was 8 percent (95% CI, 3-11 percent) higher than with comparator drugs. The NNH is 13 (95% CI, 9-29). Whether this finding can be extrapolated to comparisons of sertraline with other second-generation antidepressants remains unclear.

Discontinuation syndrome. Withdrawal syndromes (e.g., headache, dizziness, lightheadedness, nausea, anxiety) commonly occur following the abrupt discontinuation of second-generation antidepressants. A good systematic review conducted by an Expert Working Group of the UK Committee on Safety in Medicines (CSM) assessed the frequency of discontinuation syndromes in second-generation antidepressants.[169] 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.

Three studies not included in the UK systematic review provide consistent results.[170-172] One head-to-head trial compared fluoxetine with paroxetine.[170] 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.[172] A pooled analysis of six trials investigated the effects of abrupt discontinuation of duloxetine and placebo.[171] Significantly more patients receiving duloxetine than receiving placebo reported discontinuation syndromes (44.3 percent vs. 22.9 percent; $P < 0.05$).

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

Table 28 summarizes average discontinuation rates. Figures 15 through 17 depict relative risks of discontinuation rates comparing these agents with SSRIs as a class. Three sets of individual meta-analyses for overall discontinuation and for discontinuation from adverse events and lack of efficacy are presented in Appendix H. Available data for duloxetine and trazodone were insufficient to determine discontinuation rates that might be attributed to lack of efficacy.

Overall discontinuation rates did not differ significantly between SSRIs and bupropion, duloxetine, mirtazapine, nefazodone, trazodone, or venlafaxine (Figure 15). A published meta-analysis of 15 RCTs did not find any statistically significant differences in discontinuation rates because of adverse events between fluoxetine and other SSRIs as a class.[163] The only statistically significant difference in our pooled estimates of the relative risks of discontinuation because of

Table 28. Average rates of overall discontinuation, discontinuation because of adverse events, and discontinuation because of lack of efficacy

	Overall Loss to Followup (%)	Discontinuation Because of Adverse Events (%)	Discontinuation Because of Lack of Efficacy (%)
SSRIs	20.8	8.1	4.4
Bupropion	14.1	6.7	3.1
Duloxetine	17.2	5.5	NR
Mirtazapine	21.6	9.5	3.4
Nefazodone	23.6	15.0	2.0
Trazodone	20.7	7.0	NR
Venlafaxine	24.8	11.5	3.5

Figure 15. Relative risks of overall discontinuation

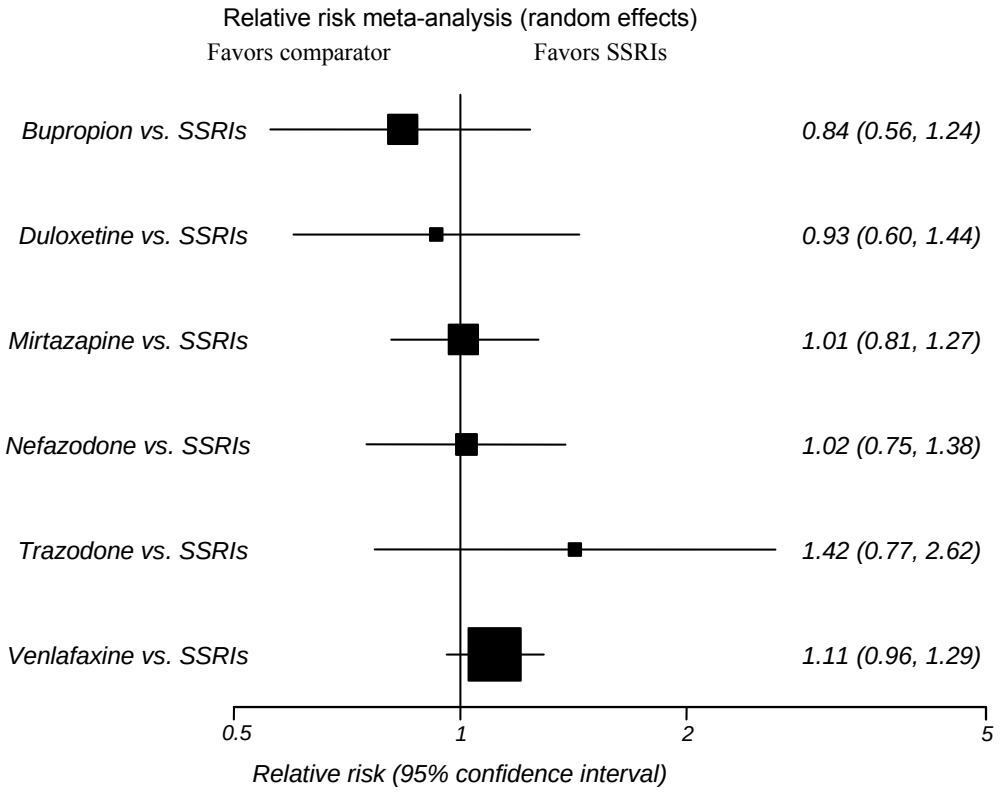


Figure 16. Relative risk of discontinuation because of adverse events

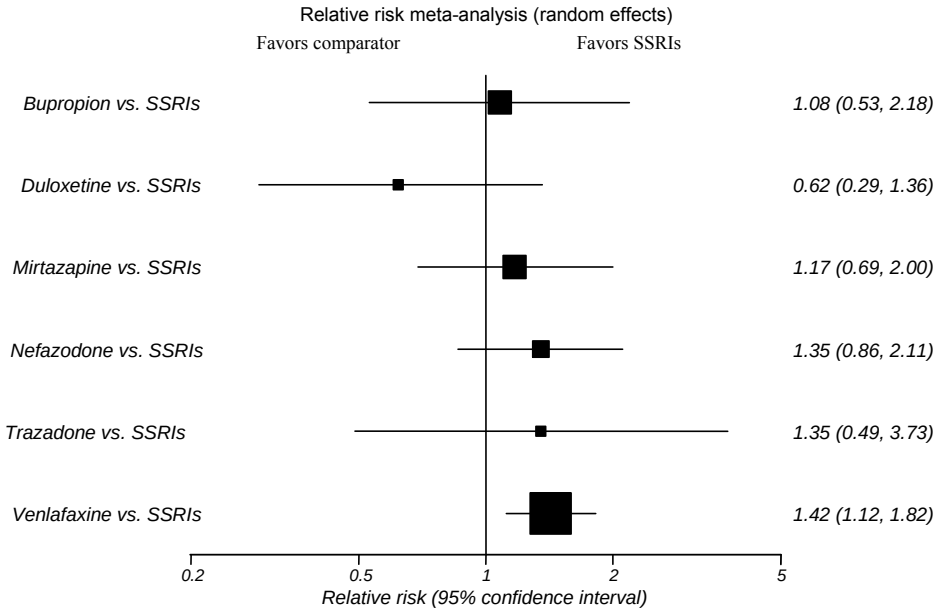
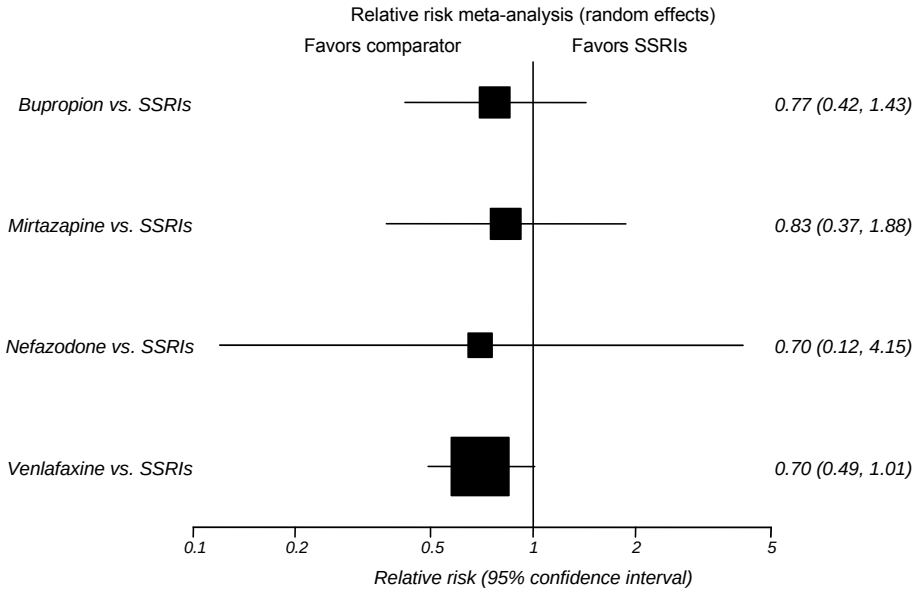


Figure 17. Relative risk of discontinuation because of lack of efficacy



adverse events was a higher rate for patients on venlafaxine than for patients on SSRIs (RR, 1.42; 95% CI, 1.12-1.82) (Figure 16). Overall, this finding was balanced by lower discontinuation rates because of lack of efficacy for venlafaxine (RR, 0.70; 95% CI, 0.49-1.01) (Figure 17).

Nefazodone and trazodone had rates of discontinuation because of adverse events similar to those of venlafaxine. However, differences with SSRIs did not reach statistical significance because of smaller sample sizes.

Severe Adverse Events: Key Points

The evidence on the comparative risk of second-generation antidepressants on most severe 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 risk of rare but severe 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.

Based on five RCTs (N = 1,489), bupropion led to a significantly lower rate of sexual adverse events than fluoxetine and sertraline.[79,80,88,89,102] The NNT to experience one additional person with high overall satisfaction of sexual functioning is 6 (95% CI, 4-9).

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).[37,41,50,86] Underreporting of absolute rates of sexual dysfunction, however, is likely in these studies. The NNH is 6 (95% CI, 4-9).

Table 29 summarizes studies included for the assessment of severe adverse events: suicidality, sexual dysfunction, cardiovascular events, seizures and other events.[173]

Table 29. Studies assessing severe adverse events

Study	Design Interventions	N	Results	Quality Rating
Suicidality (Suicidal thoughts and behavior)				
CSM Expert Working Group, 2004[169]	Systematic review and meta-analysis Second-generation antidepressants	NR	No differences in risk among second-generation antidepressants	Good
Fergusson et al., 2005[174]	Meta-analysis SSRIs vs. placebo	87,650	Higher risk of suicide attempts for SSRI-treated patients	Good
Khan et al., 2003[175]	Retrospective cohort study Bupropion, citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, venlafaxine	48,277	No difference in the rate of suicides	Fair
Gunnell et al., 2005[176]	Meta-analysis Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, all vs. placebo	40,000	Increased risk of nonfatal suicide attempts compared with placebo; no difference in risk among drugs	Good
Martinez et al., 2005[177]	Case-control study Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, TCAs	146,095	No difference in risk of suicide or nonfatal suicide attempts between SSRIs and TCAs or among individual SSRIs	Good
Didham et al., 2005[178]	Retrospective cohort study Citalopram, fluoxetine, paroxetine	57,000	Significant association between nonfatal suicide attempts and SSRIs; no difference in risk among drugs	Fair
Pedersen, 2005[173]	Retrospective cohort study Escitalopram vs. placebo	4,091	Higher rate of nonfatal suicide attempts for escitalopram than for placebo	Fair
Jick et al., 1992[179]	Database review Fluoxetine, first-generation antidepressants	8,730	No difference in suicides between fluoxetine and first-generation antidepressants	NA
Jick et al., 2004[180]	Case-control study Fluoxetine, paroxetine	159,810	No difference in risk among drugs	Fair
Jick et al., 1995[181]	Retrospective cohort study and nested case-control study Fluoxetine, trazodone, first-generation antidepressants	172,598	Significantly higher risk of suicide for fluoxetine and mianserin than for dothiepin	Fair
Aursnes et al., 2005[182]	Meta-analysis of unpublished data Paroxetine	1,466	Higher rate of suicides for paroxetine than for placebo	Fair
Lopez-Ibor, 1993[183]	Database review Paroxetine, first-generation antidepressants	4,686	No difference in suicidality	NA

CSM, Committee on Safety in Medicines; NA, not applicable; NR, not reported; RCT, randomized controlled trials; TCAs, tricyclic antidepressants.

Table 29. Studies assessing severe adverse events (continued)

Study	Design, Interventions	N	Results	Quality Rating
Sexual Dysfunction				
Clayton et al., 2002[184]	Cross-sectional survey Bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine	6,297	Highest risk for paroxetine, lowest risk for bupropion	Fair
Coleman et al., 2001[79]	RCT Bupropion SR vs. fluoxetine	456	Significantly more sexual adverse events with fluoxetine	Fair
Feighner et al., 1991[80]	RCT Bupropion vs. fluoxetine	61	Higher rate of sexual dysfunction for fluoxetine	Fair
Coleman et al., 1999[88]	RCT Bupropion SR vs. sertraline	364	Significantly more sexual adverse events with sertraline	Fair
Croft et al., 1999[89]	RCT Bupropion SR vs. sertraline	360	No differences	Fair
Segraves et al., 2000[102]	RCT Bupropion vs. sertraline	248	Significantly more sexual adverse events with sertraline	Fair
Nieuwstraten and Dolovich, 2001[191]	Meta-analysis Bupropion vs. SSRIs	1,332	Significantly higher rate of sexual satisfaction in bupropion group	Good
Montejo et al., 2001[190]	Prospective cohort study Citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine	1,022	Highest incidence of sexual dysfunction for citalopram, paroxetine, and venlafaxine; lowest for mirtazapine and nefazodone	Fair
Landen et al., 2005[189]	Cross-sectional study Citalopram vs. paroxetine	119	No differences	Fair
Ekselius et al., 2001[186]	RCT Citalopram vs. sertraline	308	No differences	Fair
Delgado et al., 2005[185]	Pooled analysis Duloxetine vs. paroxetine vs. placebo	1,466	Higher rate of sexual dysfunction for paroxetine	Fair
Philip et al., 2000[192]	Prospective cohort study Fluoxetine, fluvoxamine, paroxetine, sertraline, moclobemide	268	No difference among SSRIs	Fair
Fava et al., 1998[37]	Pooled Analysis Fluoxetine vs. paroxetine	128	Significantly more sexual adverse events with paroxetine	Fair
Kennedy et al., 2000[188]	Prospective cohort study Paroxetine, sertraline, venlafaxine	174	No difference	Fair
Kavoussi et al., 1997[90,108]	RCT Sertraline vs. bupropion	248	Higher rate of sexual adverse events with sertraline	Fair
Nemeroff et al., 1995[51]	RCT Sertraline vs. fluvoxamine	95	Higher rate of sexual adverse events with sertraline	Fair
Behnke et al., 2003[76]	RCT Sertraline vs. mirtazapine	346	Significantly more sexual adverse events with sertraline	Fair
Feiger et al., 1996[92]	RCT Sertralinenefazodone	160	Sertraline had significant adverse effects on sexual function; nefazodone had none	Fair
Aberg-Wistedt et al., 2000[53]	RCT Sertralineparoxetine	353	Significantly more libido decreases in patients taking sertraline	Fair
Ferguson et al., 2001[187]	RCT Sertraline vs. trazodone	150	Higher reemergence rate of sexual dysfunction for sertraline	Fair

Table 29. Studies assessing severe adverse events (continued)

Study	Design, Interventions	N	Results	Quality Rating
Seizures				
Dunner et al., 1998[193]	Uncontrolled, open-label trial Bupropion	3,100	Rate of seizures for bupropion within reported range of other antidepressants	Fair
Johnston et al., 1991[194]	Uncontrolled, open-label trial Bupropion	3,341	Rate of seizures for bupropion within range of other antidepressants	Fair
Whyte et al., 2003[195]	Prospective observational study SSRIs, TCAs, venlafaxine	538	Seizures more common in venlafaxine overdose than in SSRI or TCA overdose	Good
Cardiovascular Events				
Thase et al., 1998[196]	Pooled analysis Venlafaxine	3,744	Increase in diastolic blood pressure for venlafaxine	Fair
Thase et al., 2005[197]	Post hoc data analysis Fluoxetine, paroxetine, duloxetine	1,873	Greater change in heart rate for duloxetine than for fluoxetine and paroxetine	NA
Other Adverse Events				
Buckley et al., 2002[198]	Database analysis Citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine	47,329	Highest rate of fatal toxicity for venlafaxine	NA
Coogan et al., 2005[199]	Case-control SSRIs	4,996	No association between breast cancer and SSRIs	Fair
Kirby et al., 2002[200]	Retrospective cohort study SSRIs, venlafaxine	199	Increased rate of hyponatremia in patients on SSRIs and venlafaxine	Fair
Thapa et al., 1998[201]	Retrospective cohort study Fluoxetine, paroxetine, sertraline, trazodone	2,428	No difference in the risk of falls	Fair

Severe Adverse Events: Detailed Analysis

Suicidality. Eleven studies (12 articles) assessed the risk of suicidality (suicidal thinking or behavior) in patients treated with second-generation antidepressants.[169,174-183] 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.[175-178,180] However, these findings are based primarily on retrospective cohort studies,[175,177,178,180] and confounding by indication (i.e., patients who are at higher risk for suicide may be prescribed some medications rather than others) may lead to erroneous conclusions.

The largest attempt to determine whether second-generation antidepressants increase the risk of suicidality was conducted in 2004 by the CSM working group.[169] The CSM experts investigated ongoing safety concerns about suicidal behavior with some second-generation antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, venlafaxine) in patients with MDD. They used data from 477 published and unpublished RCTs on more than 40,000 individuals as well as spontaneous reporting data. However, these data were limited to studies funded by the pharmaceutical industry.

A meta-analysis limited the CSM data to placebo-controlled trials of SSRIs in ~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, 0.20-3.40).[176] The risk of suicide-related events was similar between second-generation antidepressants and active comparators, although some evidence of an increased risk of nonfatal suicide attempts was detected (OR, 1.57; 95% CI, 0.99-2.55).

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, 2.25; 95% CI, 1.14-4.55).[174] 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, 1.06-3.57). No significant difference existed in the pooled analysis of SSRIs compared with TCAs (OR, 0.88; 95% CI, 0.54-1.42). The overall rate of suicide attempts was 3.9 (95% CI, 3.3-4.6) 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 (i.e., 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.[177] It did not find any evidence that the risk of either suicide (OR, 0.57; 95% CI, 0.26-1.25) or nonfatal suicide attempts (OR, 0.99; 95% CI, 0.86-1.14) was greater in patients on second-generation antidepressants than in patients on TCAs.

Findings of other large observational studies and meta-analyses are similar.[173,175,178-183] Most detected an increase in nonfatal suicide attempts but no significant difference in suicides. In general, no significant differences in risks regarding suicidality could be detected between second-generation antidepressants and TCAs.

An internal report of all published and unpublished studies on paroxetine conducted by GlaxoSmithKline is consistent with findings from studies described above.[202]

Sexual dysfunction. Multiple studies assessed the comparative risk of sexual dysfunction among second-generation antidepressants.[79,88,89,102,190] 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.[190] 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). This study did not include data on bupropion, escitalopram, and trazodone.

A cross-sectional survey of patients on second-generation antidepressants presented similar results.[184] 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[37,51,53,76,90,92] 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; $P = 0.004$).[90] A pooled analysis of four efficacy trials comparing paroxetine and duloxetine reported significantly higher rates of sexual dysfunction for patients on paroxetine.[185]

Six RCTs assessed the comparative risk of sexual dysfunction between two or more second-generation antidepressants as primary outcome measures.[79,88,89,102,186,187]

Citalopram vs. 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.[186] 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 vs. 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.[191] We do not describe studies included in this meta-analysis individually.[80,88,89,102] The rate of sexual satisfaction was significantly higher in patients receiving bupropion than in those receiving SSRIs (RR, 1.28; 95% CI, 1.16-1.41).

An 8-week RCT (not in the meta-analysis cited above) compared efficacy and sexual dysfunction of bupropion SR (150-400 mg/day), fluoxetine (20-60 mg/day), and placebo in 456 outpatients with MDD.[79] Findings are consistent with those from the 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, 4-9).

Sertraline vs. trazodone. 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 trazodone.[187]

Seizures. Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of seizures in patients taking any of the reviewed drugs, including bupropion. Two open-label trials[193,194] examined the rate of seizures during bupropion treatment. 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.[195]

Cardiovascular adverse events. A post hoc analysis examined pooled data from 3,744 patients participating in venlafaxine trials.[196] At 6 weeks, 11.5 percent of venlafaxine patients had a supine diastolic blood pressure (DBP) greater than 90 mm Hg (placebo, 5.7 percent; $P < 0.001$). During continuation-phase treatment (up to 12 months), significantly more venlafaxine subjects than placebo subjects with normal supine DBPs developed elevated readings ($P = 0.05$).

A post hoc analysis of six RCTs (published and unpublished) comparing duloxetine with fluoxetine and paroxetine did not find any statistically significant differences in supine systolic or diastolic blood pressure.[197] Patients receiving duloxetine had a greater mean change in heart rate than those on either fluoxetine (+2.8 beats/min vs. -1.0 beat/min) or paroxetine (+1.0 beats/min vs. -1.4 beats/min).

Efficacy trials infrequently assessed cardiovascular outcomes. Two RCTs, one comparing venlafaxine XR with sertraline[78] and one comparing venlafaxine with fluoxetine,[66] detected statistically significant increases in supine DBP[78] and supine pulse rate[66] for venlafaxine relative to fluoxetine.

Other adverse events. 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.[198] A case-control study did not find an association between SSRIs and breast cancer.[199] A retrospective review of the charts of 2,428 nursing home residents did not detect differences in the risk of falls among fluoxetine, paroxetine, and sertraline.[201]

Hyponatremia. A retrospective cohort study 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, 1.4-8.9).[200] 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.[203] 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.

Hepatotoxicity. Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of liver toxicity during nefazodone treatment. Nevertheless, numerous case reports not included in this report contain low quality but potentially important evidence citing an increased risk of liver toxicity during nefazodone treatment.[204]

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.[165] 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.[205]

A postmarketing survey identified cases of the serotonin syndrome in British general practice among patients who received nefazadone.[165] In a cohort of 11,834 patients, 19 cases met criteria for the syndrome (incidence = 0.4 cases per 1,000 patient-months of treatment with nefazodone). Similar rates of the syndrome were reported for fluoxetine, sertraline, paroxetine, and venlafaxine.

Adherence: Key Points

Few efficacy studies reported rates of adherence. Lack of adherence, however, was often used as a reason to exclude patients from the study. Efficacy trials do not indicate any differences in adherence among second-generation antidepressants. However, the quality of reporting and assessment of adherence was limited. Findings from highly controlled efficacy studies may have limited generalizability to "real-world" practice especially because of the overall short duration of these trials. The evidence is insufficient to conclude on adherence in effectiveness studies. A review of a large, managed care database suggested that extended-release formulations might have greater adherence than immediate-release medications.[206] Strength of evidence is moderate for efficacy studies and low for effectiveness studies.

Adherence: Detailed Analysis

The published literature in this area 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.[207] Given the lack of a clear definition, we use the term adherence. Table 30 summarizes included studies on adherence.

The majority of RCTs that reported adherence stated a rate between 90 percent and 100 percent. Nineteen published studies, examining 18 RCTs, reported levels of adherence.[25,30,35,59,79,85,88-90,128,136,193,194,208-213] Most, however, contained only minimal information, and many did not stratify by treatment. Furthermore, they provided little or no information on the methods of assessment. For example, one fair study reported that both treatment arms exhibited 100 percent adherence, but the investigators did not describe their method of determining adherence.[60] Only 10 of 18 RCTs reported adherence rates for different treatment arms;[30,36,79,81,82,87,88,100,117,212] of these, 8 were head-to-head comparisons (Table 30).[30,79,84,88-90,97,102] None of these studies noted a significant difference in adherence.

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.

A retrospective database analysis used the Integrated Healthcare Information Services National Managed Care Benchmark Database to examine adherence levels in 116,090 patients being treated with SSRIs (immediate-release citalopram, escitalopram, fluoxetine, or sertraline) compared with controlled-release paroxetine.[206] Their primary finding was that patients on a controlled-release formula were significantly more compliant than patients on immediate-release formulations. After controlling for baseline covariates (age, sex, insurance type, titration rates, mental health specialty care, diagnoses, and comorbidity), patients initiating an immediate-release SSRI were 13.6 percent less likely to be adherent than patients on controlled-release paroxetine ($P < 0.0001$).

Table 30. Head-to-head trials reporting adherence to second-generation antidepressants

Study	N Drugs and Dose Duration	Rate of Adherence	Quality Rating
Coleman et al., 1999[88]	364 Bupropion SR 150-400 mg/d Sertraline 50-200 mg/d Placebo 8 weeks	Tablet: Bupropion SR 96% Sertraline 97% Placebo 96% Capsule: Bupropion SR 98% Sertraline 98% Placebo 98%	Fair
Coleman et al., 2001[79]	456 Bupropion SR 150-400 mg/d Fluoxetine 20-60 mg/d Placebo 8 weeks	97% to 99% in all groups	Fair
Croft et al., 1999[89]	360 Bupropion SR 150-400 mg/d Sertraline 50-200 mg/d Placebo 8 weeks	Bupropion SR 98% Sertraline 97% Placebo 98%	Fair
Ekselius et al., 1997[30]	400 Citalopram 20-60 mg/d Sertraline 50-100 mg/d 24 weeks	Citalopram 95% Sertraline 90%	Good
Kavoussi et al., 1997[90]	248 Bupropion SR 100-300 mg/d Sertraline 50-200 mg/d 16 weeks	Bupropion SR 98% Sertraline 99%	Fair
Segraves et al., 2000[102]	248 Bupropion SR 100-300 mg/day Sertraline 50-200 mg/day 16 weeks	Bupropion 98% Sertraline 99%	Fair
Weihs et al., 2000[84]	100 Bupropion SR 100-300 mg/d Paroxetine 10-40 mg/d 6 weeks	Bupropion SR 95% Paroxetine 98%	Good
Weisler et al., 1994[97]	124 Bupropion 225-450 mg/day Trazodone 150-400 mg/day 6 weeks	Bupropion 95% Trazodone 90%	Fair

CR, controlled release; IR, immediate release; SR, sustained release.

Key Question 5: Efficacy, effectiveness, and harms for selected populations

KQ 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); and
- patients taking other medications.

Overview

We did not find any studies directly comparing efficacy, effectiveness, and harms of second-generation antidepressants between subgroups and the general population for the treatment of depression syndromes (depressive disorders), which include MDD, dysthymia, and subsyndromal depression including minor depression. Numerous studies, however, conducted subgroup analyses or used subgroups as the study population.

Overall, we included 44 studies in addressing this key question: 36 RCTs, 3 pooled analyses, 2 open-label medication trials (1 randomized), 2 observational studies, and 1 systematic review. We focused on groups defined by age, sex, race or ethnicity, and comorbidities (which included HIV/AIDS, alcohol and substance abuse, Alzheimer's disease or dementia, cardiovascular disease, dialysis, and stroke). These results provide indirect evidence for KQ 5. All studies were rated as fair quality unless otherwise noted.

We present key points and detailed analyses below for the population groups noted above. Details about included studies are presented in Table 31 (listed alphabetically by author within each subgroup). Strength of evidence is moderate for comparative efficacy and effectiveness for age and low for sex, race or ethnicity, and comorbidities; it is low for harms for age.

Age: Key Points

No studies directly compared the efficacy of second-generation antidepressants between either the elderly (60 to 79 years of age) or the very elderly (80 years of age or older) and the general population. Twelve head-to-head efficacy trials[31,34,39,44,45,49,52,55,73,84,94,114,214,215] and two meta-analyses (pooled analyses of original data)[216,217] provide mixed evidence on differences in efficacy in the elderly or very elderly treated with second-generation antidepressants. Comparisons were available for less than one-fourth of the potential comparisons between the 12 second-generation antidepressants addressed in this report. Only seven head-to-head trials or meta-analyses compared the efficacy of any non-SSRI second-generation antidepressant with any other second-generation antidepressant.[55,73,84,94,215-217]

Subgroup analyses of two effectiveness studies provide mixed evidence on differences in effectiveness of second-generation antidepressants between either the elderly or very elderly and the general population for the treatment of MDD,[49] dysthymia, and minor depression.[112,113] We did not find any studies directly comparing the harms of second-generation antidepressants between either the elderly or very elderly and the general population. Some findings from randomized controlled trials and observational evidence indicate that very elderly patients might have an increased risk for some rare but potentially serious adverse events such as hyponatremia and weight loss.[167,200]

Table 31. Studies of efficacy, effectiveness, and harms for patient subgroups

Study	Interventions	N	Results	Quality Rating
Age				
Roose et al., 2004[219]	Citalopram vs. placebo	174	No significant difference in response/remission except in high severity group	Fair
Rocca et al., 2005[114]	Citalopram vs. sertraline	138	No significant difference	NA
Allard et al., 2004[55]	Citalopram vs. venlafaxine XR	151	No significant difference	Fair
Burt et al., 2005[218]	Duloxetine vs. placebo	114	Duloxetine was more efficacious (response/remission); no difference in effect in women 40-55 vs. older or younger women	Fair
Kasper et al., 2005[31]	Escitalopram vs. fluoxetine vs. placebo	517	No significant difference in response rates; remission rates lower for fluoxetine than escitalopram	Fair
Cassano et al., 2002[34]	Fluoxetine vs. paroxetine	242	No significant difference	Fair
Schone and Ludwig, 1993[39] Geretsegger et al., 1994[214]	Fluoxetine vs. paroxetine	106	Greater response rate for paroxetine	Fair
Kroenke et al., 2001[49]	Fluoxetine vs. paroxetine vs. sertraline	573	No significant difference	Fair
Devanand et al., 2005[100]	Fluoxetine vs. placebo	90	No difference in response rates and quality of life	Good
Goldstein et al., 1997[167]	Fluoxetine vs. placebo	671	Higher weight loss with fluoxetine in older patients	Fair
Tollefson et al., 1993[222] Tollefson, et al., 1995[223] Small et al., 1996[224]	Fluoxetine vs. placebo	671	Significantly greater response with fluoxetine; current physical illness not associated with response	Fair
Newhouse et al., 2000[44] Finkel et al., 1999[45]	Fluoxetine vs. sertraline	236	Overall similar efficacy, although sertraline patients experienced greater cognitive improvement and greater response among people over 70 years of age	Fair
Rossini et al., 2005[52]	Fluvoxamine vs. sertraline	93	No significant difference in response rates	Fair
Halikas et al., 1995[94]	Mirtazapine vs. trazodone vs. placebo	150	No significant difference	Fair
Weihs et al., 2000[84]	Paroxetine vs. bupropion SR	100	No differences	Good
Schatzberg et al., 2002[73]	Paroxetine vs. mirtazapine	255	Greater early efficacy for mirtazapine; similar number of CGI responders at end of continuation phase	Fair
Rapaport et al., 2003[213]	Paroxetine (CR and IR) vs. placebo	319	Significantly more responders and remitters for paroxetine (CR and IR formulations) than for placebo	Fair
Barrett et al., 2001[113] Williams et al., 2000[112]	Paroxetine vs. placebo vs. behavioral therapy	656	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

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.

Table 31. Studies of efficacy, effectiveness, and harms for patient subgroups (continued)

Study	Interventions	N	Results	Quality Rating
Schneider et al., 2003[220] Sheikh et al., 2004[221]	Sertraline vs. placebo	752	Significantly more responders in sertraline group both with and without comorbid medical illness	Fair
Wilson et al., 2003[137]	Sertraline vs. placebo	113	No difference in prevention of depression; sertraline associated with longer time to recurrence	Fair
Oslin et al., 2003[215]	Sertraline vs. venlafaxine	52	No significant difference in efficacy; tolerability was lower for venlafaxine	Poor
Kirby et al., 2002[200]	SSRIs use vs. venlafaxine	199	Higher rate of hyponatremia in patients on SSRIs and venlafaxine	Fair
Entsuah et al., 2001[217] Thase et al., 2005[216]	Venlafaxine (IR and XR) vs. SSRIs vs. placebo	2,045	Venlafaxine response not affected by age or sex; SSRI response poorer in older women; similar efficacy of venlafaxine and SSRIs except in older women, but HRT appears to eliminate the difference	Fair
Sex				
Kennedy et al., 2000[188]	Paroxetine vs. sertraline vs. venlafaxine vs. moclobemide	107	Sex difference in impairment in drive/desire; rates of dysfunction in men similar in all treatments; in women, greater levels of dysfunction with sertraline and paroxetine; favorable drug response associated with less dysfunction	Fair
Thase et al., 2005[216] and Enstuah et al., 2001[217]	SSRIs vs. venlafaxine XR vs. placebo	2,045	Venlafaxine response not affected by age or sex; SSRI response poorer in older women; similar efficacy of venlafaxine and SSRIs, except in older women, but HRT appears to eliminate the difference	Fair
Ethnicity				
Wagner et al., 1998[225]	Fluoxetine vs. placebo	118	Ethnicity not associated with side effects; whites had a higher response rate, Latinos a higher drop-out rate	Poor
Comorbidities				
HIV/AIDS				
Rabkin et al., 1999[228]	Fluoxetine vs. placebo	120	No difference in depressed HIV/AIDS patients	Fair
Wagner et al., 1998[225]	Fluoxetine vs. placebo	118	Ethnicity not associated with side effects; whites had a higher response rate, Latinos a higher drop-out rate	Poor
Rabkin et al., 2004[227]	Fluoxetine vs. testosterone vs. placebo	123	No difference in depressed HIV/AIDS patients	Fair
Ferrando et al., 1997[226]	Sertraline vs. paroxetine vs. fluoxetine	33	Completers (all treatment groups) experienced improvements in affective and somatic symptoms (many of which were attributed to HIV rather than depression)	Poor

Table 31. Studies of efficacy, effectiveness, and harms for patient subgroups (continued)

Study	Interventions	N	Results	Quality Rating
Alcohol				
Hernandez-Avila et al., 2004[208]	Nefazadone vs. placebo	41	No significant differences	Fair
Gual et al., 2003[229]	Sertraline vs. placebo	83	No significant differences	Fair
Moak et al., 2003[210]	Sertraline vs. placebo	82	Greater depression improvement in females treated with sertraline; less drinking associated with greater depression improvement	Fair
Alzheimer's disease/dementia				
Nyth et al., 1992[211]	Citalopram vs. placebo	149	Significantly greater improvement with citalopram	Poor
Lyketsos et al., 2003[230]	Sertraline vs. placebo	44	Sertraline associated with greater response	Fair
Magai et al., 2000[231]	Sertraline vs. placebo	31	No significant difference	Fair
Breast cancer				
Roscoe et al., 2005[232]	Paroxetine vs. placebo	94	Paroxetine associated with greater depression response	Poor
Cardiovascular disease				
Strik et al., 2000[235]	Fluoxetine vs. placebo	54	Significantly greater response with fluoxetine	Good
Krishnan et al., 2001[209]	Sertraline	220	Vascular comorbidity not associated with more adverse events or premature discontinuation	Fair
Glassman et al., 2002[234]	Sertraline vs. placebo	369	Significantly greater response with sertraline	Fair
Bush et al., 2005[233]	SSRIs	NR	SSRIs improve depression in post-MI patients	Fair
Dialysis				
Blumenfield et al., 1997[236]	Fluoxetine vs. placebo	14	No significant difference	Fair
Stroke				
Andersen et al., 1994[237]	Citalopram vs. placebo	285	Significantly more improvement with citalopram	Fair
Murray et al., 2005[238]	Sertraline vs. placebo	123	No difference in response; greater improvements in quality of life with sertraline	Fair
Substance abuse				
Petrakis et al., 1998[212]	Fluoxetine vs. placebo	44	No difference in depressed opioid addicts	Fair
Schmitz et al., 2001[239]	Fluoxetine vs. placebo	68	No difference in depressed cocaine abusers	Poor

Age: Detailed Analysis

Head-to-head evidence. We identified 12 head-to-head RCTs (14 articles) in elderly or very elderly patients.[31,34,39,44,45,49,52,55,73,84,94,114,214,215] We also identified one set of meta-analyses of original data from eight RCTs.[216,217] These trials evaluated numerous treatment comparisons: first, intra-SSRI comparisons (citalopram vs. sertraline, escitalopram vs. fluoxetine vs. placebo, fluoxetine vs. paroxetine, fluoxetine vs. sertraline, fluvoxamine vs. sertraline, and paroxetine vs. sertraline); second, SSRI vs. SNRI comparisons (citalopram vs. venlafaxine XR, paroxetine vs. mirtazapine, sertraline vs. venlafaxine IR, SSRIs vs. venlafaxine IR or XR vs. placebo); third,

SSRIs vs. other second-generation antidepressants (paroxetine vs. bupropion SR); and fourth, SNRIs vs. other second-generation antidepressants (mirtazapine vs. trazodone vs. placebo).

SSRIs vs. SSRIs. *Citalopram vs. sertraline.* One randomized trial evaluated citalopram and sertraline in the treatment of 138 nondemented elderly patients with minor depressive disorder and subsyndromal depressive symptomatology.[114] Although this trial does not meet eligibility criteria because of the study design (because of flawed randomization, it is essentially a nonrandomized trial) and therefore is not assigned a quality rating, we included it here because it is the only evidence pertaining to a comparison of these two SSRIs; the trial also had high loss to followup (27.5 percent). Both treatments improved depressive symptoms (as measured by the HAM-D); HAM-D remission rates were similar for citalopram and sertraline at the end of the study (53 percent and 42 percent, $P = 0.25$). Similar improvements were seen in Global Assessment of Function (GAF) and cognitive scores.

Escitalopram vs. fluoxetine vs. placebo. One 8-week study compared escitalopram, fluoxetine, and placebo in 517 participants older than 65 years of age (mean age in each treatment group, 75 years).[31] Outcome measures included the MADRS and the CGI-S. Patients on escitalopram experienced greater improvement than those on fluoxetine in MADRS score at week 8 (using an LOCF analysis) ($P < 0.01$); however, the patients treated with escitalopram and with placebo did not differ significantly. Escitalopram, placebo, and fluoxetine MADRS response rates were similar (46 percent, 47 percent, 37 percent, respectively, P = not significant).

In addition, MADRS remission rates were similar for escitalopram and placebo (40 percent and 42 percent), but for fluoxetine vs. placebo the difference was significant (30 percent vs. 42 percent, $P = 0.05$). Escitalopram- and fluoxetine-treated patients experienced significantly more nausea than placebo-treated patients ($P < 0.01$).

Fluoxetine vs. paroxetine. We identified three randomized trials (four articles) in populations older then 60 years of age.[34,39,49,214] One 6-week trial (two publications) 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).[39,214] In this trial, patients treated with paroxetine achieved statistically significantly higher HAM-D response rates than patients in the fluoxetine group ($P = 0.03$).[39,214] No significant differences were seen in overall adverse events.

By contrast, an effectiveness trial conducted in patients older than 18 years of age with major depression, dysthymia, or minor depression did not detect any differences in the effectiveness of fluoxetine and paroxetine.[49] Both treatment groups showed significant improvements in depression and other health-related quality of life domains (social function, work function, physical function) with no significant differences between study groups. It also produced no interactions between treatment groups and age (≥ 60 years of age vs. younger).

An Italian study lasting 1 year 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 persons 65 years or older.[34] Treatment groups did not differ significantly at study endpoint in CGI scores. Although there are no statistically significant differences in outcome measures, this finding does not conclusively demonstrate noninferiority.[109] Severe adverse events were significantly more common in the fluoxetine group than the paroxetine group (22 vs. 9 events; $P < 0.002$).

Fluoxetine vs. sertraline. One 12-week study (two articles) comparing sertraline (50-100 mg/day) and fluoxetine (20-40 mg/day) in 236 participants ages 60 years and older provides evidence of the comparable efficacy of these drugs.[44,45] 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]). Patients treated with these drugs did not differ significantly on primary outcome measures (MADRS, HAM-D). HAM-D response rates (sertraline, 73 percent; fluoxetine, 71 percent) and HAM-D remission rates (sertraline, 45 percent; fluoxetine, 46 percent) were similar. Adverse event rates were similar in the two treatment groups. Quality of life and other patient-rated measures were also similar for both treatment groups at endpoint. Sertraline-treated patients showed greater cognitive improvement than patients on fluoxetine on the DSST at endpoint ($P = 0.037$). A subgroup analysis of 75 patients 70 years of age or older demonstrated a greater response rate for sertraline than for fluoxetine (58.5 percent vs. 42.4 percent, respectively, $P = 0.027$).[45]

A 9-month effectiveness study yielded similar results.[49] The investigators found no differences in effectiveness between fluoxetine and sertraline in patients older than 18 years of age with major depression, dysthymia, or minor depression. Both treatment groups showed significant improvements in depression and other health-related quality of life domains (social function, work function, physical function) with no significant differences between study groups. No interactions between treatment groups and age (≥ 60 years of age vs. younger) were seen.

Fluvoxamine vs. sertraline. A 7-week trial compared fluvoxamine and sertraline for the treatment of major depression in 93 patients 59 years of age and older (mean age for both treatment groups, 68 years).[52] HAM-D response rates favored fluvoxamine over sertraline but did not reach statistical significance (71.8 percent vs. 55.6 percent, $P = 0.12$). Although the difference was not statistically significant, this finding does not conclusively demonstrate noninferiority.[109] A two-way repeated measures analysis of variance revealed a significant time-by-group interaction in HAM-D scores favoring fluvoxamine ($P = 0.007$).

Paroxetine vs. sertraline. A fair effectiveness trial conducted in patients older than 18 years of age with major depression, dysthymia, or minor depression did not detect any differences in the effectiveness of paroxetine and sertraline.[49] The investigators found no differences in effectiveness between paroxetine and sertraline in patients 18 years of age and older with major depression, dysthymia, or minor depression. Both treatment groups showed significant improvements in depression and other health-related quality of life domains (social function, work function, physical function) with no significant differences between study groups. No interactions between treatment groups and age (≥ 60 years of age vs. younger) were seen.

SSRIs vs. SNRIs. *Citalopram vs. venlafaxine XR.* A European 6-month study compared citalopram with venlafaxine XR for the treatment of depression in 151 elderly outpatients (mean age, 73 years).[55] The investigators found no statistically significant differences at study endpoint in any 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). Although outcome measures did not differ significantly, this finding does not conclusively demonstrate noninferiority.[109] More spontaneously reported adverse events were

reported by venlafaxine-treated patients than citalopram-treated patients (62 percent vs. 43 percent, respectively); tremor was more common in the citalopram group than the venlafaxine group, and nausea or vomiting was more common in the venlafaxine group than the citalopram group.

Paroxetine vs. mirtazapine. One study compared paroxetine (20-40mg/day) and mirtazapine (15-45 mg/day) for the treatment of major depression in 255 elderly patients 65 years of age and older; the trial included an acute phase (8 weeks) and a continuation phase (16 weeks).[73] Mirtazapine was associated with significantly more patients who responded (50 percent reduction in HAM-D scores) at day 14 and patients in remission at day 42 (27.8 percent and 31.0 percent, respectively) than paroxetine (13.3 percent and 19.2 percent, respectively; $P = 0.005$ and $P = 0.044$, respectively). The median time to achieving response was significantly shorter for mirtazapine than for paroxetine (26 days vs. 40 days, respectively). 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 vs. venlafaxine IR. One 10-week randomized trial compared sertraline (up to 100 mg/day) and venlafaxine IR (up to 150 mg/day) among 52 nursing home residents (61 to 99 years of age).[215] We graded the quality of this study as poor for efficacy because of high loss to followup (44 percent), but we note it here because it is the only study comparing these two agents and because the high loss to followup may be expected in this population (elderly nursing home residents) and may not be a reflection of the quality of the study. The investigators reported a significantly higher rate of loss to followup among venlafaxine- than sertraline-treated patients (63 percent vs. 24 percent). 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.

SSRIs vs. venlafaxine (IR or XR) vs. placebo. 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.[216,217] This study was not based on a systematic literature search, so results must be viewed cautiously. The trials 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.[216] 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 (response rate: 28 percent) than younger women (response rate: 36 percent) and both older and younger men (response rates: 35 percent and 36 percent, respectively). Remission rates for older women treated with venlafaxine (48 percent) were higher than remission rates for older women treated with SSRIs (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 of age) 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.[217] Among patients over 40 years of age, the rates of adverse events were similar between the treatment groups, although venlafaxine-treated patients 55 to 64 years of age reported significantly more nausea than placebo ($P \leq 0.003$), and placebo patients 41 to 54 years of age reported significantly more headache than venlafaxine ($P \leq 0.01$) .

A fair retrospective cohort study 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, 1.4-8.9).[200] 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.

SSRIs vs. other second-generation antidepressants. *Paroxetine vs. bupropion SR.* One good-quality RCT examined the efficacy of paroxetine and bupropion SR over 6 weeks in 100 outpatients ages 60 years or older (range 60-88 years).[84] The majority of patients were white (paroxetine, 90 percent; bupropion SR, 98 percent), female (paroxetine, 60 percent; bupropion SR, 54 percent), and did not use antidepressants for the current episode before enrollment (paroxetine, 88 percent; bupropion SR, 83 percent). Statistical analysis used an LOCF approach. The overall loss to followup was 16 percent, with no significant difference between treatment groups. Overall adverse events were similar in the two treatment groups. Efficacy according to any outcome measure did not differ significantly between treatment groups. Response rates ($\geq$ 50 percent reduction in HAM-D scores) were similar in both groups (paroxetine, 77 percent; bupropion SR, 71 percent).

SNRIs vs. other second-generation antidepressants. *Mirtazapine vs. trazodone vs. placebo.* One study compared mirtazapine with trazodone in patients with MDD older than 55 years of age.[94] Efficacy outcome measures in this trial favored mirtazapine, but differences did not reach statistical significance. Although outcome measures did not differ significantly, this finding does not conclusively demonstrate noninferiority.[109] More mirtazapine-treated patients discontinued treatment than did those on both trazodone and placebo. Both treatments were associated with more somnolence and dry mouth than placebo ($P \leq 0.05$); trazodone treatment was associated with significantly more dizziness and blurred vision compared to placebo ($P \leq 0.05$).

Placebo-controlled evidence. Two studies (four articles) provide evidence of the general efficacy of paroxetine (CR and IR formulations) and fluoxetine in the treatment of elderly patients with depression.[213,222-224] A good-quality trial evaluated the efficacy of fluoxetine for treating patients 60 years of age and older with dysthymia over 12 weeks.[100] ITT 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; $P < 0.4$). One study of fluoxetine vs. placebo (n = 671 patients older than 60 years of age) recorded a significant weight loss for fluoxetine compared with placebo.[167]

A study of citalopram vs. placebo yielded no significant difference between the two treatment groups in response or remission rates except in the high severity group ($P = 0.04$).[219] One sertraline trial (two publications) demonstrated that sertraline was superior to placebo in elderly patients with late-life depression with and without comorbid medical illness (HAM-D and CGI-I response rates).[220,221] Another trial reported that sertraline was not superior to placebo

in the prevention of recurrence; however, patients on sertraline experienced a longer time to recurrence than did patients on placebo (92 weeks and 48 weeks, respectively).[137]

One large, primary-care-based effectiveness study (two publications) randomized 656 patients with dysthymia or minor depression to 11 weeks of paroxetine, placebo, or behavioral therapy.[112,113] 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 ($P = 0.004$).[112] 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 scale.[113] 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.

One 9-week pooled analysis trial evaluated the efficacy of duloxetine in 114 depressed women ages 40 to 55 and women younger than 40 or older than 55.[218] In women 40 to 55, both response rates (58.2 percent vs. 32.2 percent, $P = 0.003$) and remission rates (34.6 percent vs. 18.6 percent, $P = 0.027$) were significantly higher in the women receiving duloxetine than in women receiving placebo. The magnitude of treatment effect was similar in women 40 to 55 years of age and older women (more than 55 years of age) and younger women (less than 40 years of age).

Sex: Key Points

Two head-to-head comparisons (one observational trial[188] and one pooled analysis[216,217]) were available for the potential comparisons between the 12 second-generation antidepressants addressed in this report. The effects of second-generation antidepressants do not appear to differ by sex.[188,216,217] Some differences may exist in the frequency of some adverse events (sexual side effects,[188] headache,[216,217] and nausea).[216,217] In both cases, the strength of the evidence is low.[188]

No placebo-controlled trials are available on the efficacy, effectiveness, and harms of second-generation antidepressants in men and women.

Sex: Detailed Analysis

Head-to-head evidence. One head-to-head observational study and one pooled analysis compared men and women.[188,216,217] The pooled analyses do not provide evidence of any differences in efficacy, although some difference was observed in adverse events. Men experienced higher rates of headaches with venlafaxine than with placebo, and women experienced higher rates of nausea with venlafaxine than with placebo.[216,217] Observational evidence also suggests that men and women may experience differences in sexual side effects.[188] The strength of the evidence is low.

SSRIs vs. SNRIs. One 14-week trial of paroxetine (mean dose 30.7 mg/day), sertraline (99.0 mg/day), venlafaxine (151.6 mg/day), and moclobemide (485 mg/day) evaluated disturbances in sexual drive/desire and arousal/orgasm in depressed patients who completed 8 weeks of the study.[188] Men reported greater impairment in drive/desire than 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.

SSRIs vs. venlafaxine (IR or XR) vs. placebo. As described above (head-to-head evidence for age), data were pooled 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.[216,217] Remission rates for venlafaxine-treated patients were not affected by sex.[216] Among patients treated with SSRIs, however, a significant interaction was observed between treatment and sex ($P = 0.04$): older women had a poorer SSRI response (28 percent) than younger women (36 percent) and than both older and younger men (35 percent and 36 percent, respectively). Additional analyses of the age (≤ 40, 41-54, 55-64, and ≥ 65) and sex subgroups revealed no significant sex-by-treatment or age-by-sex interactions; men and women of different ages within each treatment group had similar rates of remission, response, and absence of depressed mood.[217]

Placebo-controlled evidence. We did not identify any placebo-controlled trials on the efficacy or harms of second-generation antidepressants in men and women.

Race or Ethnicity: Key Points

One placebo-controlled efficacy study compared different racial or ethnic groups.[225] Fluoxetine and placebo did not differ significantly in outcomes, but this study may not have been powered to detect a significant difference; it was rated poor quality because it lacked an ITT analysis (completer analysis only). No studies directly compared the effectiveness and harms of second-generation antidepressants between different races or ethnicities.

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. One trial evaluated the efficacy of fluoxetine vs. placebo in the treatment of patients with comorbid HIV/AIDS.[225] We included it even though we rated it as poor for efficacy (no ITT analysis) because it is the only trial identified in the literature search that examined race or ethnicity.

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.

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.

One poor-quality head-to-head study examined the efficacy of treatment with second-generation antidepressants for patients with MDD and comorbid HIV/AIDS.[226]

Eighteen placebo-controlled trials of varying quality[208-212,225,227-232,234-239] and one systematic review[233] evaluated second-generation antidepressants in patients with various comorbid conditions. Some of these suggested that second-generation antidepressants may not be efficacious for depressed patients with comorbidities.[208,210,212,225,227-229,231,236-239] However, many of the studies may not have been powered to detect a difference between active treatment and placebo.

Comorbidities: Detailed Analysis

HIV/AIDS. One poor-quality head-to-head study compared the efficacy and tolerability of fluoxetine, paroxetine, or sertraline in depressed individuals with HIV.[226] This 6-week open-label trial evaluated 33 depressed HIV-positive men and women. This trial was rated as poor because it included a completer-only analysis (no ITT analysis); it has been included here because it is the only head-to-head trial in patients with depression and various comorbidities. The overall clinical response rate for completers (n = 24) was 83 percent (fluoxetine, 90 percent; paroxetine, 86 percent; sertraline, 71 percent). Overall, and in each treatment group, significant reductions were seen in both affective and somatic symptoms (as measured by the HAM-D, BDI, HAM-D affective subscale, BDI cognitive subscale, HAM-D vegetative subscale, and BDI somatic subscale scores among completers), including somatic symptoms that were attributed to HIV rather than depression.

Two placebo-controlled studies evaluated the efficacy of fluoxetine vs. placebo in the treatment of patients with depression and comorbid HIV/AIDS.[227,228] The first study, a 12-week randomized trial, compared fluoxetine and placebo in the treatment of depression in patients with HIV/AIDS.[228] The second trial, a 12-week, randomized trial compared fluoxetine, testosterone, and placebo in the treatment of depression in patients with HIV/AIDS.[227] In both studies, fluoxetine and placebo response rates (57 percent vs. 41 percent[228] and 54 percent vs. 44 percent[227]) did not differ significantly. However, these studies may not have been powered to detect a statistically significant difference.

A third, 8-week, placebo-controlled trial evaluated the efficacy of fluoxetine vs. placebo in the treatment of patients with comorbid HIV/AIDS (described for race and ethnicity).[225] We rated it as poor because it had no ITT analysis; however, we included it here because of the very limited evidence on this topic. Response rates among subjects who completed the study were higher in the fluoxetine group (white, 84 percent; black, 50 percent; Latino, 67 percent) than in

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.

Alcohol abuse. One randomized trial compared nefazadone and placebo in the treatment of depressed patients with comorbid alcohol dependence over a period of 10 weeks.[208] Nefazadone was superior to placebo, as measured by improvement in depression on the HAM-D from intake to study endpoint (mean change in HAM-D score for nefazadone vs. placebo: -12.25 vs. -12.55, $P = 0.51$), the difference did not achieve statistical significance, perhaps because the study was underpowered to do so.

Two randomized trials compared sertraline and placebo in the treatment of patients with depression and alcoholism.[210,229] Results suggested that, in some subgroups, sertraline was superior to placebo (i.e., in women), but overall the two treatment groups did not differ significantly. A 24-week study compared sertraline (50-150 mg/day) and placebo in recently detoxified alcohol-dependent patients with current depressive symptoms.[229] Response (≥ 50 percent decrease in MADRS) was slightly higher in sertraline-treated patients (44 percent) than in placebo-treated patients (39 percent). Both groups experienced significant improvements in HAM-D and MADRS scores during the study, although the two groups did not differ significantly. Adverse event rates were similar for the two treatment groups. A 12-week trial showed similar results.[210] In women, treatment with sertraline was associated with less depression at the end of treatment than those receiving placebo. Less drinking during the study was associated with improved depression outcomes.

Alzheimer's disease or dementia. Two randomized trials compared sertraline and placebo for patients with depression and comorbid Alzheimer's disease.[230,231] An 8-week trial of late-stage Alzheimer's disease failed to demonstrate a statistically significant difference between sertraline and placebo; 47 percent and 36 percent, respectively, achieved at least a 50 percent improvement in the Cornell Score for Depression in Dementia (CSDD) and 35 percent and 50 percent, respectively, achieved at least a 50 percent improvement in the Gestalt Depression Scale. However, this study may not have been powered to detect statistically significant differences.[231] A fair 12-week trial demonstrated that sertraline was statistically significantly superior to placebo, as measured by both the CSDD ($P = 0.002$) and the Hamilton Depression Rating Scale (HDRS) ($P = 0.01$).[230] More patients treated with sertraline responded to treatment (full responders, 38 percent; partial responders, 46 percent) than did patients treated with placebo (full responders, 20 percent; partial responders, 15 percent) ($P = 0.007$).

One poor-quality randomized trial compared citalopram and placebo for patients 65 years of age and older with depression and comorbid mild to moderate dementia.[211] We rated this trial poor because it appeared to be a completer-analysis only and had high loss to followup. In the efficacy analysis, which includes only those patients who completed the trial, the mean total HAM-D score at endpoint ($P < 0.05$) and improvement in HAM-D total score at endpoint ($P < 0.01$) were statistically significantly better for patients treated with citalopram than those receiving placebo; similar results were seen with the CGI-S. Significantly more citalopram-treated patients than placebo-treated patients improved (score of 1 or 2 on the CGI-I) (60 percent vs. 24 percent, $P < 0.001$).

Breast cancer. One randomized trial compared paroxetine and placebo for patients with breast cancer who were receiving at least four cycles of chemotherapy to evaluate whether the use of an antidepressant can alleviate symptoms of depression and reduce fatigue.[232] We rated it as poor because it appeared to be a completer-analysis only and the length of the study was not adequately described. Paroxetine was more effective in reducing depression during chemotherapy, as measured by the Center for Epidemiological Studies of Depression (CES-D) ($P = 0.006$); mean (standard deviation [SD]) scores at cycle 4 for paroxetine and placebo were 8.8 (1.11) and 12.6 (1.24), respectively. However, paroxetine and placebo did not differ significantly on all four fatigue scales.

Cardiovascular disease. AHRQ sponsored a systematic review of postmyocardial infarction (post-MI) depression that we graded fair overall. The authors concluded that SSRIs improve depression in post-MI patients.[233]

We also identified three studies evaluating second-generation antidepressants in the treatment of depression in patients with MI or angina;[209,234,235] two had been included in the AHRQ report.[234,235] The first, a 24-week randomized trial, evaluated sertraline vs. placebo for treating depression in patients with acute MI or unstable angina.[234] The second, a good-quality 25-week randomized trial, evaluated fluoxetine vs. placebo in the treatment of depression after a first MI.[235] In both trials, active treatment was associated with a significantly greater response rate than placebo (sertraline, 67 percent; placebo, 53 percent; $P = 0.01$;[234] fluoxetine, 48 percent; placebo, 26 percent; $P = 0.05$[235]).

The third study was a pooled analysis of two randomized trials of sertraline (sertraline vs. fluoxetine and sertraline vs. nortriptyline); the article evaluated sertraline only in patients older than 60 with vascular disease (fluoxetine and nortriptyline results are not reported).[209] Newhouse et al. reported the results of the sertraline vs. fluoxetine comparison in all patients (not limited to those with cardiovascular disease); this article is described in detail for KQ 5, subsection Age.[44] Results for sertraline vs. nortriptyline were reported by Bondareff et al.;[240] this article was excluded because the comparison (sertraline vs. nortyriptyline) is outside of the scope of interest of this report.

The former analysis categorized patients into one of three groups: patients with a current diagnosis of hypertension but no other past or present cardiovascular disease, patients reporting a current or past history of cardiovascular illness but excluding hypertension, and patients with no hypertension and no other comorbid vascular illness. Sertraline was safe, well tolerated, and effective as an antidepressant in elderly patients suffering from hypertension and other forms of vascular comorbidity. Rates of response (measured by the HAM-D and the CGI-I) were similar in sertraline-treated patients in all three vascular illness categories.

Dialysis. We identified one randomized trial of fluoxetine vs. placebo in depressed patients on dialysis (N = 14).[236] Patients treated with fluoxetine had slightly greater improvement than patients treated with placebo, as measured by the BDI (-9.57 vs. -8.8, $P = 0.91$), the Brief Symptom Inventory (Depression Scale) (-4.43 vs. -3.2, $P = 0.88$), the HAM-D (-9.0 vs. -7.5, $P = 0.72$), and the MADRS (-11.14 vs. -6.67, $P = 0.45$). Although the differences were not statistically significant at study endpoint, this may be attributable to the small sample size. No patients discontinued because of side effects; no side effects were judged to be severe.

Stroke. Two studies evaluated the efficacy of citalopram and sertraline in the treatment of patients with poststroke depression.[237,238] One 6-week randomized trial evaluated the efficacy of citalopram vs. placebo in poststroke depression.[237] A 26-week trial evaluated the efficacy of sertraline vs. placebo in the treatment of minor depression and less severe depression in stroke patients.[238] Citalopram was associated with significantly greater improvements in depression than placebo on the HAM-D; mean (SD) improvements for citalopram vs. placebo were 8.0 (6.0) vs. 7.2 (5.8), respectively.[237] Sertraline and placebo did not differ significantly in response rates (week 6: 56 percent vs. 46 percent, respectively; week 26: 76 percent vs. 78 percent, respectively) or week 6 or week 26 remission rates (week 6: 59 percent vs. 51 percent, respectively; week 26: 81 percent vs. 87 percent, respectively).[238] However, at week 26, sertraline was associated with greater improvements in quality of life than placebo (effect size not reported, $P < 0.05$).

Substance abuse. Two studies evaluated the efficacy of fluoxetine in the treatment of patients with depression and comorbid substance abuse (persons with methadone-maintained opioid addiction or cocaine dependence); overall, fluoxetine and placebo did not differ significantly in reducing depressive symptoms.[212,239]

One randomized 12-week trial evaluated fluoxetine vs. placebo in the treatment of depression in methadone-maintained opioid addicts.[212] 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), there were no significant differences in the rate of change of depressive symptoms by treatment group (fluoxetine vs. placebo) over time (BDI: -7.8 vs. -3.4; respectively; HDRS: -5.1 vs. -6.9, respectively). The second study, a poor-quality, 12-week randomized trial, evaluated fluoxetine vs. placebo for treating major depression in cocaine-dependent patients.[239] This trial was rated poor for efficacy (high loss to followup [52.9 percent]) but is included here because of the dearth of evidence on this topic. Fluoxetine and placebo did not differ significantly on the BDI (effect size not reported).

Discussion

General Conclusions

This report provides a comprehensive summary of the comparative efficacy, effectiveness, and harms of 12 second-generation antidepressants for the treatment of major depressive disorder (MDD), dysthymia, and subsyndromal depression. They include bupropion, citalopram, 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. Table 32 briefly summarizes our findings from evidence for all five key questions and their subquestions and notes the strength of evidence in each case.

Most of the relevant trials were conducted in patients with MDD. Therefore, we can draw some conclusions regarding the use of second-generation antidepressants for MDD. Evidence is insufficient, however, to draw firm conclusions about comparative efficacy, effectiveness, and harms of second-generation antidepressants for dysthymia and subsyndromal depression.

For MDD, 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. We could not find any substantial differences in efficacy and effectiveness for either treating the acute depressive phase or maintaining remission. Furthermore, no differences in efficacy and effectiveness are apparent in subgroups based on age and sex, although evidence within subgroups is more limited.

More than 50 percent of patients treated with second-generation antidepressants for acute-phase depression did not achieve remission, the goal of depression treatment. Almost 40 percent of patients failed to respond, a less rigorous outcome. Currently, the evidence is insufficient to determine patient factors that can reliably predict response or nonresponse to an individual drug.

Although limited evidence indicates that second-generation antidepressants are also similar in efficacy for treating patients who had failed to respond to a first-line agent, a substantial proportion of these patients do not achieve response or remission with second-line treatment. Multiple treatment options, therefore, are required for patients who do not respond to first- or second-line treatment.

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 symptoms. 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 fatigue and loss of energy, evidence is lacking.

Table 32. Summary of findings with strength of evidence

Key Question, Disorder, and Outcome of Interest	Strength of Evidence*	Findings†
Key Question 1a. Comparative efficacy and effectiveness of second-generation antidepressants		
Major depressive disorder		
Comparative efficacy	Moderate	Results from direct and indirect comparisons indicate that no substantial differences in efficacy exist among second-generation antidepressants.
Comparative effectiveness	Moderate	Direct evidence from one good and two fair effectiveness studies 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 mostly fair studies 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 fair 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	Low	No head-to head evidence exists. Findings from five placebo-controlled trials were insufficient to draw conclusions about comparative efficacy.
Comparative effectiveness	Low	One fair effectiveness study provides mixed evidence about paroxetine vs. placebo; patients older than 60 showed greater improvement on paroxetine; those younger than 50 did not show any difference.
Quality of life	No evidence	
Onset of action	No evidence	
Subsyndromal depression		
Comparative efficacy	Low	One nonrandomized, open-label trial did not detect any difference between citalopram and sertraline. Findings from two placebo-controlled trials were insufficient to draw conclusions.
Comparative effectiveness	No evidence	
Quality of life	No evidence	
Onset of action	No evidence	
Key Question 1b: Greater efficacy and effectiveness with previously effective medications		
Major depressive disorder	No evidence	
Dysthymia	No evidence	
Subsyndromal depression	No evidence	

*Strength of evidence is based on a modified version of the GRADE system.[20]
†Good, fair, or poor designations relate to quality grades given to each study; see Methods.
RCT, randomized controlled trials; SR, slow release; XR, extended release.

Table 32. Summary of findings with strength of evidence (continued)

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Key Question 2a: Efficacy and effectiveness of second-generation antidepressants for maintaining response or remission (i.e., preventing relapse or recurrence)		
Comparative efficacy	Moderate	Based on findings from three efficacy trials, no significant differences exist between fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine for preventing relapse or recurrence. Whether this finding can be extrapolated to other second-generation antidepressants is unclear.
Comparative effectiveness	No evidence	
General effectiveness/efficacy	Moderate	Based on findings from 21 placebo-controlled trials, second-generation antidepressants are effective for preventing relapse or recurrence.
Key Question 2b: Efficacy and effectiveness of second-generation antidepressants in managing treatment-resistant depression syndrome or treating recurrent depression		
Managing treatment-resistant depression		
Comparative efficacy	Low	Results from one fair trial support modestly better efficacy for venlafaxine compared with paroxetine.
Comparative effectiveness	Moderate	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 fair effectiveness trial found venlafaxine to be modestly superior to citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline.
General effectiveness/efficacy	Low	No placebo-controlled evidence exists. Uncontrolled, open-label evidence supports the general efficacy of second-generation antidepressants.
Treating recurrent depression		
Comparative efficacy	No evidence	
Comparative effectiveness	No evidence	
Key Question 3a: Comparative efficacy and effectiveness of second-generation antidepressants for treatment of depression in patients with accompanying symptom clusters		
Anxiety		
Comparative efficacy	Moderate	Results from six head-to-head trials and one placebo-control led trial (all fair quality) suggest that efficacy does not differ substantially for treatment of depression in patients with accompanying anxiety.
Comparative effectiveness	No evidence	
Insomnia		
Comparative efficacy	Low	Evidence from three fair head-to-head studies is insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting insomnia. Results are limited by study design.
Comparative effectiveness	No evidence	

Table 32. Summary of findings with strength of evidence (continued)

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Melancholia		
Comparative efficacy	Low	Evidence from two fair head-to-head studies, one poor head-to-head study, and one fair placebo-controlled trial is insufficient to draw conclusions about treating depression in patients with coexisting insomnia. Results are inconsistent across studies.
Comparative effectiveness	No evidence	
Pain		
Comparative efficacy	Low	Evidence from one fair placebo-controlled study is insufficient to draw conclusions about treating depression in patients with coexisting pain. Results from head-to-head trials are not available.
Comparative effectiveness	No evidence	
Psychomotor change		
Comparative efficacy	Low	Evidence from one fair head-to-head trial is insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting psychomotor change. Results indicate comparative outcomes for psychomotor retardation and psychomotor change may be different.
Comparative effectiveness	No evidence	
Somatization		
Comparative efficacy	No evidence	
Comparative effectiveness	No evidence	
Key Question 3b: Comparative efficacy and effectiveness of second-generation antidepressants for treatment of symptom clusters in patients with depression		
Anxiety		
Comparative efficacy	Moderate	Results from 10 fair head-to-head trials and 2 fair placebo-controlled trials suggest that no substantial differences in efficacy exist among second-generation antidepressants for treatment of accompanying anxiety symptoms.
Comparative effectiveness	No evidence	
Insomnia		
Comparative efficacy	Low	Evidence from six fair head-to-head trials is insufficient to draw conclusions about treating insomnia in depressed patients. Results are limited by study design; differences in outcomes are of unknown clinical significance.
Comparative effectiveness	No evidence	
Melancholia		
Comparative efficacy	No evidence	
Comparative effectiveness	No evidence	
Pain		
Comparative efficacy	Low	Evidence from two head-to-head trials (one fair, one poor) and three placebo-controlled trials is insufficient to draw conclusions about treating coexisting pain in depressed patients. Results indicate no difference in efficacy but are limited by study design.
Comparative effectiveness	No evidence	

Table 32. Summary of findings with strength of evidence (continued)

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Psychomotor change		
Comparative efficacy	No evidence	
Comparative effectiveness	No evidence	
Somatization		
Comparative efficacy	No evidence	
Comparative effectiveness	Low	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.
Key Question 4: Comparative risk of harms (safety, adverse events) and adherence		
General tolerability		
Adverse events profiles	High	Adverse events profiles are similar among second-generation antidepressants. Differences in the incidence of specific adverse events exist.
Nausea and vomiting	High	Meta-analysis of 15 fair-quality studies indicates that venlafaxine has a higher rate of nausea and vomiting than SSRIs as a class.
Diarrhea	Moderate	Evidence from 15 fair-quality studies indicates that sertraline has a higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine.
Weight change	Moderate	Seven fair trials indicate that mirtazapine leads to higher weight gains than citalopram, fluoxetine, paroxetine, and sertraline.
Somnolence	Moderate	Six fair studies provide evidence that trazodone has a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine.
Discontinuation syndrome	Moderate	A good systematic review provides evidence that paroxetine and venlafaxine have the highest rates of discontinuation syndrome; fluoxetine has the lowest.
Discontinuation rates	High	Meta-analyses of efficacy trials indicate that overall discontinuation rates are similar. Venlafaxine has a higher rate of discontinuations because of adverse events and a lower rate of discontinuations because of lack of efficacy than SSRIs as a class.
Severe adverse events		
Suicidality	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of suicidality.
Sexual adverse events	Moderate	Five fair trials provide evidence that bupropion causes significantly less sexual dysfunction than fluoxetine, paroxetine, and sertraline. Among SSRIs, paroxetine has the highest rates of sexual dysfunction.
Cardiovascular adverse events	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of cardiovascular adverse events. Weak evidence indicates that venlafaxine might have an increased risk of cardiovascular adverse events.
Hyponatremia	Low	The evidence is insufficient to draw conclusions about the comparative risk for hyponatremia.

Table 32. Summary of findings with strength of evidence (continued)

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Seizures	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of seizures. Weak evidence indicates that bupropion might have an increased risk of seizures.
Hepatotoxicity	Low	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.
Serotonin syndrome	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of serotonin syndrome. Observational studies indicate no differences in risk among second-generation antidepressants.
Adherence in efficacy studies	Moderate	Efficacy studies indicate no differences in adherence. One observational study suggests that extended-release formulations might have better adherence than immediate-release formulations.
Adherence in effectiveness studies	Low	Evidence from existing studies is insufficient to draw conclusions about adherence in "real-world" settings.
Key Question 5: Subgroups		
Age		
Comparative efficacy	Moderate	Results from 22 efficacy trials (2 good RCTs, 17 fair RCTs or pooled analyses of RCTs, 1 poor RCT, 1 pooled analysis that was not rated, and 1 nonrandomized controlled trial that was not rated) indicate that no substantial differences exist in efficacy among second-generation antidepressants in the elderly or the very elderly.
Comparative effectiveness	Moderate	Based on findings from one fair head-to-head effectiveness trial, no substantial differences exist among second-generation antidepressants in the elderly compared with other age groups. A second trial in patients with dysthymia or minor depression provides mixed evidence.
Comparative harms	Low	Results from two fair studies indicate that adverse events may differ somewhat across second-generation antidepressants in the elderly or very elderly.
Sex		
Comparative efficacy	Low	Results from one fair pooled analysis of RCTs indicates that efficacy among second-generation antidepressants may not differ substantially between men and women.
Comparative effectiveness	No evidence	
Comparative harms	Low	One fair head-to-head trial suggests harms (headache, nausea) may differ between men and women treated with venlafaxine vs. placebo and venlafaxine vs. SSRIs or placebo. Observational evidence (one fair study) suggests that some sexual side effects may differ between in men and women.

Table 32. Summary of findings with strength of evidence (continued)

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Race or Ethnicity		
Comparative efficacy	Low	Results from one poor RCT indicate that efficacy does not differ substantially among second-generation antidepressants in different racial subgroups.
Comparative effectiveness	No evidence	
Comparative harms	No evidence	
Comorbidities		
Comparative efficacy	Low	One poor head-to-head trial included patients with depression and HIV/AIDS; this study indicated that efficacy does not differ substantially among second-generation antidepressants. Findings from placebo-controlled trials were insufficient to draw conclusions about comparative efficacy.
Comparative effectiveness	No evidence	
Comparative harms	No evidence	

Although second-generation antidepressants are similar in efficacy, they cannot be considered identical drugs. Evidence of 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 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[60,61,72,73,76] and that bupropion has fewer sexual side effects than fluoxetine, paroxetine, and sertraline.[79,80,88-90]

Some of these differences are small and might be offset by other 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.

A considerable limitation of our conclusions is that they have been derived primarily from efficacy trials. Although findings from effectiveness studies are generally consistent with those from efficacy trials, the generalizability of some of our conclusions may be limited. Furthermore, the pharmaceutical industry funded a large percentage of these studies, and selective reporting is conceivable, although we had no way to account for missing information.

Our report is the first to assess statistically each of 66 possible drug comparisons of second-generation antidepressants. For comparative efficacy, we employed direct analyses for four comparisons and 62 indirect statistical analyses.

In the following sections we discuss major findings for individual key questions in more detail.

Results for Efficacy and Effectiveness in Major Depressive Disorders

For MDD, direct evidence from head-to-head trials and indirect comparisons using placebo-controlled trials indicate that, overall, the efficacy and effectiveness of second-generation antidepressants do not differ substantially for the treatment of adults. We rated the strength of this evidence as moderate. These findings are consistent with prior systematic reviews and meta-analyses.[8,241]

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. Accompanying meta-analyses of effect sizes, however, suggest that the actual differences in the mean treatment effects are small and most likely not clinically significant.

For example, a relative risk (RR) meta-analysis of response rates indicates that significantly more patients receiving escitalopram than receiving citalopram achieved treatment response (RR, 1.14; 95% CI, 1.04-1.26). An effect-size meta-analysis yielded a mean difference of 1.3 points on the Hamilton Depression Rating Scale (HAM-D), 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.[103] In this case, dichotomizing a continuous scale such as the HAM-D appears to overestimate the actual difference in effect sizes.

Similarly, sertraline and venlafaxine had statistically significantly greater response rates than fluoxetine. Effect size meta-analyses, however, yielded no clinically significant mean differences on HAM-D scales.

Findings from indirect comparisons yielded no statistically significant differences in response rates among other potential comparisons. The precision of some of these estimates was low, leading to inconclusive results with wide confidence intervals. Nevertheless, point estimates of treatment effects consistently indicate no substantial differences in efficacy among comparisons.

Although response and remission rates are similar among second-generation antidepressants, 54 percent of patients in these trials did not achieve remission and 34 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—an effectiveness study that randomized patients to bupropion SR, sertraline, or venlafaxine XR after they had failed treatment with citalopram[146]—indicate that, even with second-line treatments, a substantial proportion of patients do not achieve remission.

Effectiveness trials have greater generalizability of findings than efficacy studies; 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 US health systems may limit the applicability of results from French effectiveness trials to US patients.

No evidence exists on adherence in effectiveness studies. Although adherence was similar in efficacy trials, the generalizability 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.

Results for Maintaining Response or Remission

The majority of studies included in this report 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 the 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 three efficacy trials[47,96,116,117] suggests that no substantial differences in efficacy exist between fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine for preventing relapse or recurrence. 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 three head-to-head studies, one defined relapse as an increase in the lowest HAM-D or Montgomery-Asberg Depression Rating Scale (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;[47] a second study defined relapse as a HAM-D score greater than 15 with functional impairment;[116,117] and the third simply assessed discontinuation rates.[96] Eligibility for continuation- or maintenance-phase treatment also varied considerably.

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.[122] 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.

Results for Managing Treatment-Resistant or Recurrent Depression

Overall, approximately 40 percent of patients do not achieve clinical response with initial treatment; approximately 10 percent to 15 percent of patients discontinue treatment because of

adverse events. Three 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 moderate.

The best evidence comes from the STAR-D trial.[146] Although this was an open-label study, an interviewer blinded to the treatment arm did the outcomes assessment. 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,[140] we could not determine whether raters were blinded to treatment allocation, potentially limiting the ARGOS conclusions.

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; it did not include patients who initially responded and then lost response.

Results for Treating Patients with Depression and Accompanying Symptoms

The range of physical and psychological symptoms that accompany depressive disorders is wide. 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 these pharmaceuticals for treating depression in patients with such symptoms *and* treating the accompanying symptoms in patients with depression. Generally, the strength of evidence for anxiety was moderate; for all other symptom clusters, either the strength of evidence was low or no evidence was found.

The most common and distressing accompanying symptoms can be considered the highest priority for further studies. Research involving depressed populations that may be more generalizable suggests that common presenting symptom clusters in both primary care and psychiatric clinics are fatigue and loss of energy (for which no studies were identified), anxiety, insomnia, and pain and other somatic symptoms.[147]

Anxiety. Although anxiety is not a discrete MDD subtype,[242] evidence suggests that it may present as a distinctive cluster[243] and be associated with more persistent depression.[244-246] For patients with high anxiety associated with MDD, we found no difference in patients' depression treatment response by either antidepressant class or specific medication. These findings are consistent with a recent nonsystematic review sponsored by a pharmaceutical manufacturer.[247] Although all the included studies identified a high anxiety group, the definitions employed by investigators varied markedly.

In addition, for patients with anxiety symptoms associated with depression, we found no identifiable difference in anxiety response by either antidepressant class or specific medication. Therefore, the current evidence suggests that improvement in both depressive and anxiety

symptoms is likely with adequate dosing of antidepressant treatment, but evidence of clear benefit for one antidepressant over another is lacking.

Insomnia. For patients with depression and accompanying insomnia, we found no clear evidence of differences in depressive response or insomnia response by antidepressant class or specific medication.

Indirect evidence from studies that did not identify insomnia subgroups[82,96] provides results that are consistent with improved sleep quality for trazodone compared with fluoxetine[82] and venlafaxine.[96] Higher quality, direct evidence, however, was limited. Among the three studies that identified an insomnia group, only one trial involved one of these three antidepressants; it suggested greater benefit for nefazodone than fluoxetine.[81] The two other studies, which compared SSRIs, produced mixed results.[41,151]

Studies were limited by varying and incomplete assessment of insomnia and by insensitive outcome measures. Most studies used a sleep measure that is a part of HAM-D, with three items producing a total sleep score ranging from 0 to 6. The clinical meaningfulness of the small reported differences in this outcome measure is unclear.

Melancholia. Information about outcomes in the melancholic subgroup was limited to three comparative trials; they addressed only the effect on depressive outcomes. Evidence did not consistently support a difference in outcome by either class or medication.

Pain. Patients with depression commonly experience physical symptoms; the majority are pain symptoms. In addition, depression is prevalent among patients with chronic pain disorders.[248] We identified few trials addressing the use of second-generation antidepressants for treatment of pain accompanying depression. All the trials we identified tested duloxetine, an SSNRI; two compared duloxetine with paroxetine, and the other three were placebo-controlled trials.

Studies were limited by exclusion of patients with common chronic pain conditions, failure to analyze subgroups with moderate to severe pain, and failure to report outcomes in a clinically meaningful way. No study included patients with comorbid depression and chronic pain, probably the group of most interest to clinicians. The only study that required patients to have pain of at least mild intensity for inclusion excluded those with a history of any diagnosed painful condition, including common pain disorders such as migraine and arthritis.[154]

The difference in mean pain scores between duloxetine and placebo groups was statistically significant, but probably not clinically meaningful, in three studies; all used a 100 mm pain intensity visual analog scale (VAS) as the outcome measure.[153,155,156] Prior research has produced different estimates of the minimum clinically important difference on the VAS, ranging from 9 mm to 30 mm.[109,249-251] No study included in this review reported the proportion of patients achieving a clinically important improvement in pain scores.

Psychomotor changes. The evidence addressing depression outcomes in patients with psychomotor changes is limited to a single trial. It found that sertraline was more efficacious than fluoxetine in patients with psychomotor agitation but not in those with psychomotor retardation.[149]

Somatization. The evidence directly addressing treatment of somatization in patients with depression is limited to a single trial that found similar effectiveness for three SSRIs.[49] Conclusions from this study are limited because the investigators did not analyze information for a subgroup with high somatization.

Results for Harms (Adverse Events) and Adherence

On average, 61 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.

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.

Efficacy studies did not indicate any differences in adherence across agents. One observational study indicated that extended-release formulations might have a better adherence rate than immediate-release medications. This finding, however, is likely more attributable to differences in dosing regimens than to differences in efficacy and harms. The evidence is insufficient to draw any conclusions about differences in adherence in effectiveness studies.

Results for Population Subgroups

In efficacy and effectiveness studies, treatment effects were similar between different age groups and between males and females. Despite the importance of the harms of second-generation antidepressants, especially in the elderly, little evidence is available on this topic. We found very limited 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 mainly limited to placebo-controlled trials assessing the general efficacy of second-generation antidepressants in such subgroups. Some of these studies indicate 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 meaningful differences, although they may not have been powered to detect 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.

Results for Dysthymia and Subsyndromal Depression

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

For the treatment of 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.[100,113] Similarly, the evidence on the general efficacy in subsyndromal depression is limited to few studies with mixed results.

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 studies with a high rate of applicability to primary care populations are generally lacking for most drugs. 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 differences in drug doses is also poorly understood.

Management of Treatment-Resistant or Recurrent Depression

Given the fact that approximately 40 percent of patients do not respond to initial treatment, an important future research agenda is to explore whether combinations of antidepressants at treatment initiation lead to better response rates than single agents alone. Furthermore, 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.

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 psychotherapy, vagal nerve stimulation, light therapy, and alternative medicines as substitutes or complements to pharmaceutical management also needs to be better understood.

Accompanying Symptoms

More research is needed to evaluate differences between second-generation antidepressants 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, information about treatment of accompanying symptoms is key for clinicians who must select among many antidepressant drugs.

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 (e.g., a high anxiety group should be identified with a consistent definition). Analyses should then be done in such subgroups, using similarly defined outcomes to allow results to 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 fatigue or loss of energy 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 have an excess risk of severe adverse events with any second-generation antidepressant.

Addendum

As this report was going to press, a relevant study addressing sequential treatment steps among patients who did not obtain remission with initial acute-phase treatment was published. We were unable to incorporate this study fully into this report, but we found its results important in light of the general lack of high-quality evidence for treating patients who do not obtain remission with initial treatments.

The Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial – described in detail in Key Question 2b – consisted of a series of RCTs examining sequential treatment steps in patients who did not obtain remission or could not tolerate previous treatments. Key Question 2b detailed the medication switch arms of the second-step treatment in which all patients in the analysis had failed initial treatment with citalopram and were randomized to second-step treatment with bupropion SR (N = 239), sertraline (N = 238), or venlafaxine XR (N = 250); this analysis found no statistically significant differences in remission rates between second-step treatments.[146]

The more recently published study describes the acute and longer-term outcomes associated with all four treatment steps.[252] Patients not achieving remission or unable to tolerate a treatment step were encouraged to move to the next step; patients achieving acceptable benefit could enter a 12-month follow-up phase. All patients (N = 3,671) received citalopram in Step 1. Step 2 and Step 3 treatments were randomly assigned using an equipoise stratified randomized design. In this, 1,439 patients were randomized in Step 2, which included seven possible treatment alternatives (bupropion SR, sertraline, venlafaxine XR, cognitive therapy, citalopram plus bupropion, citalopram plus buspirone, or citalopram plus cognitive therapy). Step 3 randomized 390 patients to switch to mirtazapine or nortriptyline or to receive augmentation with lithium or triiodothyronine (T3). Step 4 used only a single randomization; 123 patients were randomized to tranylcypromine or venlafaxine XR plus mirtazapine.

Overall, 67 percent of patients achieved remission. Remission rates were 36.8 percent for Step 1, 30.6 percent for Step 2, 13.7 percent for Step 3, and 13.0 percent for Step 4. For patients achieving acceptable benefits who continued on in the 12-month follow-up study, relapse rates were 40.1 percent, 55.3 percent, 64.6 percent, and 71.1 percent for those achieving benefit in Steps 1, 2, 3, and 4, respectively. In all steps, patients achieving remission (Quick Inventory of Depressive Symptomatology–Self Report [QIDS-SR-16] $\leq$ 5) were less likely to relapse than patients not achieving remission (acceptable benefit but QIDS-SR-16 > 5).

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Peer Reviewers

We gratefully acknowledge the following individuals who reviewed the initial draft of this report and provided us with constructive feedback. The peer reviewers were asked to provide comments on the content, structure, and format of the evidence report and to complete a checklist. Their comments and suggestions formed the basis of our revisions to the evidence report. Acknowledgments are made with the explicit statement that this does not constitute endorsement of the report.

- Susan G. Kornstein, MD., Professor of Psychiatry and Obstetrics and Gynecology, Virginia Commonwealth University, Richmond;
- John Williams, MD, Professor of Medicine and Psychiatry, Duke University, Durham, North Carolina;
- Mark Helfand, MD, MPH, Professor of Medicine and Medical Informatics and Clinical Epidemiology, and Director, Oregon Evidence-based Practice Center, Oregon Health and Science University, Portland;
- Staff of the National Institute for Mental Health, Rockville, Maryland;
- Staff of the Oregon Health and Science University Scientific Resource Center, Portland; and
- Staff of the Agency for Healthcare Research and Quality, Rockville, Maryland

Search Strategy

#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

Excluded Studies

Background

This appendix documents that 525 publications that we identified but did not ultimately include in this report. The citations are numbered consecutively throughout the appendix, but within groupings of the major reasons for exclusion, they are listed alphabetical order by author . The groupings include publication in a language other than English, the wrong outcome, relevant drug(s) not included in the study or publication, population not included, wrong publication type, and wrong study design

Articles by Reason for Exclusion

Not Published in English

1. Berlanga C, Arechavaleta B, Heinze G, Campillo C, Torres M, Caballero A, et al. A double-blind comparison of nefazodone and fluoxetine in the treatment of depressed outpatients. Salud Mental 1997;20(3):1-8.

2. Bremner JD. Double-blind comparison of mirtazapine, amitriptyline and placebo in major depression. <ORIGINAL> DOPPELBLINDVERGLEICH VON MIRTAZAPIN, AMITRIPTYLIN UND PLAZEBO BEI 'MAJOR DEPRESSION". Nervenheilkunde 1996;15(8):533-540.

3. Peters UH, Lenhard P, Metzm M. Therapy of depression in the psychiatrist's office - A double-blind multicenter study. Nervenheilkunde 1990;9(1):28-31.

4. Schone W, Ludwig M. Paratoxetine in the treatment of geriatric depressed patients - A double-blind comparison with fluoxetine. <ORIGINAL> PAROXETIN IN DER DEPRESSIONSBEHANDLUNG GERIATRISCHER PATIENTEN - EINE DOPPELBLINDE VERGLEICHSSTUDIE MIT FLUOXETIN. Fortschr Neurol Psychiatr 1994;62(Suppl 1):16-18.

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Wrong Outcome

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MMA Abbreviations for Evidence Tables

A/S	Aktieselskap (Company type in Denmark)
AD	antidepressant
AE	adverse event
AIDS	acquired immune deficiency syndrome
AMT	awake and moving time
ARV	antiretroviral
ATVI	aortic time velocity interval
BDI	Beck Depression Inventory
BMI	body mass index
BP	blood pressure
BQOL	Battelle Quality of Life Measure
BSI	Brief Symptom Inventory of Depression
BUP SR	bupropion sustained release
BUP	bupropion
CBT	cognitive-behavioral therapy
CDC	Centers for Disease Control and Prevention
CESD	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
CIT	citalopram
cm	centimeter
CR	controlled release
D	drug
DBP	diastolic blood pressure
DESS	Discontinuation-Emergent Signs and Symptoms checklist
df	degrees of freedom
diff	difference(s)
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
ESC	escitalopram
FDA	Food and Drug Administration
FLUO	fluoxetine
FLUV	fluvoxamine
FSQ	Functional Status Questionnaire
GBS	Gottfrey-Brane-Steen
GDS	Geriatric Depression Scale
GP	general physician
GPRD	General Practice Research Database
HAM–A	Hamilton Rating Scale for Anxiety
HAM–D	Hamilton Rating Scale for Depression
HIV	Human immunodeficiency virus
HSCL-D	Hopkins Depression Scale
HTN	hypertension
ICD10	International Classification of Diseases- 10th revision
IDS	Inventory for Depressive Symptomatology

IDS-C	Inventory for Depressive Symptomatology - Clinician Rated
IDS-SR	Inventory for Depressive Symptomatology - Self Rated
IMI	imipramine
IR	immediate release
ITT	intent to treat
KQ	key question
LOCF	last-observation-carried-forward
LTF	loss to follow-up
MADRS	Montgomery Asberg Depression Rating Scale
MAF	Multidimensional
MAOI	monoamine oxidase inhibitor
m-CPP	meta-chlorophenylpiperazine
MD	medical doctor
MDD	major depressive disorder
MI	myocardial infarction
mil	milnacipran
MINI	Mini International Neuropsychiatric Interview
MIR	mirtazapine
mmHG	millimeters of mercury
MMSE	Mini Mental State Examination
mo	month(s)
N	number
N/A	not applicable
NEF	nefazodone
NIH	National Institute of Health
NIHM	Health Diagnostic Interview Schedule
NIMH	National Institute of Mental Health
NNT	number needed to treat
NoVASC	no other comorbid vascular illness
NR	not reported
NS	not sig
NV	Naamloze Vennootschap (Dutch company type)
OR	odds ratio
P	P-value
PAR	paroxetine
PCP	primary care physician
PGI	Patient Global Impression
PGIS	Patient Global Improvement Scale
Phys-SFR	physicians rating of sexual functioning
PSD	poststroke depression
px	prescription
QLDS	Quality of Life in Depression Scale
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QLSQ	Q-LES-Q
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
SCID	Structured Clinical Interview for DSM-III Revised
SD	sexual dysfunction
SDS	Self rating Depression Scale

SDS	Sheehan Disability Scale
SER	sertraline
SF-36	Medical Outcomes Study Health Survey - Short Form 36
Sig	significant/significantly
SIP	Sickness Impact Profile
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TMT-A	Trail Making Test – Part A
TMT-B	Trail Making Test – Part B
TRA	Trazodone
UK	United Kingdom
UKU	Utvalg for Kliniske Undersogelse (Side Effect Scale)
US	United States
USA	United States of America
UT	Utah
VAS	visual analog scale
VASC	patients with a history of cardiovascular illness (excluding hypertension)
VEN ER	venlafaxine extended release
VEN XR	venlafaxine extended release
VEN	venlafaxine
VF	verbal fluency test
vs.	versus
WHO	World Health Organization
wk	week(s)
WMS	Wechsler Memory Scale
yr	year(s)

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms

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 **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:** Sertraline 50-150 mg/d **D2:** Paroxetine 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% 24 wks: SER: 80.2% PAR: 73.7% 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* ≤ 0.05	**Overall attrition rate:** 35.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Venlafaxine 37.5-150 mg/d **D2:** Citalopram 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Portugal Multicenter (3 sites) **Funding:** Wyeth-Ayerst International	**Research objective:** Efficacy and tolerability of VEN and FLUO in MDD **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 87 **Intervention:** **D1:** Venlafaxine 75-150 mg/d **D2:** Fluoxetine 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%, FLUO: 74% (*P* = NR); HAM-D Remitters: VEN: 51%, FLUO: 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 FLUO 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Nefazodone 200-600 mg/d **D2:** Paroxetine 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Venlafaxine 75-150 mg/d **D2:** Paroxetine 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: VEN: 59% vs. PAR: 49%	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** United States Multicenter, primary care clinics **Funding:** Hartford and MacArthur Foundation	**Research objective:** To compare PAR vs. placebo 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:** Paroxetine 10-40 mg/d, individually titrated **D2:** placebo	**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), placebo: 0.85 (0.09); behavior therapy: 0.79 (0.09), no sig diffs between arms Remission by HAM-D-17 score < 6: PAR: 80%, placebo: 44.4%; behavior therapy: 56.8% (*P* = 0.008 for diff among all 3 arms) Minor depression: PAR 60.7%, placebo 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Country NR (appears to be United States) Multicenter **Funding:** Eli Lilly	**Research objective:** To evaluate comparative safety and efficacy of FLUO 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 placebo run-in approximately 1 wk in duration) **Study design:** RCT **Overall study N:** 126 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Trazodone: 100-400 mg/d	**Inclusion criteria:** • Adults 18 or older • 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	**Mean age (yrs):** **D1:** 40.0 **D2:** 40.0 **Sex (% female):** **D1:** 64.6 **D2:** 68.8 **Race (% white):** NROverall **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.4 (2.7) **D2:** 24.3 (3.6)	Response rates, n (%) (response = ≥ 50% decrease in HAM-D at endpoint) FLUO = 40.5 (62.3%) TRA = 42.0 (68.9%) Remission rates (remission = HAM-D ≤ 7 at endpoint) FLUO = 33.1(50.9%) TRA = 25.7(42.2%) PGIS mean change at endpoint FLUO 2.4 (1.2) vs. TRA 2.3 (1.2) (*P* = NR)	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Mirtazapine: 30-45 mg/d **D2:** Sertraline: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 Szegedi et al., 2003 **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:** Mirtazapine: 15-45 mg/d (32.7) **D2:** Paroxetine: 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)	Benkert-MIR and PAR equally effective in reducing mean HAM-D-17 score (58.3% vs. 53.7%) Szegedi-Improvement occurred in majority of analyzed patients within 2 wks, MIR: 72.7% PAR: 64.9% Early improvement was highly sensitive predictor of later stable response or stable remission for both drugs At endpoint, 40.9% of MIR group and 34.1% of PAR group were considered HAM-D remitters (score ≤ 7)	**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 fatigue-8.9 **D2:** 7.5 fatigue-8.2 **Sweating (increase):** **D1:** 2.2 **D2:** 7.5	**Overall attrition rate:** 23% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** UK Multicenter (20 centers) **Funding:** Pfizer, Inc	**Research objective:** To compare SER and FLUO in outpatients with depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 286 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Fluoxetine: 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%, FLUO: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Escitalopram: 20mg **D2:** Venlafaxine: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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 FLUO in treatment of depression **Duration of study:** 180 days **Study design:** RCT **Overall study N:** 242 **Intervention:** **D1:** Fluoxetine: 50-150 mg/d **D2:** Sertraline: 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: FLUO: 54.3% SER: 49% Day 180: FLUO: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** 491 **Intervention:** **D1:** placebo **D2:** Escitalopram 10 mg/d **D3:** Escitalopram 20 mg/d **D4:** Citalopram 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, placebo treatment (27.7%, $P < 0.01$) For QOL, diff in mean change from baseline for ESC vs. placebo 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 placebo 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Italy Multicenter (38 centers) **Funding:** SmithKline, Beecham	**Research objective:** To assess efffects of PAR and FLUO 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:** Paroxetine: 20-40 mg/d **D2:** Fluoxetine: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Canada Multicenter (8) **Funding:** SmithKline, Beecham	**Research objective:** Antidepressant and anxiolytic efficacy of PAR and FLUO were compared **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 203 **Intervention:** **D1:** Paroxetine: 20-50 mg/d **D2:** Fluoxetine: 20-80 mg/d	**Inclusion criteria:** • 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 • 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:** 96.5 **D2:** 96.5 **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: (Observed cases at 12 wks) PAR: 85.7% FLUO: 88.4% (LOCF endpoint) PAR: 67.0% FLUO: 68.4% No statistically sig diffs in remission rates: (Observed cases at 12 wks) PAR: 77.8% FLUO: 81.2% (LOCF endpoint) PAR: 58.0% FLUO: 59.2%	**Changes in weight (decrease):** **D1:** 11.88 **D2:** 2.94 **Constipation:** **D1:** 17.65 **D2:** 3.96 **Diarrhea:** **D1:** 11.76 **D2:** 18.81 **Headache:** **D1:** 36.27 **D2:** 36.63 **Insomnia:** **D1:** 26.47 **D2:** 22.77 **Nausea:** **D1:** 37.25 **D2:** 31.68 **Somnolence (fatigue):** **D1:** 18.63 **D2:** 16.83 **Sweating (increase):** **D1:** 13.73 **D2:** 5.94	**Overall attrition rate:** 36% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Coleman et al., 2001 **Country and setting:** United States Multicenter (15 centers) **Funding:** Glaxo Wellcome	**Research objective:** Comparison of BUP, FLUO and placebo 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:** Fluoxetine: 20-60 mg/d (26) placebo **D2:** Bupropion: 150-400 mg/d (319) **D3:** placebo	**Inclusion criteria:** • Adults 18 or older • 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 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 **Mean HAM-D score at baseline:** **D1:** 24.6 **D2:** 24.5 **D3:** 24.4	No diff in responders (> 50 decrease in HAM-D) FLUO: 57% vs BUP: 56% (*P* = NR), remitters (HAM-D < 8) FLUO: 40% vs. BUP: 47% (*P* = NR) More BUP SR remitters (47%) compared to placebo (32%) Orgasm dysfunction occurred sig more in FLUO patients compared with placebo or BUP SR patients (*P* < 0.001) At endpoint, more FLUO treated patients had sexual desire disorder than BUP SR treated patients (*P* < 0.05) More FLUO-treated patients dissatisfied with sexual function beginning at wk 1 (*P* < 0.05)	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Coleman et al., 1999 **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:** 364 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Bupropion: 150-400 mg/d **D3:** placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Stable relationship • Have normal sexual functioning • Sexual activity at least once every 2 wks **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 **Mean HAM-D score at baseline:** **D1:** 34.5 **D2:** 34.8 **D3:** 34.0	No sig diff between BUP SR and SER groups. HAM-D responders: SER: 61% vs. BUP: 66% (*P* = NR) CGI-I and CGI-S for BUP SR sig better than placebo but not better than SER SER not statistically better than placebo No diffs in HAM-A; 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 placebo or BUP SR patients (*P* < 0.05) Diagnosed with at least one sexual dysfunction: SER: 39%, BUP SR: 13%, placebo: 17%	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Escitalopram: 10 mg/d **D2:** Citalopram: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** South America Multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** Safety and efficacy of VEN versus FLUO in patients with depression in Latin America and Brazil **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 382 **Intervention:** **D1:** Venlafaxine: 75-225 mg/d **D2:** Fluoxetine: 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 (≥ 50% decrease in HAM-D or MADRS and CGI score of 1 or 2) was achieved by 86.8% in VEN group and 82% in FLUO group ($P = 0.074$) Remission was observed in 60.2% of patients in each group Patients who increased dose to VEN 150 mg and FLUO 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Croft et al., 1999 **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 placebo **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 360 **Intervention:** **D1:** Sertraline: 50-200 mg/d (mean = 121) **D2:** Bupropion: 150-400 mg/d (mean = 293) **D3:** placebo	**Inclusion criteria:** • Adults 18 or older • 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 **Mean HAM-D score at baseline:** NR	Mean HAM-D scores in both BUP and SER group were statistically better than placebo ($P < 0.05$) No sig diff in HAM-D scores between BUP and SER groups HAM-D responders: BUP: 66% vs. SER 68% CGI-S and CGI-I improvement compared to placebo but no diffs between drugs at any wk Orgasmic dysfunction occurred sig more in SER patients compared with placebo or BUP patients ($P < 0.001$) At day 56 no diff in overall satisfaction with sexual function between treatment groups	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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 placebo 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:** Venlafaxine: 156-160 mg/d **D2:** Trazodone: 294-300 mg/d **D3:** placebo	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Europe Multicenter **Funding:** Solvay Pharmaceuticals	**Research objective:** Comparison of efficacy and safety of FLUV and FLUO **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 184 **Intervention:** **D1:** Fluoxetine: 20 mg/d **D2:** Fluvoxamine: 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. At end of study, 60% of both groups were considered responders 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Belgium Psychiatric practices (14) **Funding:** NR	**Research objective:** To compare efficacy and safety of VEN and FLUO in patients with depression and anxiety **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 146 **Intervention:** **D1:** Venlafaxine: 75-150 mg/d **D2:** Fluoxetine: 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 FLUO 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 FLUO 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Belgium Multicenter **Funding:** SmithKline, Beecham	**Research objective:** To compare efficacy and tolerability of PAR and FLUO **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** **D1:** Paroxetine: 20-40 mg/d **D2:** Fluoxetine: 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% FLUO: ~ 62% no sig diff HAM-A score reduction statistically sig diff for PAR vs. FLUO at wk 3; no sig diff at wks 4 or 6 At wk 4, 53% of PAR patients and 23% of FLUO 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** 367 **Intervention:** **D1:** Duloxetine 80 mg/d **D2:** Duloxetine 120 mg/d **D3:** Paroxetine: 20 mg/d **D4:** placebo	**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) 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** United States Outpatient clinic **Funding:** NIMH	**Research objective:** FLUO vs. placebo for treatment of dysthymia in patients over 60 **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 90 **Intervention:** **D1:** Fluoxetine: 20-60 mg (individually titrated by protocol according to response) **D2:** placebo	**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: FLUO: 27.3% placebo: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** France NR **Funding:** Wyeth-Ayerst International	**Research objective:** Comparison of efficacy and safety of VEN and FLUO in outpatients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 314 **Intervention:** **D1:** Venlafaxine: 75-150 mg/d (mean daily dose for Venlafaxine: 109-122 mg/d from day 15 forward) **D2:** Fluoxetine: 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: VEN: 72% FLUO: 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):** **D1:** 5 - Asthenia **D2:** 2- Asthenia **Sweating (increase):** **D1:** 6 **D2:** 4	**Overall attrition rate:** 25% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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 **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 400 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Citalopram: 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: SER: 69.5%; CIT: 68.0% Wk 24: SER: 75.5%; CIT: 81.0% Compliance: SER 90.3%, CIT 94.5%	**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	**Overall attrition rate:** 22% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 (continued)					**Somnolence (fatigue):** **D1:** 5 **D2:** 4.5 **Sweating (increase):** **D1:** 13 **D2:** 17	

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Fluoxetine: 20-60 mg/d **D2:** Sertraline: 50-200 mg/d **D3:** Paroxetine: 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 FLUO, SER and PAR on all outcome measures of HAM-D No statistically sig diffs between FLUO, 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; remission rates: 54.4%, 59.4%, and 57.0% respectively	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** United States Multicenter (15 sites) **Funding:** Eli Lilly Research	**Research objective:** To compare tolerability and efficacy of FLUO, 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:** Fluoxetine: 20-60 mg/d **D2:** Sertraline: 50-200 mg/d **D3:** Paroxetine: 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 FLUO, SER and PAR in baseline-to-endpoint improvement in HAM-D total (overall $P = 0.323$) No sig diffs in efficacy and tolerability of FLUO, 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	**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	**Overall attrition rate:** NR **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** United States Multicenter (5 sites) **Funding:** SmithKline, Beecham	**Research objective:** Efficacy and tolerability of PAR and FLUO **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 128 **Intervention:** **D1:** Paroxetine: 20-50 mg/d (initial dosage of 20 mg/d could be increased wkly by 10 mg/d up to 50 mg/d) **D2:** Fluoxetine: 20-80 mg/d (initial dosage of 20 mg/d could be increased wkly by 20 mg/d up to 80 mg/d) **D3:** placebo	**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	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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), 2000 **Country and setting:** US Multicenter (22) **Funding:** Forest Laboratories, Inc.	**Research objective:** To assess efficacy and safety of ESC vs. CIT and placebo **Duration of study:** 8 weeks **Study design:** RCT **Overall study N:** 375 **Intervention:** **D1:** Escitalopram: 10-20 mg/d **D2:** Citalopram: 20-40 mg/d **D3:** placebo	**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. placebo) **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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Nefazodone: 100-600 mg/d **D2:** Sertraline: 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: NEF: 59% SER: 57% Difficulty with ejaculation: SER: had sig AEs on sexual function NEF: no sig AE on sexual function $P < 0.01$	**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):** **D1:** asthenia- 18 somnolence- 23 **D2:** asthenia- 24 somnolence- 21 **Sweating (increase):** **D1:** 6 **D2:** 17	**Overall attrition rate:** 24.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** United States Multicenter (2) **Funding:** Burroughs Wellcome Co	**Research objective:** Efficay and safety of BUP and FLUO in depressed outpatients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** **D1:** Bupropion: 225-450 mg/d (382) **D2:** Fluoxetine: 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: BUP: 62.7% FLUO: 58.3% No sig diffs in changes of CGI-S, CGI-I, and HAM-A scores	NR	**Overall attrition rate:** 7.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Gagiano, 1993 **Country and setting:** South Africa University hospital **Funding:** NR	**Research objective:** Safety and efficacy comparison of PAR and FLUO in patients with MDD **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 90 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Paroxetine: 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%, FLUO: 63%; no *P* value reported) No sig diffs in groups on HAM-D (item 3) measure for suicidal ideation, both groups showed reduction over six-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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** United States Multicenter (8 sites) **Funding:** Eli Lilly and company	**Research objective:** Evaluation of DUL for efficacy and safety versus placebo and FLUO in patients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 173 **Intervention:** **D1:** Placebo **D2:** Duloxetine: 40-120 mg/d **D3:** Fluoxetine: 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 FLUO 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 placebo (-1.95) *P* = 0.027 and FLUO (-1.82) (*P* = 0.041) Change from baseline on HAM-A subscale of anxiety was DUL (-6.87) in comparison to placebo (-5.05) *P* = 0.077 and FLUO (-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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** France, Denmark, Belgium, The Netherlands Multicenter (33) **Funding:** N.V. Organon, Oss, The 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:** Mirtazapine: 49.5 mg **D2:** Venlafaxine: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Citalopram: 20-40 mg/d **D2:** Fluvoxamine: 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 FLUO 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: CIT: 14% FLUV: 8% no sig diff Mean % reduction in score at wk 6: CIT: 33% FLUV: 26% Responders (reduction in score from baseline > 50%): CIT: 30.5%, FLUV: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Halikas, 1995 **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:** 150 **Intervention:** **D1:** Mirtazapine: 5-35 mg **D2:** Trazodone: 40-280 mg **D3:** placebo	**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 (SDS) • 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 placebo 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 placebo were statistically sig at 2, 3, 4, and 6 wks. Using MADRS, statistically sig diffs were found between both active compounds and placebo at wks 2 and 3. MIR and TRA were associated with sig higher frequencies of dizziness and blurred vision as compared to placebo At wk 6, 51% of MIR and 41% of TRA treated patients were HAM-D responders (not statistically sig)	**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	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Nefazodone: 400-600 mg/d **D2:** Paroxetine: 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	NEF sig increased objective sleep efficiency and total sleep time. Total sleep time for PAR: 388; NEF: 396 (P = 0.05) PAR decreased sleep efficiency in early treatment and some disruption remained at wk 8 % Remission for NEF = 23 PAR = 6% (P = 0.1)	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Taiwan Multicenter **Funding:** NV Organon, Oss, The Netherlands	**Research objective:** To compare efficacy and tolerability of MIR and FLUO 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:** Mirtazapine: 15 mg-45 mg/d **D2:** Fluoxetine: 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. FLUO: 51%) At day 42, diff in HAM-D remitters (MIR: 35% vs. FLUO: 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 FLUO patients Mean body weight increase MIR + 1.84 kg FLUO -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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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 FLUO in treatment of outpatients with minor depressive disorder **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 162 **Intervention:** **D1:** Fluoxetine: 10-20 mg/d **D2:** placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with minor depression according to NIHM 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 FLUO than for placebo (-1.19 vs. -0.61; $P < 0.02$) Statistically greater rate of improvement in FLUO groups than placebo 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 FLUO group (z = 2.10, $P < 0.04$). At endpoint, 40.5% (FLUO) vs. 24.1%(placebo) 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kasper S., 2005 **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:** Trazodone: (prolonged release) 150-450 mg/d **D2:** Paroxetine: 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:** **D1:** 21.0 (SE 0.21) **D2:** 20.9 (SE 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 trazodone 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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 placebo in elderly patients with MDD, using FLUO at fixed dose of 20 mg as a reference drug **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 518 **Intervention:** **D1:** placebo **D2:** Escitalopram: 10 mg **D3:** Fluoxetine: 20 mg placebo	**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	With LOCF, "responders" (≥ 50% decrease from baseline in MADRS total score) = 46% ESC group, 47% placebo group, 37% FLUO group (all NS). At last assessment (LOCF), "remitters" (MADRS total score ≤ 12): 40% ESC group, 42% placebo group, 30% FLUO group. Diff between placebo and ESC groups NS, but fewer remitters in FLUO vs. placebo groups ($P < 0.05$)	**Overall adverse events:** **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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 Goes with Rush et al., 2001 **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:** Bupropion: 100-300 mg/d (mean 238 mg/d) **D2:** Sertraline: 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	**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 **Sexual dysfunction :** **D1:** 10 **D2:** 61 **Somnolence (fatigue):** **D1:** 2 **D2:** 13 **Sweating (increase):** **D1:** 2 **D2:** 10	**Overall attrition rate:** 31.5% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Fluvoxamine: 50-150 mg/d **D2:** Paroxetine: 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: FLUV: 1.93 PAR: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kroenke et al., 2001 **Country and setting:** United States Primary care (76 physicians) **Funding:** Eli Lilly	**Research objective:** To compare efficacy of PAR, FLUO. and SER in depressed primary care patients **Duration of study:** 9 mos **Study design:** Open-label, randomized trial **Overall study N:** 601 **Intervention:** **D1:** Paroxetine: 20 mg/d **D2:** Fluoxetine: 20 mg/d **D3:** Sertraline: 50 mg/d	**Inclusion criteria:** • Adults 18 or older • Depressive disorder as determined by PCP • Had home telephone **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 47.2 **D2:** 47.1 **D3:** 44.1 **Sex (% female):** **D1:** 76 **D2:** 86 **D3:** 75 **Race (% white):** **D1:** 85 **D2:** 88 **D3:** 79 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	All 3 treatment groups showed sig improvements in depression and other health related QOL domains (social function, work function, physical function) No sig diffs between treatment groups in any of 3 and 9 mos outcome measures Subgroup analysis showed no diffs in treatment effects for patients with MDD and for patients older than 60 yrs Switch rate to other medication: PAR: 22% FLUO: 14% SER: 17%	NR	**Overall attrition rate:** 24.3% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Multinational **Funding:** Clinical research grant from NV Organon, Oss, The 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:** Mirtazapine: 15-60 mg/d **D2:** Citalopram: 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 placebo-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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Europe and Canada Primary care **Funding:** H. Lundbeck A/S	**Research objective:** Efficacy and tolerability of ESC compared to CIT and placebo in depression in primary care setting **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 471 **Intervention:** **D1:** Citalopram: 20-40 mg/d (mean 28.4) **D2:** Escitalopram: 10-20 mg/d (mean 14.0) **D3:** placebo	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Venlafaxine: XR 75 mg/d **D2:** Paroxetine: 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 (HAM-D, CGI, MADRS rates were at 76% for both treatment groups Remission rates (6 or less on MADRS) were 48% for VEN XR and 46% 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Venlafaxine: 75-150 mg/d **D2:** Sertraline: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Escitalopram: 10-20 mg/d (12.1) **D2:** Venlafaxine: 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: ESC 77.4% and VEN 79.6% responders ESC 69.9% and VEN. 69.7% remitters	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Escitalopram: 20 mg/d **D2:** Citalopram: 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) ESC 76.1% CIT 61.3 (P = 0.008) Remitters: ESC 56.1% CIT 43.6% (P = 0.04); NNT for remission: 9 MADRS-S ESC -9.9 CIT -8.6 (P < 0.05) CGI-S ESC -2.3 CIT -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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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., 2005 **Country and setting:** United States Multicenter (13 university-affiliated and private research clinics) **Funding:** NR	**Research objective:** To assess relative efficacy and safety of VEN and FLUO **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 308 **Intervention:** **D1:** Venlafaxine: 75-225 mg/d **D2:** Fluoxetine: 20-60 mg/d **D3:** placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Symptoms present 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 • Investigational drug use within last 30 days • ECT within last 3 mos • Suicidal tendencies • History of nonresponse to VEN or FLUO • Received VEN within 6 mos	**Mean age (yrs):** **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 **Mean HAM-D score at baseline:** **D1:** 23.5 (3.2) **D2:** 23.7 (3.2) **D3:** 23.7 (3.3)	Overall diffs among treatment groups on HAM-D did not quite reach statistical significance, although diff between VEN and placebo was statistically sig HAM-D response: VEN: 53% vs. FLUO: 45% (P = 0.034); HAM-D remission rates: VEN: 32% vs. FLUO: 28% (P = 0.25) Fluoxetine was sig more effective than placebo according to CGI and PGI definitions in response only; neither active therapy separated sig from placebo on remission definitions A statistically sig diff observed on only 1 of 5 QOL measures; greater improvement in VEN compared with both FLUO and placebo groups on variable	**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 **Somnolence (fatigue):** **D1:** 10 **D2:** 10 **D3:** 5 **Sweating (increase):** **D1:** 14 **D2:** 4 **D3:** 2	**Overall attrition rate:** 22% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Sertraline: 50-200 mg/d (137.1) **D2:** Fluvoxamine: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 Finkel et al., 1999 **Country and setting:** United States Outpatient **Funding:** NR	**Research objective:** To assess efficacy of SER vs. FLUO 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:** Sertraline: 50-100 mg/d **D2:** Fluoxetine: 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 FLUO on primary efficacy measures Responders: SER: 73% FLUO: 71% Remitters: SER: 45% FLUO: 46% **Sugroup analysis:** Sig more responders in SER group (P = 0.027): 58.5% (SER) vs. 42.4% (FLUO) Psychological Health subscale: SER group improved from 46.0 (9.2) to 51.4 (8.8) and FLUO 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** France Multicenter (general practices) **Funding:** NR	**Research objective:** To compare CIT with FLUO 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:** Citalopram: 20 mg/d **D2:** Fluoxetine: 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: CIT: -20.7 FLUO: -19.4 Responders (reduction in score from baseline > 50%) at endpoint: CIT: 78% FLUO: 76% Remitters (MADRS ≤ 12) at endpoint: CIT: 75% FLUO: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** United States **Funding:** NR	**Research objective:** To compare clinical efficacy of FLUO and TRA in patients with major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 40 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Trazodone: 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 (% female):** **D1:** Male:female ratio = 9:12 **D2:** Male:female ratio = 10:9 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 23.2 (2.8) **D2:** 23.6 (3.0)	At endpoint no sig diffs in health outcomes between FLUO and TRA	**Overall adverse events:** **D1:** 43% reported 2+ events **D2:** 37% reported 2+ events **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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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., 1996 **Country and setting:** United States Multicenter **Funding:** Solvay Pharmaceuticals, Inc.; The Upjohn Company	**Research objective:** To compare efficacy, safety, and tolerance of FLUV and FLUO in a depressed outpatient population **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** **D1:** Fluvoxamine: 100-150 mg; endpoint mean = 101.85 (25.22) **D2:** Fluoxetine: 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 • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies: acute (score of ≥ 21 on Modified Scale for Suicidal Ideation) • Previous treatment with FLUO 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 **Mean HAM-D score at baseline:** **D1:** 25.2 **D2:** 25.6	No statistically sig diffs observed between 2 groups on any efficacy parameter. Medications well tolerated, with only 2 patients in each group terminated because of side effects. FLUV was associated with less nausea than FLUO	**Headache:** **D1:** 50 **D2:** 53 **Insomnia:** **D1:** 36 **D2:** 28 **Nausea:** **D2:** 42.5 **Suicidality:** **D1:** 2 **D2:** 2	**Overall attrition rate:** 16% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Canada and Europe Multicenter **Funding:** Pfizer, Inc	**Research objective:** To determine safety, tolerability, and efficacy of SER vs. placebo in treatment of dysthymia **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 310 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** placebo	**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: SER: 51.9%, placebo: 33.8% (P = 0.001) MADRS: SER: 53.2%, placebo: 37.5% (P = 0.006) CGI-I: SER: 60.1%, placebo: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rocca et al., 2005 **Country and setting:** Italy University clinic **Funding:** University of Turin, Italy	**Research objective:** To compare effect of SER and CIT on depression symptoms and cognitive functions in nondemented elderly patients with minor depressive disorder or sybsyndromal depressive symptomatology **Duration of study:** 12 mos **Study design:** Nonrandomized controlled trial **Overall study N:** 138 **Intervention:** **D1:** Citalopram: 20 mg/d **D2:** Sertraline: 50 mg/d	**Inclusion criteria:** • Minimum HAM-D score of 10 • Nondemented elderly (65 or older) • Minor depressive disorder or subsyndromal depressive disorder according to SCID **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Any other current Axis I or II psychiatric disorder • Impairment and decline of global cognitive functions on MMSE • Score of at least 12 on Alzheimer's Disease Assessment Scale-Cognitive Subscale	**Mean age (yrs):** **D1:** 72.4 **D2:** 71.9 **Sex (% female):** **D1:** 24.2 **D2:** 31.9 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 12.9 **D2:** 12.9	Both treatments induced a sig, sustained, comparable improvement in depressive symptoms and social functioning Change from baseline to endpoint on HAM-D CIT and SER groups decrease 55% vs. 52.7%; *(P* = NR) or GDS Remission observed at any timepoint between treatment groups 12 mos: 53% vs. 42%; *P* = 0.25 Sig within-group improvements seen in all cognitive measures for both SER and CIT WMS, TMT-A, TMT-B, VF, and MMSE	**Dizziness:** **D1:** 15.2 **D2:** 9.7 **Headache:** **D1:** 10.1 **D2:** 9.7 **Nausea:** **D1:** 24.2 **D2:** 18.1	**Overall attrition rate:** 27.5 **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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 placebo washout) **Study design:** RCT **Overall study N:** 93 **Intervention:** **D1:** Fluvoxamine: 200 mg/d (100mg twice daily) **D2:** Sertraline: 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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 FLUO **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 301 **Intervention:** **D1:** Venlafaxine: XR 75-225 mg/d **D2:** Fluoxetine: 20-60 mg/d **D3:** placebo	**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 FLUO treatment on 21-HAM-D or MADRS at endpoint in LOCF analysis At wk 8 of LOCF, 57% of VEN group and 50% of FLUO group (P = 0.07) were HAM-D responders At end of treatment 37% of VEN group and 22% of FLUO ($P \leq 0.05$) group were in remission (HAM-D score ≤ 7) At endpoint in LOCF analysis, VEN patients showed a sig diff from placebo in MADRS, CGI, and HAM-D depressed mood item FLUO 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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., 1998 **Country and setting:** United States and Canada Multicenter **Funding:** please list name: Seay Center for Research (UT Southwestern), NIMH	**Research objective:** Effect of NEF and FLUO on sleep in patients with MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 125 **Intervention:** **D1:** Nefazodone: 200-500 mg/d (mean = 424) **D2:** Fluoxetine: 20-40 mg/d (mean = 32)	**Inclusion criteria:** • Adults 19 to 55 • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 18 • Concomitant condition: sleep disturbances **Exclusion criteria:** • Pregnant • Lactating • Clinically sig medical disease	**Mean age (yrs):** **D1:** 36 **D2:** 37 **Sex (% female):** **D1:** 59 **D2:** 70 **Race (% white):** **D1:** 78 **D2:** 85 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 22.9 (2.9) **D2:** 23.3 (2.7)	No diff in efficacy between groups as measured by change in HAM-D17 Response (< 10 on HAM-D17): NEF: 47% FLUO: 45% On EEG: increased sleep efficiency, decreased awakenings and decreased % AMT for NEF as compared to FLUO Also sig diffs on sleep disturbance factors of HAM-D and IDS-C and IDS-SR favoring NEF over FLUO	**Constipation:** **D1:** 17 **D2:** 11 **Diarrhea:** **D1:** 16 **D2:** 26 **Dizziness:** **D1:** 22 **D2:** 8 **Headache:** **D1:** 56 **D2:** 48 **Insomnia:** **D1:** 6 **D2:** 11 **Nausea:** **D1:** 36 **D2:** 25 **Somnolence (fatigue):** **D1:** 22 **D2:** 21	**Overall attrition rate:** 17% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Mirtazapine: 15 mg/d up to 45 mg/d **D2:** Paroxetine: 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 MIR (80) 64.0% PAR (68) 56.7% 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Austria and Germany 6 centers **Funding:** SmithKline, Beecham	**Research objective:** Comparison of efficacy and safety with PAR and FLUO in geriatric outpatients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 108 **Intervention:** **D1:** Paroxetine: 20-40 mg/d **D2:** Fluoxetine: 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:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • ECT within last 3 mos	**Mean age (yrs):** **D1:** 74.3 **D2:** 73.7 **Sex (% female):** **D1:** 83 **D2:** 90 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	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 FLUO group MADRS responders at wk 6 (i.e., reduction > 50% from baseline MADRS) sig greater in PAR than FLUO	**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:** NR **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** France Multicenter (45) **Funding:** Pfizer, Inc	**Research objective:** Comparison of efficacy and safety in patients being treated with SER and FLUO with MDD **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 234 **Intervention:** **D1:** Sertraline: 50-150 (mean = 76.5) **D2:** Fluoxetine: 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 • FLUO 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 FLUO patients on HAM-D 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

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 **Country and setting:** Canada Multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** Comparison of VEN XR and FLUO in outpatients with depression and anxiety **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 368 **Intervention:** **D1:** placebo **D2:** Venlafaxine: 75-225 mg/d (could be increased to 150 mg/d on day 14 and 225 mg/d on day 28) **D3:** Fluoxetine: 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 FLUO and VEN (just placebo) At wk 12 response rates were 67% for VEN and 62% for FLUO ($P < 0.05$) HAM-D scores in VEN and FLUO groups dropped sig when compared with placebo VEN had sig more HAM-A responders at wk 12 than FLUO HAM-D remission rate in VEN group was sig compared to placebo at wks 3, 4, 6, 8, 12 and final HAM-D remission rate in FLUO group was sig compared to placebo at wks 8, 12, and final Patients in VEN group showed a sig decrease in HAM-D and HAM-A scores compared to placebo ($P < 0.05$)	**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% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Sertraline: 50-150 mg/d **D2:** Venlafaxine: 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: SER: 70.9% VEN: 70.9% (*P* = 0.95) HAM-D remitters: SER: 59.5% VEN: 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: SER 16.8 + 1.77 VEN 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 Kocsis et al., 1997 **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:** Sertraline: 50-200 mg/d **D2:** Imipramine: 50-300 mg/d **D3:** placebo	**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 placebo (59.0% vs. 44.3%; $P < 0.02$) A sig greater proportion of patients in SER group increased in psychosocial functioning compared to placebo (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 placebo 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Tignol, 1993 **Country and setting:** France Multicenter **Funding:** SmithKline Beecham Pharmaceuticals	**Research objective:** To compare PAR and FLUO in treatment of inpatients with major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 178 **Intervention:** **D1:** Paroxetine: 20 mg **D2:** Fluoxetine: 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 FLUO patients. MADRS scores fell to ≤ 11 among 67% of PAR and 64% of FLUO patients After 6 wks of treatment, CGI-S scores were 1 or 2 among 78% of PAR and 73% of FLUO patients	**Nausea:** **D1:** 4 **D2:** 10	**Overall attrition rate:** 1.1% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** UK **Funding:** Wyeth-Ayerst International	**Research objective:** Safety and efficacy of VEN and FLUO 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:** Venlafaxine: 75 mg/d **D2:** Fluoxetine: 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: FLUO: 62.8% VEN: 55.1% (*P* = NR) MADRS remitters (MADRS ≤ 6): FLUO: 34.1% VEN: 35.4% (*P* = NR) 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Greece and Italy Hospitalized and day care **Funding:** Wyeth-Ayerst International	**Research objective:** Efficacy and tolerability of VEN and FLUO in patients with major depression and melancholia **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 109 **Intervention:** **D1:** Venlafaxine: 225 mg/d **D2:** Fluoxetine: 60 mg/d	**Inclusion criteria:** • Adults 18 to 64 • Diagnosed with MDD according to DSM-III or -IV • Concomitant condition: melancholia • MADRS ≥ 25 **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, 70% of patients with VEN and 66% with FLUO had ≥ 50% reduction in MADRS score, and 70% with VEN and 62% with FLUO 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 FLUO (P = 0.018). Final HAM-D score < 7 was attained in 41% of VEN and 36% of FLUO patients	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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 FLUO 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:** Sertraline: 50-100 mg/d **D2:** Fluoxetine: 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% FLUO = 77% **CONTINUATION PHASE** Relapse rates SER = 10% FLUO = 13% Response rate (see defintion above) SER = 81% FLUO = 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Mirtazapine: 24-72 mg/d **D2:** Trazodone: 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) 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** France, Psychiatric centers **Funding:** NR	**Research objective:** To investigate whether FLUO 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:** Fluoxetine: 20 mg/d (Phase I), 20-40 mg/d (Phase II) **D2:** placebo	**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 • FLUO 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), FLUO = 42 placebo = 14 (P = 0.03) Remission n at mo 3 (HAM-D $\leq$ 7), FLUO = 32, placebo = 10 (P = 0.07) # of responders at mo 6: FLUO = 33 placebo = 9 (P = 0.48) Remission n at mo 6: FLUO: 29 placebo: 4 (P = 0.01) Increase in GAF scores by mo 3 sig greater in FLUO (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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Versiani et al., 2005 **Country and setting:** Multinational, Multicenter (30 sites) **Funding:** Organon, NV	**Research objective:** To compare effectiveness and tolerability of MIR and FLUO in severe MDD and compare effects on anxiety, sleep and QOL **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 299 **Intervention:** **D1:** Mirtazapine: 30-60 mg **D2:** Fluoxetine: 20-40 mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 25 **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 3 mos • Suicidal tendencies	**Mean age (yrs):** **D1:** 43 **D2:** 47 **Sex (% female):** **D1:** 74 **D2:** 69 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 29 (3) **D2:** 28(3)	No sig diff in percent of responders at day 56, (MIR: 40.1% vs. FLUO: 41.4 %) Both treatment groups showed 18 point improvement on QLSQ	**Overall adverse events:** **D1:** 50 **D2:** 45 **Changes in weight (increase):** **D1:** 6.9 **D2:** 1.3 **Dizziness:** **D1:** 9 **D2:** 12.8 **Headache:** **D1:** 19.3 **D2:** 18.8 **Insomnia:** **D1:** 4.8 **D2:** 8.7 **Nausea:** **D1:** 15.9 **D2:** 24.1 **Somnolence (fatigue):** **D1:** 13.8 **D2:** 9.4	**Overall attrition rate:** 14% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **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:** Bupropion: 100-300 mg/d (197) **D2:** Paroxetine: 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 ≥ 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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Country NR, appears to be United States 2 private psycho-pharmacology 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 placebo lead-in to eliminate placebo responders and placebo nontolerators) **Study design:** RCT **Overall study N:** 124 **Intervention:** **D1:** Bupropion: 225-450 mg/d **D2:** Trazodone: 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 at least 4 wks but < 2 yrs • Clinically appropriate 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 history of priapism or being treated with meds 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 **D2:** 25.0	**HAM-D (LOCF)** **Center 1** BUP: at day 42, BUP stat sig better than TRA ($P < 0.01$) When centers combined, no statistically sig diffs between TRA and BUP were observed Responder analysis (responder = > 50% reduction in HAM-D score between baseline and discontinuation) BUP = 33 (55.9%) TRA = 21 (40.4%) Remitters (>50% reduction and a HAM-D score<10) BUP = 27 (46%) TRA = 16 (31%) CGI-I responders BUP = 34 (57.6%) TRA = 24 (46.2%)	**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. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (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 **Country and setting:** Multinational Multicenter **Funding:** NV Organon	**Research objective:** To compare efficacy and tolerability of MIR and FLUO in depressed inpatients and outpatients **Duration of study:** 6 wks (after a 3-7 day single-blind, placebo washout period) **Study design:** RCT **Overall study N:** 133 **Intervention:** **D1:** Mirtazapine: 15-60 mg/d **D2:** Fluoxetine: 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% FLUO 25.4% (*P* = 0.39) CGI responders (much or very much approved): MIR 63.3% FLUO 54.0% (*P* = 0.677) Q-LES-Q estimated treatment diff (MIR minus FLUO): 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%	**Overall attrition rate:** 28.6% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 1. KQ1: Efficacy or effectiveness of antidepressants for treating depressive symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Williams, 2000 **Country and setting:** United States Multicenter, primary care clinics **Funding:** Hartford and MacArthur Foundations	**Research objective:** To compare effectiveness of PAR vs. placebo 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:** Paroxetine: 10-40, individually titrated **D2:** placebo	**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: PAR: 0.61 (*P* = 0.05) placebo: 0.40 (*P* = 0.05) Behavior Therapy 0.52 (*P* = 0.05) *P* = 0.004 for PAR vs. placebo PAR only statistically and clinically sig better than placebo for subjects with dysthymia and high baseline mental health function HAM-D results NR for ITT population	**Overall adverse events:** NR	**Overall attrition rate:** 25.1% **TT Analysis:** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse

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 **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:** Venlafaxine: 75-225 mg/d **D2:** Conventional txt: Citalopram: 20-40 mg/d Fluoxetine: 20-40 mg/d Mirtazapine: 30-45 mg/d Paroxetine: 20-40 mg/d Sertraline: 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 psychotheraputic 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%) FLUO 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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **Country and setting:** United States, outpatient **Funding:** SmithKline Beecham	**Research objective:** To compare effectiveness of PAR vs. IMI and placebo 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 placebo-controlled trial **Overall study N:** 219 of 717 patients randomized to acute phase continued in double-blind extension **Intervention:** **D1:** Paroxetine: 10-50 mg/d **D2:** Placebo	**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% (placebo). 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 placebo group. CGI-S: 4.2 baseline to 2.0 at 1 yr (PAR) vs. 4.3 baseline to 1.6 at 1 yr (placebo) Relapse rates in responders: PAR 15%, placebo 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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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 placebo in outpatients with major depression **Duration of study:** Short-term study: 6 wks Long-term study: 1 yr **Study design:** RCT **Overall study N:** Enrolled: 227 Analyzed: 225 **Intervention:** Average daily doses after titration: **D1:** Venlafaxine: 156-160 mg/d **D2:** Trazodone: 294-300 mg/d **D3:** Placebo	**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 • Suicidial tendencies • No formal psychotherapy allowed during study period	**Mean age (yrs):** Overall: 40.7 **Sex (% female):** Overall: F:M ratio 2:1 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** **D1:** 25.02 **D2:** 24.66 **D3:** 24.41	CGI response rates (score or 1 or 2): VEN 72% TRA 60% placebo 55% (*P* = NR) 30 TRA- and 37 VEN-treated clinical responders (CGI-I score of 1 or 2) were allowed to continue on in long-term phase Relapse rates: TRA 13% VEN, 8% placebo 14% (*P* = NR)	**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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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 placebo period; 295 entered double-blind therapy **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Placebo	**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 placebo 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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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:** Nefazodone: 400-600 mg/d **D2:** Placebo	**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 nefazodone (1.8%) group vs. placebo (18.3%) group Discontinuation due to lack of efficacy 17.3% for NEF and 32.8% for placebo Relative risk of relapse (HAM-D)was sig lower for NEF than placebo 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 placebo (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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **Country and setting:** United States Multiclinic **Funding:** Bristol-Myers-Squibb	**Research objective:** Comparison of nefazodone and placebo in prevention of depression recurrence **Duration of study:** 52 wks **Study design:** RCT **Overall study N:** 165 for maintenance phase **Intervention:** **D1:** Nefazodone: 300-600 mg/d (495.2) **D2:** Placebo **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 placebo-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 dysfunctional (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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **Country and setting:** Spain; multicenter (10) **Funding:** Eli Lilly and Co	**Research objective:** To evaluate efficacy and safety of FLUO compared to placebo 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:** Fluoxetine: 20-40 mg/d **D2:** Placebo	**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 FLUO vs. 40% with placebo (P = 0.010); symptom-free period sig longer for FLUO vs. placebo (295 days vs. 192 days, P = 0.002); mean end-point HAMD sig lower in FLUO vs. placebo (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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **Country and setting:** Multinational, multicenter **Funding:** H. Lundbeck A/S	**Research objective:** To compare prophylactic efficacy of CIT vs. placebo 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:** Citalopram: 20, 40, or 60 mg (3 groups + placebo) **D2:** Placebo	**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 placebo CIT 24/132 (18.2%); placebo 59/132 (44.7%) ($P < 0.001$). Prophylactic treatment well tolerated. Risk ratio related to recurrence of depression (CIT / placebo) estimated at 0.321 (95% CI: 0.199-0.516). Diff in time to recurrence between CIT and placebo 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 placebo 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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 Kocsis et al., 2002 **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:** Sertraline: 50-200 mg/d **D2:** Placebo	**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 • This was a 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: SER = 6%, placebo = 23% (P = 0.002) By consensus agreement: SER = 26%, placebo = 50% (P = 0.001) Showed first symptoms of recurrence by consensus agreement: SER = 34%, placebo = 60% (P = 0.001) Patients receiving placebo 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 the full population **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **Country and setting:** Denmark Single center study - out patient **Funding:** H.Lundbeck A/S	**Research objective:** To compare prophylactic efficacy of CIT and placebo 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:** Citalopram: 20-40 mg/d **D2:** Placebo	**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 • FLUO 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 placebo had recurrence. Time to recurrence was sig different between CIT- and placebo-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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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:** Sertraline 50 **D2:** Sertraline 100 **D3:** Placebo	**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 placebo (SER, 50 mg: 16 [16.8%] of 95; SER, 100 mg: 16 [17.0%] of 94; placebo: 33 [33.3%] of 99). Patients treated with SER also had sig longer time until recurrence compared with placebo-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):** **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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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:** Venlafaxine: 100-200 mg/d **D2:** Placebo	**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 placebo group ($P < 0.001$) More than twice as many placebo-treated patients (48%) as VEN-treated patients (21%) discontinued treatment because of lack of efficacy ($P < 0.001$)	**Overall adverse events:** **D1:** TAES- 80 **D2:** TAES- 79 **Diarrhea:** **D1:** 12 **D2:** 7 **Dizziness:** **D1:** 17 **D2:** 25 **Headache:** **D1:** 27 **D2:** 21 **Nausea:** **D1:** 19 **D2:** 14 **Somnolence (fatigue):** **D1:** asthenia-11 **D2:** asthenia-7	**Overall attrition rate:** 63% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events	Analysis and Quality Rating
Author: Montgomery and Dunbar 1993 **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**: Paroxetine: 20-30 mg/d **D2**: Placebo	**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. placebo 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. placebo 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. placebo 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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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., 1993 **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 placebo-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 placebo 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:** Citalopram: 20 mg/d **D2:** Citalopram: 40 mg/d **D3:** Placebo	**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 placebo (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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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:** Paroxetine: 30-40 mg/d **D2:** Venlafaxine: 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 ≥ 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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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:** Escitalopram: 10-20 mg/d **D2:** Placebo	**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% placebo; hazard ratio = 0.56; P = 0.01). ESC-treated subjects had sig lower depression ratings than placebo-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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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, placebo-controlled continuation study of patients who responded to acute FLUO treatment for major depression **Duration of study:** 50 wks **Study design:** RCT **Overall study N:** 395 (randomized) **Intervention:** **D1:** Fluoxetine 20 mg/d 14 wks **D2:** Fluoxetine 20 mg/d 38 wks **D3:** Fluoxetine 20 mg/d 50 wks **D4:** Placebo	**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 FLUO compared with those transferred to placebo in both first interval, after 24 total wks of treatment (FLUO, 26.4%; placebo, 48.6%, $P < 0.001$), and second interval, after 38 total wks of treatment (FLUO, 9.0%; placebo, 23.2% $P < 0.04$) In third interval, after 62 total wks of treatment, rates were not sig different between groups (FLUO, 10.7%; placebo, 16.2% $P = 0.54$)	NR	**Overall attrition rate:** N/A **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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
 	
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: Citalopram: 20-60 mg/d
	D2: Placebo
		Inclusion criteria:
		• Diagnosed with MDD according to DSM-III or -IV
		• MADRS < 12 after 8 wks on CITor placebo
		
		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):
				CIT = 21 (13.8%)
				placebo = 18 (24.3%)
				P = 0.04
					Constipation:
					D1: 15
					D2: 5
						Overall attrition rate:
						N/A
						
						ITT Analysis
						Yes
						
						Quality rating:
						Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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:** Bupropion: SR 150-400 mg/d **D2:** Sertraline: 50-200 mg/d **D3:** Venlafaxine: 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: • BUP 21.3% • SER 17.6% • VEN XR 24.8% (*P* = 0.16) QIDS-SR-16 Remission: • BUP 25.5% • SER 26.6% • VEN XR 25.0% (*P* = NR; ns) QIDS-SR-16 Response: • BUP 26.1% • SER 26.7% • VEN XR 25.0% (*P* = NR; ns)	NR	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Good Effectiveness trial

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 Dinan et al and Schmidt et al. 2002 and 2001 **Country and setting:** United States Multicenter **Funding:** Eli Lilly	**Research objective:** To assess efficacy of FLUO 20 mg daily vs. FLUO 90 mg wkly vs. placebo in continuation treatment of MDD **Duration of study:** 25 wks **Study design:** RCT **Overall study N:** 501 **Intervention:** **D1:** Fluoxetine 90 mg/wk **D2:** Fluoxetine 20 mg/wk **D3:** Placebo	**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: • FLUO 90 37% • FLUO 20 26% • placebo 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:** NA **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (continued)

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 **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:** Venlafaxine XR 75-225 mg/d **D2:** Placebo	**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 • FLUO within 30 days	**Mean age (yrs):** **D1:** 43 **D2:** 41 **Sex (% female):** **D1:** 102 (66%) **D2:** 86 (62%) **Race (% white):** NR **Baseline HAM-A:** NA **Baseline HAM-D:** **D1:** 6.5 **D2:** 6.4	HAM-D-6.4 (at day 56) placebo 6.5 (at day 56) VEN XR MADRS-7.2 (56 day) placebo 7.4 (day 56) VEN XR 6-mo relapse rates were sig higher for placebo (52%) than for VEN XR (28%) ($P < 0.001$)	**Overall adverse events:** **D1:** 97% **D2:** 93% **Cardiovascular adverse events:** **D1:** 6% **D2:** 2% **Constipation:** **D1:** 7% **D2:** 3% **Sexual dysfunctional:** **D1:** 5% **D2:** 2% **Sweating (increase):** **D1:** 11% **D2:** 5%	**Overall attrition rate:** 62% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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:** Fluvoxamine: 100 mg/d **D2:** Placebo	**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 placebo (35.1%) ($P < 0.001$) Highly sig diff between FLUV and placebo in distribution of time to recurrence ($P < 0.001$). time to recurrence sig longer for FLUV and placebo (181 vs. 96 days, $P < 0.005$)	**Changes in weight (decrease):** **D1:** 1 **Headache:** **D1:** 5 **Sexual dysfunctional:** **D1:** 0 **Somnolence (fatigue):** **D1:** 4	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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:** Mirtazapine: 15-45 mg/d **D2:** Placebo	**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 placebo ($P < 0.001$) 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 placebo 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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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 FLUO 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:** Acute 165 Continuation 105 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Fluoxetine: 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 • Suicidial ideation • MADRS score greater than 40 • History of mania, hypomania or psychosis • 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 **Baseline HAM-D:** **D1:** 24.5 **D2:** 23.2	Relapse during 32 wk continuation SER 10/49 (20%) FLUO 13/53 (23%) Partial relapse during 32 wk continuation SER 6/49 (12%) FLUO 2/53 (4%)	**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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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:** Bupropion: 300 mg/d **D2:** Placebo	**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 placebo (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 2. KQ2: Efficacy or effectiveness of antidepressants for treating remission, nonresponse, or relapse (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 **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 placebo) (article focuses on results of this maintenance phase) **Study design:** RCT **Overall study N:** 113 (randomised to double-blind phase) **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 65 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Geriatric Mental State AGECAT depression ≥ 3 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Clinically sig medical disease • 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 placebo, log rank test = 1.55, df = 1, (*P* = 0.21) Cumulative survival function SER = 39%, median survival 92 wks placebo 31%, median survival 48 wks Reduction in risk of recurrence: 8.4% over 100 wks (SER vs. placebo) % experiencing recurrence in first 26 wks: SER = 57% placebo = 60% % experiencing recurrence between wks 27 and 52 SER = 16% placebo = 32% Cox regression model predicting recurrence: hazard ratio (95% CI) included variables: SER vs. placebo = 1.21 (0.704, 2.082)	NR	**Overall attrition rate:** 72.6% **ITT Analysis** N/A because recurrence trial **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms

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 **Country and setting:** Europe, multicenter (20 psychiatric clinics) **Funding:** Bristol-Myers Squibb	**Research objective:** To compare efficacy of NEF and PAR for treatment of moderate-severe major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 206 randomized; 196 included in analysis **Intervention:** **D1:** Nefazodone 200-600 mg/d (mean 472) **D2:** Paroxetine 20-40 mg/d (mean 32.7)	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-III-R • Minimum HAM-D-17 score of 18 • Rated at least moderately ill on CGI-S **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant psychotherapeutic medications • ECT within 6 mos • Substance abuse or dependence (within 1 yr) • Clinically sig medical disease • Pregnant or lactating • Suicidal (serious risk) • Lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** **D1:** 38.3 **D2:** 37.9 **Sex (% female):** **D1:** 60 **D2:** 50 **Race (% white):** **D1:** NR **D2:** NR **Baseline HAM-D-17:** **D1:** 24.6 **D2:** 24.8 **Baseline HAM-A:** **D1:** 19 **D2:** 18.3	**Anxiety outcomes:** Improvement in HAM-A score was 6.5 for NEF vs. 8.0 for PAR (95% CI for diff between groups: -0.7 to 3.8)	**Overall adverse events:** **D1:** 84 **D2:** 78 **Dizziness:** **D1:** 17 **D2:** 9 **Headache:** **D1:** 35 **D2:** 25 **Nausea:** **D1:** 27 **D2:** 30 **Somnolence:** **D1:** 16 **D2:** 24	**Overall attrition rate:** 23.1% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **Country and setting:** United States, multicenter (3 sites) **Funding:** Eli Lilly and Company	**Research objective:** To compare FLUO and TRA for treatment of major depression and to evaluate activation and sedation effects **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 126 randomized; 120 included in analysis **Intervention:** **D1:** Fluoxetine 20-40 mg/d (median 20 mg/d) **D2:** Trazodone 50-400 mg/d (median 250 mg/d)	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-III • Minimum HAM-D-21 score of 20 • Duration at least 4 wks **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant psychotherapeutic medications • Substance abuse (within one yr) • Placebo response during lead-in	**Mean age (yrs):** **D1:** 40.0 **D2:** 40.0 **Sex (% female):** **D1:** 64.6 **D2:** 68.8 **Race (% white):** **D1:** 98.5 **D2:** 98.4 **Baseline HAM-D-21:** **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) **Baseline HAM-A:** NR	**Sleep outcomes** Improvement in HAM-D Sleep Disturbance Factor was 1.6 points in FLUO-treated group vs. 2.7 points in TRA group (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:** **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 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **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:** Duloxetine 60 mg/d **D2:** Placebo	**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 placebo, $P = 0.544$). Response rates were similar for DUL and placebo (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 placebo ($P = 0.066$). 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 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **Country and setting:** Canada, multicenter (8 sites) **Funding:** SmithKline Beecham	**Research objective:** To evaluate antidepressant and anxiolytic efficacy of FLUO and PAR in patients with major depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 203 randomized; 198 included in analysis **Intervention:** **D1:** Fluoxetine 20-80 mg/d (mean 27.5) **D2:** Paroxetine 20-50 mg/d (mean 25.5)	**Inclusion criteria:** • Outpatients • MDD according to DSM-III-R • Minimum HAM-D-21 score of 20 and score of 2 on HAM-D item 1 • Depression symptoms for at least 1 mo **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic drugs • ECT within 2 mos • Concurrent formal psychotherapy • Illicit drug or alcohol abuse (past or present) • Suicidal (sig risk) • Pregnant or lactating • Clinically sig medical disease	**Mean age (yrs):** **D1:** 41.2 **D2:** 40.6 **Sex (% female):** **D1:** 59.4 **D2:** 63.7 **Race (% white):** **D1:** 98.0 **D2:** 95.1 **Baseline HAM-D-21:** **D1:** 25.45 (0.46) **D2:** 25.91 (0.46) **Baseline HAM-A:** NR	**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 1.21 for FLUO and 1.17 for PAR (*P* = 0.823). Improvement from baseline in HAM-D Agitation item was 0.39 for FLUO and 0.40 for PAR (*P* = 0.978)	**Changes in weight (decrease):** **D1:** 11.9 **D2:** 2.9 **(increase):** **D1:** 13.9 **D2:** 10.8 **Constipation:** **D1:** 4.0 **D2:** 17.7 **Diarrhea:** **D1:** 18.8 **D2:** 11.8 **Headache:** **D1:** 36.6 **D2:** 36.3 **Insomnia:** **D1:** 22.8 **D2:** 26.5 **Nausea:** **D1:** 31.7 **D2:** 37.3 **Sexual dysfunction:** **D1:** 7.3 of males **D2:** 10.8 of males **Somnolence:** **D1:** 16.8 **D2:** 18.6 **Suicidality:** **D1:** 2.0 **D2:** 2.0 **Sweating (increase):** **D1:** 5.9 **D2:** 13.7	**Overall attrition rate:** 36% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Clerc et al., 1994 **Country and setting:** France and Belgium, multicenter (hospitals) **Funding:** Wyeth-Ayerst	**Research objective:** To compare efficacy and short-term safety of VEN and FLUO in hospitalized patients with MDD and melancholia **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 68 **Intervention:** **D1:** Fluoxetine 40 mg/d **D2:** Venlafaxine 200 mg/d	**Inclusion criteria:** • Adults 18 or older • Hospitalized patients • MDD with melancholia according to DSM-III-R • Depression duration at least 1 mo • MADRS at least 25 **Exclusion criteria:** • Clinically sig medical disease • Concurrent ECT • Concurrent psychotherapy	**Mean age (yrs):** **D1:** 53.6 **D2:** 49.0 **Sex (% female):** NR **Race (% white):** NR **Baseline HAM-D-21:** **D1:** 29.7 (4.2) **D2:** 29.1 (5.2) **Baseline HAM-A:** NR	**Depression outcomes in patients with melancholia:** Mean decrease in HAM-D score was sig better for VEN (-18) compared to FLUO (-12.4) (*P* = 0.027) HAM-D response rates were 73% in VEN-treated group compared to 50% in FLUO-treated group. Diff not statistically sig (*P* = NR)	**Headache:** **D1:** 9 **D2:** 3 **Insomnia:** **D1:** 9 **D2:** 9 **Nausea:** **D1:** 12 **D2:** 9	**Overall attrition rate:** 23% **ITT Analysis** Yes **Quality rating:** Poor High differential attrition

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **Country and setting:** United States and Canada, multicenter (6 sites) **Funding:** Wyeth-Ayerst	**Research objective:** To compare efficacy and safety of TRA, VEN, and placebo in outpatients with major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 227 randomized; 225 included in analysis **Intervention:** **D1:** Trazodone 150-400 mg/d **D2:** Venlafaxine 75-200 mg/d **D3:** Placebo	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-III-R • Minimum HAM-D-21 score of 20 • Depression duration at least 1 mo **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic drugs • Drug or alcohol dependence (within 2 yrs) • ECT within 14 days • Investigational drug use within 2 yrs • Suicidal (serious risk) • Pregnant, lactating, or child-bearing potential without contraception • Unstable medical disease • History of seizure disorder • Placebo response during washout (20% improvement on HAM-D)	**Mean age (yrs):** Overall: 40.7 **Sex (% female):** NR **Race (% white):** NR **Baseline HAM-D-21:** **D1:** 24.66 **D2:** 25.02 **D3:** 24.41 **Baseline HAM-D Sleep Factor:** **D1:** 3.60 **D2:** 3.52 **D3:** 3.20 **Baseline HAM-A:** NR	**Sleep outcomes** HAM-D Sleep Factor scores at endpoint were sig better for TRA (1.42) than for VEN (2.22; $P < 0.05$) and placebo (1.95; $P < 0.05$)	**Constipation:** **D1:** 9 **D2:** 22 **D3:** 4 **Dizziness:** **D1:** 36 **D2:** 17 **D3:** 5 **Nausea:** **D1:** 19 **D2:** 44 **D3:** 5 **Somnolence:** **D1:** 61 **D2:** 43 **D3:** 12 **Sweating (increase):** **D1:** 3 **D2:** 12 **D3:** 1	**Overall attrition rate:** 33.78% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Detke, 2004 **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:** 367 **Intervention:** **D1:** Duloxetine 80 mg/d **D2:** Duloxetine 120 mg/d **D3:** Paroxetine: 20 mg/d **D4:** placebo	**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) PGI scores were sig superior in patients receiving PAR than patients receiving 80 mg/d DUL (*P* < 0.05) Improvments in pain scores similar between active medications: DUL 80 mg and placebo (*P* = 0.063), DUL 120 mg and placebo (*P* = 0.086). Improvement in pain was superior to placebo (*P* = 0.035)	**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 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **Country and setting:** United States, multicenter (18 sites) **Funding:** Eli Lilly and Company	**Research objective:** To evaluate efficacy of DUL vs. placebo for treatment of MDD and associated painful symptoms **Duration of study:** 9 wks **Study design:** RCT **Overall study N:** 245 **Intervention:** **D1:** Duloxetine 60 mg/d **D2:** Placebo	**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 duloxetine (~8.5 mm) compared to placebo (~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 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **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 placebo for treatment of emotional and painful physical symptoms of MDD **Duration of study:** 9 wks **Study design:** RCT **Overall study N:** 267 **Intervention:** **D1:** Duloxetine 60 mg/d **D2:** Placebo	**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 placebo 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 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **Country and setting:** United States, multicenter (15 sites) **Funding:** Eli Lilly and Company	**Research objective:** To compare efficacy and tolerability of FLUO 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:** Fluoxetine: 20-60 mg/d **D2:** Paroxetine: 20-60 mg/d **D3:** Sertraline: 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 placebo 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 FLUO, 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: FLUO (-3.1), PAR (-2.9), SER (-3.1) (overall *P* = 0.852)	**Changes in weight (increase 7%):** **D1:** 1.6 **D2:** 9.0 **D3:** 2.9 **Diarrhea:** **D3:** 26.0 **Headache:** **D1:** 25.0 **D2:** 21.9 **D3:** 28.1 **Insomnia:** **D2:** 20.8 **D3:** 26.0 **Nausea:** **D2:** 25.0 **D3:** 20.8 **Sexual dysfunction (abnormal ejaculation):** **D2:** 20.0 (of males)	**Overall attrition rate:** 49% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **Country and setting:** United States, multicenter (15 sites) **Funding:** Eli Lilly and Company	**Research objective:** To compare efficacy and tolerability of FLUO vs. PAR and SER for treatment of anxious depression **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:** 108 (subset of patients with high anxiety from larger trial involving 284 patients with MDD) **Intervention:** **D1:** Fluoxetine: 20-60 mg/d (mean 44) **D2:** Paroxetine: 20-60 mg/d (mean 36) **D3:** Sertraline: 50-200 mg/d (mean 104)	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-IV • Minimum HAM-D-17 score of 16 Note: High anxiety defined as HAM-D Anxiety/Somatization Factor score of at least 7 **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 • Seizure within 1 yr • Response to placebo in lead-in phase	**Mean age (yrs):** **D1:** 40.3 **D2:** 41.4 **D3:** 44..1 **Sex (% female):** **D1:** 65.7 **D2:** 66.7 **D3:** 62.8 **Race (% white):** NR **Baseline HAM-D-17:** **D1:** 23.6 (3.9) **D2:** 25.0 (3.8) **D3:** 23.9 (3.4) **Baseline HAM-D Anxiety/Somatization factor:** **D1:** 7.8 (0.9) **D2:** 8.2 (1.3) **D3:** 8.1 (1.3) **Baseline HAM-A:** NR	**Depression outcomes in patients with anxiety:** No statistically sig diffs between FLUO, SER and PAR in improvement on HAM-D-17 total scores (overall *P* = 0.323) Response rates were similar for FLUO, PAR, and SER (73%, 77%, and 86%, overall *P* = 0.405). Remission rates were also similar (53%, 50%, and 62%, overall *P* = 0.588) **Anxiety outcomes:** No statistically sig diffs between FLUO, SER and PAR in improvement on HAM-D Anxiety/ Somatization Factor scores (overall *P* = 0.199)	**Diarrhea:** **D2:** 20.0 **D3:** 25.6 **Headache:** **D1:** 22.9 **D2:** 23.3 **D3:** 25.6 **Insomnia:** **D1:** 17.1 **D2:** 23.3 **D3:** 23.3 **Nausea:** **D2:** 26.7 **Somnolence:** **D1:** 11.4 **D2:** 10.0 **D3:** 16.3	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **Country and setting:** United States, multicenter (5 sites) **Funding:** SmithKline Beecham	**Research objective:** To evaluate efficacy of FLUO vs. PAR vs. placebo for treatment of depression **Duration of study:** 12 wks **Study design:** Pooled analysis of data from 5 sites of 2 multicenter trials **Overall study N:** 128 **Intervention:** **D1:** Fluoxetine 20-80 mg/d **D2:** Paroxetine 20-50 mg/d **D3:** Placebo	**Inclusion criteria:** • Outpatients • Minimum HAM-D-17 score of 18 • Raskin Depression score of 8 or more • Raskin score higher than Covi Anxiety Scale score **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant psychotherapeutic medications • Alcohol or drug abuse (within 6 mos) • ECT within 3 mos • Investigational drug within 1 mo • Suicidal (high risk) • Clinically sig medical disease • Pregnant, lactating, or child-bearing potential without contraception • Placebo response during washout (25% improvement on HAM-D)	**Mean age (yrs):** Overall: 41.3 **Sex (% female):** Overall: 50 **Race (% white):** NR **Baseline HAM-D-17:** **D1:** 23.9 (3.8) **D2:** 23.1 (3.4) **D3:** 23.7 (2.7) **Baseline Covi Anxiety score:** **D1:** 6.3 (1.7) **D2:** 6.2 (1.7) **D3:** 5.8 (1.2) **Baseline HAM-A:** NR	**Anxiety outcomes:** Improvement in Covi Anxiety was similar for FLUO (1.2), PAR (1.2) and placebo (1.1; *P* = NR)	**Cardiovascular adverse events:** **D1:** 11 **D2:** 5 **D3:** 11 **Insomnia:** **D1:** 20 **D2:** 29 **D3:** 11 **Sexual dysfunction:** **D1:** 7 **D2:** 25 **D3:** 0 **Somnolence:** **D1:** 26 **D2:** 35 **D3:** 11	**Overall attrition rate:** 28% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **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 FLUO 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:** Fluoxetine 20-40 mg/d (mean 25) **D2:** Sertraline 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 • Placebo 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 FLUO vs. -11.0 SER). Response rates were higher for SER (59%) vs. FLUO (44%) ($P < 0.05$) **Depression results in anxiety:** FLUO 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 FLUO vs. -9.1/ 48% for SER; P = NR). In agitation, HAM-D improvement was 8.7 for FLUO vs. 12.4 for SER ($P = 0.02$); response rate was 39% for FLUO 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 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Gagiano, 1993 **Country and setting:** South Africa University hospital **Funding:** NR	**Research objective:** To evaluate efficacy of FLUO and PAR in patients with MDD **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 90 **Intervention:** **D1:** Fluoxetine 20-60 mg/d **D2:** Paroxetine 20-40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Outpatients • MDD according to DSM-III-R • Minimum HAM-D-21 score of 18 **Exclusion criteria:** • Additional mental illness or organic mental disorder • Recent psychotherapeutic medications • ECT within 3 mos • Alcohol or drug abuse • Pregnant or lactating • Clinically sig medical disease • Suicidal (severe risk)	**Mean age (yrs):** **D1:** 39.6 **D2:** 37.8 **Sex (% female):** **D1:** 80 **D2:** 80 **Race (% white):** NR **Baseline HAM-D-21:** **D1:** 24.5 (5.0) **D2:** 25.0 (4.7) **Baseline HAM-A:** **D1:** 22.6 (5.1) **D2:** 23.4 (5.5)	**Anxiety outcomes:** Improvement in HAM-A scores was similar for FLUO and PAR groups (*P* = NR)	**Diarrhea:** **D1:** 13 **D2:** 13 **Headache:** **D1:** 47 **D2:** 53 **Insomnia:** **D1:** 20 **D2:** 11 **Nausea:** **D1:** 33 **D2:** 36	**Overall attrition rate:** 21% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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., 2004 **Country and setting:** United States, multicenter (19 psychiatric research centers) **Funding:** Eli Lilly and Company	**Research objective:** To evaluate DUL vs. PAR and placebo for treatment of emotional and painful physical symptoms in patients with MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 353 **Intervention:** **D1:** Duloxetine 40 mg/d **D2:** Duloxetine 80 mg/d **D3:** Paroxetine 20 mg/d **D4:** Placebo	**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 illnesses or organic mental disorder (except anxiety disorders) • Substance abuse or dependence (within 1 yr) • Positive urine drug screen • Lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** **D1:** 41 **D2:** 41 **D3:** 40 **D4:** 40 **Sex (% female):** **D1:** 56 **D2:** 62 **D3:** 64 **D4:** 64 **Race (% white):** **D1:** 84 **D2:** 85 **D3:** 74 **D4:** 83 **Baseline HAM-D-17:** **D1:** 18.74 (5.97) **D2:** 17.86 (4.66) **D3:** 17.83 (5.19) **D4:** 17.20 (5.08) **Baseline HAM-A:** **D1:** 15.24 (5.87) **D2:** 14.70 (4.83) **D3:** 14.70 (6.00) **D4:** 14.47 (5.3) **Median baseline 100mm VAS (overall pain):** **D1:** 17.5 **D2:** 18.0 **D3:** 15.0 **D4:** 15.0	**Pain outcomes:** Median change in VAS overall pain was 0 for placebo, -4 mm for DUL 40 mg (*P* vs. placebo = 0.172), -7.5 mm for DUL 80 mg (*P* vs. placebo = 0.005), and -3 for placebo (*P* vs. placebo = 0.088)	**Constipation:** **D1:** 8.1 **D2:** 8.8 **D3:** 13.8 **D4:** 3.4 **Dizziness:** **D1:** 4.7 **D2:** 16.5 **D3:** 10.3 **D4:** 5.6 **Insomnia:** **D1:** 17.4 **D2:** 19.8 **D3:** 8.0 **D4:** 5.6 **Nausea:** **D1:** 22.1 **D2:** 25.3 **D3:** 16.1 **D4:** 2.2 **Somnolence:** **D1:** 17.4 **D2:** 11.0 **D3:** 8.0 **D4:** 2.2 **Sweating (increase):** **D1:** 9.3 **D2:** 12.1 **D3:** 6.9 **D4:** 0.0	**Overall attrition rate:** 41% **ITT Analysis:** Yes **Quality rating:** Poor: High overall attrition

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Joliat et al., 2004 Pooled data from 1. Reimherr et al., 1998 2. Schmidt et al., 2000 **Country and setting:** United States, multicenter **Funding:** Eli Lilly and Company	**Research objective:** To assess efficacy of FLUO 20 mg daily vs. FLUO 90 mg wkly vs. placebo in continuation treatment of depression in patients with MDD and associated anxiety who initially responded to therapy **Duration of study:** 25 wks **Study design:** Pooled analysis of data from 2 RCTs **Overall study N:** 374 with anxiety (data for 425 patients without anxiety not considered for KQ 3) **Intervention:** **D1:** Fluoxetine 20 mg/d **D2:** Fluoxetine 90 mg/wk **D3:** Placebo	**Inclusion criteria:** • Adults 18 to 65 (Study 1) and 18 to 80 (Study 2) • Outpatients • MDD according to DSM-III-R or IV • Minimum HAM-D-17 score of 16 for Study 1 and 18 for Study 2. Study 2 also required CGI-S score of 4 or more • Duration of 1 mo or more Note: High anxiety defined as score of 7 or more on HAM-D Anxiety-Somatization subscale **Exclusion criteria:** • Additional mental illness or organic mental disorder • Substance abuse (within 1 yr) • Pregnant or lactating • Unstable medical conditions • Lack of response of current episode to FLUO or to 2 prior courses of therapy	**Mean age (yrs):** **D1:** 40.6 **D2:** 40.8 **D3:** 41.5 **Sex (% female):** **D1:** 72.1 **D2:** 70.1 **D3:** 76.2 **Race (% white):** **D1:** 84.3 **D2:** 91.8 **D3:** 86.7 **Baseline HAM-D:** **D1:** 3.79(2.56) **D2:** 4.17(2.77) **D3:** 3.45(2.34) **Baseline HAM-A:** NR	**Depression outcomes in patients with anxiety:** Relapse rates for patients with anxiety were 28.5% in FLUO wkly group, 27.8% in FLUO daily group, and 53.3% in placebo-treated group (*P* = NR) **Anxiety outcomes:** HAM-D Anxiety-Somatization scores increased (worsened) 1.92 and 1.93 in FLUO daily and wkly groups, respectively, and 3.12 points in placebo group (*P* = NR)	NR	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **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. placebo 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:** Venlafaxine 75 mg/d **D2:** Venlafaxine 150 mg/d **D3:** Venlafaxine 200 mg/d **D4:** Placebo	**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 placebo 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 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kroenke et al., 2001 **Country and setting:** United States, multicenter (37 primary care clinics) **Funding:** Eli Lilly and Company	**Research objective:** To compare effectiveness of PAR, FLUO and SER for treatment of depression in primary care **Duration of study:** 9 mos **Study design:** RCT **Overall study N:** 601 randomized; 546 included in analysis **Intervention:** **D1:** Fluoxetine: 20 mg/d (mean 23.4) **D2:** Paroxetine: 20 mg/d (mean 23.5) **D3:** Sertraline: 50 mg/d (mean 72.8)	**Inclusion criteria:** • Adults 18 or older • Depressive disorder diagnosed by primary care physician • Access to telephone at home **Exclusion criteria:** • Concomitant psychotherapeutic medications (SSRI within 2 mos or current non-SSRI antidepressant) • Suicidal tendencies (active) • Bipolar disorder, severe cognitive impairment, terminal illness • Active cocaine or opiate abuse • Pregnant, lactating or pregnancy planned within 9 mos • Unable to read, write, or speak English	**Mean age (yrs):** **D1:** 47.1 **D2:** 47.2 **D3:** 44.1 **Sex (% female):** **D1:** 86 **D2:** 76 **D3:** 75 **Race (% white):** **D1:** 88 **D2:** 85 **D3:** 79 **Baseline HAM-D:** NR **Baseline HAM-A:** NR	**Somatization severity outcomes:** Scores on Patient Health Questionnaire Somatization Severity scale (possible range 0-28) improved similarly in all 3 treatment groups. Scores decreased 3.1, 3.2, and 4.1 points for FLUO, PAR, and SER-treated groups (nonsig diff; *P* value NR)	**Dropouts due to changes in weight (increase):** **D1:** 0 **D2:** 1 **D3:** 1 **Dropouts due to gastrointestinal symptoms:** **D1:** 4 **D2:** 8 **D3:** 4 **Dropouts due to headache:** **D1:** 2 **D2:** 3 **D3:** 1 **Dropouts due to sexual dysfunction:** **D1:** 1 **D2:** 2 **D3:** 0	**Overall attrition rate:** 24.3% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Lader et al., 2005 Pooled data from 1. Burke et al., 2002 2. Rapaportet al., 2004 3. Lepola et al., 2003 **Country and setting:** United States and Europe **Funding:** H. Lundbeck A/S, Forest Laboratories	**Research objective:** To evaluate effect of ESC vs. CIT and placebo on sleep in patients with depression **Duration of study:** 8 wks **Study design:** Pooled analysis of 3 RCTs **Overall study N:** 1321 included in analysis; 638 with sleep problems **Intervention:** **D1:** Citalopram: 20-40 mg/d (mean 28.9) **D2:** Escitalopram: 10-20 mg/d (mean 13.3) **D3:** Placebo	**Inclusion criteria:** • Adults 18 to 65 (Study 1, 3), 18 to 80 (Study 2) • Outpatients • MDD according to DSM-IV • Minimum MADRS score of 22 Note: Sleep problems defined as MADRS item 4 score of 4 or more (possible range 0-6) **Exclusion criteria:** • Concomitant psychotherapeutic medications • Full criteria not reported	**Mean age (yrs):** **D1:** 42 **D2:** 41 **D3:** 42 **Sex (% female):** **D1:** 61 **D2:** 67 **D3:** 64 **Race (% white):** NR **Baseline HAM-D:** NR **Baseline MADRS:** **D1:** 28.9 (4.6) **D2:** 28.7 (4.5) **D3:** 29.0 (4.6) **Baseline HAM-A:** NR	**Depression outcomes in patients with sleep problems** Mean improvement in MADRS total score was 16.47 points for ESC group ($P < 0.05$ vs. CIT; $P < 0.05$ vs. placebo) compared to 14.02 for CIT (P vs. placebo not sig) and 12.2 for placebo **Sleep outcomes:** Mean improvement in MADRS item 4 was 1.65 points for ESC ($P < 0.01$ vs. CIT; $P < 0.01$ vs. placebo), 1.31 for CIT (P vs. placebo not sig), and 1.26 for placebo. Rate of improvement (end MADRS sleep score of 0 or 1) was 43.6% for ESC vs. 28.4% for CIT and 24.4% for placebo ($P < 0.001$)	**Insomnia:** **D1:** 8.6 **D2:** 9.2 **D3:** 3.9 **Somnolence:** **D1:** 4.7 **D2:** 6.9 **D3:** 2.2	**Overall attrition rate:** 16.7% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **Country and setting:** European, multicenter (21 psychiatric sites) **Funding:** Organon	**Research objective:** To evaluate efficacy of MIR vs. CIT for treatment of major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 270 randomized; 269 included in analysis **Intervention:** **D1:** Citalopram 20-60mg/d (mean 36.6) **D2:** Mirtazapine 15-60mg/d (mean 35.9)	**Inclusion criteria:** • Adults 18 to 65 • Outpatient and inpatient • MDD according to DSM-IV • Minimum MADRS score of 22 • Duration of current depression episode less than 12 mos **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic medications • ECT within 3 mos • Substance abuse (within 12 mos) • Pregnant or lactating • Clinically sig medical disease • Suicidal (high risk) • Lack of response of current MDD episode to 2 prior courses of therapy • Placebo response during washout (25% improvement on MADRS)	**Mean age (yrs):** **D1:** 41.1 **D2:** 42.1 **Sex (% female):** **D1:** 57.1 **D2:** 66.9 **Race (% white):** NR **Baseline HAM-D:** NR **Baseline MADRS:** **D1:** 29.1 (4.5) **D2:** 29.6 (4.9) **Baseline HAM-A:** **D1:** 20.9 (6.1) **D2:** 21.1 (6.2)	**Anxiety outcomes:** Mean reduction in HAM-A scores was similar (approximately -13 points) in both treatment groups (change estimated from figure; *P* = 0.75)	**Overall adverse events:** **D1:** 70.7 **D2:** 66.4 **Changes in weight (increase):** **D1:** 4.5 **D2:** 15.3 **Diarrhea:** **D1:** 6.0 **D2:** 2.9 **Dizziness:** **D1:** 4.5 **D2:** 8.8 **Headache:** **D1:** 14.3 **D2:** 9.5 **Nausea:** **D1:** 20.2 **D2:** 10.2 **Somnolence:** **D1:** 6 **D2:** 8 **Fatigue:** **D1:** 13.5 **D2:** 12.4 **Sweating (increase):** **D1:** 15.0 **D2:** 2.2	**Overall attrition rate:** 19.1% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Mallinckrodt et al., 2005 **Country and setting:** United States, multicenter **Funding:** Eli Lilly and Company	**Research objective:** To compare efficacy of DUL for treatment of depression in patients with melancholia to those without melancholia **Duration of study:** 9 wks **Study design:** Pooled analysis of 8 RCTs (all RCTs included in DUL's New Drug Application to FDA) **Overall study N:** 1572 with melancholia **Intervention:** **D1:** Duloxetine 40-120 mg **D2:** Placebo	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Minimum HAM-D-17 score of 15 • CGI-S score of 4 or more Note: Melancholic features defined by DSM-IV criteria **Exclusion criteria:** • Additional mental illness or organic mental disorder • Concomitant psychotherapeutic or chronic prescription analgesic drugs • Substance abuse or dependence (within one yr); positive urine drug screen • Clinically sig medical disease • Suicidal (serious risk) • Lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** All melancholic: 42.1 **Sex (% female):** All melancholic: 69.5 **Race (% white):** NR **Baseline HAM-D:** All melancholic: 22.3 (3.9) **Baseline HAM-A:** NR	**Depression outcomes in patients with melancholia:** Mean reduction in HAM-D-17 score was 8.97 for DUL-treated group and 6.57 for those receiving placebo ($P < 0.001$)	NR	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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., 1998 **Country and setting:** United States, multicenter (10 sites) **Funding:** Bristol-Myers Squibb	**Research objective:** To evaluate effects of FLUO vs. NEF on sleep in patients with depression and insomnia **Duration of study:** 8 wks **Study design:** Pooled analysis of 3 RCTs **Overall study N:** 125 randomized; 122 included in analysis **Intervention:** **D1:** Fluoxetine 20-40 mg/d (mean 32) **D2:** Nefazodone 200-500 mg/d (mean 424)	**Inclusion criteria:** • Adults 19 to 55 • Outpatients • MDD according to DSM-III-R • Minimum HAM-D-17 score of 18 • One of following sleep problems was required: difficulty falling asleep, waking up during night, or inability to fall asleep again after getting up **Exclusion criteria:** • Additional mental illness or organic mental disorder • Substance use disorder (within 1 yr) • Clinically sig medical disease • Pregnant, lactating, or child-bearing potential without contraception • Shift-workers; sleep/wake disorder on polysomnograph	**Mean age (yrs):** **D1:** 37 **D2:** 36 **Sex (% female):** **D1:** 70 **D2:** 59 **Race (% white):** **D1:** 85 **D2:** 78 **Baseline HAM-D:** **D1:** 23.3 (2.7) **D2:** 22.9 (2.9) **Baseline HAM-D Sleep Disturbance Factor:** **D1:** 4.2 (1.3) **D2:** 4.2 (1.3) **Baseline Depression Symptomatology-Self Report (IDS-SR) Sleep Factor:** **D1:** 5.8 (2.1) **D2:** 5.3 (2.2) **Baseline HAM-A:** NR	**Depression outcomes in patients with insomnia:** Mean improvement in HAM-D-17 was 12.2 for FLUO-treated group and 11.4 for NEF-treated group (95% CI for diff: -1.7, 2.8) Response rates were similar for FLUO (45%) and NEF (47%; *P* = NR) **Sleep outcomes:** Mean improvement in HAM-D Sleep Disturbance Factor was 1.6 points for FLUO-treated group and 2.3 for NEF-treated group (*P* < 0.05) Improvement in IDS-SR Sleep Factor was 1.7 points for FLUO-treated group and 2.4 for NEF-treated group (*P* < 0.01)	**Constipation:** **D1:** 11 **D2:** 17 **Diarrhea:** **D1:** 26 **D2:** 16 **Dizziness:** **D1:** 8 **D2:** 22 **Headache:** **D1:** 48 **D2:** 56 **Insomnia:** **D1:** 11 **D2:** 6 **Nausea:** **D1:** 25 **D2:** 36 **Sexual dysfunction:** **D1:** 11 of males **D2:** 0 of males **Somnolence:** **D1:** 21 **D2:** 22	**Overall attrition rate (%):** 17% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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., 2001 (original report: Kavoussi, 1997) **Country and setting:** United States, multicenter **Funding:** Glaxo-Wellcome	**Research objective:** To determine whether baseline anxiety levels are associated with response to BUP SR and SER **Duration of study:** 16 wks **Study design:** RCT **Overall study N:** 248 **Intervention:** **D1:** Bupropion SR 100-300 mg/d **D2:** Sertraline 50-200 mg/d	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Minimum HAM-D-21 score of 18 • Depression duration 1 to 24 mos **Exclusion criteria:** • Concomitant or recent psycho-therapeutic drugs • Suicidal (active) • Pregnant or lactating • History of eating disorder or predisposition to seizures • Previous treatment with BUP or SER	**Mean age (yrs):** **D1:** 39 **D2:** 40 **Sex (% female):** **D1:** 48 **D2:** 48 **Race (% white):** **D1:** 93 **D2:** 94 **Baseline HAM-D:** **D1:** 24.8 (4.6) **D2:** 24.8 (4.6) **Baseline HAM-A:** **D1:** 16.6 (5.2) **D2:** 16.6 (5.4)	**Depression outcomes in patients with high anxiety:** In patients with high anxiety (top quartile of HAM-A scores), response and remission rates were similar for BUP SR and SER (estimated from figure: approximately 60% remission and 70% response in both groups, *P* = NR) **Anxiety outcomes in all patients:** Mean reduction in HAM-A was 9.7 for BUP-treated group and 10.0 for SER treated group (*P* = NR)	**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 **Sexual dysfunction (orgasm in men):** **D1:** 10 **D2:** 61 **Sexual dysfunction (orgasm in women):** **D1:** 7 **D2:** 41 **Somnolence:** **D1:** 2 **D2:** 13 **Sweating (increase):** **D1:** 2 **D2:** 10	**Overall attrition rate (%):** 31% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **Country and setting:** Australia and Turkey (13 sites) **Funding:** Pfizer, Inc	**Research objective:** To evaluate diffs in efficacy between SER and VEN XR on measures of QOL, depression, anxiety and pain in patients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 163 overall; 120 in anxiety subgroup **Intervention:** **D1:** Sertraline 50-150 mg/d **D2:** Venlafaxine XR 75-225 mg/d	**Inclusion criteria:** • Adults 18 or older • Outpatients • MDD according to DSM-IV • Minimum HAM-D-17 score of 18 Note: Anxious depression subgroup defined by HAM-D Anxiety-Somatization score of 7 or more **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Substance abuse or dependence (within 6 mos) • Pregnant or child-bearing potential without contraception • Lack of response of current MDD episode to 2 prior courses of therapy • History of nonresponse to SER or VEN	**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-D:** **D1:** 23.4 (4.4) **D2:** 23.5 (4.4) **Baseline HAM-A:** NR	**Depression outcomes in anxiety subgroup:** Mean reduction in HAM-D was 17.3 for SER and 14.8 for VEN XR (P = 0.70) Response rates SER 79.6% VEN 68.9% (P = 0.26) Remission rates were SER 63.0% VEN 54.1 (P = 0.44) **Anxiety outcomes:** In overall study population, mean reduction in HAM-A was similar for treatment groups: 14.1 for SER vs. 12.9 for VEN XR (P = 0.32) In high-anxiety subgroup, response on HAM-D Anxiety-Somatization subscale was similar for treatment arms: 83.3% for SER, 70.5% for VEN (P = 0.12)	**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:** **D1:** 21.5 **D2:** 26.2 **Sweating (increase):** **D1:** 31.6 **D2:** 21.4	**Overall attrition rate (%):** 23% **ITT Analysis:** **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Trivedi et al., 2001 and Rush et al., 2001 **Country and setting:** United States, multicenter **Funding:** Glaxo Wellcome Inc	**Research objective:** To compare effects of bupropion SR and SER on anxiety in patients with MDD **Duration of study:** 8 wks **Study design:** Analysis of pooled data from 2 RCTs **Overall study N:** 724 randomized; 692 included in analysis **Intervention:** **D1:** Bupropion SR 150-400 mg/d **D2:** Sertraline 50-200 mg/d **D3:** Placebo	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Recurrent major depression episode of 2 to 24 mo duration • Minimum HAM-D-21 score of 18 Note: Anxiety subgroup defined as top quartile on HAM-A (score > 24) **Exclusion criteria:** • Additional mental illness or organic mental disorder (except GAD) • Concomitant psychotherapeutic medications (within one wk) • Substance abuse or dependence (within one yr) • Pregnant or lactating • Prior treatment with BUP or SER	**Mean age (yrs):** **D1:** 37 **D2:** 37 **D3:** 38 **Sex (% female):** **D1:** 53 **D2:** 51 **D3:** 55 **Race (% white):** **D1:** 87 **D2:** 91 **D3:** 88 **Baseline HAM-D:** **D1:** 25.2 (5.2) **D2:** 25.2 (5.2) **D3:** 24.9 (5.2) **Baseline HAM-A:** **D1:** 18.8 (7.3) **D2:** 18.6 (7.4) **D3:** 18.6 (7.1)	**Depression outcomes in patients with anxiety:** Response rates were similar for BUP SR, SER, and placebo (approximately 70%, 64% and 58%; rates estimated from figure; *P* = NR). Remission rates were also similar for all 3 treatment groups (*P* = NR) **Anxiety outcomes in all patients:** Mean reduction in HAM-A was similar for BUP SR and SER-treated groups (9.9 and 9.4 points) and slightly less for those receiving placebo (8.4 points). No statistically sig diff between active drug groups (*P* > 0.41). Diff between active drug and placebo was statistically sig for BUP group (*P* = 0.04) but not for SER (*P* = NR)	**Dizziness:** **D1:** 7 **D2:** 8 **D3:** 5 **Insomnia:** **D1:** 16 **D2:** 18 **D3:** 5 **Somnolence:** **D1:** 3 **D2:** 13 **D3:** 5	**Overall attrition rate:** 28% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (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 **Country and setting:** Greece and Italy, multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** To evaluate efficacy of FLUO vs. VEN in patients with major depression and melancholia **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 109 **Intervention:** **D1:** Fluoxetine 60 mg/d **D2:** Venlafaxine 225 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:** • Additional mental illnesses or organic mental disorder • Concomitant or recent psycho-therapeutic drugs • ECT within 30 days • Drug or alcohol dependence (within 2 yrs) • Pregnant or without contraception • Clinically sig medical disease • Investigational drug use within 30 days • Suicidal (acute)	**Mean age (yrs):** **D1:** 49 **D2:** 47 **Sex (% female):** **D1:** 83 **D2:** 75 **Race (% white):** NR **Baseline HAM-D:** **D1:** 27.1 (5.6) **D2:** 27.8 (5.6) **Baseline HAM-A:** NR	**Depression outcomes in melancholia:** Response rates were similar for FLUO-treated group (58%) and VEN group (65%; *P* = NR). Remission rates were similar for FLUO (36%) and VEN (41%; *P* = NR)	**Overall adverse events:** **D1:** 46.3 **D2:** 49.1 **Constipation:** **D1:** 1.9 **D2:** 7.3 **Dizziness:** **D1:** 0 **D2:** 5.5 **Headache:** **D1:** 1.9 **D2:** 5.5 **Insomnia:** **D1:** 1.9 **D2:** 12.7 **Nausea:** **D1:** 14.8 **D2:** 5.5 **Sweating (increase):** **D1:** 3.7 **D2:** 5.5	**Overall attrition rate:** 22% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 3. KQ3: Efficacy or effectiveness of antidepressants for treating depression and its accompanying symptoms (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Versiani, 2005 **Country and setting:** Europe and South America, multicenter (30 sites) **Funding:** Organon	**Research objective:** To compare efficacy and tolerability of MIR and FLUO in severe MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 299 randomized; 292 included in analysis **Intervention:** **D1:** Fluoxetine 20-40 mg/d **D2:** Mirtazapine 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 placebo washout (25% improvement in HAM-D-17)	**Mean age (yrs):** **D1:** 47 **D2:** 43 **Sex (% female):** **D1:** 69 **D2:** 74 **Race (% white):** NR **Baseline HAM-D:** **D1:** 28 (3) **D2:** 29 (3) **Baseline HAM-A:** NR	**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 4. KQ4: Safety, adverse events or adherence of antidepressants

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 **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:** Sertraline 50-150 mg/d **D2:** Paroxetine 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% 24 wks: SER: 80.2% PAR: 73.7% 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* ≤ 0.05	**Overall attrition rate:** 35.4% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Mirtazapine: 30-45 mg/d **D2:** Sertraline: 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 Szegedi et al., 2003 **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:** Mirtazapine: 15-45 mg/d (32.7) **D2:** Paroxetine: 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)	Benkert-MIR and PAR equally effective in reducing mean HAM-D-17 score (58.3% vs. 53.7%) Szegedi-Improvement occurred in majority of analyzed patients within 2 wks, MIR: 72.7% PAR: 64.9% Early improvement was highly sensitive predictor of later stable response or stable remission for both drugs At endpoint, 40.9% of MIR group and 34.1% of PAR group were considered HAM-D remitters (score ≤ 7)	**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 fatigue-8.9 **D2:** 7.5 fatigue-8.2 **Sweating (increase):** **D1:** 2.2 **D2:** 7.5	**Overall attrition rate:** 23% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Buckley et al., 2005 **Country and setting:** United Kingdom Database **Funding:** NR	**Research objective:** To establish relative frequency with which venlafaxine 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) FLUO: 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:** N/A

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** 6297 **Intervention:** Bupropion: IR: 255.0; SR: 273.7 Citalopram: 24.9 Fluoxetine: 25.5 Mirtazapine: 28.6 Nefazodone: 293.2 Paroxetine: 23.3 Sertraline: 81.4 Venlafaxine: Regular: 124.9; XR: 114.9	**Inclusion criteria:** • Adults 18+ • Taking monotherapy for depression (no trazodone 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **Country and setting:** United States Multicenter (15 centers) **Funding:** Glaxo Wellcome	**Research objective:** Comparison of BUP, FLUO and placebo 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:** Fluoxetine: 20-60 mg/d (26) **D2:** Bupropion: 150-400 mg/d (319) **D3:** Placebo	**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 placebo (32%) Orgasm dysfunction occurred sig more in FLUO patients compared with placebo or BUP SR patients ($P < 0.001$) At endpoint, more FLUO 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** 364 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Bupropion: 150-400 mg/d **D3:** Placebo	**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 placebo (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 placebo or BUP SR patients ($P < 0.05$) Diagnosed with at least one sexual dysfunction: SER: 39%, BUP SR: 13%, placebo: 17% Sig more BUP patients were satisfied with their sexual functioning (endpoint BUP 85% vs. SER 62%; $P< 0.05$) Mean Compliance: Tablet: placebo: 96.1%, BUP 96.4%, SER 97.1% Capsule: placebo: 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 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Coogan et al., 2005 **Country and setting:** United States, inpatient, multicenter (3 hospitals) **Funding:** Not reported	**Research objective:** To evaluate SSRI use and breast cancer risk **Duration of study:** Enrollment was from 1998 to 2002. Duration of treatment was not specified and use ranged from <2 yrs to ge 4 yrs **Study design:** Case control study **Overall study N:** 4,996 **Intervention:** **D1:** Fluoxetine **D2:** Paroxetine **D3:** Sertraline	**Inclusion criteria:** • Adults 18 to 79 • Concomitant condition: breast cancer for cases • Able to complete interview • Lived in eligible zip code **Exclusion criteria:** • Patients did not have certain excluded diagnoses (e.g., psychiatric diagnoses)	**Mean age (yrs):** NR **Sex (% female):** 100 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Adjusted OR (95% CI) for breast cancer and breast cancer association = 1.1 (0.8, 1.7) OR for use of SSRI for 4 or more yrs = 0.7 (0.4, 1.5) OR for recent use of SSRIs = 1.2 (0.8, 1.8) OR for SSRI use stopped at least a yr prior to interview = 1.1 (0.5, 2.6) OR for sporadic SSRI use = 1.1 (0.6, 2.1)	NR	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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 placebo **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 360 **Intervention:** **D1:** Sertraline: 50-200 mg/d (mean = 121) **D2:** Bupropion: 150-400 mg/d (mean = 293) **D3:** Placebo	**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 placebo ($P < 0.05$) At day 56, both BUP and SER had higher sexual arousal disorder ($P < 0.05$) than placebo Orgasmic dysfunction occurred sig more in SER patients compared with placebo 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% Placebo 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 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: CSM Expert Working Group, 2004 **Country and setting:** UK **Funding:** Not reported **Research objective:** Evaluating safety of SSRI antidepressants (CIT, ESC, FLUO, 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:** Venlafaxine **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 FLUO	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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Duloxetine: 40, 80, or 120 mg/d **D2:** Paroxetine: 20 mg/d **D3:** Placebo	**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	Acute Phase Treatment-Emergent Dysfunction (ASEX) in 475 patients who did not have sexual dysfunction at baseline, incidence of treat-emergent sexual dysfunction was sig higher for DUL vs. placebo DUL = 46.4% placebo = 28.8% t = 2.69, df = 1337, *P* = 0.007 PAR vs. Placebo PAR = 61.4% placebo = 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Citalopram Fluoxetine Paroxetine	**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 FLUO: 0.80 (0.22-2.89) PAR: 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 FLUO; 1.30 (0.96-1.75) PAR 1.21 (0.84-1.72)	Not Reported	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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 one yr **Study design:** Uncontrolled, open-label trial **Overall study N:** 3100 **Intervention:** **D1:** Bupropion: 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 3094 evaluable patients, or 0.06% and for acute and continuation phases combined was 3 seizures in 3094 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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 **Duration of study:** 24 wks **Study design:** RCT **Overall study N:** 400 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Citalopram: 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: SER: 69.5% CIT: 68.0% Wk 24: SER: 75.5% CIT: 81.0% Compliance: SER 90.3% CIT 94.5%	**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 **Sweating (increase):** **D1:** 13 **D2:** 17	**Overall attrition rate:** 22% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Ekselius et al., 2001 **Country and setting:** Sweden General practice **Funding:** Pfizer AB Swedish Medical Research Council	**Research objective:** Examination of occurance and severity of sexual dysfunction symptoms in depressed patients before and after 6 mos of treatment **Duration of study:** 24 wks **Study design:** RCT, completers only analysis **Overall study N:** 308 **Intervention:** **D1:** Citalopram: 20-60 mg/d (33.9) **D2:** Sertraline: 50-150 mg/d (82.4)	**Inclusion criteria:** • Adults 18 and over • Diagnosed with MDD according to DSM-III or -IV • MADRS of 21 or more **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	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% reported decreased sexual desire, 18.9% reported orgasmic dysfunction, 25% experienced ejaculatory dysfunction	**Overall adverse events:** NR	**Overall attrition rate:** N/A **ITT Analysis** No, completers analysis **Quality rating:** Fair for adverse event reporting

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **Country and setting:** United States Multicenter (15 sites) **Funding:** Eli Lilly Research	**Research objective:** To compare tolerability and efficacy of FLUO, 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:** Fluoxetine: 20-60 mg/d **D2:** Sertraline: 50-200 mg/d **D3:** Paroxetine: 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 FLUO, SER and PAR in baseline-to-endpoint improvement in HAM-D total (overall $P = 0.323$) No sig diffs in efficacy and tolerability of FLUO, 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	**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	**Overall attrition rate:** NR **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **Country and setting:** United States Multicenter (5 sites) **Funding:** SmithKline, Beecham	**Research objective:** Efficacy and tolerability of PAR and FLUO **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 128 **Intervention:** **D1:** Paroxetine: 20-50 mg/d (initial dosage of 20 mg/d could be increased wkly by 10 mg/d up to 50 mg/d) **D2:** Fluoxetine: 20-80 mg/d (initial dosage of 20 mg/d could be increased wkly by 20 mg/d up to 80 mg/d) **D3:** placebo	**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	**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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **Country and setting:** United States Multicenter (2 sites) **Funding:** Burroughs Wellcome Co	**Research objective:** Efficacy and safety of BUP and FLUO in depressed outpatients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** **D1:** Bupropion: 225-450 mg/d (382) **D2:** Fluoxetine: 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, BUP: 62.7%, FLUO: 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 FLUO (*P* = NR)	NR	**Overall Attrition rate:** 7.3% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Nefazodone: 200-400 mg/d **D2:** Sertraline: 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **Country and setting:** United States multicenter, outpatient trial **Funding:** Lilly	**Research objective:** To assess effect of FLUO 20 mg/d on weight loss in older patients **Duration of study:** 6 wks (after a 1-wk placebo lead-in) **Study design:** RCT **Overall study N:** 671 **Intervention:** **D1:** Fluoxetine: 20 mg/d **D2:** Placebo	**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 FLUO • 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: FLUO -0.88 (2.11) Placebo 0.11 (1.96) (P < 0.001) High BMI: FLUO -1.14 (1.99) Placebo 0.04 (1.72) (P < 0.001) Pooled: FLUO -1.01 (2.05) Placebo 0.08 (1.85) (P < 0.001) % with weight loss of at least 5% low/normal BMI: FLUO 2.4 Placebo 1.1 (P = 0.225) High BMI: FLUO 3.7 Placebo 0 (P = 0.021) Pooled: FLUO 3.1 Placebo 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 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Halikas, 1995 **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:** 150 **Intervention:** **D1:** Mirtazapine: 5-35 mg **D2:** Trazodone: 40-280 mg **D3:** placebo	**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 placebo 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 placebo were statistically sig at 2, 3, 4, and 6 wks. Using MADRS, statistically sig diffs were found between both active compounds and placebo at wks 2 and 3. MIR and TRA were associated with sig higher frequencies of dizziness and blurred vision as compared to placebo 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	**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	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Harto et al., 1988 **Country and setting:** United States NR **Funding:** Not Reported	**Research objective:** To determine if FLUO produces weight loss and to examine predictive factors **Duration of study:** 6 wks **Study design:** Cannot determine **Overall study N:** 35 **Intervention:** **D1:** Placebo **D2:** Fluoxetine 5mg **D3:** Fluoxetine 20 **D4:** Fluoxetine 40	**Inclusion criteria:** • Adults 18 to 65 • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Investigational drug is within last 28 days • Additional mental illnesses or organic mental disorder • Concomitant psychotheraputic or psychtropic medications • History of seizure	**Mean age (yrs):** **D1:** 39 **D2:** 38.4 **D3:** 43.8 **D4:** 36.4 **Sex (% female):** **D1:** 75 **D2:** 50 **D3:** 70 **D4:** 56 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	FLUO reduces sig reduction of body mass in depressed patients BMI change score- at wk 6 a statistically sig diff was evident between placebo and FLUO (F 3.23) = 6.81 ($P < 0.002$)	NR	**Overall attrition rate:** NR **ITT analysis:** No **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Fluoxetine Trazodone Dothiepin Amitriptyline Clomipramine Imipramine Flupenthixol Lofepramine Mianserin Doxepin	**Inclusion criteria:** • Received a prescription for 1 or more antidepressant in VAMP database (General Practice Research Database) • All patients who committed suicide identified in cohort evaluation were included as cases **Exclusion criteria:** • Not reported	**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); FLUO: 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 FLUO 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **Country and setting:** United Kingdom General practice **Funding:** Burroughs Wellcome	**Research objective:** Evaluate whether FLUO 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:** 8730 **Intervention:** Mianserin and Lofepramine **D1:** Fluoxetine **D2:** Trazodone	**Inclusion criteria:** • Age 15 to 74 • Patients who received a px for FLUO, 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	FLUO 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** 3341 **Intervention:** **D1:** Bupropion: 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **Country and setting:** Multinational; outpatient **Funding:** Eli Lillly	**Research objective:** To compare mean number of interruption-emergent events during 3 to 5 day placebo interruption period in remitted, depressed patients on maintenance therapy with FLUO or PAR **Duration of study:** Placebo interruption period = 3-5 days, but unclear total duration of observation **Study design:** Open-label, parallel-group study with double-blind, crossover, placebo interruption phase **Overall study N:** 150 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Paroxetine: 20-50 mg/d	**Inclusion criteria:** • Adults 18 and older • Unipolar depression on effective maintenance with FLUO 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	FLUO 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 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Keene et al., 2005 **Country and setting:** United States IHCIS National Managed Care Benchmark Database **Funding:** GlaxoSmithKline	**Research objective:** To evaluate differential compliance rates between IR SSRIs and CR SSRIs in patients initiating SSRI therapy **Duration of study:** 6 mos of follow-up **Study design:** Observational **Overall study N:** 116,090 **Intervention:** Citalopram Escitalopram Fluoxetine Paroxetine(IR and CR formulations) Sertraline **D1:** SSRI IR **D2:** Paroxetine CR	**Inclusion criteria:** • Adults 18 and older • Anxiety or depression according to ICD9CM • Patients with an SSRI script but no diagnosis also included **Exclusion criteria:** • Antidepressant in 6 mos prior to index date, continuously eligible for 6 mos prior to index date and during follow-up period • Patients with a psychosis-related diagnosis of schizophrenia or bipolar disorders • Antipsychotic within 6 mos previous to or within 1 yr of index date	**Mean age (yrs):** **D1:** 42.9 **D2:** 41.8 **Sex (% female):** **D1:** 69.3 **D2:** 62.6 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	After controlling for baseline covariates (age, gender, insurance type, titration rates, mental health specialty care, diagnoses, and comorbidity) patients initiating IR SSRIs were 13.6% less likely to be compliant than patients initiating par CR (P = 0.0001) Patients on PAR IR least likely to be compliant when compared to PAR CR (21.2% less likely, P = 0.0001), followed by ESC (15.0% less likely, P = 0.0179), SER (12.3% less likely, P = 0.0005), CIT (9.1% less likely, P = 0.0114), and FLUO (8.4% less likely, P = 0.0250)	NR	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Sertraline: 50-200 mg/d **D2:** Paroxetine: 10-80 mg/d **D3:** Venlafaxine: 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 FLUO) **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 [mean (SD) = 2.26 (2.02) vs. 1.43(2.12), t = 6.23, df = 107, (P < 0.05) No signficant diffs between anti-depressants among men reporting antidepressant-induced sexual dysfunction Women showed lower rates of dysfunction on VEN compared to PAR and SER, however, only one item ("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 completer analysis only **Quality rating:** Fair for AE reporting

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Landen et al., 2005 **Country and setting:** Sweden and Norway Multicenter (13 sites) **Funding:** NR	**Research objective:** To determine: 1) concordance of sexual dysfunction AE rates between open-ended questioning and directed questioning 2) incidence of sexual side effects of CIT and PAR 3) correlation between sexual side effects and illness severity, treatment duration and drug/dose combination **Duration of study:** 4 wks **Study design:** Non-randomized trial of AE elicitation methods embedded in RCT **Overall study N:** 119	**Inclusion criteria:** • No response to CP or px for a minimum of 4 wks prior to start of study **Exclusion criteria:** • Epilepsy	**Mean age (yrs):** 46 **Sex (% female):** 69 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	By objective 1. Side effect elicitation method: sig more patients (49 versus 6) reported sexual side effects in response to direct questioning than open questioning ($P < 0.001$) 2. Incidence of side effects by drug: no statistically sig diffs between paroxetine and paroxetine groups in sexual side effects reported or sexual dysfunction score; open-ended questioning: CIT 5%, PAR 7% ($P = 0.98$); direct questioning: CIT 44%, PAR 36% ($P = 0.37$) 3. Correlations with illness severity and treatment parameters: only weak correlation with duration of current depression episode ($P = 0.043$)	NR	**Overall attrition rate:** N/A **ITT Analysis** NR **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Lopez-Ibor, 1993 **Country and setting:** Spain Database analysis **Funding:** Not reported	**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:** Paroxetine **D2:** Placebo	**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 palcebo 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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, 1999 **Country and setting:** UK General practice **Funding:** Reported as "many pharmacetical companies"	**Research objective:** To compare safety and side-effect profiles of four selective serotonin reuptake inhibitor antidepressants (SSRIs), FLUV, FLUO, SER and PAR in a cohort study **Duration of study:** NA **Study design:** Cross sectional – prescription event monitoring **Overall study N:** 50,150 **Intervention:** **D1:** Fluvoxamine **D2:** Fluoxetine **D3:** Sertraline **D4:** Paroxetine	**Inclusion criteria:** • Patients prescribed SSRIs **Exclusion criteria:** None	**Survey Response rate:** 60% **Mean age (yrs):** **D1:** 51 **D2:** 50 **D3:** 49 **D4:** 49 **Sex (% female):** **D1:** 70.1 **D2:** 69.8 **D3:** 68.6 **D4:** 67.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	FLUV had a considerably higher incidence of side-effects associated with its use than other 3 SSRIs and 36% of GPs expressing an opinion reported FLUV as effective, compared with approximately 60% for FLUO, SER, and PAR The most common reason for stopping treatment was nausea/vomitting for all 4 SSRIs	**Dizziness:** **D1:** 9.6 **D2:** 2.7 **D3:** 2.8 **D4:** 4.0 **Headache:** **D1:** 10.1 **D2:** 5.7 **D3:** 5.4 **D4:** 4.8 **Nausea:** **D1:** 42.8 **D2:** 9.0 **D3:** 8.6 **D4:** 13.0	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Citalopram **D2:** Fluoxetine **D3:** Fluvoxamine **D4:** Paroxetine **D5:** Sertraline	**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 CI: 0.86 to 1.14) No diff in risk of suicide between SSRIs and tricyclic antidepressants (OR: 0.57 CI: 0.26 to 1.25)	N/A	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Good

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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 versus 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:** Sertraline **D2:** Other SSRIs (Fluoxetine Fluvoxamine Paroxetine)	**Inclusion criteria:** • All patients with a new SER prescription; consecutive patients taking FLUO, 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 serious adverse event (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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 (goes with Reimherr et al., 1998) **Country and setting:** United States Academic centers (5 sites) **Funding:** Eli Lilly	**Research objective:** To assess changes in weight during long-term treatment with FLUO or placebo **Duration of study:** 50 wks **Study design:** RCT **Overall study N:** 839 acute phase 395 remission phase **Intervention:** **D1:** Fluoxetine: 20 mg/d **D2:** Placebo	**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 FLUO and placebo 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Citalopram Fluoxetine Fluvoxamine Mirtazapine Nefazodone Paroxetine Sertraline Venlafaxine	**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: FLUO, 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Sertraline: 50-200 mg/d (137.1) **D2:** Fluvoxamine: 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Fluoxetine: 20-60 mg/d **D2:** Fluvoxamine: 50-300 mg/d **D3:** Paroxetine: 10-50 mg/d **D4:** Sertraline: 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 (FLUO, 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **Country and setting:** United States, multicenter **Funding:** Solvay Pharmaceuticals, Inc.; The Upjohn Company	**Research objective:** To compare efficacy, safety, and tolerance of FLUV and FLUO in a depressed outpatient population **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 100 **Intervention:** **D1:** Fluvoxamine: 100-150 mg; endpoint mean = 101.85 (25.22) **D2:** Fluoxetine: 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 FLUO 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 FLUO	**Headache:** **D1:** 50 **D2:** 53 **Insomnia:** **D1:** 36 **D2:** 28 **Nausea:** **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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Mirtazapine: 15 mg/d up to 45 mg/d **D2:** Paroxetine: 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 MIR (80) 64.0% PAR (68) 56.7% 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Trazodone (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) FLUO- 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 4. KQ4: Safety, adverse events or adherence of antidepressants (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Versiani et al., 2005 **Country and setting:** Multinational, Multicenter (30 sites) **Funding:** Organon, NV	**Research objective:** To compare effectiveness and tolerability of MIR and FLUO in severe MDD and compare effects on anxiety, sleep and QOL **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 299 **Intervention:** **D1:** Mirtazapine: 30-60 mg **D2:** Fluoxetine: 20-40 mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 25 **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 3 mos • Suicidal tendencies	**Mean age (yrs):** **D1:** 43 **D2:** 47 **Sex (% female):** **D1:** 74 **D2:** 69 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 29 (3) **D2:** 28(3)	No sig diff in percent of responders at day 56, (MIR: 40.1% vs. FLUO: 41.4 %) Both treatment groups showed 18 point improvement on QLSQ	**Overall adverse events:** **D1:** 50 **D2:** 45 **Changes in weight (increase):** **D1:** 6.9 **D2:** 1.3 **Dizziness:** **D1:** 9 **D2:** 12.8 **Headache:** **D1:** 19.3 **D2:** 18.8 **Insomnia:** **D1:** 4.8 **D2:** 8.7 **Nausea:** **D1:** 15.9 **D2:** 24.1 **Somnolence (fatigue):** **D1:** 13.8 **D2:** 9.4	**Overall attrition rate:** 14% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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:** Bupropion: 100-300 mg/d (197) **D2:** Paroxetine: 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 ≥ 50% reduction in HAM-D) were similar in both groups: BUP sr: 71% PAR: 77% No sig diffs in QOL scales (QLDS, SF-36) between treatment groups at endpoint; overall sig improvement in QLDS and QOL at day 42 ($P < 0.0001$) Compliance: BUP 95% PAR 98%	**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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **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 placebo lead-in to eliminate placebo responders and placebo nontolerators) **Study design:** RCT **Overall study N:** 124 **Intervention:** **D1:** Bupropion: 225-450 mg/d **D2:**Trazodone: 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) BUP = 33 (55.9%) TRA = 21 (40.4%) Remitters (>50% reduction and a HAM-D score<10) BUP = 27 (46%) TRA = 16 (31%) CGI-I responders BUP = 34 (57.6%) TRA = 24 (46.2%) Compliance BUP 94.7% TRA 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 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **Country and setting:** Multinational Multicenter **Funding:** NV Organon	**Research objective:** To compare efficacy and tolerability of MIR and FLUO in depressed inpatients and outpatients **Duration of study:** 6 wks (after a 3-7 day single-blind, placebo washout period) **Study design:** RCT **Overall study N:** 133 **Intervention:** **D1:** Mirtazapine: 15-60 mg/d **D2:** Fluoxetine: 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% FLUO 25.4% (*P* = 0.39) CGI responders (much or very much approved): MIR 63.3% FLUO 54.0% (*P* = 0.677) Q-LES-Q estimated treatment diff (MIR minus FLUO): 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%	**Overall attrition rate:** 28.6% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 4. KQ4: Safety, adverse events or adherence of antidepressants (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 **Country and setting:** Australia Hospital (Hunter Area Toxicology Service Database) **Funding:** NR	**Research objective:** To assess toxicity in overdose of venlafaxine 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 venlafaxine and other SSRI records) **Intervention:** **D1:** Venlafaxine **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 venlafaxine: **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 venlafaxine and SSRI overdoses	NR	**Overall attrition rate:** N/A **ITT Analysis** NR **Quality rating:** Good

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Aursnes et al., 2005 **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 paroxetine as presented to world's drug regulatory agencies in 1989 **Included Populations** NR **Interventions:** Paroxetine versus placebo, no other info provided	**Study Results:** 7 suicide attempts in patients on drug and 1 in a patient on placebo. Probability of increased intensity of suicide attempts per yr in adults taking paroxetine 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 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Brambilla et al., 2005 **Country and setting**: NR **Funding:** Multinational **Research objective:** To assess frequency of side-effects in FLUO 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 FLUO or any other anti-depressant • Cross-over studies and those with patients with concomitant medical illness were excluded **Included Populations** Patients with MDD **Interventions:** • Fluoxetine vs. tricyclic antidepressant (65 studies) • Fluoxetine vs. SSRI (22 studies) • Fluoxetine vs. another AD (44 studies)	**Study Results:** • 59.4% of patients treated with FLUO and 59.3% of patients treated with other SSRIs experienced AEs.RR 1.00 95% CI 0.95, 1.04 • FLUO 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 • FLUO had less side effects (50.9%) than TCAs (60.3%) RR = 0.84 95% CI 0.76 to 0.94(P = 0.03) • FLUO 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 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Fergusson et al., 2005 **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 placebo or an active non-SSRI **Included Populations** • All patients included in trials comparing SSRIs to either placebo or non-SSRI control • No age, gender, or diagnosis restrictions **Interventions:** Patients randomized to either an SSRI, placebo, 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 placebo (OR: 2.28; CI: 1.144 - 4.55, *P* = 0.02) No diffs in actual suicides between SSRIs and placebo were found (OR: 0.95; 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; 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 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Greist et al., 2004 **Country and setting:** US (6 studies); Europse (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 • Detke et al., 2002 • Goldstein et al., 2002 • Goldstein et al., 2004 • 4 unpublished studies submitted for FDA approval of DUL	**Included Studies:** Double-blind, randomized, placebo or active-controlled trials of DUL **Included Populations** Adult outpatients with MDD **Interventions:** • Duloxetine vs. Placebo (8 studies) • Duloxetine vs. Paroxetine (4 studies) • Duloxetine vs. Fluoxetine (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 FLUO (20mg) (17.1% vs. 15.7%, *P* -NR) No sig diffs between DUL (120 mg/d) and FLUO (20 mg/d) (17.1% vs. 15.7%, *P* -NR) Sig more DUL- than placebo-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 placebo (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 placebo	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:** N/A

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Gunnell et al., 2005 **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 Medicine and Healthcare Products Regulatory Agency (MHRA) (2004) • 342 placebo controlled trials included in report – citations not given in bibliography	**Included Studies:** Randomized, placebo controlled trials of SSRIs (CIT, ESC, FLUO, FLUV, PAR, and SER) submitted by pharmaceutical companies **Included Populations** Adult patients with various indications included in trials comparing SSRIs to placebo **Interventions:** Patients randomized to either SSRI or placebo	**Study Results:** No sig diff was found between SSRI treatment and placebo 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 placebo 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 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Khan et al., 2003 **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:** Fluoxetine, Sertraline, Paroxetine, Citalopram, Fluvoxamine, Nefazodone, Mirtazapine, Bupropion, Venlafaxine, Imipramine, Amitrptyline, Maprotiline, Trazodone, Mianserin, Dothiepin	**Study Results:** No statistically sig diff in suicide rates between SSRIs, other antidepressants, and placebo ($P > 0.05$) Absolute Suicide Rate • SSRI: 0.15% (0.10-0.20% 95% CI) • "Other": 0.20% (0.09-0.27% 95% CI) • Placebo: 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) • Placebo: 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 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Nieuwstraten and Dolovich, 2001 **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:** Bupropion vs. sertraline (3 trials) Bupropion vs. paroxetine (1 trial) Bupropion vs. fluoxetine (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 bupropion 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 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Pedersen, 2005 **Country and setting:** Denmark **Funding:** Drug Development, H. Lundbeck A/S	**Study design:** Retrospective cohort study **Number of Patients:** 4091 **Studies Included:** 12 placebo-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:** Escitalopram and placebo	**Study Results:** MADRS item 10 (suicidal thoughts): ESC patients had fewer suicidal thoughts than placebo from wks 1 ($P < 0.05$) to 8 ($P < 0.001$) Suicides in placebo-controlled studies: ESC n = 0 Rate = 0 Incidence = 0 Placebo n = 1 Rate = 0.003 Incidence = 0.1 Non-fatal self harm in placebo controlled studies: ESC n = 5 Rate = 0.011 Incidence = 0.2 Placebo 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 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Perahia et al., 2005 **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, placebo controlled trials, examining 8-9 wks of acute treatment (2 had 26-wk placebo-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 • Placebo-controlled trials, placebo given during lead-out phase	**Study Results:** In 6-study pooled analysis, significanlty more DUL patients (44.3%) had > 1 DEAE than placebo (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 placebo. Withdrawal due to DEAEs occured in 3.1% of DUL patients and 0% of placebo. 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 placebo-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 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events	Assessments	Study Appraisals and Quality Rating
Author: Thase et al., 2005 **Country and setting:** Multinational **Funding:** Eli Lilly and Mental Health Intervention Center	**Study design:** Pooled analysis **Number of Patients:** 2,345 **Studies Included:** 8 placebo-controlled studies	**Included Studies:** • Placebo-controlled studies **Included Populations** • 18 yrs of age or older • Current primary MDD diagnosis as defined in DSM-IV • HAM-D score >15 • CGI-S score >4 **Interventions:** Duloxetine Fluoxetine Paroxetine	**Study Results:** Greater change in heart rate for DUL vs. FLUO and PAR: mean change of 2.8 bpm for DUL vs. -1.0 bpm for FLUO ($P < 0.01$); mean change of 1.0 bpm for DUL vs. -1.4 bpm for PAR ($P < 0.001$) DUL had slightly lower mean change in systolic BP than FLUO (2.3 mm Hg vs. 3.2 mm Hg) No statistically sig diffs in systolic and diastolic BP for DUL vs. FLUO or PAR Mean changes in QTcF and QRS intervals not sig different for DUL vs. PAR	N/A	**Publication Bias:** No **Heterogeneity:** No	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy:** No **Quality Rating:** Fair

Evidence Table 5. KQ4: Systematic reviews and meta-analyses on safety, adverse events, or adherence (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Thase et al., 1998 **Country and setting:** United States **Funding:** NR **Research objective:** To assess effects of VEN on BP	**Study design:** Meta-analysis **Number of Patients**: 3,744 **Studies Included:** Original data for statistical analysis were provided by Wyeth-Ayerst Laboratories	**Included Studies:** Acute and continuation phase data from randomized controlled trials comparing VEN with placebo and IMI (21 outpatient and 6 inpatient trials at 180 different sites) **Included Populations** • Meet DSM-III-R criteria for a current principal diagnosis of major depression • Score at least 20 on 21-item HAM-D • Have no poorly controlled or serious medical illness **Interventions:** **D1:** Venlafaxine **D2:** Imipramine **D3:** Placebo	**Study Results:** Acute phase at 6 wks: • Mean increase in supine DBP: VEN 1.02 mmHG • Sustained elevation in supine DBP: VEN: 4.8%, placebo 2.1% (P = 0.015 for crude group comparison and P = 0.086 after adjustment for age/sex) • Incidence of supine DBP > 90 mmHg: VEN: 11.5%, placebo 5.7% (P < 0.001 VEN vs placebo) Continuation Phase Results: • Mean supine DBP: no drug effect P = 0.58 • 4.5% (21 of 467) with normal supine DBPs developed elevated readings during this phase and it was sig higher in VEN group P = 0.058 • A sig dose response effect on BP was seen in VEN group (P < 0.001)	NR	**Publication Bias:** Yes **Heterogeneity:** Yes	**Standard Method of Study Appraisals:** Yes **Comprehensive Search Strategy**: No **Quality Rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations

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 **Country and setting:** Sweden and Denmark Multicenter (12) **Funding:** Wyeth	**Research objective:** Compare efficacy and tolerability of VEN ER 75-150 mg/d with CIT 10-20 mg/d in elderly patients with major depression according to DSM-IV criteria **Duration of study:** 6 mos **Study design:** RCT **Overall study N:** 151 **Intervention:** **D1:** Venlafaxine: 37.5-150 mg/d **D2:** Citalopram: 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **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:** Citalopram: 10-40 mg/d **D2:** Placebo	**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 placebo ($P < 0.05$)	NR	**Overall attrition rate:** 13.6% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **Country and setting:** United States Multicenter, primary care clinics **Funding:** Hartford and MacArthur Foundation	**Research objective:** To compare PAR vs. placebo 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:** Paroxetine 10-40 mg/d, individually titrated **D2:** placebo	**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), placebo: 0.85 (0.09); behavior therapy: 0.79 (0.09), no sig diffs between arms Remission by HAM-D-17 score < 6: PAR: 80%, placebo: 44.4%; behavior therapy: 56.8% (*P* = 0.008 for diff among all 3 arms) Minor depression: PAR 60.7%, placebo 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Blumenfield et al., 1997 **Country and setting:** United States (New York) 2 inpatient centers **Funding:** Lilly Research Laboratories	**Research objective:** To test safety and efficacy of FLUO in patients with renal failure on dialysis **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 14 **Intervention:** **D1:** Fluoxetine: 20mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • Concomitant condition: renal failure **Exclusion criteria:** • Pregnant • 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	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	At wk 4 sig improvements in depression were seen in BDI and BSI ($P < 0.05$) At endpoint, wk 8, there were no longer any diffs between fluo and placebo in depression scores No withdrawals due to AEs	**Cardiovascular adverse events:** **D1:** 67 **D2:** 14 **Constipation:** **D1:** 0 **D2:** 14 **Diarrhea:** **D1:** 17 **D2:** 14 **Dizziness:** **D1:** 17 **D2:** 0 **Headache:** **D1:** 50 **D2:** 0 **Insomnia:** **D1:** 33 **D2:** 14 **Nausea:** **D1:** 83 **D2:** 29	**Overall attrition rate:** 7.1% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Burt et al., 2005 **Country and setting:** US; multicenter **Funding:** Eli Lilly and Co	**Research objective:** To assess efficacy of DUL in depressed women ages 40 to 55 yrs **Duration of study:** 9 wks **Study design:** Post-hoc analysis of pooled data from 2 identical, but independent, randomized, double-blind studies **Overall study N:** 114 **Intervention:** **D1:** Duloxetine: 60 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to no max given • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 15 • CGI-S ≥ 4 at 2 consecutive screening visits **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Treatment-resistant depression; lack of response of current depression episode to 2+ adequate treatment courses	**Mean age (yrs):** **D1:** 47.7 **D2:** 46.4 **Sex (% female):** **D1:** 100 **D2:** 100 **Race (% white):** **D1:** 80.0 **D2:** 72.6 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 21.3 (4.4) **D2:** 21.5 (3.5)	Using LOCF, response rates were 58.2% in DUL vs. 32.2% in placebo group (P = 0.003, cell = 1, 1, P = 0.008). Remission rates were 34.6% in DUL and 18.6% in placebo group (P = 0.027, cell = 1, 1, P = 0.006). Magnitude of treatment effect was similar in women aged 40-55 compared to older and younger women	NR	**Overall attrition rate:** N/A **ITT Analysis** N/A Post-hoc analysis **Quality rating:** Fair Post-hoc analysis

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **Country and setting:** Italy Multicenter (38 centers) **Funding:** SmithKline, Beecham	**Research objective:** To assess efffects of PAR and FLUO 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:** Paroxetine: 20-40 mg/d **D2:** Fluoxetine: 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 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Devanand, 2005 **Country and setting:** United States Outpatient clinic **Funding:** NIMH	**Research objective:** FLUO vs. placebo for treatment of dysthymia in patients over 60 **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 90 **Intervention:** **D1:** Fluoxetine: 20-60 mg (individually titrated by protocol according to response) **D2:** placebo	**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 differences in response rates between treatment groups Responders: FLUO: 27.3%, placebo: 19.6% (*P* = 0.4) No sig differences in QOL measures on Q-LES-Q	NR	**Overall attrition rate:** 21% **ITT analysis:** Yes **Quality rating:** Good

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Ferrando et al., 1997 **Country and setting**: US appears to be a university outpatient clinic (outpatients referred from Northwestern Memorial Hospital) **Funding:** Chicago Consortium for Psychiatric Research	**Research objective:** To assess effectiveness and tolerability of SER, PAR, and FLUO in treatment of depressed patients with medically symptomatic HIV or AIDS **Duration of study:** 6 wks **Study design:** Other: open-label medication trial **Overall study N:** 33 **Intervention:** **D1:** Sertraline: 50 mg/d to a maximum of 150 mg/d as tolerated **D2:** Paroxetine: 20 mg/d to a maximum of 40 mg/d **D3:** Fluoxetine: 20 mg/d to a maximum of 40 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 17 • Symptomatic HIV infection (CDC stage B2, or B3) or AIDS (CDC stage C2 or C3) as determined by CD4 count, physical exam by physician, and medical records review • BDI ≥ 20 **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Clinically sig medical disease • Actively suicidal • Had been treated with other psychotropics in past mo • Unable to sign informed consent	**Mean age (yrs):** Overall: 38 **Sex (% female):** Overall: 18 **Race (% white):** Overall: 73 **Baseline (HAM-A):** NR **Baseline HAM-D:** Overall: 23.3 (4.8)	Clinical response (response = CGI of much or very much improved) Overall = 83% SER = 71% PAR = 86% FLUO = 90% Subjects who completed 6 wks of SSRI treatment experienced sig reductions in both affective and somatic symptoms (as measured by HAM-D, BDI, HAM-D affective, BDI cognitive subscale, HAM-D vegetative, and BDI somatic subscale scores among completers), many of the latter having been attributed to HIV rather than depression Nine subjects dropped out early due to AEs	**Diarrhea:** Overall: 9 **Headache:** Overall: 21 **Insomnia:** Overall: 21 **Nausea:** Overall: 15	**Overall attrition rate**: 27.3% **ITT Analysis** No- completer analysis **Quality rating:** Poor: open-label, no ITT

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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
 	
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: Sertraline: 50-200 mg/d
	D2: Placebo
		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:
				SER = 19.6 (5.3) and -8.4 (0.41)
				Placebo = 19.6 (5.4) and -7.6 (0.41)
				
				Any recurrent depression:
				SER = 20.6 (5.1) and -9.8 (0.59)
				placebo = 20.8 (5.6) and -7.6 (0.61)
				
				Patients with 2 prior episodes, plus HAM-D score $\geq$ 18:
				SER = 22.9 (3.6) and -12.3 (0.88)
				Placebo = 24.5 (4.4) and -8.9 (0.98)
				
				# CGI responders total sample:
				SER = 125 (67%)
				Placebo = 97 (53%)
				(P = 0.01)
				
				Any recurrent MDD:
				SER = 69 (72%)
				Placebo = 46 (51%)
				(P = 0.003)
				
				Patients with more severe (2 prior episodes plus HAM-D score ≥ 18):
				SER = 39 (78%)
				Placebo = 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **Country and setting:** United States multicenter, outpatient trial **Funding:** Lilly	**Research objective:** To assess effect of FLUO 20 mg/d on weight loss in older patients **Duration of study:** 6 wks (after a 1-wk placebo lead-in) **Study design:** RCT **Overall study N:** 671 **Intervention:** **D1:** Fluoxetine: 20 mg/d **D2:** Placebo	**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 FLUO • 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: FLUO -0.88 (2.11) Placebo 0.11 (1.96) (P < 0.001) High BMI: FLUO -1.14 (1.99) Placebo 0.04 (1.72) (P < 0.001) Pooled: FLUO -1.01 (2.05) Placebo 0.08 (1.85) (P < 0.001) % with weight loss of at least 5% low/normal BMI: FLUO 2.4 Placebo 1.1 (P = 0.225) High BMI: FLUO 3.7 Placebo 0 (P = 0.021) Pooled: FLUO 3.1 Placebo 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **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:** Placebo **D2:** Sertraline: 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), % SER = 44% placebo = 39% No sig diff in SF-36 physical component score, mean (SD) SER = 48.6 (9.6); change from baseline ~ 2.5 points Placebo = 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:** 61% **ITT Analysis** Yes **Quality rating:** Fair:

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Halikas, 1995 **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:** 150 **Intervention:** **D1:** Mirtazapine: 5-35 mg **D2:** Trazodone: 40-280 mg **D3:** placebo	**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 (SDS) • 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 placebo 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 placebo were statistically sig at 2, 3, 4, and 6 wks. Using MADRS, statistically sig diffs were found between both active compounds and placebo at wks 2 and 3. MIR and TRA were associated with sig higher frequencies of dizziness and blurred vision as compared to placebo At wk 6, 51% of MIR and 41% of TRA treated patients were HAM-D responders (not statistically sig)	**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	**Overall attrition rate:** 27% **ITT analysis:** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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., 2003 **Country and setting:** United States Outpatient **Funding:** Bristol-Meyers Squibb NIH Grants	**Research objective:** To compare NEF or placebo 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:** Nefazodone: 200-600 mg/d (412.9) **D2:** Placebo	**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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **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 placebo in elderly patients with major depressive disorder, using FLUO at fixed dose of 20 mg as a reference drug **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 517 **Intervention:** **D1:** Placebo **D2:** Escitalopram: 10 mg **D3:** Fluoxetine: 20 mg	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Age 65+ • MADRS total score of 22-40 at screening and baseline • MMSE 22+ at screening **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 ≥ 5 on Item 10 (suicidal thoughts) • 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 **Baseline HAM-D:** NR	"Responders" (≥ 50% decrease from baseline in MADRS total score) = 46% ESC group, 47% placebo group, 37% FLUO group (all NS) "Remitters" (MADRS total score < = 12): 40% ESC group, 42% placebo group, 30% FLUO group. Diff between placebo and ESC groups NS, but fewer remitters in FLUO vs. placebo groups ($P < 0.05$) ESC-treated patients experienced greater improvement than FLUO-treated patients in MADRS score at wk 8 (last observation carried forward) ($P < 0.01$); however, there was no sig diff between ESC- and placebo-treated patients	**Overall adverse events:** **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:** Good

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **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:** Sertraline: 50-200 mg/d **D2:** Paroxetine: 10-80 mg/d **D3:** Venlafaxine: 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 FLUO) **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 one 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcomes Results	Adverse Events (%)	Analysis Quality Rating
Author: Kirby et al.; 2002 **Country and setting:** Australia; inpatient **Funding:** Not reported	**Research objective:** To determine prevalence of hyponatremia associated with SSRI use vs. VEN in elderly compared to elderly not on these drugs **Duration of study:** 1 yr. (inpatients treated between 1997 to 1998) **Study design:** Observational **Overall study N:** 199 **Intervention:** Fluoxetine Fluvoxamine Paroxetine Sertraline Venlafaxine	**Inclusion criteria:** • Inpatient in North-West Hospital psychogeriatric unit between 1997 and 1998 **Exclusion criteria:** • Patients with no sodium test during admission	**Mean age (yrs):** Overall: 74.2 **Sex (% female):** Overall: 65 **Race (% white):** Overall: NR **Baseline (HAM-A):** NR **Baseline HAM-D:**	SSRIs/VEN were sig associated with hyponatremia after controlling for confounding factors (OR 3.5, 95% CI 1.4-8.9) OR adjusted for thiazide use: 2.5 (95% CI 1.1 - 5.4) VEN had a higher rate of hyponatremia than other drugs (71.4%; PAR: 32.0%; FLUO: 60.0%; SER: 28.6%)	NR	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Krishnan et al., 2001 Newhouse et al. 2000 **Country and setting:** US **Funding:** Pfizer, Inc	**Research objective:** To evaluate safety and efficacy of SER in treatment of moderate-to-severe major depression in elderly outpatients with comorbid vascular disease **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 220 **Intervention:** Fluoxetine: 50-100 mg/d Sertraline: 50-150 mg/d Other: nortriptyline **D1:** HTN **D2:** VASC **D3:** NoVasc	**Inclusion criteria:** • Adults 60 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Minimal improvement at most on CGI-I **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 • Suicidal tendencies • MMSE < 23 • Current diagnosis of dysthmia • Previous history of non-response to 6-wks adequate doses of 2 or more antidepressants	**Mean age (yrs):** **D1:** 68.6 **D2:** 68.9 **D3:** 67.3 **Sex (% female):** **D1:** 69 **D2:** 44 **D3:** 62 **Race (% white):** NR **Baseline (HAM-A):** **D1:** 14.4 **D2:** 14.4 **D3:** 15.2 **Baseline HAM-D:** NR	SER found to be safe, well-tolerated, and effective as an antidepressant in elderly patients suffering from hypertension and other forms of vascular comorbidity Both completer analysis and more conservative endpoint (LOCF) analysis found similar numbers of patients achieving "responder" status by end of study treatment (responder status defined as 50% or greater reduction from baseline in HAM-D total score); SER treatment yielded comparable levels of response in all 3 groups at treatment endpoint on both completer analysis (HTN, 86%, VASC, 89%, NoVASC, 58%; $P < 0.05$)	**Constipation:** **D1:** 18 **D2:** 13 **D3:** 6 **Diarrhea:** **D1:** 21 **D2:** 19 **D3:** 22 **Headache:** **D1:** 44 **D2:** 28 **D3:** 25 **Insomnia:** **D1:** 18 **D2:** 19 **D3:** 20 **Nausea:** **D1:** 19 **D2:** 9 **D3:** 20 **Somnolence (fatigue):** **D1:** 12 **D2:** 16 **D3:** 7 **Sweating (increase):** **D1:** 17 **D2:** 6 **D3:** 8	**Overall attrition rate:** NR **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Kroenke et al., 2001 **Country and setting:** US Primary care (76 physicians) **Funding:** Eli Lilly	**Research objective:** To compare efficacy of PAR, FLUO, and SER in depressed primary care patients **Duration of study:** 9 mos **Study design:** Open-label, randomized trial **Overall study N:** 573 **Intervention:** **D1:** Paroxetine: 20 mg/d **D2:** Fluoxetine: 20 mg/d **D3:** Sertraline: 50 mg/d	**Inclusion criteria:** • Adults 18 and up • Depressive disorder as determined by PCP • Home telephone **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** **D1:** 47.2 **D2:** 47.1 **D3:** 44.1 **Sex (% female):** **D1:** 76 **D2:** 86 **D3:** 75 **Race (% white):** **D1:** 85 **D2:** 88 **D3:** 79 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	All 3 treatment groups showed sig improvements in depression and other health related QOL domains (social function, work function, physical function) No sig diffs between treatment groups in any of 3 and 9 mos outcome measures Subgroup analysis showed no diffs in treatment effects for patients with MDD and for patients older than 60 yrs Switch rate to other medication: PAR: 22% FLUO: 14% SER: 17%	NR	**Overall attrition rate:** 24.3% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **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 a one-wk single-blind placebo phase) **Study design:** RCT **Overall study N:** 44 **Intervention:** **D1:** Placebo **D2:** Sertraline: 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%) placebo patients (P = 0.007) SER was statistically sig superior to placebo 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Magai et al., 2000 **Country and setting:** US, nursing homes **Funding:** Pfizer Pharmaceuticals New York State Dept. of Health Dementia Grants Program; Minority Biomedical Research Support Program and National Institute on Aging	**Research objective:** To evaluate efficacy of SER in treatment of depressive symptoms and signs in late-stage dementia patients **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 31 **Intervention:** **D1:** Sertraline: 25-100 mg **D2:** Placebo	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Concomitant condition: dementia • Minor depression **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Clinically sig medical disease	**Mean age (yrs):** **D1:** 88.4 **D2:** 90.1 **Sex (% female):** **D1:** 100 **D2:** 100 **Race (% white):** **D1:** 94 **D2:** 71 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	On all measures, both treatment and placebo groups improved over time, with 3 of 6 measures showing a sig time effect. "Knit-brow" facial feature approached significance for a treatment by time effect. In sum, SER had no sig benefits over placebo	**Overall adverse events:** **D1:** 11.8 **D2:** 14.3	**Overall attrition rate:** 12.9% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **Country and setting:** USA Single center **Funding:** National Institute on Alcohol Abuse and Alcoholism	**Research objective:** Comparison of SER and placebo in conjunction with CBT in treatment of depressed alcoholics **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 82 **Intervention:** **D1:** Sertraline: 50-200 mg/d **D2:** Placebo	**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 placebo, 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 placebo. Less drinking during study was associated with improved depression outcomes	NR	**Overall attrition rate:** 28% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **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:** Sertraline: 50-100 mg/d **D2:** Placebo	**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) SER = 76% placebo = 78% % remission (defined as a MADRS score < 10) (percent of those who completed 26 wks of treatment) SER = 81% placebo = 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 and Finkel et al., 1999 **Country and setting:** USA Multicenter **Funding:** Pfizer, Inc	**Research objective:** Examined efficacy and safety of FLUO and SER in depressed elderly outpatients **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 236 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Fluoxetine: 20-40 mg/d	**Inclusion criteria:** • Adults 60 yrs or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Additional mental illnesses or organic mental • Clinically sig medical disease • Failure to respond to ECT	**Mean age (yrs):** **D1:** 68 **D2:** 67 **Sex (% female):** **D1:** 63.2 **D2:** 51.3 **Race (% white):** **D1:** 95.7 **D2:** 100 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 25.1 (4.2) **D2:** 25.0 (4.7) **Subgroup analysis: Mean age (yrs):** **D1:** 74 **D2:** 75 **Sex (% female):** **D1:** 57 **D2:** 49 **Race (% white):** **D1:** 95 **D2:** 100 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 24.2 **D2:** 25.4	HAM-D Responders: SER: 73% FLUO: 71% *P* = NS HAM-D remitters: SER: 45% FLUO: 46% *P* = NS Q-LES-Q and other patient-rated secondary efficacy measures were similar for both treatment groups at endpoint SER-treated patients showed a greater cognitive improvement than patients on FLUO on Digit Symbol Substitution Test at endpoint (*P* = 0.037) Patients 70 yrs of age and older, HAM-D responders at endpoint in SER group (*P* = 0.027): 58.5% (SER) vs. 42.4% (FLUO)	**Diarrhea:** **D1:** 22.4 **D2:** 16.1 **Dizziness:** **D1:** 7.8 **D2:** 10.2 **Headache:** **D1:** 33.6 **D2:** 31.4 **Insomnia:** **D1:** 13.7 **D2:** 14.4 **Nausea:** **D1:** 14.7 **D2:** 18.6 **Subgroup analysis: Overall adverse events:** **D1:** 93 **D2:** 94 **Headache:** **D1:** 23.8 **D2:** 33.3 **Nausea:** **D1:** 16.7 **D2:** 15.2	**Overall attrition rate:** 32.2% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Nyth et al., 1992 **Country and setting:** Denmark, Norway, Sweden Multicenter (7) **Funding:** NR	**Research objective:** To assess efficacy and safety of CIT vs. placebo in depressed elderly patients who might also suffer from somatic disorders and/or senile dementia **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 149 **Intervention:** **D1:** Citalopram: 10-30 mg **D2:** Placebo	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 14 • Mild to moderate dementia and somatic disorders acceptable but not required for inclusion **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Receipt of anti-cancer treatment; recent treatment with monoamine oxidase inhibitors; GBS geriatric rating scale with score >4	**Mean age (yrs):** **D1:** F: 77.0, M: 74.4 **D2:** F: 77.7; M: 77.8 **Sex (% female):** **D1:** 67 **D2:** 73 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 22.1 (6.2) **D2:** 21.1 (5.8)	Rate of response as measured by HAM-D was similar in CIT and placebo groups (no data given) GBS dementia rating scale indicated that intellectual function-time orientation, recent memory, and ability to increase tempo and symptoms common to dementia-anxiety, fear-panic, depressed mood all improved sig more in CIT-treated subgroup of patients with dementia than in placebo-treated subgroup ($P < 0.05$)	**Overall adverse events:** **D1:** 37 **D2:** 25 **Changes in weight (decrease):** **D1:** 9.2 **D2:** 3.9 **Constipation:** **D1:** 3.1 **D2:** 5.9 **Dizziness:** **D1:** 7.1 **D2:** 0 **Nausea:** **D1:** 5.1 **D2:** 7.8 **Somnolence (fatigue):** **D1:** 18.4 **D2:** 5.9	**Overall attrition rate:** 36.9% **ITT Analysis** Efficacy analysis; ITT done and ITT **Quality rating:** Poor Completer analysis only

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Oslin et al., 2003 **Country and setting:** US VA nursing facilities (13) **Funding:** National Institute of Mental Health; Department of Veterans Affairs	**Research objective:** To examine efficacy and tolerability of VEN and SER among nursing home residents **Duration of study:** 10 wks **Study design:** RCT **Overall study N:** 52 **Intervention:** **D1:** Sertraline: 25-100 mg/d **D2:** Venlafaxine: 18.75-150 mg/d	**Inclusion criteria:** • Age 60 or more • Diagnosed with MDD according to DSM-III or -IV • HAM-D ≤ 12 • Sig dysphoria with score ≥ 10 on GDS and/or rating >2 on depressed mood item of HAM-D • Minor depression, dementia with depression, or dysthymia • Blessed Memory Information Concentration test score < 21 **Exclusion criteria:** • 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 wks • Suicidal tendencies	**Mean age (yrs):** **D1:** 83.8 **D2:** 81.2 Overall: 82.5 **Sex (% female):** **D1:** 56 **D2:** 33 Overall: 44.2 **Race (% white):** **D1:** 92 **D2:** 63 Overall: 76.9 **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 20.2 (3.4) **D2:** 20.3 (3.7)	Mean change from baseline to endpoint: HAM-D (F 3.45, *P* 0.069) = 8.0 (SER) vs. 4.6 (VEN); GDS (F 2.13, *P* 0.151) = 3.5 (ser) vs. 0.8 (ven); Cornell (F 7.65, *P* 0.008) = 8.5 (ser) vs. 4.0 (ven). Endpoint CGI = 2.3 (ser) vs. 3.0 (ven) with F = 2.83 and *P* = 0.98. Tolerability lower for VEN	NR	**Overall attrition rate:** 38.5% **ITT Analysis** Yes **Quality rating:** Poor

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **Country and setting:** US Teaching hospital **Funding:** National Institute on Drug Abuse	**Research objective:** To evaluate efficacy of FLUO in treating depression in methadone-maintained opioid addicts **Duration of study:** 3 mos **Study design:** RCT **Overall study N:** 44 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Placebo	**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 ($z = 2.37$; $P = 0.01$; $z = 5.85$, $P < 0.01$); no sig diffs between placebo and FLUO 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **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 FLUO is superior to placebo for depression, fatigue, or both **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** **D1:** Fluoxetine: 20-60 mg/d **D2:** Placebo 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% [placebo] [*P* = 0.66]) and remission (50% [fluox] vs. 51% [placebo] [*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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **Country and setting:** US and Canada Multicenter (31) **Funding:** GlaxoSmithKline	**Research objective:** Efficacy and safety of PAR CR and IR versus placebo in late life depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 310 **Intervention:** **D1:** Paroxetine CR 12.5-50 **D2:** Paroxetine IR 10-40 mg/d **D3:** Placebo	**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 placebo, 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 placebo. Response (a score of 1 or 2 on CGI-I scale) was achieved by 72% of PAR CR patients (P < 0.002 vs. placebo), 65% of PAR IR patients (P = 0.06 vs. placebo), and 52% of placebo patients. Remission, defined as HAM-D total score ≤ 7, was achieved by 43% of PAR CR patients (P = 0.009 vs. placebo), 44% of PAR IR patients (P = 0.01 vs. placebo), and 26% of placebo patients	**Insomnia:** **D1:** 9.6 **D2:** 14.2 **D3:** 8.3	**Overall attrition rate:** 24.4% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Rocca et al., 2005 **Country and setting:** Italy University clinic **Funding:** University of Turin, Italy	**Research objective:** To compare effect of SER and CIT on depression symptoms and cognitive functions in nondemented elderly patients with minor depressive disorder or sybsyndromal depressive symptomatology **Duration of study:** 12 mos **Study design:** Nonrandomized controlled trial **Overall study N:** 138 **Intervention:** **D1:** Citalopram: 20 mg/d **D2:** Sertraline: 50 mg/d	**Inclusion criteria:** • Minimum HAM-D score of 10 • Nondemented elderly (65 or older) • Minor depressive disorder or subsyndromal depressive disorder according to SCID **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Any other current Axis I or II psychiatric disorder • Impairment and decline of global cognitive functions on MMSE • Score of at least 12 on Alzheimer's Disease Assessment Scale-Cognitive Subscale	**Mean age (yrs):** **D1:** 72.4 **D2:** 71.9 **Sex (% female):** **D1:** 24.2 **D2:** 31.9 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** **D1:** 12.9 **D2:** 12.9	Both treatments induced a sig, sustained, comparable improvement in depressive symptoms and in social functioning Change from baseline to endpoint on HAM-D CIT and SER groups decrease 55% vs. 52.7%; *(P* = NR) or GDS Remission observed at any timepoint between treatment groups 12 mos: 53% vs. 42%; *P* = 0.25 Sig within-group improvements seen in all cognitive measures for both SER and CIT WMS, TMT-A, TMT-B, VF, and MMSE)	**Dizziness:** **D1:** 15.2 **D2:** 9.7 **Headache:** **D1:** 10.1 **D2:** 9.7 **Nausea:** **D1:** 24.2 **D2:** 18.1	**Overall attrition rate:** 27.5 **ITT Analysis:** Yes **Quality rating:** N/A

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Roose et al., 2004 **Country and setting:** US, multicenter **Funding:** Forest Laboratories	**Research objective:** To evaluate efficacy of CIT for treatment of depression in "old-old" **Duration of study:** 8 wks (after a single-blind placebo lead-in) **Study design:** RCT **Overall study N:** 184 **Intervention:** **D1:** Citalopram: 10-40 mg/d **D2:** Placebo	**Inclusion criteria:** • Age 75 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 (HAM-D 24) **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Current suicide intent or serious suicide attempt within past yr • Probable Alzheimer's disease or probable vascular dementia • MMSE score ≤ 18 • Parkinson's disease • Failure to respond to either a trial of an SSRI for at least 4 wks, or trials of 2 or more different classes of antidepressants other than SSRIs	**Mean age (yrs):** **D1:** 79.8 **D2:** 79.3 **Sex (% female):** **D1:** 53.6 **D2:** 62.2 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 24.4 (4.3) **D2:** 24.2 (3.9)	Number of responders (reduction of ≥ 50% in HAM-D score) CIT = 34 placebo = 34 f = 0.97 (*P* = 0.32) Number of remitters (HAM-D ≤ 10) CIT = 29 placebo = 30 f = 0.29 (*P* = 0.59) CGI improvement of 1 or 2 CIT = 37 placebo = 39 f = 1.53 (*P* = 0.22) Higher rate of response, CIT vs. placebo, in high severity group: chi-square = 4.03, df = 1 (*P* = 0.04) Patients with onset of major depression before 60 yrs of age had poorer outcome when treated with placebo than any other 3 subgroups (*P* < 0.05)	**Constipation:** **D1:** 11.5 **D2:** 4.4 **Diarrhea:** **D1:** 14.9 **D2:** 6.7 **Dizziness:** **D1:** 9.2 **D2:** 7.8 **Headache:** **D1:** 11.5 **D2:** 4.4 **Insomnia:** **D1:** 3.4 **D2:** 5.6 **Nausea:** **D1:** 6.9 **D2:** 6.7 **Somnolence (fatigue):** **D1:** 5.7 **D2:** 4.4	**Overall attrition rate:** 16.7% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Roscoe et al., 2005 **Country and setting:** US University medical center **Funding:** SmithKline Beecham (supplied medication), Department of Defense	**Research objective:** To evaluate effect of PAR on fatigue and depression in breast cancer patients receiving chemotherapy **Duration of study:** Undefined (visits conducted 7 days after each of 4 on-study treatments) PAR: 20 mg/d placebo **Study design:** RCT **Overall study N:** 122 **Intervention:** **D1:** Paroxetine **D2:** Placebo	**Inclusion criteria:** • Breast cancer • Beginning or currently receiving treatment for breast cancer • Females **Exclusion criteria:** • Concurrent radiation, interferon, history of seizures or mania, treatment cycles less than 2 wks apart, radiation okay if occurs between chemo cycles (it was regarded as a treatment cycle) • Concomitant psychotherapeutic or psychotropic medications	**Mean age (yrs):** **D1:** 52.2 **D2:** 52.2 **Sex (% female):** **D1:** 100 **D2:** 100 **Race (% white):** **D1:** 93 **D2:** 86 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Controlling for cycle 1, PAR was more effective in reducing depression during chemotherapy as measured by CESD (P = 0.006) [mean (SD) at cycle 4 for PAR and placebo: 8.8 (1.11) vs. 12.6 (1.24)] No sig diff between PAR and placebo on all 4 fatigue scales MAF question 1, Fatigue/Inertia Scale, Fatigue Symptom Checklist, and Interference with Daily Activities Sub-Scale from MAF (Interference)]; mean at cycle 4: MAF 4.6 vs. 5.0; Fatigue/Inertia Scale 6.0 vs. 7.1, Fatigue Symptom Checklist 44.6 vs. 48.0, Interference 3.1 vs. 3.8) (all Ps >0.27)	NR	**Overall attrition rate:** 23% **ITT Analysis** No **Quality rating:** Poor: Appears to be completer analysis only, study length is not defined

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 Study has 13-20% bipolars **Country and setting:** Italy One inpatient center **Funding:** Not reported	**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 placebo washout) **Study design:** RCT **Overall study N:** 93 **Intervention:** **D1:** Fluvoxamine: 200 mg/d (100mg twice daily) **D2:** Sertraline: 150 mg/d (75mg twice daily)	**Inclusion criteria:** • Age 59 or more • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 21 • MDD diagnosed by MD using unstructured interviews and medical records according to DSM-IV, and after 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 • No psychotic features	**Mean age (yrs):** **D1:** 67.80 **D2:** 68.24 **Sex (% female):** **D1:** 61.5 **D2:** 82.2 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 31.23 (5.12) **D2:** 29.23 (3.45)	No sig diff in final response rates was found between 2 treatment groups, 55.6% (25/45) and 71.8% (28/39) for SER and FLUV, respectively (P = 0.12). A repeated-measures analysis of variance on Hamilton Rating Scale for Depression 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **Country and setting:** US 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:** Paroxetine: 20 mg/d up to 40 mg/d	**Inclusion criteria:** • Adults 65 or older • MDD diagnosis according to DSM-III or -IV • HAM-D ≥ 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 MIR = (80) 64.0% PAR = (68) 56.7% chi square = 1.23 *P* = 0.267 Greater early efficacy for mirtazapine, similar number of CGI responders at end of continuation phase	**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	**Attrition:** 26.8% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schmitz et al., 2001 **Country and setting:** US **Funding:** National Institute on Drug Abuse and Department of Pscyhiatry and Behavioral Sciences, University of Texas-Houston	**Research objective:** To test hypothesis that FLUO would produce favorable effects onoutcome measures of retention, depression, and cocaine use compared with placebo for treatment of comorbid cocaine dependence and depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 68 **Intervention:** **D1:** Fluoxetine: 40 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 18 to 50 • Diagnosed with MDD according to DSM-III or -IV • Diagnosed dually with MDD and cocaine dependence • BDI score > 10 • English speaking • Free of serious legal and medical problems **Exclusion criteria:** • Current dependence on alcohol or any other psychoactive substance (except nicotine or cannabis) • Met criteria for current primary Axis I disorders other than depression	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	No sig diff in response among depressed cocaine abusers	NR	**Overall attrition rate:** 52.9% **ITT Analysis:** NR **Quality rating:** Poor High LTF

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schneider et al., 2003 and Sheikh et al., 2004 **Country and setting:** US; psychiatric and primary care **Funding:** Pfizer	**Research objective:** To confirm results of non-placebo controlled efficacy trials of SER for treating late-life derpession and to report on efficacy, safety, and tolerability of SER in treatment of elderly depres-sed patients with and without comorbid medical illness **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 752 **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Placebo	**Inclusion criteria:** • Age 60 or more • Diagnosed with MDD according to DSM-III or -IV • HAM-D > 17 • Community-dwelling • Episode ≥ 4 wks • HAM-D depressed mood score ≥ 2 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses • Illicit drug and alcohol abuse • Investigational drug in last 2 wks • Any need for ECT • Suicidal tendencies • Psychotic features, dementia, seizure disorder • Previous nonresponse/ hypersensitivity • Clinically sig unstable medical disease • Psychotherapy within 3 mos	**Mean age (yrs):** **D1:** 70 **D2:** 69.6 **Overall**: 69.8 **Sex (% female):** **D1:** 54 **D2:** 58 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 21.4 (2.7) **D2:** 21.4 (2.6)	Mean changes in HAM-D = -7.4 (SD 6.3) for SER and -6.6 (SD 6.4) for placebo with $P = 0.01$ HAM-D responders = 35% for SER vs. 26% for placebo ($P = 0.007$) CGI responders = 45% for SER vs. 35% for placebo (chi sq = 7.8, df = 1, $P = 0.005$) SER was superior to placebo on all three primary outcome measures, HAM-D, and overall clinical severity and change (CGI-S/CGI-I). Furthermore, therapeutic response to SER was comparable in those with or without medical comorbidity, and there were no treatment by comorbidity group interactions	**Diarrhea:** **D1:** 19 **Dizziness:** **D1:** 8 **Headache:** **D1:** 17 **Insomnia:** **D1:** 9 **Nausea:** **D1:** 16 **Somnolence (fatigue):** **D1:** 10	**Overall attrition rate:** 20.9% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Schone et al., 1993 and Geretsegger et al., 1994 **Country and setting:** NR (but assume Germany, based on authors' affiliations), inpatient and outpatient clinics **Funding:** Not reported	**Research objective:** To compare efficacy of PAR vs. FLUO in treatment of depression among elderly clients, and to assess drugs' effects on clients' cognitive and behavioral function **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 106 **Intervention:** **D1:** Paroxetine: 20-40 mg **D2:** Fluoxetine: 20-60 mg	**Inclusion criteria:** • 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 placebo run-in period (3-7 days)	**Mean age (yrs):** **D1:** 74.3 **D2:** 73.7 **Sex (% female):** **D1:** 83.3 **D2:** 90.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** **D1:** 24.2 **D2:** 26.0	Wk 6 (endpoint) mean changes from baseline, PAR vs. FLUO, respectively: (1) SCAG total score = -14.5 vs. -8.9. (2)SCAG Cognitive dysfunction factor scores = -2.9 vs. -0.6. (3) HAM-D cognitive factor scores = -1.5 vs. -1.0. (4)MMS total scores = 2.3 vs. 1.1 Sig higher proportion of responders (reduction of 50% or more in HAM-D [37.5% vs. 17.5%, *P* = 0.03] or MADRS [*P* = 0.04] total scores) at end of treatment in PAR group. No sig diff between treatment groups in proportion of responders on CGI-S	**Overall adverse events:** **D1:** 61 **D2:** 77 **Constipation:** **D1:** 10 **D2:** 0 **Dizziness:** **D1:** 0 **D2:** 7	**Overall attrition rate:** 17% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **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 FLUO in patients with depression after their 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:** Fluoxetine: 20-60 mg/d **D2:** Placebo	**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 FLUO - 8.34(5.87) vs. placebo 5.84(5.92) (P = 0.06) but mildly depressed patients in FLUO group had endpoint HAM-D scores sig different (by 5.4 points) than placebo (P = 0.01). At wk 25- responder rates 48% (fluox) vs. 26% (placebo) (P = 0.05) and remission rates 26% (fluox) vs. 14.8% (placebo)(P = 0.60)	**Cardiovascular adverse events:** **D1:** 18.5 **D2:** NR	**Overall attrition rate:** 25.9% **ITT Analysis** Yes **Quality rating:** Good

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (continued)

Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Health Outcome Results	Adverse Events (%)	Analysis and Quality Rating
Author: Tollefson et al., 1993 Tollefson et al., 1995 Small et al., 1996 and Heiligenstein et al., 1995 **Country and setting:** US Mulitcenter **Funding:** Not reported	**Research objective:** To compare HAM-D scores of FLUO-treated vs. placebo-treated elderly depressed patients (not explicitly stated) **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 671 **Intervention:** **D1:** Fluoxetine: 20 mg/d **D2:** Placebo	**Inclusion criteria:** • Adults 60 yrs or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 16 • MMSE < 25 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	FLUO had sig better rates of response and remission than placebo. Response of FLUO group was 36% versus 27% placebo (P = 0.014) and remission of FLUO group was 21% versus 13% for placebo (P = 0.008) FLUO was statistically sig more efficacious than placebo in overall response (43.9% vs. 31.6%, P = 0.002) and remission (31.6% vs. 18.6%, P < 0.001) Number of physical illnesses did not affect treatment response, though historic illness was associated with greater fluoxetine repsone and poorer placebo repsonse	**Overall adverse events:** **D1:** 11.6% discontinuation rate **Dizziness:** **D1:** 0.3% discontinuation rate **Insomnia:** **D1:** 0.9% discontinuation rate **Suicidality:** **D1:** n = 4	**Overall attrition rate:** 20.4% **ITT Analysis** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **Country and setting:** US 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:** Bupropion: 100-300 mg/d (197) **D2:** Paroxetine: 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 ≥ 50% reduction in HAM-D) were similar in both groups: BUP sr: 71% PAR: 77% No sig diffs in QOL 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	**Attrition:** 16% **ITT Analysis:** Yes **Quality rating:** Fair

Evidence Table 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **Country and setting:** United States Multicenter, primary care clinics **Funding:** Hartford and MacArthur Foundations	**Research objective:** To compare effectiveness of PAR vs. placebo 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:** Paroxetine: 10-40, individually titrated **D2:** placebo	**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: PAR: 0.61 (P = 0.05) placebo: 0.40 (P = 0.05) Behavior Therapy 0.52 (P = 0.05) P = 0.004 for PAR vs. placebo PAR only statistically and clinically sig better than placebo 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 6. KQ5: Efficacy, effectiveness, or harms of antidepressants in subpopulations (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 **Country and setting:** UK, outpatient clinic(s) **Funding:** Not reported	**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 placebo) (article focuses on results of this maintenance phase) **Study design:** RCT **Overall study N:** 113 (randomised to double-blind phase) **Intervention:** **D1:** Sertraline: 50-100 mg/d **D2:** Placebo	**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 placebo, log rank test = 1.55, df = 1 (*P* = 0.21) Cumulative survival function SER = 39%, median survival 92 wks; placebo = 31%, median survival 48 wks Reduction in risk of recurrence: 8.4% over 100 wks (SER vs. placebo) % with recurrence in first 26 wks and wks 27-52, respectively: SER = 57%, 16% placebo = 60%, 32% Cox regression model predicting recurrence: hazard ratio (95% CI) included variables: SER vs. placebo = 1.21 (0.704, 2.082)	NR	**Overall attrition rate:** 72.6% **ITT Analysis** Not applicable: recurrence trial **Quality rating:** Fair

Evidence Table 7. KQ5: Systematic reviews and meta-analyses on antidepressants in subpopulations

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Bush et al., 2005 **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 7. KQ5: Systematic reviews and meta-analyses on antidepressants in subpopulations (continued)

Study Characteristics	Study Information	Study Characteristics	Results	Adverse Events (%)	Assessments	Study Appraisals and Quality Rating
Author: Entsuah et al., 2001 Thase et al., 2005 **Country and setting:** Multinational **Funding:** NR **Research objective:** To compare response and remission rates in different sub-populations	**Study design:** Pooled analysis **Number of Patients:** 2,045 **Studies Included:** 8 double-blind, active controlled	**Included Studies:** Studies that compared VEN to FLUO or PAR **Included Populations** • 18 yrs of age or more • HAM-D of 20 or more or MADRS of 25 or more **Interventions:** • **D1:** Venlafaxine 75-225 mg/d • **D2:** Fluoxetine 20-50 mg/d • **D3:** Paroxetine 20-40 mg d	**Study Results:** No sig age by treatment; gender by treatment; or age-by-gender by treatment interactions (all *P* -values >0.1) Among women, but not men, there was a sig interaction reflecting poorer SSRI response in older age group (*P* = 0.04). HRT appeared to eliminate this diff. Diff among older women taking and not taking HRT was 23% Remission (HAMD at endpoint ≤ 7): VEN = 45% SSRI = 35% placebo = 25% (VEN vs SSRI, *P* < 0.0001; SSRI vs placebo, *P* = 0.0003)	**Adverse Events:** Women on VEN had more nausea than other groups	**Publication Bias:** No **Heterogeneity:** No	**Standard Method of Study Appraisals:** NR **Comprehensive Search Strategy:** No **Quality Rating:** Fair

Table E-1. Characteristics of Studies with Poor Internal Validity

Study	Design	Sample Size	Intervention	Reason for Exclusion
Aguglia et al., 1993[1]	RCT	108	Fluoxetine vs. sertraline	High LTF
Amini et al., 2005[2]	RCT	36	Mirtazapine vs. fluoxetine	No ITT analysis
Clerc et al., 1994[3]	RCT	68	Fluoxetine vs. venlafaxine	High differential attrition
Falk et al., 1989[4]	RCT	27	Trazadone vs. fluoxetine	High LTF
Ferrando et al., 1997[5]	RCT	33	Sertraline vs. paroxetine vs. fluoxetine	No ITT analysis
Flament et al., 2001[6]	RCT	286	Sertraline vs. fluoxetine	No ITT analysis
Goldstein et al., 2004[7]	RCT	353	Duloxetine vs. paroxetine	High LTF
Grigoriadis et al., 2003[8]	Observational	201	Citalopram vs. fluoxetine	No ITT analysis (completer analysis only)
Gülseren et al., 2005[9]	RCT	25	Fluoxetine vs. paroxetine	No ITT analysis; high rate of post-randomization exclusions
Mesters et al., 1993[10]	RCT	308	Fluoxetine	No ITT analysis
Oslin et al., 2003[11]	RCT	52	Sertraline vs. venlafaxine IR	High attrition
Roscoe et al., 2005[12]	RCT	94	Paroxetine vs. placebo	No ITT analysis
Rosenbaum et al., 1998[13]	Observational	242	Sertraline, fluoxetine, paroxetine	No ITT analysis
Schmitz et al., 2001[14]	RCT	68	Fluoxetine vs. placebo	High LTF
Stahl et al., 2000[15]	RCT	323	Citalopram vs. sertraline	High attrition
Thase et al., 2001[16]	Pooled analysis	2,045	Venlafaxine vs. SSRIs	No systematic literature search
Tollefson et al., 1994[17] and Beasley et al., 1991[18]	Meta-analysis	3,065	Fluoxetine vs. placebo	No systematic literature search
Wade et al., 2003[19]	RCT	197	Mirtzapine vs paroxetine	High LTF; high post-randomization exclusions
Wagner et al., 1998[20]	RCT	118	Fluoxetine vs. placebo	No ITT analysis
Winokur et al., 2003[21]	RCT	21	Fluoxetine vs. mirtazapine	No ITT analysis, small sample size
Zanardi et al., 1996[22]	RCT	46	Paroxetine vs. sertraline	High LTF (41%)

ITT, intent to treat analysis; LTF, loss to followup; RCT, randomized controlled trial.

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Placebo Studies Included in Meta-Regression

Study	Design	Sample Size	Intervention	Quality Rating
Addington et al., 2002[1]	RCT	48	Sertraline vs. placebo	Fair
Brannan et al., 2005[2]	RCT	282	Duloxetine vs. placebo	Fair
Burke et al., 2001[3]	RCT	70	Fluoxetine vs. placebo	Fair
Claghorn et al., 1992[4]	RCT	71	Paroxetine vs. placebo	Fair
Claghorn et al., 1992[5]	RCT	341	Paroxetine vs. placebo	Fair
Cohn et al., 1996[6]	RC	81	Nefazodone vs. placebo	Fair
Cunningham et al., 1997[7]	RCT	268	Venlafaxine vs. placebo	Fair
Detke et al., 2002[8]	RCT	267	Duloxetine vs. placebo	Fair
Detke et al., 2002[9]	RCT	236	Duloxetine vs. placebo	Fair
Feighner et al., 1999[10]	RCT	650	Citalopram vs. placebo	Fair
Fontaine et al., 1994[11]	RCT	135	Nefazodone vs. placebo	Fair
Hypericum Depression Trial Study Group, 2002[12]	RCT	227	Sertraline vs. placebo	Good
Khan et al., 1991[13]	RCT	93	Venlafaxine vs. placebo	Fair
Kocsis et al., 1997[14,15]	RCT	416	Sertraline vs. placebo	Fair
Lineberry et al., 1990[16]	RCT	224	Bupropion vs. placebo	Fair
Lydiard et al., 1989[17]	RCT	36	Fluvoxamine vs. placebo	Fair
Lydiard et al., 1997[18]	RCT	234	Sertraline vs. placebo	Fair
Mendels et al., 1993[19]	RCT	312	Venlafaxine vs. placebo	Fair
Mendels et al., 1995[20]	RCT	240	Nefazodone vs. placebo	Fair
Olie et al., 1997[21]	RCT	258	Sertraline vs. placebo	Fair
Reimherr et al., 1990[22]	RCT	290	Sertraline vs. placebo	Fair
Reimherr et al., 1988[23]	RCT	77	Sertraline vs. placebo	Fair
Rickels et al., 1989[24]	RCT	102	Paroxetine vs. placebo	Fair
Shrivastava et al., 1992[25]	RCT	69	Paroxetine vs. placebo	Fair
Strik et al., 2000[26]	RCT	54	Fluoxetine vs. placebo	Fair
Thase et al., 1997[27]	RCT	197	Venlafaxine vs. placebo	Fair
Tollefson et al., 1993[28]	RCT	534	Fluoxetine vs. placebo	Fair
Tollefson et al., 1995[29,30]	RCT	671	Fluoxetine vs. placebo	Fair
Trivedi et al., 2004[31]	RCT	459	Paroxetine vs. placebo	Fair
Wade et al., 2002[32]	RCT	380	Escitalopram vs. placebo	Fair
Walczak et al., 1996[33]	RCT	577	Fluvoxamine vs. placebo	Fair

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Placebo Studies Excluded from Meta-Regression

Study	Design	Sample Size	Intervention	Reason for Exclusion
Brown et al., 2005[1]	RCT	90	Citalopram vs. placebo	High attrition
Byerley et al., 1988[2]	RCT	97	Fluoxetine vs. placebo	No ITT analysis
Claghorn et al., 1995[3]	RCT	90	Mirtazapine vs. placebo	No ITT analysis
Claghorn et al., 1996[4]	RCT	150	Fluvoxamine vs. placebo	No ITT analysis
Claghorn, 1992[5]	RCT	72	Paroxetine vs. placebo	No ITT analysis
Cohn et al., 1990[6]	RCT	120	Paroxetine vs. placebo	No ITT analysis
Cohn et al., 1992[7]	RCT	120	Paroxetine vs. placebo	No ITT analysis; high rate of post-randomization exclusions
Corrigan et al., 2000[8]	RCT	70	Fluoxetine vs. placebo	No ITT analysis
Croft et al., 2002[9]	RCT	432	Bupropion vs. placebo	High LTF
Dunbar et al., 1991[10]	RCT	480	Paroxetine vs. placebo	High Attrition
Dunbar et al., 1993[11]	RCT	273	Paroxetine vs. placebo	High Attrition
Elliot et al., 1998[12]	RCT	75	Paroxetine vs. placebo	High LTF; no ITT analysis
Evans et al., 1997[13]	RCT	82	Fluoxetine vs. placebo	High Attrition
Fabre et al., 1996[14]	RCT	100	Fluvoxamine vs. placebo	High Attrition
Fabre et al., 1995[15]	RCT	369	Sertraline vs. placebo	No ITT analysis
Fabre et al.,1992[16]	RCT	74	Paroxetine vs. placebo	High Attrition
Fabre et al., 1987[17]	RCT	84	Fluoxetine vs. placebo	No ITT analysis
Fava et al., 2005[18]	RCT	90	Fluoxetine vs. placebo	High Attrition
Fava et al., 1997[19]	RCT	20	Venlafaxine vs. placebo	No ITT analysis
Feighner et al., 1989[20]	RCT	45	Nefazodone vs. placebo	Not enough data
Feighner et al., 1992[21]	RCT	430	Paroxetine vs. placebo	High Attrition
Feighner et al., 1992[22]	RCT	76	Paroxetine vs. placebo	High Attrition
Feighner et al., 1993[23]	RCT	480	Paroxetine vs. placebo	High Attrition
Feighner et al., 1998[24]	RCT	117	Nefazodone vs. placebo	High Attrition
Gilaberte et al., 2001[25]	RCT	140	Fluoxetine vs. placebo	High attrition
Lapierre et al., 1987[26]	RCT	63	Fluvoxamine vs. placebo	No ITT analysis
March et al., 1990[27]	RCT	54	Fluvoxamine vs. placebo	No ITT analysis

Study	Design	Sample Size	Intervention	Reason for Exclusion
McGrath et al., 2000[28]	RCT	154	Fluoxetine vs. placebo	High rate of post-randomization exclusions
Montgomery et al., 1992[29]	RCT	199	Citalopram vs. placebo	High rate of post-randomization exclusions
Muijen et al., 1988[30]	RCT	81	Fluoxetine vs. placebo	No ITT analysis
Petracca et al., 2001[31]	RCT	41	Fluoxetine vs. placebo	No ITT analysis
Ravindram et al., 1995[32]	RCT	103	Sertraline vs. placebo	High attrition; no ITT analysis
Reimherr et al., 1998[33]	RCT	362	Bupropion vs. placebo	High Attrition
Rickels et al., 1994[34]	RCT	191	Nefazodone vs. placebo	High Attrition
Rickels et al., 1982[35]	RCT	202	Trazadone vs. placebo	No ITT analysis
Rickels et al., 1992[36]	RCT	111	Paroxetine vs. placebo	No ITT analysis
Roth et al., 1990[37]	RCT	90	Fluvoxamine vs. placebo	No ITT analysis
Roy-Byrne et al., 2000[38]	RCT	64	Nefazodone vs. placebo	High Attrition
Rudolph et al., 1998[39]	RCT	358	Venlafaxine vs. placebo	High Attrition
Schweizer et al., 1991[40]	RCT	60	Venlafaxine vs. placebo	High Attrition
Smith et al., 1990[41]	RCT	150	Mirtazapine vs. placebo	No ITT analysis
Smith et al., 1992[42]	RCT	77	Paroxetine vs. placebo	No ITT analysis
Sramek et al., 1995[43]	RCT	144	Fluoxetine vs. placebo	Not enough data
Vartiainen et al., 1994[44]	RCT	114	Mirtazapine vs. placebo	High Attrition
Wernicke et al., 1987[45]	RCT	345	Fluoxetine vs. placebo	High Attrition
Wernicke et al., 1988[46]	RCT	363	Fluoxetine vs. placebo	Not enough data

ITT, intent to treat; RCT, randomized controlled trial; LTF, lost to follow-up

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Discontinuation Rates

Background

Presented in this appendix are relative risk meta-analyses that compare selective serotonin reuptake inhibitors (SSRIs) with individual drugs with respect to discontinuation. The specific comparisons with SSRIs are shown below: bupropion, duloxetine, mirtazapine; nefazodone; trazodone, and venlafaxine The first six figures are for overall discontinuation. The two sets of figures following those are for discontinuation specifically for adverse events and then for discontinuation for lack of efficacy. All are random effects models.

Relative Risk of Overall Discontinuation

Figure H-1. Bupripion vs. SSRIs

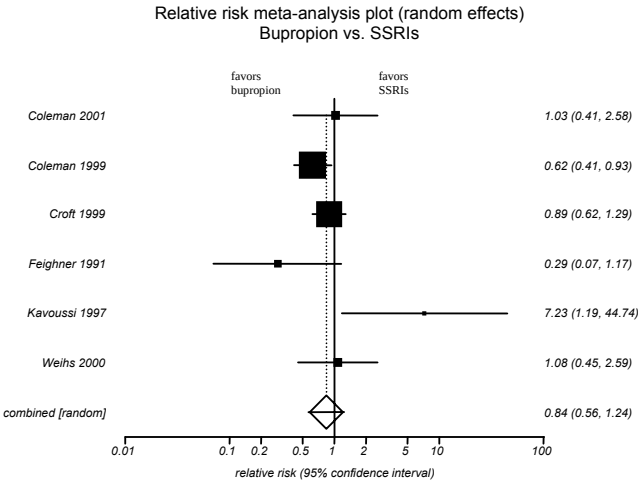


Figure H-2. Duloxetine vs. SSRIs

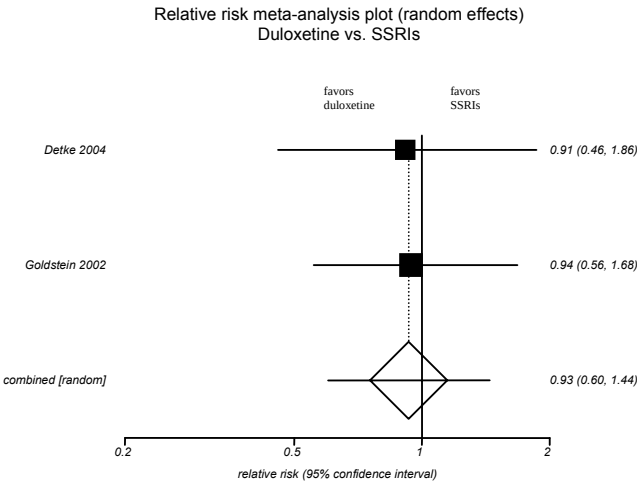


Figure H-3. Mirtazapine vs. SSRIs

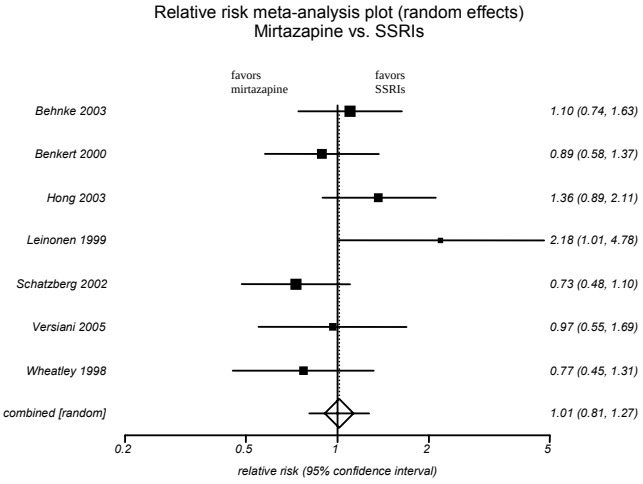


Figure H-4. Nefazodone vs. SSRIs

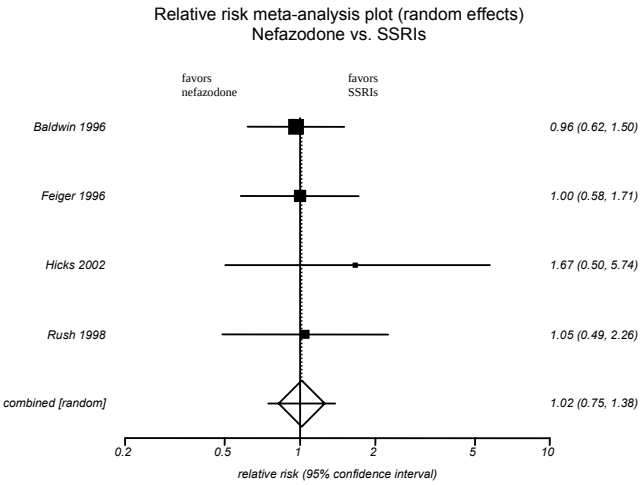


Figure H-5. Trazadone vs. SSRIs

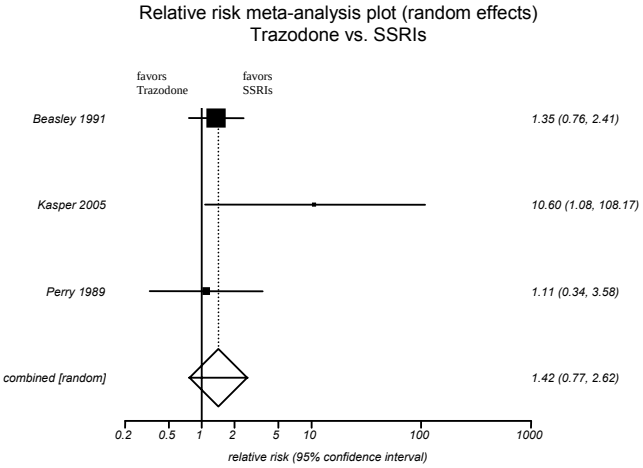
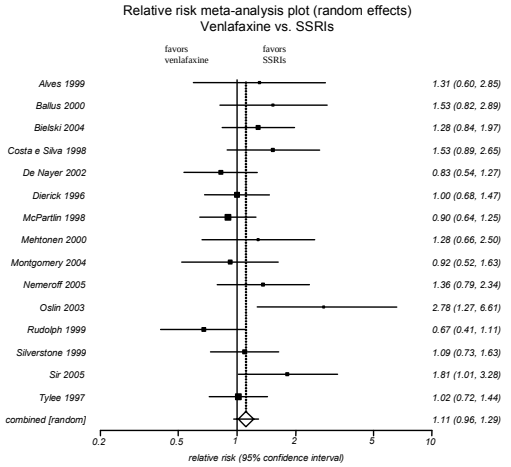


Figure H-6. Venlafaxine vs. SSRIs



Relative Risk of Discontinuation because of Adverse Events

Figure H-7: Bupropion vs. SSRIs: Adverse Events

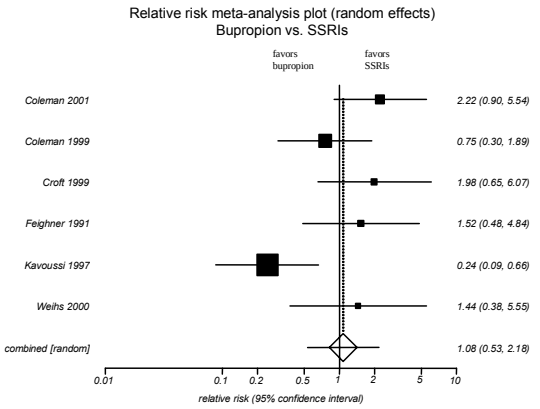


Figure H-8: Duloxetine vs. SSRIs: Adverse Events Only

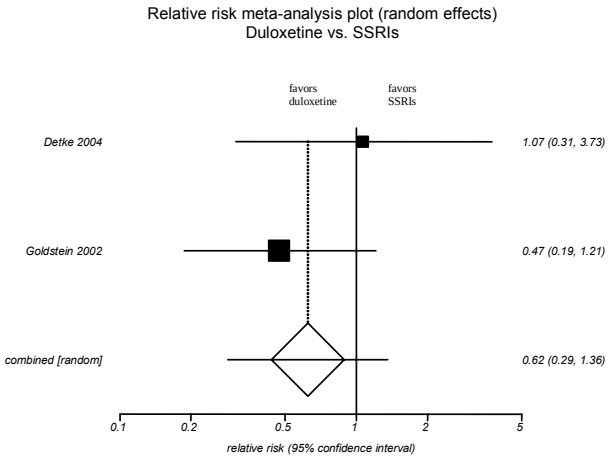


Figure H-9: Mirtzapine vs SSRIs: Adverse Events Only

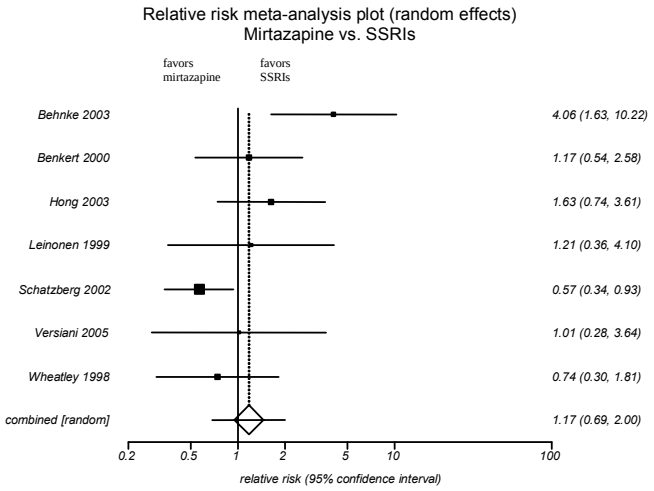


Figure H-10: Nefazodone vs SSRIs: Adverse Events Only

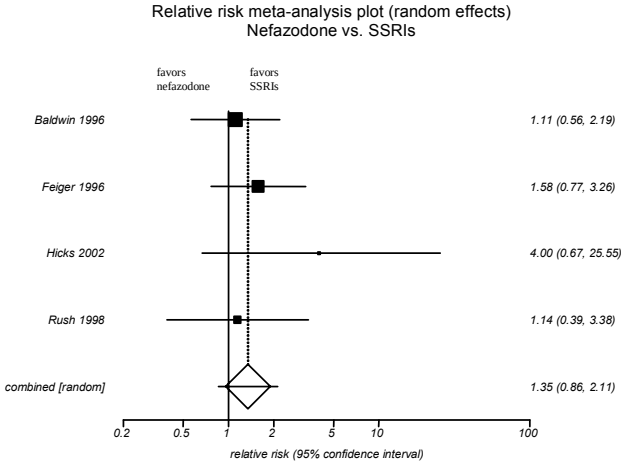


Figure H-11: Trazodone vs SSRIs: Adverse Events Only

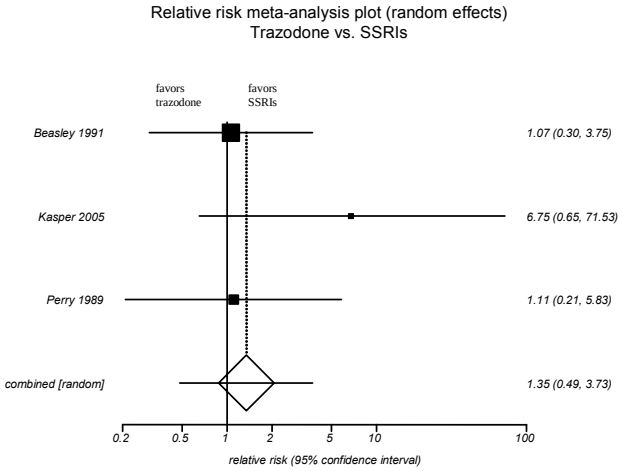
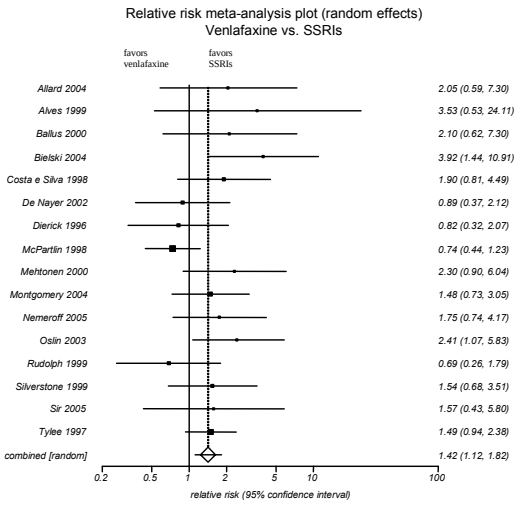


Figure H-12: Venlafaxine vs SSRIs: Adverse Events Only



Relative Risk of Discontinuation because of Lack of Efficacy

Figure H-13. Bupropion vs. SSRIs: Lack of Efficacy

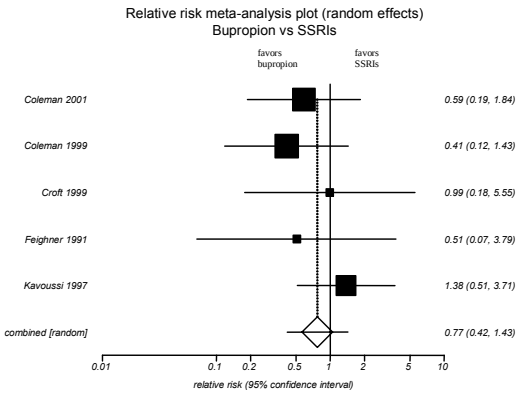


Figure H-14: Mirtzazpine vs. SSRIs: Lack of Efficacy

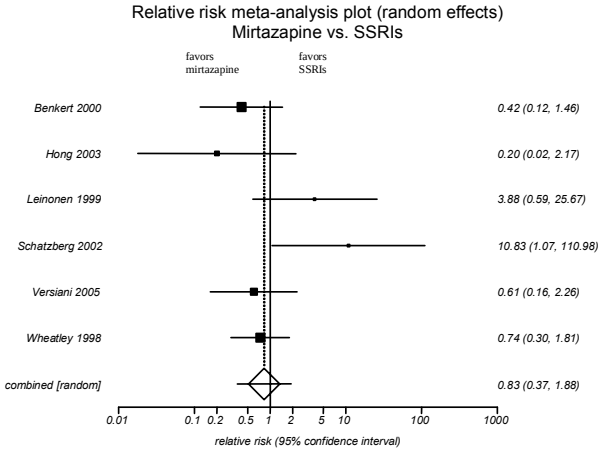


Figure H-15: Nefazodone vs SSRIs: Lack of Efficacy

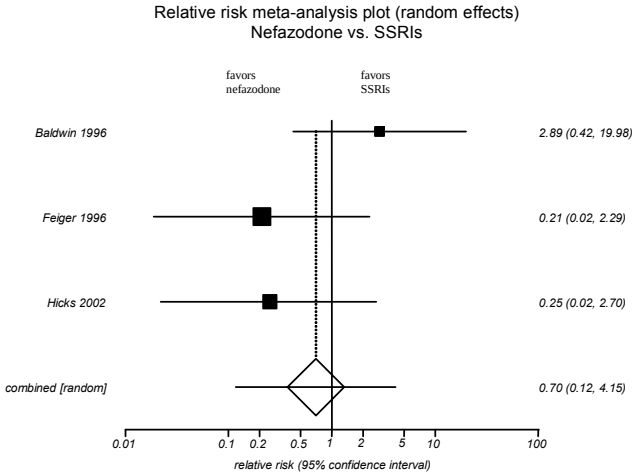
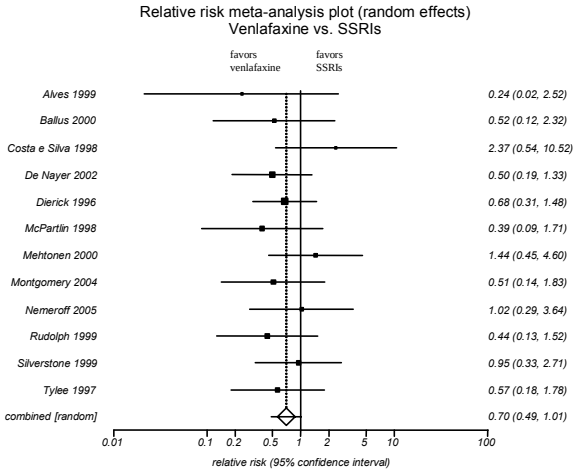


Figure H-16: Venlaxafine vs SSRIs: Lack of Efficacy



Appendix I. Publications Appearing Only as Abstracts

1. Ansseau M, Gabriels A, Loyens J, Bartholome F, Evrard J, Linhart R, et al. A double-blind comparison of paroxetine and fluvoxamine in major depression. Eur Neuropsychopharmacol 1993;3(3):323-324.

2. Montgomery SA. Comparative efficacy and tolerability of escitalopram oxalate versus venlafaxine XR. Data on file at Forest Laboratories. 2004.

3. Skinner EP, Cantrell R, Chaffin J, et al. Adherence with once-daily bupropion XL versus twice-daily bupropoion SR. J Am Pharm Assoc 2005;45:265.

ACKNOWLEDGMENTS

This study was supported by Contract 290-02-0016 from the Agency for Healthcare Research and Quality (AHRQ), Task No. 7. We acknowledge the continuing support of Beth Collins Sharp, PhD, RN, Acting Director of the AHRQ Evidence-Based Practice Center (EPC) Program, and Lia Snyder, MPH, the AHRQ Task Order Officer for this project.

We extend our appreciation to our Technical Expert Panel (TEP): Susan G. Kornstein, MD., Professor of Psychiatry and Obstetrics and Gynecology, Virginia Commonwealth University, Richmond; Anand Kumar, MD, Professor of Psychiatry and Director of Geriatric Ambulatory Care Programs, University of California at Los Angeles; and John Williams, MD, Professor of Medicine and Psychiatry, Duke University, Durham, North Carolina. 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 (UNC). We would particularly acknowledge Timothy Carey, MD, MPH, for insightful comments on the first draft and helpful suggestions throughout the project; Lynn Whitener, DrPH, MSLS, our EPC Librarian; and UNC supporting staff Stacey Williams and Jonathan Ward. We also express our gratitude to RTI staff Tammeka Swinson, Research Analyst, and both Jennifer Drolet, MA and Melissa Fisch, BA, editors.