Comparative Benefits and Harms of Second-Generation Antidepressants: Background Paper for the American College of Physicians

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Background: Second-generation antidepressants dominate the management of major depressive disorder, dysthymia, and subsyndromal depression. Evidence on the comparative benefits and harms is still accruing.

Purpose: To compare the benefits and harms of second-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine) for the treatment of depressive disorders in adults.

Data Sources: MEDLINE, EMBASE, PsychLit, Cochrane Central Register of Controlled Trials, and International Pharmaceutical Abstracts from 1980 to April 2007, limited to English-language articles. Reference lists of pertinent review articles were manually searched and the Center for Drug Evaluation and Research database was explored to identify unpublished research.

Study Selection: Abstracts and full-text articles were independently reviewed by 2 persons. Six previous good- or fair-quality systematic reviews or meta-analyses were included, as were 155 good- or fair-quality double-blind, placebo-controlled, or head-to-head randomized, controlled trials of at least 6 weeks' duration. For harms, 35 observational studies with at least 100 participants and follow-up of at least 12 weeks were also included.

Data Extraction: Using a standard protocol, investigators abstracted data on study design and quality-related details, funding, settings, patients, and outcomes.

Data Synthesis: If data were sufficient, meta-analyses of head-to-head trials were conducted to determine the relative benefit of response to treatment and the weighted mean differences on specific depression rating scales. If sufficient evidence was not available, adjusted indirect comparisons were conducted by using meta-regressions and network meta-analyses. Second-generation antidepressants did not substantially differ in efficacy or effectiveness for the treatment of major depressive disorder on the basis of 203 studies; however, the incidence of specific adverse events and the onset of action differed. The evidence is insufficient to draw conclusions about the comparative efficacy, effectiveness, or harms of these agents for the treatment of dysthymia and subsyndromal depression.

Limitation: Adjusted indirect comparisons have methodological limitations and cannot conclusively rule out differences in efficacy.

Conclusion: Current evidence does not warrant the choice of one second-generation antidepressant over another on the basis of differences in efficacy and effectiveness. Other differences with respect to onset of action and adverse events may be relevant for the choice of a medication.

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Major depressive disorder (MDD) is the most prevalent axis I disorder, affecting more than 16% of U.S. adults during their lifetime (1). In 2000, the economic burden of depressive disorders was an estimated $83.1 billion (2), more than 30% of which was attributable to direct medical expenses.

Pharmacotherapy dominates the medical management of MDD. Since the mid-1980s, second-generation antidepressants have gradually replaced tricyclic antidepressants and monoamine oxidase inhibitors as first-line medications, primarily because of their lower toxicity in overdose and similar general efficacy (3). These newer treatments include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, and other second-generation drugs (**Table 1**).

To date, only 2 systematic reviews have assessed the comparative efficacy and harms of second-generation antidepressants (3, 4). These studies reported no substantial differences in efficacy or harms among agents. However, because of a lack of direct head-to-head comparisons, assessments in both studies were primarily qualitative. Consequently, uncertainties persist about the differences among the drugs for which sufficient head-to-head evidence is lacking.

We systematically assessed evidence on the comparative benefits and harms of second-generation antidepressants for the acute, continuation, and maintenance phases of treatment of MDD; subsyndromal depression; and dysthymia and the comparative efficacy and effectiveness for such accompanying symptoms as anxiety, insomnia, or

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Table 1. **Second-Generation Antidepressants Approved for Use in the United States**

Generic Name	U.S. Trade Name; Manufacturer	Dosage Forms*	Therapeutic Classification	Labeled Uses	Generic Available?*
Bupropion	Bupropion SR, Bupropion XL, Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban; GlaxoSmithKline, Research Triangle Park, NC	75, 100 mg tablets; 50, 100, 150, 200 mg SR tablets; 150, 300 mg XL tablets	Other second-generation antidepressant	MDD, seasonal affective disorder	Yes (immediate-release formulation only)
Citalopram	Celexa; Forest Laboratories, New York, NY	10, 20, 40 mg tablets; 1, 2 mg/mL solution	SSRI	MDD	Yes
Duloxetine	Cymbalta; Eli Lilly and Company, Indianapolis, IN	20, 30, 60 mg capsules	SSNRI	MDD, DPNP	No
Escitalopram	Lexapro; Forest Laboratories, New York, NY	10, 20 mg tablets; 1 mg/mL solution	SSRI	MDD, GAD	No
Fluoxetine	Prozac, Prozac Weekly, Sarafem; GlaxoSmithKline, Research Triangle Park, NC	10, 20, 40 mg capsules; 10 mg tablets; 4 mg/mL solution; 90 mg pellets (weekly)	SSRI	MDD (adults or children), OCD, PMDD, panic disorder	Yes (immediate-release formulation only)
Fluvoxamine	Luvox; Solvay Pharmaceuticals and the Upjohn Company, Marietta, GA	25, 50, 100 mg tablets	SSRI	OCD (children age ≥8 y or adults)	Yes
Mirtazapine	Remeron; Organon USA, West Orange, NJ	15, 30, 45 mg tablets; 15, 30, 45 mg orally disintegrating tablets	SNRI	MDD	Yes
Nefazodone	Serzone†; Bristol-Myers Squibb, New York, NY	50, 100, 150, 200, 250 mg tablets	Other second-generation antidepressant	MDD	Yes
Paroxetine	Paxil, Paxil CR; GlaxoSmithKline, Research Triangle Park, NC	10, 20, 30, 40 mg tablets; 2 mg/mL solution; 12.5, 25, 37.5 mg CR tablets	SSRI	MDD (adult), OCD, panic disorder, social anxiety disorder, GAD, PTSD, PMDD‡	Yes
Sertraline	Zoloft; Pfizer, New York, NY	25, 50, 100 mg tablets; 20 mg/mL solution	SSRI	MDD (adult), OCD, panic disorder, PTSD, PMDD, social anxiety disorder	Yes
Trazodone	Desyrel; Bristol-Myers Squibb, New York, NY	50, 100, 150, 300 mg tablets	Other second-generation antidepressant	MDD	Yes
Venlafaxine	Effexor, Effexor XR; Wyeth Pharmaceuticals, Madison, NJ	25, 37.5, 50, 75, 100 mg tablets; 37.5, 75, 150 mg XR capsules	SNRI	MDD, GAD§, social anxiety disorder§	No

CR = controlled release; DPNP = diabetic peripheral neuropathic pain; GAD = generalized anxiety disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = posttraumatic stress disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SR = sustained release; SSNRI = selective serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; XL = extended length; XR = extended release.
* Generic available for some dosage forms.
† Brand-name product no longer available.
‡ Only Paxil CR (not Paxil) is approved for the treatment of PMDD.
§ Only Effexor XR is approved for the treatment of GAD and social anxiety disorder.

neurovegetative symptoms. We also sought to determine whether efficacy, effectiveness, and harms differed among subgroups of patients on the basis of age, sex, race or ethnicity, or comorbid conditions.

To our knowledge, this is the first meta-analysis of second-generation antidepressants to assess quantitatively all possible comparisons among drugs in this class. We update findings of an earlier report on these pharmaceuticals (5) for the Agency for Healthcare Research and Quality.

METHODS

An open process (described at www.effectivehealthcare.ahrq.gov) involving the public, the Agency for Healthcare Research and Quality's Scientific Resource Center for Effective Health Care program, and various stakeholder groups produced key questions. We followed a standardized protocol for all review steps (5).

Data Sources

We searched MEDLINE, EMBASE, PsychLit, Cochrane Central Register of Controlled Trials, and International Pharmaceutical Abstracts from 1980 to April 2007. We used Medical Subject Heading terms when available and keywords when appropriate. We combined terms for depressive disorders with a list of 12 specific second-generation antidepressants—bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine—and their specific trade names. We limited electronic searches to "adult 19 + years," "human," and "English language."

We manually searched reference lists of pertinent review articles and letters to the editor and used the Center for Drug Evaluation and Research database (up to April 2007) to identify unpublished research submitted to the U.S. Food and Drug Administration. The Scientific Resource Center invited pharmaceutical manufacturers to submit dossiers on completed research for each drug. We received dossiers from 3 pharmaceutical companies (Eli Lilly and Company, Indianapolis, Indiana; GlaxoSmithKline, Philadelphia, Pennsylvania; and Wyeth, Madison, New Jersey).

Study Selection

Two persons independently reviewed abstracts and relevant full-text articles. To assess efficacy or effectiveness regarding response, speed of onset, remission, maintenance of remission, and quality of life, we included head-to-head controlled trials of at least 6 weeks' duration that compared 1 drug with another. Because head-to-head evidence was lacking for many comparisons, we included placebo-controlled trials for indirect comparison models. To assess harms (specific adverse events, rates of adverse events, and discontinuations attributable to adverse events), we also examined data from observational studies with at least 100 participants and follow-up of at least 12 weeks. To assess differences of benefits and harms in subgroups and patients with accompanying symptoms, we reviewed both head-to-head and placebo-controlled trials. We included meta-analyses if we found them to be relevant for a key question and of good or fair methodological quality (6).

If both reviewers agreed that a study did not meet eligibility criteria, we excluded it. We also excluded studies that met eligibility criteria but were reported only as an abstract. Investigators resolved disagreements about inclusion or exclusion by consensus or by involving a third reviewer.

Data Extraction and Quality Assessment

We used a structured, Web-based data abstraction form (SRS 4.0, TrialStat, Ottawa, Ontario, Canada) onto which trained reviewers abstracted data from each study and assigned an initial quality rating. A senior reviewer read each abstracted article, evaluated completeness of data abstraction, and confirmed the quality rating. Investigators resolved disagreements by discussion and consensus or by consulting an independent party.

We assessed the internal validity (quality) of trials on the basis of predefined criteria and applied ratings of good, fair, or poor (5, 7, 8). Primary elements of quality assessment included randomization and allocation concealment, similarity of compared groups at baseline, blinding, use of intention-to-treat analysis, and overall and differential loss to follow-up. To assess observational studies, we used criteria involving selection of case patients or cohorts and control participants, adjustment for confounders, methods of outcomes assessment, length of follow-up, and statistical analysis (9). We rated studies with a fatal flaw in 1 or more categories as poor quality (**Appendix Table 1**, available at www.annals.org) and did not include them in our analyses for this review unless no other head-to-head evidence was available. To identify effectiveness studies, we used a tool that distinguishes efficacy trials from effectiveness studies on the basis of certain elements of study design (10). Such studies have greater generalizability of results than efficacy trials because they enroll less selected study populations, use treatment modalities that mimic clinical practice, and assess health outcomes along with adverse events.

Lacking clear definitions about the equivalence of dosages among second-generation antidepressants in the published literature, we developed a roster of low, medium, and high dosages for each drug based on the interquartile dosing range (5). We used this roster, which does not indicate dosing equivalence, to detect gross inequalities in dosing that could affect comparative efficacy and effectiveness.

Data Synthesis

If data were sufficient, we conducted meta-analyses of head-to-head comparisons. Efficacy outcomes included the relative benefit of achieving response (more than 50% improvement from baseline), which reflects the ratio of benefits in one treatment group to benefits in another, and the weighted mean difference of changes on the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression Rating Scale.

For each meta-analysis, we conducted a test of heterogeneity (I^2 index) and applied both random- and fixed-effects models. We report the random-effects results because the results from both models were very similar in all meta-analyses. We assessed publication bias by using funnel plots and the Begg adjusted rank correlation test (11) based on the Kendall τ coefficient.

Because no head-to-head evidence was available for the majority of drug comparisons, we conducted adjusted indirect comparisons (5). We employed meta-regressions of placebo-controlled trials by using individual drugs as covariates. When the number of trials was insufficient for meta-regressions, we used modified network meta-analysis (12). 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 included in different trials (13), although these assumptions are usually not verifiable.

All statistical analyses used StatsDirect Statistical Software program, version 2.3.8 (StatsDirect, Sale, United Kingdom); Stata, version 9.1 (StataCorp, College Station, Texas); and SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Rating the Strength of Evidence

We rated the strength of the available evidence for specific key questions and outcomes in a 3-part hierarchy (high, moderate, and low) (5) by using a modified GRADE (Grading of Recommendations, Assessment, De-

velopment, and Evaluation) approach (14, 15) that incorporates 4 key elements: study design, study quality, consistency of results, and directness (availability of data on outcomes or populations of interest).

Role of Funding Source

The Agency for Healthcare Research and Quality participated in formulating the key questions and reviewed and commented on planned methods and data analysis. The Agency had no role in study selection, quality ratings, or interpretation and synthesis of the evidence, although staff reviewed interim and final evidence reports and distributed them for external peer review by outside experts.

RESULTS

We identified 2318 citations from searches and reviews of reference lists (**Figure 1**). Of the 203 included studies (**Appendix Tables 2** to **11**, available at www.annals.org), 140 (69.0%) were financially supported by pharmaceutical companies and 19 (9.3%) by governmental agencies or independent funds. For 44 (21.7%) studies, we could not determine the funding source.

Major Depressive Disorder

Overall, we found no substantial differences in comparative efficacy and effectiveness of second-generation antidepressants for treatment of MDD (**Tables 2** to **4** and **Figures 2** to **4**). This finding pertains to the acute, continuation, and maintenance phases of treatment; to patients with accompanying symptom clusters; and to subgroups defined by age, race or ethnicity, sex, or comorbid conditions (we found only sparse evidence for subgroups). Nevertheless, second-generation antidepressants are not identical drugs. They differ somewhat with respect to onset of action and frequency of some adverse events. Generally, effectiveness studies with less stringent eligibility criteria provided results similar to those of efficacy trials, indicating good generalizability of our findings to primary care populations.

Comparative Efficacy for Acute-Phase Treatment of MDD

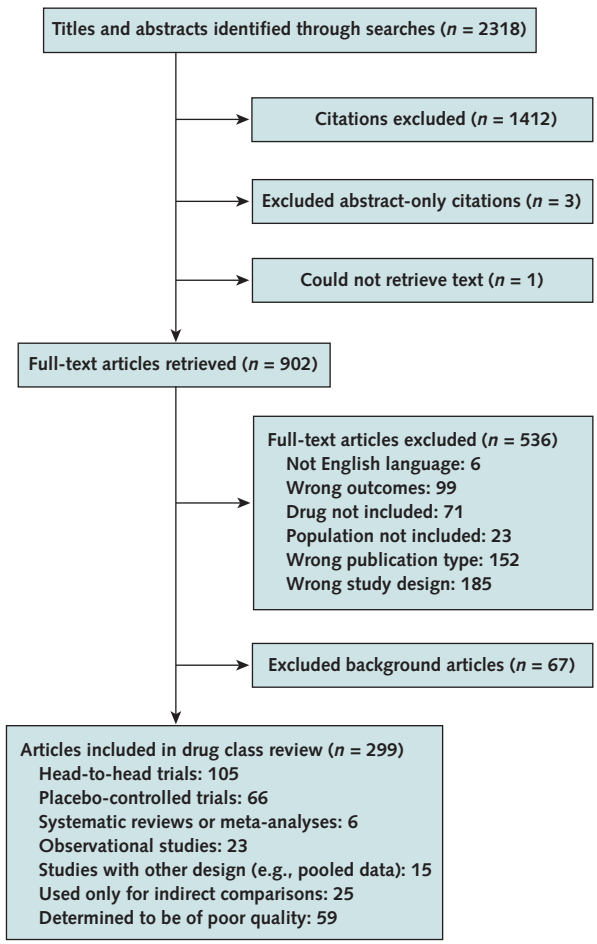
Eighty good- or fair-quality head-to-head, randomized, controlled trials (RCTs), comprising more than 17 000 patients, compared efficacy or effectiveness for acute-phase MDD treatment. These studies provided direct evidence for 36 of 66 possible comparisons among these drugs. Only 5 trials directly compared any second-generation nonselective serotonin reuptake inhibitor with another; of these, only 1 comparison was evaluated in more than 1 trial.

For the 62 comparisons of 1 drug with another for which data were available, we conducted indirect evaluations of response rates, incorporating an additional 34 placebo-controlled trials of good or fair quality comprising 26 349 patients (**Appendix Table 11**, available at www.annals.org).

For almost all comparisons, no statistically significant differences in response rates were apparent (**Figures 2** to **4**). For some indirect comparisons, however, the precision of estimates was low and confidence intervals encompassed differences that would be clinically significant.

Findings from some meta-analyses yielded statistically significant differences among treatments, but the modest effect sizes of the differences are probably not clinically significant (5). For example, the meta-analytic comparison of response rates to citalopram versus escitalopram (16–20) yielded a statistically significant additional treatment effect for escitalopram (relative benefit favoring escitalopram, 1.14 [95% CI, 1.04 to 1.26]) (5). Pooled differences of points on the Montgomery-Asberg Depression Rating Scale presented a mean additional treatment effect (weighted mean difference) of a 1.13-point reduction (CI, 0.18 to 2.09) for escitalopram (5). A 1.13-point change on the Montgomery-Asberg Depression Rating Scale represents about one fifth to one quarter of a standard deviation, so the clinical significance of this finding may be questionable. Methods research suggests that half a standard devia-

Figure 1. **Study flow diagram.**



The number of included articles differs from the number of included studies because some studies have multiple publications.

Table 2. **Summary of Findings on General Effectiveness**

Key Question, Disorder, and Outcome of Interest	Strength of Evidence*	Findings
Acute-phase treatment of MDD		
Major depressive disorders		
Comparative efficacy	Moderate	Results from direct and indirect comparisons indicate that clinical response and remission rates are similar among second-generation antidepressants.
Comparative effectiveness	Moderate	One good-quality and 2 fair-quality effectiveness studies indicate that second-generation antidepressants do not differ in effectiveness.
Quality of life	Moderate	Consistent results from 18 studies, mostly of fair quality, indicate that the efficacy of second-generation antidepressants does not differ.
Onset of action	Moderate	Consistent results from 7 fair-quality trials suggest that mirtazapine has a significantly faster onset of action than citalopram, fluoxetine, paroxetine, or 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.
Maintaining response or remission (i.e., preventing relapse or recurrence)		
Comparative efficacy	Moderate	On the basis of findings from 3 efficacy trials, fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine do not significantly differ for preventing relapse or recurrence. Whether this finding can be extrapolated to other second-generation antidepressants is unclear.
Managing treatment-resistant depression		
Comparative efficacy	Low	Results from 1 fair-quality trial support modestly better efficacy for venlafaxine compared with paroxetine.
Comparative effectiveness	Moderate	Results from 2 effectiveness studies are conflicting. On the basis of 1 good trial, bupropion SR, sertraline, and venlafaxine XR do not significantly differ in effectiveness. One fair-quality effectiveness trial found venlafaxine to be modestly superior to citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline.
Treatment of recurrent depression	No evidence	–
Treatment of depression in patients with accompanying symptom clusters		
Anxiety		
Comparative efficacy	Moderate	Results from 6 fair-quality head-to-head trials and 1 fair-quality placebo-controlled trial suggest that clinical response is similar in patients with accompanying anxiety.
Insomnia		
Comparative efficacy	Low	Evidence from 3 fair-quality head-to-head studies is insufficient to draw conclusions about treating depression in patients with coexisting insomnia. Results are limited by study design.
Melancholia		
Comparative efficacy	Low	Evidence from 2 fair-quality head-to-head studies, 1 poor-quality head-to-head study, and 1 fair-quality placebo-controlled trial is insufficient to draw conclusions about treating depression in patients with coexisting melancholia. Results are inconsistent across studies.
Pain		
Comparative efficacy	Low	Evidence from 2 fair placebo-controlled studies is insufficient to draw conclusions about treating depression in patients with coexisting pain. Results from head-to-head trials are not available.
Psychomotor change		
Comparative efficacy	Low	Evidence from 1 fair-quality 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.
Somatization	No evidence	–
Treatment of symptom clusters in patients with depression		
Anxiety		
Comparative efficacy	Moderate	Results from 10 fair-quality head-to-head trials and 2 fair-quality placebo-controlled trials suggest that second-generation antidepressants do not substantially differ for treatment of accompanying anxiety symptoms.
Insomnia		
Comparative efficacy	Low	Evidence from 6 fair-quality head-to-head trials is insufficient to draw conclusions about treating insomnia in depressed patients. Results are limited by study design, and differences in outcomes are of unknown clinical significance.
Melancholia	No evidence	–
Pain		
Comparative efficacy	Low	Evidence from 4 head-to-head trials (3 fair-quality, 1 poor-quality) and 4 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.

Table 2—**Continued**

Key Question, Disorder, and Outcome of Interest	Strength of Evidence*	Findings
Psychomotor change	No evidence	–
Somatization		
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.

MDD = major depressive disorder; SR = sustained-release; XR = extended-release.
* Based on a modified approach of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) working group (14). 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.

tion constitutes a minimally important difference for health-related quality-of-life outcomes (21).

Meta-analyses yielded significantly lower response rates for fluoxetine than for sertraline (22–25) or venlafaxine (26–33). The small effect sizes of the differences are probably not clinically relevant.

Eighteen trials (18, 23, 33–48), mostly of fair quality, included health-related quality of life or functional capacity as secondary outcome measures. We found no differences among second-generation antidepressants for these outcomes.

Comparative Effectiveness for Acute-Phase Treatment of MDD

Three studies (23, 49, 50) can be considered effectiveness rather than efficacy trials. Their findings were consistent with those of the efficacy trials. Two fair-quality effec-

Table 3. **Summary of Findings on Adverse Events: Comparative Risk for Harms**

Outcome of Interest and Disorder	Strength of Evidence*	Findings
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-quality studies indicates that venlafaxine has a higher rate of nausea and vomiting than selective serotonin reuptake inhibitors as a class (33% vs. 22%).
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, or venlafaxine (11% vs. 8%).
Weight change	Moderate	Seven fair-quality trials indicate that mirtazapine leads to higher weight gain than citalopram, fluoxetine, paroxetine, or sertraline (0.8 to 3.0 kg after 6 to 8 weeks).
Somnolence	Moderate	Six fair-quality studies provide evidence that trazodone has a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine (42% vs. 25%).
Discontinuation syndrome	Moderate	A good-quality systematic review provides evidence that paroxetine and venlafaxine have the highest rates of the discontinuation syndrome; fluoxetine has the lowest (data not reported).
Discontinuation rates	High	Meta-analyses of efficacy trials indicate that mean overall discontinuation rates are similar (23%). Venlafaxine has a higher rate of discontinuations from adverse events and a lower rate of discontinuations from lack of efficacy than selective serotonin reuptake inhibitors as a class.
Severe adverse events		
Sexual dysfunction	Moderate	Evidence from 5 fair-quality trials provide evidence that bupropion causes significantly less sexual dysfunction than fluoxetine, paroxetine, or sertraline. Among selective serotonin reuptake inhibitors, paroxetine has the highest rates of sexual dysfunction. Overall, more than 50% report sexual dysfunction.
Suicidality	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for suicidality.
Seizures	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for seizures. Weak evidence indicates that bupropion may increase risk for seizures.
Cardiovascular events	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for cardiovascular adverse events. Weak evidence indicates that venlafaxine might increase risk for cardiovascular adverse events.
Hyponatremia	Low	Evidence is insufficient to draw conclusions about the comparative risk for hyponatremia.
Hepatotoxicity	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for hepatotoxicity. Weak evidence indicates that nefazodone might increase risk for hepatotoxicity.
Serotonin syndrome	Low	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for the serotonin syndrome. Observational studies indicate no differences in risk among second-generation antidepressants.

* Based on a modified approach of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) working group (14). 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.

Table 4. **Summary of Findings on Effectiveness in Subgroups**

Selected Population and Outcome of Interest	Strength of Evidence*	Findings
Age		
Comparative efficacy	Moderate	Results from many different types of studies indicate that second-generation antidepressants do not substantially differ in efficacy among elderly or very elderly persons.
Comparative effectiveness	Moderate	On the basis of findings from 1 fair-quality head-to-head effectiveness trial, effectiveness of second-generation antidepressants in elderly persons is similar to that with other age groups. A second trial in patients with dysthymia or minor depression provides mixed evidence.
Comparative harms	Low	Results from 2 fair-quality studies indicate that adverse events may differ among second-generation antidepressants in elderly or very elderly persons.
Sex		
Comparative efficacy	Low	Results from 1 fair-quality pooled analysis of randomized, controlled trials indicate that efficacy among second-generation antidepressants may not differ substantially between men and women.
Comparative harms	Low	One fair-quality head-to-head trial suggests that harms (e.g., headache, nausea) may differ between men and women treated with venlafaxine vs. placebo and venlafaxine vs. selective serotonin reuptake inhibitors or placebo. Observational evidence (1 fair study) suggests that some sexual side effects may differ between men and women.
Race or ethnicity		
Comparative efficacy	Low	Results from 1 poor-quality randomized, controlled trial indicate that efficacy does not differ substantially among second-generation antidepressants in different racial subgroups.
Comorbid conditions		
Comparative efficacy	Low	One poor-quality head-to head trial included patients with depression and HIV/AIDS; this study indicated that efficacy does not differ substantially among second-generation antidepressants.

* Based on a modified approach of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) working group (14). 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.

tiveness trials indicated that improvement of health-related quality of life (work, social and physical functioning, concentration and memory, and sexual functioning) was similar for fluoxetine, paroxetine, and sertraline (23, 50).

Speed of Response

Seven fair-quality studies (39, 40, 45, 51–55) reported that mirtazapine had a significantly faster onset of action than citalopram, fluoxetine, paroxetine, or sertraline after 1 or 2 weeks of treatment. All studies were supported by the manufacturer of mirtazapine. After 4 weeks of treatment, most response rates were similar. The extent to which the faster onset of mirtazapine can be extrapolated to other second-generation antidepressants is unclear. Mirtazapine and venlafaxine did not differ in speed of action (42).

Response to a Second Agent after Initial Treatment Failure

Overall, 38% of patients did not achieve a treatment response during 6 to 12 weeks of treatment with second-generation antidepressants; 54% did not achieve remission. The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial (56) provides the best evidence for assessing alternative medications among those for whom initial therapy failed. About 1 in 4 of the 727 people who participated in the switch of medications became symptom-free; this did not differ significantly among those who received sustained-release bupropion, sertraline, or extended-release venlafaxine. One open-label study (57) and a smaller efficacy study (58) reported significantly greater response rates for venlafaxine than for other second-generation drugs. Given the STAR*D findings, the clinical significance of this difference is questionable.

Maintaining Response or Remission after Treatment Success

Findings from 4 fair-quality head-to-head RCTs assessing relapse or recurrence prevention (59–63) were similar for the comparisons of fluoxetine and sertraline, fluvoxamine and sertraline, duloxetine and paroxetine, and trazodone and venlafaxine. In 1 trial (59), among 105 patients who demonstrated a response at 8 weeks, 5 (10%) of 49 sertraline-treated patients and 7 (13%) of 56 of fluoxetine-treated patients had relapse over 24 weeks of continuation-phase treatment.

Efficacy or Effectiveness for Depression or Accompanying Symptoms

Clinicians may use symptom clusters that accompany depression (such as anxiety or insomnia) to guide antidepressant selection. This might improve outcomes for the depressive episode, the symptom cluster, or both. We reviewed available evidence for clinically relevant symptom clusters to address each possibility.

Treatment of Depression in Patients with Accompanying Symptom Clusters

Anxiety

Six fair-quality head-to-head trials (31, 35, 64–68) suggest that antidepressants have similar antidepressive ef-

ficacy for patients with MDD and anxiety symptoms. These studies compared either fluoxetine or paroxetine with sertraline (259 patients with accompanying anxiety) (64, 65); sertraline with bupropion (972 patients; number with anxiety not provided) (66–68); and sertraline with venlafaxine (20 patients with anxiety) (35). One fair-quality, 12-week trial (31) of 146 patients reported significantly greater response (75.0% vs. 49.3%) and remission rates (59.4% vs. 40.3%) with venlafaxine than with fluoxetine.

Insomnia

Two fair-quality head-to-head trials (441 patients with insomnia) (24, 69) provide limited evidence for similar efficacy of fluoxetine, nefazodone, paroxetine, or sertraline for treating depression in patients with accompanying insomnia. A pooled analysis of 3 RCTs (447 patients) (70) reported that the reduction on the Montgomery-Asberg Depression Rating Scale total score was significantly greater for patients receiving escitalopram than for those receiving citalopram (16.5 vs. 14.0); however, the clinical significance of this difference remains uncertain.

Melancholia

Two fair-quality head-to-head trials (286 patients) (28, 65) and 1 poor-quality head-to-head trial (68 patients) (71) assessed the effects of medications for treating depression in patients with melancholia. Although 2 studies reported greater response rates for sertraline than for fluoxetine (59% vs. 44%) (65) and for venlafaxine than for fluoxetine (70% vs. 50%) (71), the small sample sizes (87 and 68 patients) and high attrition rate (71) limit confidence in these findings.

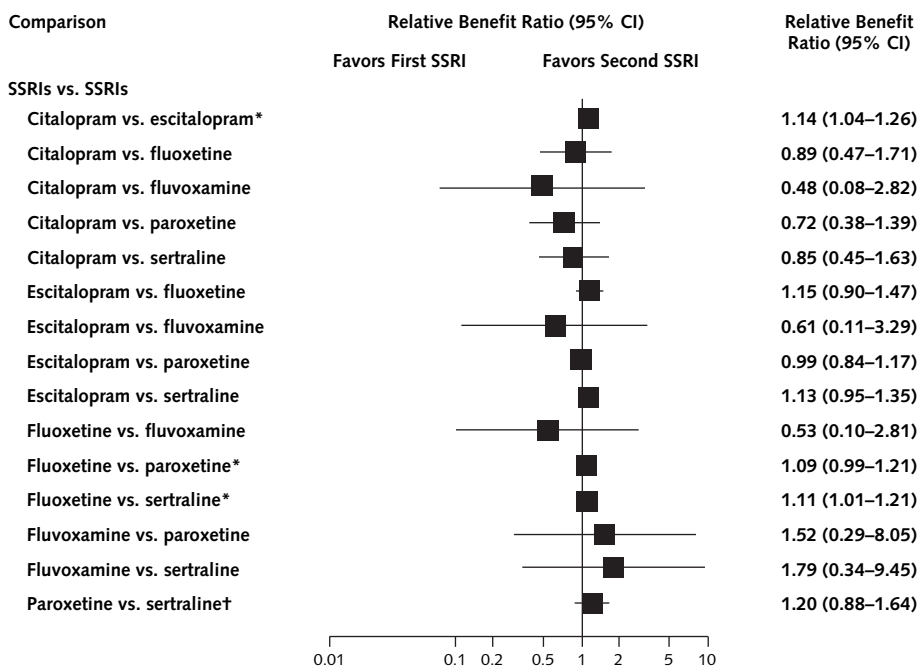
Pain

We found no head-to-head evidence. Two placebo-controlled trials reported similar response rates for patients with MDD and pain who received duloxetine (72) or paroxetine (73) compared with those who received placebo.

Psychomotor Changes

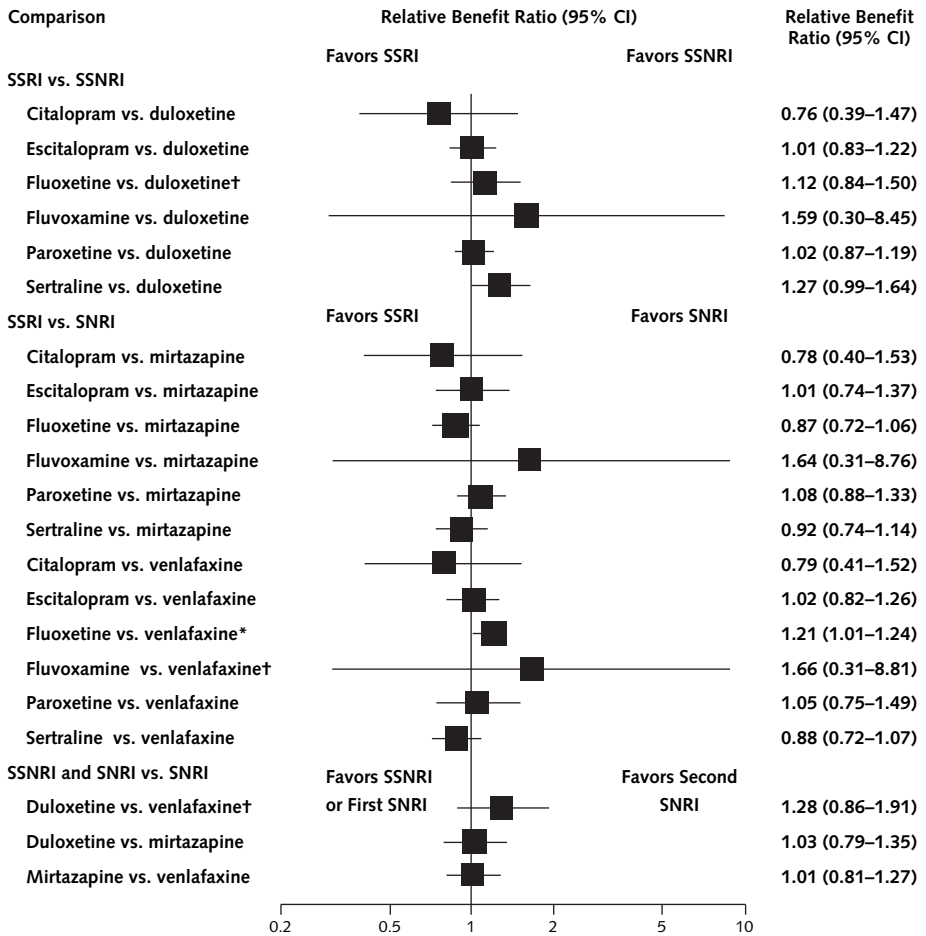
The evidence is limited to subgroup analyses from 1 fair-quality head-to-head trial (65). Fluoxetine and sertraline had similar antidepressive efficacy among 47 patients with psychomotor retardation, but sertraline had higher efficacy among 78 patients with psychomotor agitation (65). Results should be interpreted cautiously because small sample sizes and multiple testing can lead to erroneous results in such subgroup analyses.

Figure 2. **Relative benefit of response comparing selective serotonin reuptake inhibitors (*SSRIs*) with other SSRIs.**



All estimates are based on network meta-analyses except for those marked with an asterisk or a dagger.
* Based on meta-analysis of head-to-head trials.
† Based on indirect comparisons with meta-regression.

Figure 3. **Relative benefit of response comparing selective serotonin reuptake inhibitors (*SSRIs*) with selective serotonin and norepinephrine reuptake inhibitors (*SSNRIs*) and SSRIs with serotonin and norepinephrine reuptake inhibitors (SNRIs).**



All estimates are based on network meta-analyses except for those marked with an asterisk or a dagger.
* Based on meta-analysis of head-to-head trials.
† Based on indirect comparisons with meta-regression.

Treatment of Symptom Clusters in Patients with Accompanying Depression

Anxiety

Ten fair-quality head-to-head trials (31, 35, 40, 64, 66, 68, 74–77) provide evidence that antidepressant medications do not differ substantially in efficacy for treatment of anxiety associated with MDD. Improvement of anxiety did not differ substantially among fluoxetine, paroxetine, and sertraline (549 patients) (64, 75–77); sertraline and bupropion (243 patients) (66, 68); sertraline and venlafaxine (120 patients) (35); citalopram and mirtazapine (270 patients) (40); or paroxetine and nefazodone (206 patients) (74). One trial (146 patients) (31) reported significantly greater reductions in Covi Anxiety Scale scores of patients receiving venlafaxine than those receiving fluoxetine (5.7 vs. 3.9). The clinical significance of this difference remains uncertain.

Insomnia

Five fair-quality head-to-head trials (24, 37, 45, 62, 69) and a pooled analysis of 3 RCTs (70) involving 1540 patients provide limited evidence about the comparative effects of antidepressants on insomnia in patients with depression. Individual trials favored escitalopram over citalopram (70), nefazodone over fluoxetine (69), and trazodone over fluoxetine (37) and venlafaxine (62) in improving sleep scores. The comparisons were limited to single studies, and it is difficult to assess the clinical significance of these findings.

Pain

Three fair-quality head-to-head trials (63, 78, 79) and 1 poor-quality trial (80) compared duloxetine with paroxetine. These trials (1466 patients) found no substantial difference in pain relief between duloxetine and paroxetine.

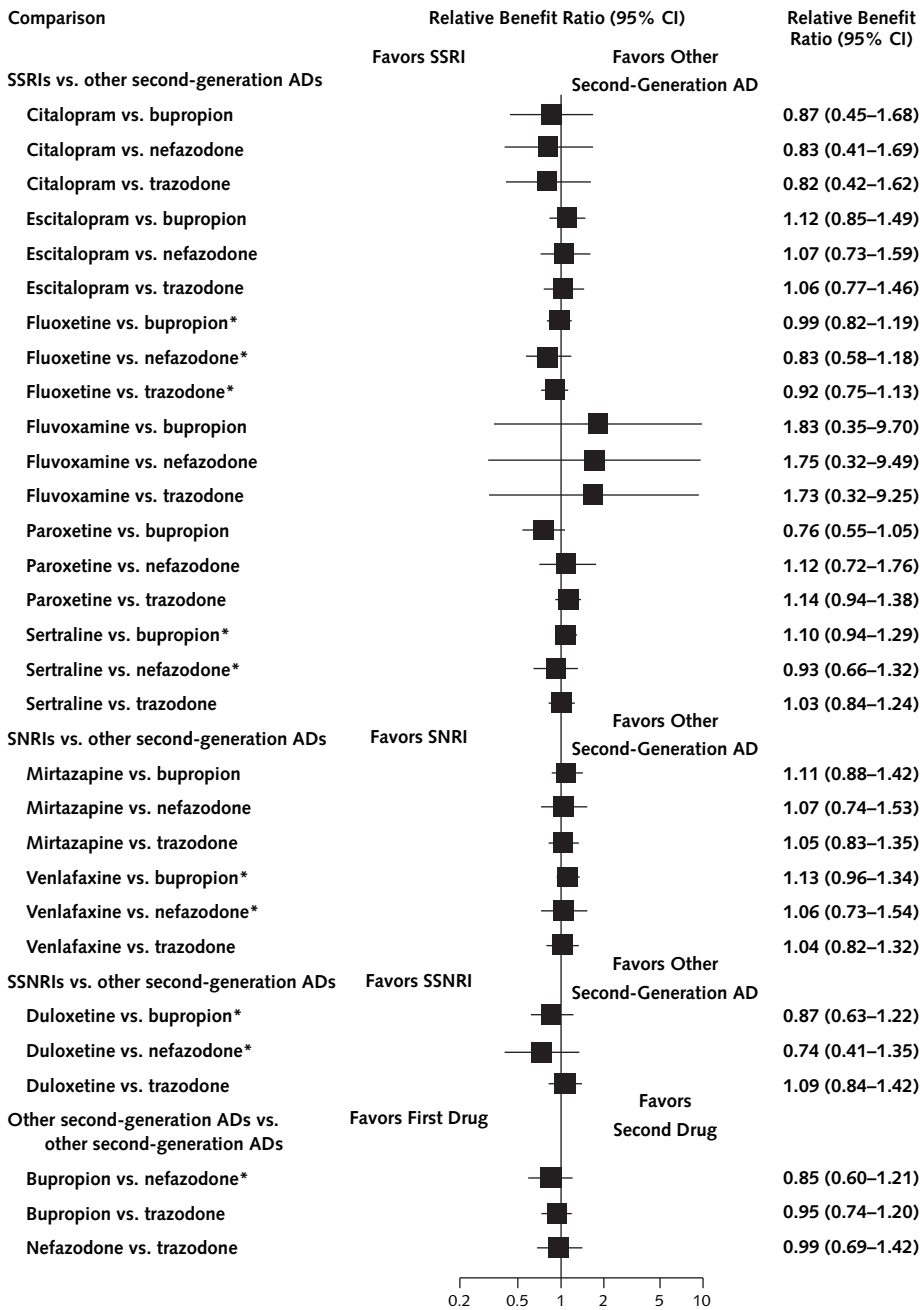
Somatization

A fair-quality, 9-month open-label effectiveness trial reported similar improvement of somatization among 573 patients receiving fluoxetine, paroxetine, or sertraline (50).

Risk for Harms

We analyzed adverse events data from 80 head-to-head efficacy studies and 42 additional studies of both experimental and observational designs. Methods of adverse events assess-

Figure 4. **Relative benefit of response comparing selective serotonin reuptake inhibitors (*SSRIs*), selective serotonin and norepinephrine reuptake inhibitors (*SSNRIs*), serotonin and norepinephrine reuptake inhibitors (*SNRIs*), and other second-generation antidepressants (*ADs*) with other second-generation ADs.**



All estimates are based on network meta-analyses except for those marked with an asterisk.
* Based on meta-analysis of head-to-head trials.

Table 5. **Main Differences in Specific Adverse Events**

Drug	Comparators	Differences in Adverse Events
Mirtazapine	Fluoxetine, paroxetine, trazodone, venlafaxine	Higher mean weight gain than with comparator drugs (0.8–3.0 kg after 6–8 wk)
Paroxetine	Fluoxetine, sertraline	Higher weight gains (data not reported) than with comparator drugs
Paroxetine	Fluoxetine, fluvoxamine, nefazodone, sertraline	Higher mean incidence of sexual dysfunction than with comparator drugs (21% [95% CI, 18%–25%] vs. 5% [CI, 0%–10%])
Sertraline	Bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine	Higher mean incidence of diarrhea than with comparator drugs (11% [CI, 8%–15%] vs. 8% [CI, 4%–13%])
Trazodone	Bupropion, fluoxetine, mirtazapine, paroxetine, venlafaxine	Higher mean incidence of somnolence than with comparator drugs (42% [CI, 19%–64%] vs. 25% [CI, 3%–46%])
Venlafaxine	SSRIs as a class	Higher mean incidence of nausea and vomiting than with SSRIs as a class (33% [CI, 25%–43%] vs. 22% [CI, 16%–24%])

SSRIs = selective serotonin reuptake inhibitors.

ment in efficacy trials differed greatly. Few studies used objective scales. Determining whether assessment methods were unbiased and adequate was often difficult.

Adverse Events Profiles

Constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence were commonly and consistently reported adverse events. On average, 61% of patients in efficacy trials experienced at least 1 adverse event. Nausea and vomiting were the most common reasons for discontinuation in efficacy studies.

Overall, second-generation antidepressants had similar adverse events profiles. **Table 5** summarizes some differences in the incidence of specific adverse events.

Sexual Dysfunction

A fair-quality prospective observational study (1022 patients) from Spain reported that 59% of patients treated with second-generation antidepressants experienced sexual dysfunction (81). On the basis of 5 RCTs (1489 patients), bupropion led to a significantly lower rate of sexual adverse events than fluoxetine and sertraline (82–86). Paroxetine frequently led to higher rates of sexual dysfunction than did fluoxetine, fluvoxamine, nefazodone, or sertraline (16% vs. 6%) (24, 76, 87, 88). Underreporting of absolute rates of sexual dysfunction is likely in these studies.

Suicidality

Eleven studies (89–99) assessed the risk for suicidality (suicidal thinking or behavior) in patients treated with second-generation antidepressants; comparative data are sparse. No particular drug has an excess risk compared with any other drug in this class (94, 98). These findings are based primarily on retrospective cohort studies (91, 93, 94, 98). Confounding by indication (patients at higher risk for suicide being prescribed certain medications rather than others) may have led to erroneous conclusions.

The United Kingdom's Committee on Safety of Medicines conducted the largest attempt to determine whether second-generation antidepressants increase the risk for suicidality in 2004 (89). A good meta-analysis of placebo-controlled trials of selective serotonin reuptake inhibitors, comprising more than 40 000 adults, yielded no evidence that these agents increase the risk for suicide (odds ratio, 0.85 [CI, 0.20 to 3.40]) but did reveal an increased risk for nonfatal suicide attempts (odds ratio, 1.57 [CI, 0.99 to 2.55]) (92).

Another good meta-analysis of published trial data (90), comprising more than 87 000 patients, reported a significantly higher risk for suicide attempts among patients receiving selective serotonin reuptake inhibitors than among those receiving placebo (odds ratio, 2.25 [CI, 1.14 to 4.55]). This study estimated the overall rate of suicide attempts as 3.9 (CI, 3.3 to 4.6) per 1000 patients treated with these drugs, with an incidence of 18.2 suicide attempts per 1000 patient-years.

Other Severe Adverse Events

Evidence on the comparative risk for rare but severe adverse events, such as seizures, cardiovascular events (events relating to systolic and diastolic blood pressure and pulse or heart rate), hyponatremia, hepatotoxicity, and the serotonin syndrome, is insufficient to draw firm conclusions. Clinicians should keep in mind the risk for such harms when treating patients with a second-generation antidepressant.

Treatment of MDD in Subgroups

No study directly compared efficacy, effectiveness, and harms of second-generation antidepressants between subgroups and the general population for treatment of depression syndromes. Numerous studies, however, conducted subgroup analyses or used subgroups as the study population.

Age

Multiple head-to-head trials (22, 44, 48, 50, 54, 100–107) and 2 fair-quality meta-analyses (108, 109) indicated that the efficacy of second-generation antidepressants does not differ in elderly patients (65 to 80 years of age) or very elderly patients (>80 years of age) compared with younger patients. These findings are consistent with placebo-controlled trials (110–116) conducted in elderly or very

elderly patients, which reported effect sizes similar to those from trials in younger patients.

Sex

Efficacy trials did not show differences between men and women (108, 109, 117). Observational evidence supports this conclusion (118).

Race or Ethnicity

One trial that evaluated efficacy differences in racial subgroups (119) did not show any differences, but this trial was rated poor quality because it lacked an intention-to-treat analysis.

Comorbid Conditions

No study directly compared efficacy, effectiveness, and harms of second-generation antidepressants between depressed patients with comorbid conditions and the general population.

One poor-quality head-to-head study did not detect differences in efficacy and tolerability among fluoxetine, paroxetine, or sertraline in depressed individuals with HIV or AIDS (120).

Seventeen placebo-controlled trials of varying quality (119, 121–136) and 1 fair-quality systematic review (137) evaluated second-generation antidepressants in patients with various comorbid conditions. Some studies suggested that these drugs may not be efficacious for depressed patients with such comorbid conditions as HIV or AIDS (119, 121, 122), alcohol abuse (123–125), Alzheimer disease (127), stroke (133, 134), or substance abuse (135, 136). Many of the studies were not powered to detect a meaningful difference between active treatment and placebo.

Dysthymia

Dysthymia is a chronic depressive disorder that is characterized by depressed mood for more days than not for at least 2 years (138). We found no head-to-head trial that studied patients with dysthymia. One good-quality trial (38) and 4 fair-quality placebo-controlled trials (36, 43, 139–142) provide mixed evidence on the general efficacy and effectiveness of fluoxetine, paroxetine, and sertraline for the treatment of dysthymia.

Subsyndromal Depression

Subsyndromal depression (also called *minor depression*) is a mood disturbance of at least 2 weeks' duration with fewer symptoms of depression than MDD (138). One nonrandomized, open-label trial (100) compared citalopram with sertraline but found no difference in efficacy. Findings from 2 placebo-controlled trials (141–143) were insufficient to draw any conclusions about comparative efficacy and effectiveness of second-generation antidepressants for the treatment of subsyndromal depression.

Discussion

In this systematic review of data from 203 studies, direct and indirect comparisons yielded no substantial differences in efficacy for the treatment of MDD. Statistically significant results were small and are unlikely to have clinical significance.

Existing evidence on efficacy does not warrant the choice of one second-generation antidepressant over another, although we could not conclusively establish equivalence in efficacy for many comparisons. No differences in efficacy were apparent for patients with accompanying symptoms or subgroups based on age, sex, race or ethnicity, or comorbid conditions, although evidence within subgroups was limited.

Nevertheless, second-generation antidepressants cannot be considered identical drugs. Moderate-strength evidence supports some differences among individual drugs with respect to speed of onset of response and incidence of some adverse events. For example, consistent evidence from multiple trials demonstrated that mirtazapine has a faster onset of action than citalopram, fluoxetine, paroxetine, or sertraline (39, 45, 52–55) and that bupropion has fewer sexual adverse events than fluoxetine, paroxetine, or sertraline (82, 86, 144). These differences may be clinically significant and may influence medication choice for a given patient.

Across all efficacy trials, more than 50% of patients treated with second-generation antidepressants for acute-phase depression did not achieve remission, the primary goal of depression treatment. Almost 40% did not achieve response, a less rigorous outcome. Current evidence is insufficient to identify patient factors that can reliably predict response or nonresponse to an individual drug. Although limited evidence indicates that the efficacy of second-generation antidepressants is similar among patients for whom treatment with a first-line agent failed, a substantial proportion of these patients do not achieve response or remission with second-line treatment (56). Multiple treatment options are required for patients who do not respond to first- or second-line treatment.

Our statistical comparisons confirm the results of previous systematic reviews (3, 4, 145), although our interpretation of findings differs from that of Cipriani and colleagues (145) in their recent meta-analysis comparing fluoxetine with other antidepressants. Their pooled estimates of response rates for fluoxetine compared with sertraline and venlafaxine were slightly larger than our results. These differences might be attributable to their inclusion of open-label trials or their use of odds ratios, which overestimate differences when event rates are high. As in our study, the effect size meta-analysis by Cipriani and colleagues did not reach statistical significance, but they interpreted these differences as clinically significant.

Our review has several limitations. First, most of the studies were efficacy trials conducted in highly selected

populations. The applicability of their results to the average patient with acute MDD might be limited. However, the fact that the effectiveness trial results (23, 49, 50) were consistent with the efficacy study results strengthens our findings.

Indirect comparisons have methodological limitations, most notably a lack of power that resulted in wide confidence intervals, which can encompass clinically significant differences between treatments. Nevertheless, we believe that the consistent similarity of treatment effects across all comparisons supports our conclusion that no substantial differences exist.

Publication bias is a concern for all systematic reviews. Selective availability of studies with positive results can seriously bias conclusions, particularly when a pharmaceutical company compares 2 of its own drugs (as in the case of citalopram and escitalopram). Selective reporting is conceivable; however, we found no evidence to prove publication bias. The validity of statistical methods to explore publication bias, such as funnel plots, is limited because of the small number of studies for individual comparisons.

Although our review included more than 200 studies, many questions remain. More evidence is needed on the most appropriate duration of antidepressant treatment for maintaining response and remission. Future studies should evaluate whether different formulations (for example, controlled release vs. immediate release) lead to differences in adherence and subsequent relapse or recurrence. In addition, although most trials maintained the dose used in acute-phase treatment throughout the continuation and maintenance phases of treatment, little is known about how drug dose affects the risk for relapse or recurrence. Future research is also needed to reliably establish the general efficacy of second-generation antidepressants for the treatment of dysthymia and subsyndromal depression.

How do our findings—that pharmacologic differences between second-generation antidepressants do not translate into substantial clinical differences, although tolerability may differ—inform the practicing clinician? Given the difficulty in predicting what medication will be both efficacious for and tolerated by an individual patient, familiarity with a broad spectrum of antidepressants is prudent. An emphasis on providing treatment trials of adequate dose and duration, with recent evidence providing support for maximum but tolerable doses for at least 8 weeks (146), seems at least as important as the choice of specific drug.

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Appendix Table 1. Characteristics of Studies with Poor Internal Validity

Study, Year (Reference)	Sample Size, *n*	Comparison	Reason for Exclusion
Aguglia et al., 1993 (147)	108	Fluoxetine vs. sertraline	High LTF
Amini et al., 2005 (148)	36	Mirtazapine vs. fluoxetine	No ITT analysis
Brown et al., 2005 (149)	90	Citalopram vs. placebo	High attrition
Byerley et al., 1988 (150)	97	Fluoxetine vs. placebo	No ITT analysis
Claghorn and Lesem, 1995 (151)	90	Mirtazapine vs. placebo	No ITT analysis
Claghorn et al., 1996 (152)	150	Fluvoxamine vs. placebo	No ITT analysis
Claghorn, 1992 (153)	72	Paroxetine vs. placebo	No ITT analysis
Cohn et al., 1990 (154)	120	Paroxetine vs. placebo	No ITT analysis
Cohn and Wilcox, 1992 (155)	120	Paroxetine vs. placebo	No ITT analysis, high rate of postrandomization exclusions
Corrigan et al., 2000 (156)	70	Fluoxetine vs. placebo	No ITT analysis
Croft et al., 2002 (157)	432	Bupropion vs. placebo	High LTF
Dunbar et al., 1991 (158)	480	Paroxetine vs. placebo	High attrition
Dunbar et al., 1993 (159)	273	Paroxetine vs. placebo	High attrition
Elliott et al., 1998 (160)	75	Paroxetine vs. placebo	High LTF, no ITT analysis
Evans et al., 1997 (161)	82	Fluoxetine vs. placebo	High attrition
Fabre et al., 1996 (162)	100	Fluvoxamine vs. placebo	High attrition
Fabre et al., 1995 (163)	369	Sertraline vs. placebo	No ITT analysis
Fabre, 1992 (164)	74	Paroxetine vs. placebo	High attrition
Fabre and Putman, 1987 (165)	84	Fluoxetine vs. placebo	No ITT analysis
Falk et al., 1989 (166)	27	Trazodone vs. fluoxetine	High LTF
Fava et al., 2005 (167)	90	Fluoxetine vs. placebo	High attrition
Fava et al., 1997 (168)	20	Venlafaxine vs. placebo	No ITT analysis
Feighner, 1992 (169)	430	Paroxetine vs. placebo	High attrition
Feighner and Boyer, 1992 (170)	76	Paroxetine vs. placebo	High attrition
Feighner et al., 1993 (171)	480	Paroxetine vs. placebo	High attrition
Feighner et al., 1998 (172)	117	Nefazodone vs. placebo	High attrition
Flament and Lane, 2001 (173)	286	Sertraline vs. fluoxetine	No ITT analysis
Gilaberte et al., 2001 (174)	140	Fluoxetine vs. placebo	High attrition
Grigoriadis et al., 2003 (175)	201	Citalopram vs. fluoxetine	No ITT analysis (completer analysis only)
Gülseren et al., 2005 (176)	25	Fluoxetine vs. paroxetine	No ITT analysis, high rate of postrandomization exclusions
Kennedy et al., 2006 (177)	141	Bupropion vs. paroxetine	No ITT analysis
Lapierre et al., 1987 (178)	63	Fluvoxamine vs. placebo	No ITT analysis
March et al., 1990 (179)	54	Fluvoxamine vs. placebo	No ITT analysis
McGrath et al., 2000 (180)	154	Fluoxetine vs. placebo	High rate of postrandomization exclusions
Mesters et al., 1993 (181)	308	Fluoxetine	No ITT analysis
Montgomery et al., 1992 (182)	199	Citalopram vs. placebo	High rate of postrandomization exclusions
Muijen et al., 1988 (183)	81	Fluoxetine vs. placebo	No ITT analysis
Petracca et al., 2001 (184)	41	Fluoxetine vs. placebo	No ITT analysis
Ravindran et al., 1995 (185)	103	Sertraline vs. placebo	High attrition, no ITT analysis
Reimherr et al., 1998 (186)	362	Bupropion vs. placebo	High attrition
Rickels et al., 1994 (187)	191	Nefazodone vs. placebo	High attrition
Rickels and Case, 1982 (188)	202	Trazadone vs. placebo	No ITT analysis
Rickels et al., 1992 (189)	111	Paroxetine vs. placebo	No ITT analysis
Rosenbaum et al., 1998 (190)	242	Sertraline vs. fluoxetine vs. paroxetine	No ITT analysis
Roth et al., 1990 (191)	90	Fluvoxamine vs. placebo	No ITT analysis
Roy-Byrne et al., 2000 (192)	64	Nefazodone vs. placebo	High attrition
Rudolph et al., 1998 (193)	358	Venlafaxine vs. placebo	High attrition
Schweizer et al., 1991 (194)	60	Venlafaxine vs. placebo	High attrition
Smith et al., 1990 (195)	150	Mirtazapine vs. placebo	No ITT analysis
Smith and Glaudin, 1992 (196)	77	Paroxetine vs. placebo	No ITT analysis
Stahl, 2000 (197)	323	Citalopram vs. sertraline	High attrition
Thase et al., 2001 (198)	2045	Venlafaxine vs. SSRIs	No systematic literature search
Tollefson et al., 1994 (199); Beasley et al., 1991 (200)	3065	Fluoxetine vs. placebo	No systematic literature search
Vartiainen and Leinonen, 1994 (201)	114	Mirtazapine vs. placebo	High attrition
Wade et al., 2003 (202)	197	Mirtazapine vs. paroxetine	High LTF, high rate of postrandomization exclusions
Wernicke et al., 1987 (203)	345	Fluoxetine vs. placebo	High attrition
Winokur et al., 2003 (204)	21	Fluoxetine vs. mirtazapine	No ITT analysis, small sample size
Zanardi et al., 1996 (205)	46	Paroxetine vs. sertraline	High LTF

ITT = intention-to-treat; LTF = loss to follow-up; SSRI = selective serotonin reuptake inhibitor.

Appendix Table 2. **Comparative Efficacy and Effectiveness Studies on Therapy for Major Depressive Disorder**

Study, Year (Reference)	Sample Size, *n*	Duration	Comparison and Dosage, *mg/d*	Response		Remission		Quality Rating
				Rate, %	*P* Value	Rate, %	*P* Value	
SSRIs vs. SSRIs								
Aberg-Wistedt et al., 2000 (34)	353	8 wk	Paroxetine, 20–40; sertraline, 50–150	63 vs. 63	NS	57.3 vs. 51.6	NS	Fair
	353	24 wk	Paroxetine, 20–40; sertraline, 50–150	69 vs. 72	NS	73.7 vs. 80.2	NS	
Baldwin et al., 2006 (206)	323	8 wk	Paroxetine, 13.9; escitalopram, 26.3	71.2 vs. 67.9	NR	61 vs. 56.4	NR	Fair
Bennie et al., 1995 (25)	286	6 wk	Fluoxetine, 20–40; sertraline, 50–100	51 vs. 59	NR	NR	NR	Fair
Boulenger et al., 2006 (207)	451	24 wk	Paroxetine, 40; escitalopram, 20	76.7 vs. 82	<0.05	66.8 vs. 75.0	<0.050	Fair
Boyer et al., 1998 (46)	242	180 d	Fluoxetine, 50–150; sertraline, 20–60	42.6 vs. 47.4	NR	NR	NR	Fair
Burke et al., 2002 (18)	491	8 wk	Citalopram, 40; escitalopram, 20	45.6 vs. 51.2	NS	NR	NR	Fair
		8 wk	Citalopram, 40; escitalopram, 10	45.6 vs. 50	NS	NR	NR	
Chouinard et al., 1999 (75)	203	12 wk	Fluoxetine, 20–80; paroxetine, 20–50	88.4 vs. 85.7	NS	81.2 vs. 77.8	NS	Fair
Colonna et al., 2005 (17)	357	8 wk	Citalopram, 20; escitalopram, 10	55 vs. 63	<0.05	45 vs. 55	NR	Fair
		24 wk	Citalopram, 20; escitalopram, 10	78 vs. 80	NS	71 vs. 76	NR	
Dalery and Honig, 2003 (208)	184	6 wk	Fluoxetine, 20; fluvoxamine, 100	60 vs. 60	NS	NR	NR	Fair
Cassano et al., 2002 (104)	242	52 wk	Fluoxetine, 20–60; paroxetine, 20–40	NR	NR	NR	NR	Fair
De Wilde et al., 1993 (209)	100	6 wk	Fluoxetine, 20–60; paroxetine, 20–40	62 vs. 67	NR	NR	NR	Fair
Ekselius et al., 1997 (49); Ekselius and von Knorring, 2001 (210)	400	24 wk	Citalopram, 20–60; sertraline, 50–150	81 vs. 75.5	NS	NR	NR	Good
Fava et al., 2002 (24)	284	10–16 wk	Fluoxetine, 20–60; paroxetine, 20–60; sertraline, 50–200	64.8 vs. 68.8 vs. 72.9	NR	54.4 vs. 57.0 vs. 59.4	NR	Fair
Fava et al., 2000 (211)	284	26–32 wk	Fluoxetine, 20–60; sertraline, 50–200; paroxetine, 20–60	NR	NR	NR	NR	Fair
Fava et al., 1998 (76)	128	12 wk	Fluoxetine, 20–80; paroxetine, 20–50	NR	NR	NR	NR	Fair
Gagiano, 1993 (77)	90	6 wk	Fluoxetine, 20–60; paroxetine, 20–40	63 vs. 70	NR	NR	NR	Fair
Haffmans et al., 1996 (212)	217	6 wk	Citalopram, 20–40; fluvoxamine, 100–200	30.5 vs. 28.4	NR	14 vs. 8	NS	Fair
Kasper et al., 2005 (101)	518	8 wk	Escitalopram, 10; fluoxetine, 20	46 vs. 37	NS	40 vs. 30	NS	Fair
Kiev and Feiger, 1997 (88)	60	7 wk	Fluvoxamine, 50–150; paroxetine, 20–50	NR	NS	NR	NR	Fair
Kroenke et al., 2001 (50)	601	36 wk	Fluoxetine, 20; sertraline, 50; paroxetine, 20	NR	NR	NR	NR	Fair
Lepola et al., 2003 (16)	471	8 wk	Citalopram, 20–40; escitalopram, 10–20	52.6 vs. 63.7	0.021	42.8 vs. 52.1	0.036	Fair
Moore et al., 2005 (19)	280	8 wk	Citalopram, 40; escitalopram, 20	61.3 vs. 76.1	0.008	43.6 vs. 56.1	0.040	Fair
Nemeroff et al., 1995 (213)	95	7 wk	Fluvoxamine, 50–150; sertraline, 50–200	NR	NS	NR	NR	Fair
Newhouse et al., 2000 (22)	236	12 wk	Fluoxetine, 20–40; sertraline, 50–100	71 vs. 73	NR	46 vs. 45	NR	Fair
Patris et al., 1996 (214)	357	8 wk	Citalopram, 20; fluoxetine, 20	78 vs. 76	NS	75 vs. 68	0.26	Fair
Rapaport et al., 1996 (215)	100	7 wk	Fluoxetine, 20–80; fluvoxamine, 100–150	NR	NR	NR	NR	Fair
Rossini et al., 2005 (105)	93	7 wk	Fluvoxamine, 150; sertraline, 200	NR	NS	NR	NR	Fair

Appendix Table 2—**Continued**

Study, Year (Reference)	Sample Size, *n*	Duration	Comparison and Dosage, *mg/d*	Response		Remission		Quality Rating
				Rate, %	*P* Value	Rate, %	*P* Value	
Schöne and Ludwig, 1993 (102)	108	6 wk	Fluoxetine, 20–60; paroxetine, 20–40	37.5 vs. 16	0.03	NR	NR	Fair
Sechter et al., 1999 (23)	234	24 wk	Fluoxetine, 20–60; sertraline, 50–150	64 vs. 74	NR	NR	NR	Fair
Unpublished FDA review (20)	375	8 wk	Citalopram, 20–40; escitalopram, 10–20	51 vs. 46	NR	NR	NR	Fair
Tignol, 1993 (216)	178	6 wk	Fluoxetine, 20; paroxetine, 20	78 vs. 75	NS	NR	NR	Fair
van Moffaert et al., 1995 (59)	165	8 wk	Fluoxetine, 20; sertraline, 50	NR	NS	NR	NR	Fair
Ventura et al., 2007 (217)	212	8 wk	Escitalopram, 10; sertraline, 50–200	75 vs. 74	NR	51 vs. 57	NR	Fair
SSRIs vs. SSNRIs and SNRIs								
Allard et al., 2004 (106)	150	22 wk	Citalopram, 10–20; venlafaxine, 75–100	93 vs. 93	NS	23 vs. 19	NS	Fair
Alves et al., 1999 (27)	87	12 wk	Fluoxetine, 20–40; venlafaxine, 75–150	74 vs. 87	NR	41 vs. 51	NR	Fair
Ballús et al., 2000 (218)	84	12 wk	Paroxetine, 20–40; venlafaxine, 75–150	NR	NS	33 vs. 57	0.011	Fair
		24 wk	Paroxetine, 20–40; venlafaxine, 75–150	49 vs. 59	NS	NR	NS	
Behnke et al., 2003 (55)	345	8 wk	Sertraline, 50–150; mirtazapine, 30–45	NR; faster onset of mirtazapine	NS	NR	NR	Fair
Benkert et al., 2000 (52)	275	6 wk	Paroxetine, 20–40; mirtazapine, 15–45	53.7 vs. 58.3; faster onset of mirtazapine	NS	34.1 vs. 40.9	NS	Fair
Bielski et al., 2004 (47)	198	8 wk	Escitalopram, 20; venlafaxine, 225	61 vs. 48	NS	36 vs. 32	NS	Fair
Costa e Silva, 1998 (26)	382	8 wk	Fluoxetine, 20–40; venlafaxine, 75–225	82 vs. 86.8	0.074	60.2 vs. 60.2	NR	Fair
De Nayer et al., 2002 (31)	146	12 wk	Fluoxetine, 20–40; venlafaxine, 75–150	49.3 vs. 75	0.001	40.3 vs. 59.4	0.028	Fair
Detke et al., 2004 (78)	367	8 wk	Paroxetine, 20; duloxetine, 80; duloxetine, 120	74 vs. 65 vs. 71	NS	44 vs. 46 vs. 52	NS	Fair
Dierick et al., 1996 (32)	314	8 wk	Fluoxetine, 20; venlafaxine, 75–150	60 vs. 72	0.023 (at week 6)	NR	NR	Fair
Goldstein et al., 2002 (219)	173	8 wk	Fluoxetine, 20; duloxetine, 40–120	45 vs. 49	0.39	30 vs. 43	0.072	Fair
Hong et al., 2003 (51)	133	6 wk	Fluoxetine, 20–40; mirtazapine, 15–45	51 vs. 58; faster onset of mirtazapine	NS	27 vs. 35	NS	Fair
Leinonen et al., 1999 (40)	270	8 wk	Citalopram, 20–60; mirtazapine, 15–60	89 vs. 85; faster onset of mirtazapine	0.53	NR	NR	Fair
McPartlin et al., 1998 (41)	361	12 wk	Paroxetine, 20; venlafaxine XR, 75	76 vs. 76	NS	46 vs. 48	NS	Fair
Mehtonen et al., 2000 (220)	147	8 wk	Sertraline, 50–100; venlafaxine, 75–150	68 vs. 83	0.05	45 vs. 68	0.008	Good
Montgomery et al., 2004 (221)	293	8 wk	Escitalopram, 10–20; venlafaxine, 75–150	77 vs. 80	NS	70 vs. 70	NS	Fair
Nemeroff and Thase, 2007 (33)	308	6 wk	Fluoxetine, 20–60; venlafaxine, 75–225	45 vs. 53	0.034	28 vs. 32	0.25	Fair
Nierenberg et al., 2007 (222)	547	8 wk	Escitalopram, 10; duloxetine, 60	45.3 vs. 48.7	NR	33 vs. 40.1	NR	Fair
Perahia et al., 2006 (63)	293	8 wk	Paroxetine, 20; duloxetine, 80; duloxetine, 120	61 vs. 65 vs. 68	NR	43 vs. 44 vs. 40	NR	Fair
Rudolph and Feiger, 1999 (30)	301	8 wk	Fluoxetine, 20–60; venlafaxine, 75–225	50 vs. 57	0.07	22 vs. 37	<0.05	Fair
Schatzberg et al., 2002 (54)	255	8 wk	Paroxetine, 20–40; mirtazapine, 15–45	56.7 vs. 64.0; faster onset of mirtazapine	NS	NR	NR	Fair
Schatzberg and Roose, 2006 (223)	204	8 wk	Fluoxetine, 20–60; venlafaxine IR, 37.5–225	No significant differences, data NR	NR	20 vs. 27	0.55	Fair

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Appendix Table 2—**Continued**

Study, Year (Reference)	Sample Size, *n*	Duration	Comparison and Dosage, *mg/d*	Response		Remission		Quality Rating
				Rate, %	*P* Value	Rate, %	*P* Value	
Shelton et al., 2006 (224)	160	8 wk	Sertraline, 150; venlafaxine XR, 225	55 vs. 65	NS	38 vs. 49	NS	Fair
Silverstone and Ravindran, 1999 (225)	368	12 wk	Fluoxetine, 20–60; venlafaxine, 75–225	62 vs. 67	<0.05	NR	NR	Fair
Sir et al., 2005 (35)	163	8 wk	Sertraline, 50–150; venlafaxine XR, 75–225	70.9 vs. 70.9	0.95	59.5 vs. 54.4	0.47	Good
Tzanakaki et al., 2000 (28)	109	6 wk	Fluoxetine, 60; venlafaxine, 225	66 vs. 70	NR	36 vs. 41	NR	Fair
Tylee et al., 1997 (29)	341	12 wk	Fluoxetine, 20; venlafaxine, 75	62.8 vs. 55.1	NR	34.1 vs. 35.4	NS	Fair
Versiani et al., 2005 (45)	297	8 wk	Fluoxetine, 20–40; mirtazapine, 15–60	NR; faster onset of mirtazapine	NS	41.4 vs. 40.1	NS	Fair
Wheatley et al., 1998 (39)	133	6 wk	Fluoxetine, 20–40; mirtazapine, 15–60	NR; faster onset of mirtazapine	NS	25.4 vs. 23.3	NS	Fair
SSRIs vs. other second-generation antidepressants								
Baldwin et al., 1996 (74)	206	8 wk	Paroxetine, 20–40; nefazodone, 200–600	60 vs. 58	NS	NR	NR	Fair
Beasley et al., 1991 (37)	126	6 wk	Fluoxetine, 20–60; trazodone, 100–400	62 vs. 69	NS	51 vs. 42	NS	Fair
Coleman et al., 2001 (82)	456	8 wk	Fluoxetine, 20–60; bupropion SR, 150–400	57 vs. 56	NS	40 vs. 47	NS	Fair
Coleman et al., 1999 (84)	364	8 wk	Sertraline, 50–200; bupropion SR, 150–400	61 vs. 66	NS	NR	NR	Fair
Croft et al., 1999 (85)	360	8 wk	Sertraline, 50–200; bupropion SR, 150–400	68 vs. 66	NS	NR	NR	Fair
Feiger et al., 1996 (226)	160	6 wk	Sertraline, 50–200; nefazodone, 100–600	57 vs. 59	NS	NR	NR	Fair
Feighner et al., 1991 (86)	123	6 wk	Fluoxetine, 20–80; bupropion SR, 225–450	58 vs. 63	NS	NR	NR	Fair
Hicks et al., 2002 (87)	40	8 wk	Paroxetine, 20–40; nefazodone, 400–600	NR	NS	NR	NR	Fair
Kasper et al., 2005 (227)	108	6 wk	Paroxetine, 20–40; trazodone, 150–450	91 vs. 87	NS	68 vs. 69	NS	Fair
Kavoussi et al., 1997 (144)	248	16 wk	Sertraline, 50–200; bupropion SR, 100–300	NR	NR	NR	NR	Fair
Munizza et al., 2006 (228)	122	6 wk	Sertraline, 50–100; trazodone PR, 150–450	63 vs. 74	NS	49 vs. 60	NR	Fair
Perry et al., 1989 (229)	40	6 wk	Fluoxetine, 20–60; trazodone, 50–400	NR	NR	NR	NR	Fair
Rush et al., 1998 (69)	125	8 wk	Fluoxetine, 20–40; nefazodone, 200–500	45 vs. 47	NS	NR	NR	Fair
Weihs et al., 2000 (44)	100	6 wk	Paroxetine, 10–40; bupropion SR, 100–300	77 vs. 71	NS	NR	NR	Fair
SNRIs vs. SNRIs								
Guelfi et al., 2001 (42)	157	8 wk	Mirtazapine, 45–60; venlafaxine, 225–375	62 vs. 52	NS	NR	NR	Fair
SNRIs vs. other second-generation antidepressants								
Cunningham et al., 1994 (62)	225	6 wk	Venlafaxine, 75–200; trazodone, 150–400	72 vs. 60	NS	NR	NR	Fair
Halikas, 1995 (230)	150	6 wk	Mirtazapine, 5–35; trazodone, 40–280	51 vs. 41	NS	NR	NR	Fair
van Moffaert et al., 1995 (231)	200	6 wk	Mirtazapine, 24–72; trazodone, 150–450	61 vs. 51	<0.05	NR	NR	Fair
Other second-generation antidepressants vs. other second-generation antidepressants								
Weisler et al., 1994 (232)	124	6 wk	Bupropion, 225–450; trazodone, 150–400	55.9 vs. 40.4	NR	46 vs. 31	NR	Fair

FDA = U.S. Food and Drug Administration; IR = immediate-release; NR = not reported; NS = not significant; PR = prolonged-release; SNRIs = serotonin and norepinephrine reuptake inhibitors; SR = sustained-release; SSRIs = selective serotonin reuptake inhibitors; SSNRIs = selective serotonin and norepinephrine reuptake inhibitors; XR = extended-release.

Appendix Table 3. Comparative Efficacy and Effectiveness Studies on Therapy for Dysthymia

Study, Year (Reference)	Intervention	Sample Size, *n*	Results	Quality Rating
Devanand et al., 2005 (38)	Fluoxetine vs. placebo	90	No difference in response rates and quality of life	Good
Vanelle et al., 1997 (43)	Fluoxetine vs. placebo	111	Significantly more responders to fluoxetine	Fair
Barrett et al., 2001 (142); Williams et al., 2000 (141)	Paroxetine vs. placebo vs. behavioral therapy	656	In patients ≥60 y, significantly greater improvement in symptom scores for paroxetine than for placebo; in patients <60 y, no difference	Fair
Thase et al., 1996 (140)	Sertraline vs. imipramine vs. placebo	412	Significantly more responders for sertraline than placebo	Fair
Ravindran et al., 2000 (36)	Sertraline vs. placebo	310	Significantly more responders and remitters for sertraline	Fair

Appendix Table 4. Comparative Efficacy and Effectiveness Studies on Therapy for Subsyndromal Depressive Disorders

Study, Year (Reference)	Intervention	Sample Size, *n*	Results	Quality Rating
Rocca et al., 2005 (100)	Citalopram vs. sertraline	138	No difference	Not applicable
Judd et al., 2004 (143)	Fluoxetine vs. placebo	162	Greater improvements on depression scales for fluoxetine than for placebo; no difference in psychosocial outcomes	Fair
Barrett et al., 2001 (142); Williams et al., 2000 (141)	Paroxetine vs. placebo vs. behavioral therapy	656	In patients ≥60 y, significantly greater improvement in symptom scores for paroxetine than for placebo; in patients <60 y, no difference	Fair

Appendix Table 5. Comparative Efficacy and Effectiveness Studies on Maintaining Remission and Preventing Relapse

Study, Year (Reference)	Treatment Phase	Duration, *wk*	Sample Size, *n*	Comparison and Dose, *mg/d*	Relapse or Recurrence		Quality Rating
					Patients, *n* (%)	*P* Value	
van Moffaert et al., 1995 (59)	Acute	8	82	Fluoxetine, 20–40	–		Fair
			83	Sertraline, 50–100	–		
	Continuation	24	56	Fluoxetine, 20–40	7 (13)	NS	
			49	Sertraline, 50–100	5 (10)		
Franchini et al., 1997 (60) and 2000 (61)	Acute	NR	NR	NR	–		Fair
	Continuation	16	NR	NR	–		
	Maintenance (2 y) (60)	104	32	Fluvoxamine, 200	6 (19)	0.88	
			32	Sertraline, 100	7 (22)		
	Maintenance (4 y) (61)	208	25	Fluvoxamine, 200	5 (20)	0.92	
			22	Sertraline, 100	3 (14)		
Cunningham et al., 1994 (62)	Acute	6	77	Trazodone, 150–400	–		Fair
			72	Venlafaxine, 75–200	–		
			76	Placebo	–		
	Continuation/maintenance	52	30	Trazodone, 150–400	4 (13)	NS	
			37	Venlafaxine, 75–200	3 (8)		
			29	Placebo	4 (14)		

NR = not reported; NS = not significant.

Appendix Table 6. Comparative Efficacy and Effectiveness Studies on Therapy for Recurrent and Treatment-Resistant Depression

Study, Year (Reference)	Duration, *wk*	Sample Size, *n*	Comparison and Dose, *mg/d*	Response		Remission		Quality Rating
				Patients, *n* (%)	*P* Value	Patients, *n* (%)	*P* Value	
Baldomero et al., 2005 (57)	24 (open)	1465	Conventional therapy (pooled)	1034 (71)	<0.001	754 (52)	<0.001	Fair
		294	Citalopram, 20–40	209 (71)	0.024	153 (52)	0.020	
		248	Fluoxetine, 20–40	174 (70)	0.012	128 (52)	0.030	
		116	Mirtazapine, 30–45	75 (65)	0.004	52 (45)	0.003	
		312	Paroxetine, 20–40	226 (73)	0.078	161 (52)	0.015	
		279	Sertraline, 50–150	197 (71)	0.014	147 (53)	0.040	
		1632	Venlafaxine, 75–225	1262 (78)		963 (59)		
Poirier and Boyer, 1999 (58)	4	62	Paroxetine, 30–40	18 (36)	0.070	11 (18)	0.020	Fair
		61	Venlafaxine, 200–300	27 (45)		22 (37)		
Rush et al., 2006 (56)	14	239	Bupropion, 150–400	62 (26)	NS	51 (21)	0.160	Good
		238	Sertraline, 50–200	63 (27)		42 (18)		
		250	Venlafaxine, 37.5–375	62 (25)		62 (25)		

NS = not significant.

Appendix Table 7. Placebo-Controlled Studies of Relapse and Recurrence

Study, Year (Reference)	Treatment Phase	Duration, *wk*	Sample Size, *n*	Comparison and Dose, *mg/d*	Relapse or Recurrence		Quality Rating
					Patients, *n (%)*	*P* Value	
Weihs et al., 2002 (233)	Acute	8	816	Bupropion SR, 300	–		Fair
	Continuation	44	210	Bupropion SR, 300	78 (37)	0.004	
			213	Placebo	111 (52)		
Hochstrasser et al., 2001 (234)	Acute	6–9	427	Citalopram, 20–60	–		Fair
	Continuation	16	327	Citalopram, 20–60	–		
	Maintenance	48	132	Citalopram, 20–60	24 (18)	<0.001	
			137	Placebo	59 (43)		
Klysner et al., 2002 (235)	Acute	8	230	Citalopram, 20–40	–		Fair
	Continuation	16	172	Citalopram, 20–40	–		
	Maintenance	48	60	Citalopram, 20–40	19 (32)	NR	
			61	Placebo	41 (67)		
Kornstein et al., 2006 (236)	Acute	8	131	Citalopram, 20–60	–		Fair
			129	Fluoxetine, 20–80			
			128	Paroxetine, 20–50			
			127	Sertraline, 50–200			
	Continuation	18	234	Escitalopram, 10–20	–		
	Maintenance	52	73	Escitalopram, 10–20	20 (27)	NR	
			66	Placebo	43 (65)		
Montgomery and Rasmussen, 1992 (237)	Acute	6	NR	Citalopram, 20–40	–		Fair
	Continuation	24	48	Citalopram, 20	4 (8)	<0.020	
			57	Citalopram, 40	7 (12)		
			42	Placebo	13 (31)		
Robert and Montgomery, 1995 (238)	Acute	8	391	Citalopram, 20–60	–		Fair
	Continuation	24	152	Citalopram, 20–60	21 (14)	0.040	
			74	Placebo	18 (24)		
Rapaport et al., 2004 (239)	Acute	8	502	Escitalopram, 10–20	–		Fair
	Continuation	36	181	Escitalopram, 10–20	47 (26)	0.010	
			93	Placebo	37 (40)		
Schmidt et al., 2000 (240); Dinan, 2001 (241)	Acute	13	932	Fluoxetine, 20	–		Fair
	Continuation	25	189	Fluoxetine 20	49 (26)	<0.010	
			190	Fluoxetine, 90 mg/wk	70 (37)		
			122	Placebo	61 (50)		
Reimherr et al., 1998 (242); Michelson et al., 1999 (243)	Acute	12–14	839	Fluoxetine, 20	–		Fair
	Continuation	14	299	Fluoxetine, 20	77 (26)	<0.001	
			95	Placebo	46 (49)		
	Continuation	38	105	Fluoxetine, 20	9 (9)	<0.040	
			52	Placebo	12 (23)		
	Continuation	50	28	Fluoxetine, 20	3 (11)	0.54	
			34	Placebo	6 (16)		
Terra and Montgomery, 1998 (244)	Acute	6	436	Fluvoxamine, 100	–		Fair
	Continuation	18	283	Fluvoxamine, 100	–		
	Maintenance	52	110	Fluvoxamine, 100	14 (13)	<0.001	
			94	Placebo	33 (35)		
Thase et al., 2001 (245)	Acute	8–12	410	Mirtazapine, 15–45	–		Fair
	Continuation	40	76	Mirtazapine, 15–45	15 (20)	0.001	
			80	Placebo	35 (44)		
Gelenberg et al., 2003 (246)	Acute	12	681	Nefazodone, 300–600	–		Fair
	Continuation	16	269	Nefazodone, 300–600	–		
	Maintenance	52	76	Nefazodone, 300–600	23 (30)	0.043	
			84	Placebo	40 (48)		
Feiger et al., 1999 (247)	Acute	16	467	Nefazodone, 400–600	–		Fair
	Continuation	36	65	Nefazodone, 400–600	1 (2)	0.009	
			66	Placebo	12 (18)		
Claghorn and Feighner, 1993 (248)	Acute	6	240	Paroxetine, 10–50	–		Fair
			237	Imipramine, 65–275	–		
			240	Placebo	–		
	Continuation	52	94	Paroxetine, 10–50	11 (12)	NR	
			79	Imipramine, 65–275	3 (4)		
			46	Placebo	10 (22)		

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Appendix Table 7—**Continued**

Study, Year (Reference)	Treatment Phase	Duration, *wk*	Sample Size, *n*	Comparison and Dose, *mg/d*	Relapse or Recurrence		Quality Rating
					Patients, *n* (%)	*P* Value	
Montgomery and Dunbar, 1993 (249)	Acute	8	172	Paroxetine, 20–30	–		Fair
	Continuation	16	68	Paroxetine, 20–30	2 (3)	<0.010	
			67	Placebo	13 (19)		
	Maintenance	36	66	Paroxetine, 20–30	9 (14)	<0.050	
			54	Placebo	16 (30)		
Reynolds et al., 2006 (250)	Acute	NR	195	Paroxetine, 10–40	–		Fair
	Continuation	16	151	Paroxetine, 10–40	–		
	Maintenance	110	35	Paroxetine, 10–40	12 (34)	0.060	
			18	Placebo	10 (56)		
Lépine et al., 2004 (251)	Remission stability	8	371	Placebo	–		Good
	Maintenance	72	189	Sertraline, 50–100	32 (17)	0.002	
			99	Placebo	33 (33)		
Doogan and Caillard, 1992 (252)	Acute	8	480	Sertraline, 50–200	–		Fair
	Continuation	44	185	Sertraline, 50–200	24 (13)	<0.001	
			110	Placebo	48 (46)		
Keller et al., 1998 (253); Kocsis et al., 2002 (254)	Acute	12	426	Sertraline, 50–200	–		Fair
	Continuation	16	209	Sertraline, 50–200	–		
	Maintenance	76	77	Sertraline, 50–200	5 (6)	0.002	
			84	Placebo	19 (23)		
Lustman et al., 2006 (255)	Acute	16	351	Sertraline, 50–200	–		Good
	Maintenance	52	79	Sertraline, 50–200	27 (34)	NR	
			73	Placebo	38 (52)		
Wilson et al., 2003 (256)	Acute	8	318	Sertraline, 50–200	–		Fair
	Continuation	16–20	254	Sertraline, 50–200	–		
	Maintenance	100	56	Sertraline, 50–100	25 (45)	0.21	
			57	Placebo	31 (54)		
Montgomery et al., 2004 (221)	Acute/Continuation	26	495	Venlafaxine, 100–200	–		Fair
	Maintenance	52	109	Venlafaxine, 100–200	24 (22)	<0.001	
			116	Placebo	64 (55)		
Simon et al., 2004 (258)	Acute	8	490	Venlafaxine, 75–225	–		Fair
	Continuation	26	161	Venlafaxine XR, 75–225	45 (28)	<0.001	
			157	Placebo	82 (52)		

NR = not reported; SR = sustained-release; XR = extended-release.

Appendix Table 8. **Comparative Efficacy and Effectiveness Studies of Treatment in Adults with Major Depressive Disorder and Accompanying Symptoms**

Study, Year (Reference)	Intervention	Sample Size, *n*	Results	Quality Rating
Accompanying anxiety				
Chouinard et al., 1999 (75)	Fluoxetine and paroxetine	203	Improvement in anxiety scores was similar for both treatment groups (P = NR).	Fair
Fava et al., 1998 (76)	Fluoxetine, paroxetine, placebo	128	Improvement in anxiety scores was similar for both treatment groups and placebo (P = NR).	Fair
Fava et al., 2000 (64)	Fluoxetine, paroxetine, sertraline	128 (all with anxiety)	Improvement in depression scores (P = 0.323), depression response rates (P = 0.405), and remission rates were similar for all groups (P = 0.588). Improvement in anxiety scores were similar for all 3 treatment groups (P = 0.199).	Fair
Flament et al., 1999 (65)	Fluoxetine and sertraline	286 overall; 131 with anxiety	Improvement in depression scores and depression response rates were similar for both treatment groups (P = NR).	Fair
Gagiano, 1993 (77)	Fluoxetine and paroxetine	90	Improvement in anxiety scores was similar for both treatment groups (P = NR).	Fair
Baldwin et al., 1996 (74)	Paroxetine and nefazodone	206	Improvement in anxiety scores was similar for both treatment groups (CI for difference, −0.7 to 3.8).	Fair
De Nayer et al., 2002 (31)	Fluoxetine and venlafaxine	146 (all with anxiety)	Improvement in depression scores was greater and response rates were higher for venlafaxine compared with fluoxetine (P < 0.05). Improvement in anxiety scores was greater for venlafaxine than for fluoxetine (P < 0.001).	Fair
Joliat et al., 2004 (259)	Fluoxetine (weekly vs. daily) and placebo	799 overall; 374 with anxiety	Depression relapse rates were similar for both medication groups and appeared better than those for placebo, but no statistical comparisons were reported (P = NR). Worsening of anxiety scores appeared better for medication groups than for placebo, but no statistical comparisons were made (P = NR).	Fair
Khan et al., 1998 (260)	Venlafaxine (3 doses) and placebo	403 overall; 346 with anxiety	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
Leinonen et al., 1999 (40)	Citalopram and mirtazapine	270	Improvement in anxiety scores was similar for both treatment groups (P = 0.75).	Fair
Rush et al., 2001 (66)	Sertraline and buproprion SR	248 overall; top quartile of HAM-A score with anxiety (number not provided)	Depression response and remission rates were similar for both treatment groups (P = NR). Improvement in anxiety scores was similar for both treatment groups (P = NR).	Fair
Sir et al., 2005 (35)	Sertraline and venlafaxine XR	163 overall; 120 with anxiety	Improvement in depression scores (P = 0.70), depression response rates (P = 0.26), and remission rates (P = 0.44) were similar for both groups. Improvement in anxiety scores was similar for both treatment groups (P = 0.32).	Fair
Trivedi et al., 2001 (68); Rush et al., 2001 (67)	Sertraline, bupropion SR, placebo	724 overall; top quartile of HAM-A score with anxiety (number not provided)	Depression response and remission rates were similar for both active groups and placebo (P = NR). Improvement in anxiety scores was similar for treatment groups (P > 0.41).	Fair

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Appendix Table 8—**Continued**

Study, Year (Reference)	Intervention	Sample Size, *n*	Results	Quality Rating
Accompanying insomnia				
Beasley et al., 1991 (37)	Fluoxetine and trazodone	126	Improvement in sleep scores was greater for trazodone than for fluoxetine ($P = 0.001$).	Fair
Cunningham et al., 1994 (62)	Venlafaxine and trazodone	227	Improvement in sleep scores was greater for trazodone than for venlafaxine ($P < 0.050$).	Fair
Fava et al., 2002 (24)	Fluoxetine, paroxetine, sertraline	284 overall; 125 with insomnia	Improvement in depression scores was similar for all groups ($P = 0.853$). Improvement in sleep was similar for all groups ($P = 0.852$).	Fair
Lader et al., 2005 (70)	Citalopram, escitalopram, placebo	1321 overall; 638 with insomnia	Improvement in depression scores for escitalopram was superior to citalopram and placebo ($P < 0.050$). Improvement in sleep for escitalopram was superior to citalopram and placebo ($P < 0.010$).	Fair
Rush et al., 1998 (69)	Fluoxetine and nefazodone	125 (all with insomnia)	Improvement in depression scores (CI for difference between groups, −1.7 to 2.8) and depression response rates (P = NR) were similar for both groups. Improvement in sleep for nefazodone was superior to fluoxetine ($P < 0.050$).	Fair
Versiani et al., 2005 (45)	Fluoxetine and mirtazapine	299	Sleep quality improved similarly for both groups (overall score NR).	Fair
Accompanying melancholia				
Clerc et al., 1994 (71)	Fluoxetine and venlafaxine	68 (all with melancholia)	Improvement in depression scores was better for venlafaxine than fluoxetine ($P = 0.027$); response rates did not differ ($P = 0.080$).	Poor
Flament et al., 1999 (65)	Fluoxetine and sertraline	286 overall; 197 with melancholia	Depression response rates for sertraline were superior to fluoxetine ($P < 0.050$); improvement in depression scores was similar for both groups (P = NR).	Fair
Mallinckrodt et al., 2005 (262)	Duloxetine and placebo	2342 overall; 1572 with melancholia	Improvement in depression scores was better for duloxetine than for placebo ($P < 0.001$).	Fair
Tzanakaki et al., 2000 (28)	Fluoxetine and venlafaxine	109 (all with melancholia)	Depression response and remission rates were similar for both groups (P = NR).	Fair
Accompanying pain				
Brannan et al., 2005 (72)	Duloxetine and placebo	282	Improvement in depression scores ($P = 0.544$), depression response rates ($P = 0.901$), and remission rates ($P = 0.887$) was similar. Improvement in pain scores was similar ($P = 0.066$).	Fair
Detke et al., 2002 (263)	Duloxetine and placebo	245	Pain score improvement was slightly greater for duloxetine than for placebo ($P = 0.019$).	Fair
Detke et al., 2002 (264)	Duloxetine and placebo	267	Pain score improvement was slightly greater for duloxetine than for placebo ($P = 0.037$).	Fair
Detke et al., 2004 (78)	Duloxetine, paroxetine, placebo	367	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

Appendix Table 8—**Continued**

Study, Year (Reference)	Intervention	Sample Size, *n*	Results	Quality Rating
Eli Lilly and Company, 2004 (79)	Duloxetine, paroxetine, placebo	354	No statistically significant differences among treatment groups at end point.	Fair
Goldstein et al., 2004 (80)	Duloxetine, paroxetine, placebo	353	Improvement in pain scores was similar among 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
Accompanying psychomotor change				
Flament et al., 1999 (65)	Fluoxetine and sertraline	286	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 = 0.020) and response rates (P = 0.040) were superior for sertraline.	Fair
Accompanying somatization				
Kroenke et al., 2001 (50)	Fluoxetine, paroxetine, sertraline	601	Improvement in somatization scores was similar in all groups (P = NR).	Fair

HAM-A = Hamilton Anxiety Rating Scale; NR = not reported; SR = sustained-release; XR = extended-release.

Appendix Table 9. **Studies of Comparative Risk for Harms in Adults with Major Depressive Disorder**

Study, Year (Reference)	Design; Intervention	Sample Size, *n*	Results	Quality Rating
General tolerability and discontinuation				
Baldwin et al., 2006 (206)	RCT; paroxetine vs. escitalopram	321	No significant difference in discontinuations due to adverse events	Fair
Boulenger et al., 2006 (207)	RCT; paroxetine vs. escitalopram	451	Significantly more discontinuations with paroxetine, with higher rates of nausea, headache, and insomnia	Fair
Brambilla et al., 2005 (265)	Systematic review; fluoxetine vs. SSRIs	NR	No difference in discontinuation rates because of adverse events	Good
Greist et al., 2004 (266)	Pooled analysis; duloxetine vs. paroxetine vs. fluoxetine	2345	No differences in nausea between duloxetine and paroxetine or duloxetine and fluoxetine	–
Haffmans et al., 1996 (212)	RCT; fluvoxamine vs. paroxetine	217	Significantly more diarrhea and nausea with fluvoxamine	Fair
Mackay et al., 1997 (267) and 1999 (268, 269)	Prescription event monitoring; fluoxetine, fluvoxamine, nefazodone, paroxetine, venlafaxine	>60 000	Venlafaxine had highest rate of nausea and vomiting; paroxetine had highest rate of sexual dysfunction; among SSRIs, fluvoxamine was associated with the most overall adverse events	–
Meijer et al., 2002 (270)	Observational study; sertraline vs. SSRIs	1251	Significantly more diarrhea with sertraline	Fair
Munizza et al., 2006 (228)	RCT; sertraline vs. trazodone PR	122	More clinical tolerability with trazodone	Fair
Nierenberg et al., 2007 (222)	RCT; escitalopram vs. duloxetine	547	Significantly more nausea with duloxetine	Fair
Perahia et al., 2006 (63)	RCT; paroxetine vs. duloxetine vs. high-dose duloxetine	293	No significant differences between treatment groups	Fair
Rapaport et al., 1996 (215)	RCT; fluoxetine vs. fluvoxamine	100	Significantly more nausea with fluoxetine	Fair
Ventura et al., 2007 (217)	RCT; escitalopram vs. sertraline	212	No significant differences between treatment groups	Fair
Changes in body weight				
Benkert et al., 2000 (52)	RCT; paroxetine vs. mirtazapine	275	Greater weight gain with mirtazapine	Fair
Croft et al., 2002 (157)	RCT; bupropion vs. placebo	423	Small weight loss with bupropion over 44 weeks	Fair
Fava et al., 2002 (24) and 2000 (211)	RCT; fluoxetine vs. paroxetine vs. sertraline	284	Greatest weight gain with paroxetine	Fair
Goldstein et al., 1997 (271)	RCT; fluoxetine vs. placebo	671	Greater weight loss with fluoxetine in older patients	Fair
Guelfi et al., 2001 (42)	RCT; venlafaxine vs. mirtazapine	157	Greater weight gain with mirtazapine	Fair
Halikas, 1995 (230)	RCT; trazodone vs. mirtazapine	150	More weight gain with mirtazapine	Fair
Harto et al., 1988 (272)	RCT; fluoxetine vs. placebo	35	Greater weight loss with fluoxetine	Fair
Hong et al., 2003 (51)	RCT; fluoxetine vs. mirtazapine	133	Significantly greater weight gain with mirtazapine	Fair
Reimherr et al., 1998 (242); Michelson et al., 1999 (243)	RCT; fluoxetine vs. placebo	395	Patients receiving fluoxetine and placebo gained weight	Fair
Nierenberg et al., 2007 (222)	RCT; escitalopram vs.duloxetine	547	Significantly greater weight loss with duloxetine	Fair
Schatzberg et al., 2002 (54)	RCT; paroxetine vs. mirtazapine	255	Greater weight gain with mirtazapine	Fair
Versiani et al., 2005 (45)	RCT; fluoxetine vs. mirtazapine	297	Greater weight gain with mirtazapine	Fair
Wheatley et al., 1998 (39)	RCT; fluoxetine vs. mirtazapine	133	Significantly greater weight gain with mirtazapine	Fair
Discontinuation syndrome				
Committee on Safety of Medicines, 2004 (89)	Systematic review and meta-analysis; second-generation antidepressants	NR	No differences in risk among second-generation antidepressants	Good
Judge et al., 2002 (273)	Open-label trial; fluoxetine and paroxetine	150	Significantly fewer symptoms in the fluoxetine group than in the paroxetine group	Fair
Perahia et al., 2005 (274)	Pooled analysis; duloxetine vs. placebo	3624	Significantly higher rate of discontinuation syndrome with duloxetine than with placebo (44% vs. 23%)	Fair

Appendix Table 9—**Continued**

Study, Year (Reference)	Design; Intervention	Sample Size, *n*	Results	Quality Rating
Zajecka et al., 1998 (275)	RCT; fluoxetine vs. placebo	395	Dizziness significantly less frequent in fluoxetine patients at 4 and 6 weeks	Fair
Suicidality (suicidal thoughts and behavior)				
Aursnes et al., 2005 (97)	Meta-analysis of unpublished data; paroxetine	1466	Higher rate of suicides for paroxetine than for placebo	Fair
Baldwin et al., 2006 (206)	RCT; paroxetine vs. escitalopram	321	More suicide attempts with paroxetine, but may not be study drug–related	Fair
Committee on Safety of Medicines, 2004 (89)	Systematic review and meta-analysis; second-generation antidepressants	NR	No differences in risk among second-generation antidepressants	Good
Didham et al., 2005 (93)	Retrospective cohort study; citalopram, fluoxetine, paroxetine	57 000	Significant association between nonfatal suicide attempts and SSRIs; no difference in risk among drugs	Fair
Fergusson et al., 2005 (90)	Meta-analysis; SSRIs vs. placebo	87 650	Higher risk for suicide attempts in SSRI-treated patients	Good
Gunnell et al., 2005 (92)	Meta-analysis; citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline—all vs. placebo	40 000	Increased risk for nonfatal suicide attempts compared with placebo; no difference in risk among drugs	Good
Jick et al., 2004 (94)	Case–control study; fluoxetine and paroxetine	159 810	No difference in risk among drugs	Fair
Jick et al., 1995 (95)	Retrospective cohort study and nested case–control study; fluoxetine, trazodone, first-generation antidepressants	172 598	Significantly higher risk for suicide with fluoxetine and mianserin than with dothiepin	Fair
Jick et al., 1992 (96)	Database review; fluoxetine and first-generation antidepressants	8730	No difference in suicides between fluoxetine and first-generation antidepressants	–
Khan et al., 2003 (98)	Retrospective cohort study; bupropion, citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, venlafaxine	48 277	No difference in suicide rate	Fair
Lopez-Ibor, 1993 (99)	Database review; paroxetine and first-generation antidepressants	4686	No difference in suicidality	–
Martinez et al., 2005 (91)	Case–control study; citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, TCAs	146 095	No difference in risk for suicide or nonfatal suicide attempts between SSRIs and TCAs or among individual SSRIs	Good
Pedersen, 2005 (276)	Retrospective cohort study; escitalopram vs. placebo	4091	Higher rate of nonfatal suicide attempts with escitalopram than with placebo	Fair
Sexual dysfunction				
Baldwin et al., 2006 (206)	RCT; paroxetine vs. escitalopram	321	No significant differences between treatment groups	Fair
Clayton et al., 2002 (277)	Cross-sectional survey; bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine	6297	Highest risk with paroxetine, lowest risk with bupropion	Fair
Clayton et al., 2006 (278)	Pooled analysis; bupropion vs. escitalopram and placebo	830	Higher rate of sexual dysfunction with escitalopram	–
Coleman et al., 2001 (82)	RCT; bupropion SR vs. fluoxetine	456	Significantly more sexual adverse events with fluoxetine	Fair
Coleman et al., 1999 (84)	RCT; bupropion SR vs. sertraline	364	Significantly more sexual adverse events with sertraline	Fair
Croft et al., 1999 (85)	RCT; bupropion SR vs. sertraline	360	No differences	Fair
Delgado et al., 2005 (279)	Pooled analysis; duloxetine vs. paroxetine vs. placebo	1466	Higher rate of sexual dysfunction with paroxetine	Fair
Ekselius and von Knorring, 2001 (210)	RCT; citalopram vs. sertraline	308	No differences	Fair
Feighner et al., 1991 (86)	RCT; bupropion vs. fluoxetine	61	Higher rate of sexual dysfunction with fluoxetine	Fair
Ferguson et al., 2001 (280)	RCT; sertraline vs. trazodone	150	Higher re-emergence rate of sexual dysfunction with sertraline	Fair
Kennedy et al., 2000 (117)	Prospective cohort study; paroxetine, sertraline, venlafaxine	174	No differences	Fair
Landén et al., 2005 (281)	Cross-sectional study; citalopram, paroxetine	119	No differences	Fair
Montejo et al., 2001 (81)	Prospective cohort study; citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine	1022	Highest incidence of sexual dysfunction with citalopram, paroxetine, and venlafaxine; lowest with mirtazapine and nefazodone	Fair

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Appendix Table 9—**Continued**

Study, Year (Reference)	Design; Intervention	Sample Size, *n*	Results	Quality Rating
Nierenberg et al., 2007 (222)	RCT; escitalopram vs. duloxetine	547	Significantly more men improved or had no change with duloxetine and significantly more men worsened with escitalopram; no difference for women	Fair
Nieuwstraten and Dolovich, 2001 (282)	Meta-analysis; bupropion vs. SSRIs	1332	Significantly higher rate of sexual satisfaction in the bupropion group	Good
Philipp et al., 2000 (283)	Prospective cohort study; fluoxetine, fluvoxamine, paroxetine, sertraline, moclobemide	268	No difference among SSRIs	Fair
Segraves et al., 2000 (83)	RCT; bupropion and sertraline	248	Significantly more sexual adverse events with sertraline	Fair
Fava et al., 1998 (76)	Pooled analysis; fluoxetine and paroxetine	128	Significantly more sexual adverse events with paroxetine	Fair
Aberg-Wistedt et al., 2000 (34)	RCT; sertraline and paroxetine	353	Significantly more libido decreases in patients receiving sertraline	Fair
Nemeroff et al., 1995 (213)	RCT; sertraline and fluvoxamine	95	Higher rate of sexual adverse events with sertraline	Fair
Behnke et al., 2003 (55)	RCT; sertraline and mirtazapine	346	Significantly more sexual adverse events with sertraline	Fair
Kavoussi et al., 1997 (144)	RCT; sertraline and bupropion	248	Higher rate of sexual adverse events with sertraline	Fair
Feiger et al., 1996 (226)	RCT; sertraline and nefazodone	160	Sertraline had significant adverse effects on sexual function; nefazodone had none	Fair
Seizures				
Dunner et al., 1998 (284)	Uncontrolled, open-label trial; bupropion	3100	Rate of seizures for bupropion within reported range of other antidepressants	Fair
Johnston et al., 1991 (285)	Uncontrolled, open-label trial; bupropion	3341	Rate of seizures for bupropion within range of other antidepressants	Fair
Whyte et al., 2003 (286)	Prospective observational study; SSRIs, TCAs, venlafaxine	538	Seizures more common in venlafaxine overdose than in SSRI or TCA overdose	Good
Cardiovascular events				
Thase, 1998 (287)	Pooled analysis; venlafaxine	3744	Increase in diastolic blood pressure with venlafaxine	Fair
Thase et al., 2005 (288)	Post hoc data analysis; fluoxetine, paroxetine, duloxetine	1873	Greater change in heart rate with duloxetine than with fluoxetine and paroxetine	–
Other adverse events				
Buckley and McManus, 2002 (289)	Database analysis; citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine	47 329	Highest rate of fatal toxicity with venlafaxine	–
Coogan et al., 2005 (290)	Case-control; SSRIs	4996	No association between breast cancer and SSRIs	Fair
Kirby et al., 2002 (291)	Retrospective cohort study; SSRIs and venlafaxine	199	Increased rate of hyponatremia in patients receiving SSRIs and venlafaxine	Fair
Thapa et al., 1998 (292)	Retrospective cohort study; fluoxetine, paroxetine, sertraline, trazodone	2428	No difference in the risk for falls	Fair

NR = not reported; PR = prolonged-release; RCT = randomized, controlled trial; SR = sustained-release; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Appendix Table 10. Comparative Efficacy and Effectiveness Studies in Subgroups

Study, Year (Reference)	Intervention	Sample Size, *n*	Results	Quality Rating
Age				
Allard et al., 2004 (106)	Citalopram vs. venlafaxine XR	151	No significant difference	Fair
Barrett et al., 2001 (142); Williams et al., 2000 (141)	Paroxetine vs. placebo vs. behavioral therapy	656	In patients ≥60 y, significantly greater improvement in symptom scores for paroxetine than for placebo; in patients <60 y, no difference	Fair
Burt et al., 2005 (293)	Duloxetine vs. placebo	114	Duloxetine was more efficacious (response/remission); no difference in effect in women 40–55 y vs. older or younger women	–
Cassano et al., 2002 (104)	Fluoxetine vs. paroxetine	242	No significant difference	Fair
Devanand et al., 2005 (38)	Fluoxetine vs. placebo	90	No difference in response rates and quality of life	Good
Entsuah et al., 2001 (109); Thase et al., 2005 (108)	Venlafaxine (IR and XR) vs. SSRIs vs. placebo	2045	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 seems to eliminate the difference	Fair
Goldstein et al., 1997 (271)	Fluoxetine vs. placebo	671	Greater weight loss with fluoxetine in older patients	Fair
Halikas, 1995 (230)	Mirtazapine vs. trazodone vs. placebo	150	No significant difference	Fair
Kasper et al., 2005 (101)	Escitalopram vs. fluoxetine vs. placebo	517	No significant difference in response rates; remission rates lower for fluoxetine than for escitalopram	Fair
Kirby et al., 2002 (291)	SSRI vs. venlafaxine	199	Higher rate of hyponatremia in patients receiving SSRIs and venlafaxine	Fair
Kroenke et al., 2001 (50)	Fluoxetine vs. paroxetine vs. sertraline	573	No significant difference	Fair
Newhouse et al., 2000 (22); Finkel et al., 1999 (48)	Fluoxetine vs. sertraline	236	Overall similar efficacy, although patients >70 y who received sertraline experienced greater cognitive improvement and greater response	Fair
Oslin et al., 2003 (107)	Sertraline vs. venlafaxine	52	No significant difference in efficacy; tolerability was lower for venlafaxine	Poor
Rapaport et al., 2003 (110)	Paroxetine (CR and IR) vs. placebo	319	Significantly more cases of response and remission for paroxetine (CR and IR formulations) than for placebo	Fair
Rocca et al., 2005 (100)	Citalopram vs. sertraline	138	No significant difference	–
Roose et al., 2004 (116)	Citalopram vs. placebo	174	No significant difference in response or remission except in high-severity group	Fair
Rossini et al., 2005 (105)	Fluvoxamine vs. sertraline	93	No significant difference in response rates	Fair
Schatzberg et al., 2002 (54)	Paroxetine vs. mirtazapine	255	Greater early efficacy for mirtazapine; similar number of CGI responders at end of continuation phase	Fair
Schneider et al., 2003 (114); Sheikh et al., 2004 (115)	Sertraline vs. placebo	752	Significantly more responders in sertraline group both with and without comorbid medical illness	Fair
Schöne and Ludwig, 1993 (102); Geretsegger et al., 1994 (103)	Fluoxetine vs. paroxetine	106	Greater response rate for paroxetine	Fair
Tollefson and Holman, 1993 (112); Tollefson et al., 1995 (111); Small et al., 1996 (113)	Fluoxetine vs. placebo	671	Significantly greater response with fluoxetine; current physical illness not associated with response	Fair
Wilson et al., 2003 (256)	Sertraline vs. placebo	113	No difference in prevention of depression; sertraline associated with longer time to recurrence	Fair
Sex				
Kennedy et al., 2000 (117)	Paroxetine vs. sertraline vs. venlafaxine vs. moclobemide	107	Sex difference in impairment in drive or 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 (108); Entsuah et al., 2001 (109)	SSRI vs. venlafaxine XR vs. placebo	2045	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
Race or ethnicity				
Wagner et al., 1998 (119)	Fluoxetine vs. placebo	118	Ethnicity not associated with side effects; whites had a higher response rate, Latinos a higher dropout rate	Poor

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Appendix Table 10—**Continued**

Study, Year (Reference)	Intervention	Sample Size, *n*	Results	Quality Rating
Comorbid conditions				
HIV/AIDS				
Ferrando et al., 1997 (120)	Sertraline vs. paroxetine vs. fluoxetine	33	Persons who completed treatment (all treatment groups) experienced improvements in affective and somatic symptoms (many of which were attributed to HIV rather than depression)	Poor
Rabkin et al., 1999 (122)	Fluoxetine vs. placebo	120	No difference in depressed patients with HIV/AIDS	Fair
Rabkin et al., 2004 (121)	Fluoxetine vs. testosterone vs. placebo	123	No difference in depressed patients with HIV/AIDS	Fair
Wagner et al., 1998 (119)	Fluoxetine vs. placebo		Ethnicity not associated with side effects; whites had a higher response rate, Latinos a higher drop-out rate	Poor
Alcohol				
Gual et al., 2003 (123)	Sertraline vs. placebo	83	No significant differences	Fair
Hernandez-Avila et al., 2004 (124)	Nefazadone vs. placebo	41	No significant differences	Fair
Kranzler et al., 2006 (294)	Sertraline vs. placebo	328	No significant differences	Fair
Moak et al., 2003 (125)		82	Greater depression improvement in women treated with sertraline; less drinking associated with greater depression improvement	Fair
Alzheimer disease/dementia				
Lyketsos et al., 2003 (126)	Sertraline vs. placebo	44	Sertraline associated with greater response	Fair
Magai et al., 2000 (127)	Sertraline vs. placebo		No significant difference	Fair
Nyth et al., 1992 (128)	Citalopram vs. placebo	149	Significantly greater improvement with citalopram	Poor
Breast cancer				
Roscoe et al., 2005 (129)	Paroxetine vs. placebo	94	Paroxetine associated with greater depression response	Poor
Cardiovascular diseases				
Bush et al., 2005 (137)	SSRIs	NR	SSRIs improve depression after MI	Fair
Glassman et al., 2002 (130)	Sertraline vs. placebo	369	Significantly greater response with sertraline	Fair
Krishnan et al., 2001 (131)	Sertraline	220	Vascular comorbid conditions not associated with more adverse events or premature discontinuation	Fair
Strik et al., 2000 (132)	Fluoxetine vs. placebo	54	Significantly greater response with fluoxetine	Good
Stroke				
Andersen et al., 1994 (133)	Citalopram vs. placebo	285	Significantly more improvement with citalopram	Fair
Murray et al., 2005 (134)	Sertraline vs. placebo	123	No difference in response; greater improvements in quality of life with sertraline	Fair
Petrakis et al., 1998 (136)	Fluoxetine vs. placebo	44	No difference in depressed opioid addicts	Fair
Schmitz et al., 2001 (135)	Fluoxetine vs. placebo	68	No difference in depressed cocaine abusers	Poor

CGI = Clinical Global Impressions; CR = controlled-release; HRT = hormone replacement therapy; IR = immediate-release; MI = myocardial infarction; NR = not reported; SSRI = selective serotonin reuptake inhibitor; XR = extended-release.

Appendix Table 11. **Randomized, Placebo-Controlled Trials Included for Indirect Comparisons**

Study, Year (Reference)	Sample Size, *n*	Comparison	Quality Rating
Addington et al., 2002 (295)	48	Sertraline vs. placebo	Fair
Brannan et al., 2005 (72)	282	Duloxetine vs. placebo	Fair
Burke and McArthur-Miller, 2001 (296)	70	Fluoxetine vs. placebo	Fair
Claghorn, 1992 (297)	71	Paroxetine vs. placebo	Fair
Claghorn et al., 1992 (298)	341	Paroxetine vs. placebo	Fair
Cohn et al., 1996 (299)	81	Nefazodone vs. placebo	Fair
Cunningham, 1997 (300)	268	Venlafaxine vs. placebo	Fair
Detke et al., 2002 (264)	267	Duloxetine vs. placebo	Fair
Detke et al., 2002 (263)	236	Duloxetine vs. placebo	Fair
Feighner and Overø, 1999 (301)	650	Citalopram vs. placebo	Fair
Fontaine et al., 1994 (302)	135	Nefazodone vs. placebo	Fair
Hypericum Depression Trial Study Group, 2002 (303)	227	Sertraline vs. placebo	Good
Khan et al., 1991 (304)	93	Venlafaxine vs. placebo	Fair
Kocsis et al., 1997 (139)	416	Sertraline vs. placebo	Fair
Lineberry et al., 1990 (305)	224	Bupropion vs. placebo	Fair
Lydiard et al., 1989 (306)	36	Fluvoxamine vs. placebo	Fair
Lydiard et al., 1997 (307)	234	Sertraline vs. placebo	Fair
Mendels et al., 1993 (308)	312	Venlafaxine vs. placebo	Fair
Mendels et al., 1995 (309)	240	Nefazodone vs. placebo	Fair
Olie et al., 1997 (310)	258	Sertraline vs. placebo	Fair
Rabkin et al., 2004 (121)	85	Fluoxetine vs. placebo	Fair
Reimherr et al., 1990 (311)	290	Sertraline vs. placebo	Fair
Reimherr et al., 1988 (312)	77	Sertraline vs. placebo	Fair
Rickels et al., 1989 (313)	102	Paroxetine vs. placebo	Fair
Roose et al., 2004 (116)	174	Citalopram vs. placebo	Fair
Schneider et al., 2003 (114); Sheikh et al., 2004 (115)	747	Sertraline vs. placebo	Fair
Shrivastava et al., 1992 (314)	69	Paroxetine vs. placebo	Fair
Strik et al., 2000 (132)	54	Fluoxetine vs. placebo	Fair
Thase, 1997 (315)	197	Venlafaxine vs. placebo	Fair
Tollefson and Holman, 1993 (112)	534	Fluoxetine vs. placebo	Fair
Tollefson et al., 1995 (111); Heiligenstein et al., 1995 (316)	671	Fluoxetine vs. placebo	Fair
Trivedi et al., 2004 (317)	459	Paroxetine vs. placebo	Fair
Wade et al., 2002 (318)	380	Escitalopram vs. placebo	Fair
Walczak et al., 1996 (319)	577	Fluvoxamine vs. placebo	Fair