



**Second Generation
Antidepressants
DRAFT- Update 4
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Produced by:
The Health Resources Commission
Office for Oregon Health Policy & Research
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Health Resources Commission

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In the summer of 2007 the Oregon Health Resources Commission (HRC) appointed a Pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee consist of three Physicians, a Nurse Practitioner, a PhD, RPh and a PharmD. All meetings are held in public with appropriate notice provided. For this report the HRC director worked with the Center for Evidence-based

Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, "Second Generation Antidepressants- update 4" was completed in October 2008, circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. The report will be updated if indicated after that assessment.

The full OHSU Evidence-based Practice Center's draft report, *Second Generation Antidepressants- update 4*

is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission

– “Clinical outcomes are the most important indicators of comparative effectiveness”
– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Overview

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

Pharmacotherapy dominates the medical management of Axis I psychiatric disease. Before the late 1980s, pharmacologic treatment was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (with the exception of premenstrual disorder, which historically was untreated). TCAs and MAOIs sometimes are referred to as traditional or first-generation antidepressants. These drugs are often accompanied by multiple side effects that many patients find intolerable; e.g., TCAs tend to cause anticholinergic effects including dry mouth and eyes, urinary hesitancy, and sometimes retention and constipation and MAOIs have the potential to produce hypertensive crisis if taken along with certain foods or dietary supplements containing excessive amounts of tyramine. Thus, first-generation antidepressants are no longer agents of choice in many circumstances.

Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs. The first of the second-generation drugs was introduced to the US market in 1985, when bupropion was approved for the treatment of major depressive disorders. In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine. Since then, five other SSRIs have been introduced: sertraline (1991), paroxetine (1992), citalopram

(1999), fluvoxamine (2000), and escitalopram (2002). The SNRIs were first introduced to the market in 1993 with the approval of venlafaxine. In 1994, nefazodone, which is essentially an SSRI with additional 5- hydroxytryptamine-2 (5-HT₂) and 5- hydroxytryptamine-3 (5-HT₃) antagonist properties, was FDA-approved. Mirtazapine, a drug that acts centrally on adrenergic autoreceptors, was added to the therapeutic arsenal in 1996. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), was approved for the treatment of MDD and diabetic peripheral neuropathic pain in 2004. The mechanism of action of most second-generation antidepressants is only poorly understood. In general, these drugs work through their effect on prominent neurotransmitters in the central nervous system. The SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) act by selectively inhibiting the reuptake of serotonin (5-hydroxy-tryptamine, 5-HT) at the presynaptic neuronal membrane. The SNRIs (venlafaxine) are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Mirtazapine, sometimes characterized as an SNRI, is believed to enhance central noradrenergic and serotonergic activity as a 5-HT₂ and 5-HT₃ receptor antagonist. Nefazodone is believed to inhibit neuronal uptake of serotonin and norepinephrine. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine. Preclinical studies of duloxetine suggest that it is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. With the exception of fluvoxamine, which is approved only for the treatment of obsessive compulsive disorder (OCD), all of the other second-generation antidepressants are approved for the treatment of MDD. Table 1 (page 7) summarizes the newer products that are available in the US by mechanism of action.

Compared to the first-generation antidepressants, the SSRIs and other second-generation antidepressant have comparable efficacy and comparable or better side effect profiles.^{3,4} However, comparative differences in efficacy, tolerability, and safety are not well defined for the second-generation drugs. The tremendous volume and large variability in the quality of evidence to support use of these products makes it difficult for clinicians and decision makers to make evidence-based decisions.

The purpose of this review is to help policymakers and clinicians make informed choices about the use of SSRIs and newer antidepressants. Given the prominent role of drug therapy in psychiatric disease and the prevalent use of these drugs, our goal is to summarize comparative data on the efficacy, tolerability, and safety of newer antidepressants.

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding

- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

The subcommittee's task was to evaluate the use of SSRIs and newer antidepressants.

Scope

Sources were searched from 1980 to 2008 (April) to capture literature relevant to the scope of our topic.

This review will focus on newer antidepressant agents: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, mirtazapine, duloxetine, venlafaxine, bupropion, and nefazodone. We will examine the role of these agents in treating patients with conditions in diagnostic categories classified by the Diagnostic and Statistical Manual of Mental Disorders (DSM); these include depressive disorders (MDD, subsyndromal depression, seasonal affective disorder and dysthymic disorder), generalized anxiety disorder (GAD), OCD, panic disorder, post-traumatic stress disorder (PTSD), and social anxiety disorder. We focus this review on these disorders in adult outpatient populations. Also, we examine the role of these agents in treating premenstrual dysphoric disorder (PMDD, known as late luteal phase dysphoric disorder [LLPDD] in the DSM, version III revised [III-R]) among adult outpatient populations. Technically, PMDD is not considered a discrete diagnostic entity by DSM version IV; instead, it is listed as an example of a Depressive Disorder Not Otherwise Specified. It does, however, have specific research criteria defined in DSM-IV; these are identical to LLPDD in DSM III-R except for the addition of one item. Of note, as of 1999, the FDA Neuropharmacology Advisory Committee supported the concept of PMDD as a distinct clinical entity. Finally, we examine the role of these agents in treating MDD in pediatric outpatient populations.

This report addresses the initial use of antidepressants. The uses of these agents for patients who are not responding to initial treatment are not addressed in this report. Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most *efficacy* studies.

Table 1: Approved Second-Generation Antidepressants

Class	Generic Name	US Trade Name*	Dosage Forms**	Labeled Uses**
Selective Serotonin Reuptake Inhibitors (SSRI)	Fluoxetine†	Prozac®; Prozac Weekly®; Sarafem®	10, 20, 40mg caps; 10 mg tabs; 4 mg/ml solution; 90 mg pellets (weekly)	MDD (adult/ped); OCD; PMDD; Panic disorder
	Sertraline	Zoloft®	25, 50, 100 mg tabs; 20 mg/ml solution	MDD (adult); OCD; Panic disorder; PTSD; PMDD; Social anxiety disorder
	Paroxetine†	Paxil®; Paxil CR®	10, 20, 30, 40 mg tabs; 2 mg/ml solution; 12.5, 25, 37.5 mg CR tabs	MDD (adult); OCD; Panic disorder; Social anxiety disorder; GAD; PTSD; PMDD††
Selective Serotonin and Norepinephrine Reuptake Inhibitor (SSNRI)	Citalopram	Celexa®	10, 20, 40mg tabs; 1, 2 mg/ml solution	MDD
	Fluvoxamine†	Luvox®	25, 50, 100 mg tabs	OCD (peds ≥ 8 years of age/adults)
	Escitalopram	Lexapro®‡	10, 20 mg tabs 1 mg/ml solution	MDD; GAD
	Duloxetine	Cymbalta®	20, 30, 60 mg caps	MDD DPNP**
	Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)	Venlafaxine	Effexor®; Effexor XR®	25, 37.5, 50, 75, 100 mg tabs; 37.5, 75, 150 mg XR caps
Other second-generation antidepressants	Bupropion†	Wellbutrin®; Wellbutrin SR®; Wellbutrin XL®; Zyban®	75, 100 mg tabs; 50, 100, 150, 200 mg SR tabs 150, 300 mg XL tabs	MDD Seasonal affective disorder
	Mirtazapine†	Remeron®	15, 30, 45 mg tabs; 15, 30, 45 mg orally disintegrating tabs	MDD
	Nefazodone†	Serzone®	50, 100, 150, 200, 250 mg tabs	MDD

*CR, SR, XL, and XR are registered trademarks referring to controlled, sustained, or extended-release dosage forms
 **GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; PMDD, premenstrual dysphoric disorder; DPNP, diabetic peripheral neuropathic pain
 † Generic available for some dosage forms.
 †† 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
 ‡ Lexapro was denied approval for social anxiety disorder 3/30/2005

Key Questions

Initially, the Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed, revised, and approved by representatives of organizations participating in the DERP in conjunction with experts in the fields of health policy, psychiatry, pharmacotherapy, and research methods. The participating organizations approved the following key questions:

1. For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders, do second-generation antidepressants differ in efficacy or effectiveness?
2. For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders, do second-generation antidepressants differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, and sex), other medications, or comorbidities for which one second-generation antidepressant is more effective or associated with fewer adverse events than another?

Conclusions:***Limitations of the evidence***

1. Duration of studies was much shorter than the usual duration of treatment.
2. High drop out rates.
3. No effectiveness studies.

Conclusions- Efficacy:

1. Evidence suggests that for initial use of second generation antidepressants in adults with major depressive disorder that there is no significant difference in overall effectiveness or efficacy.
2. Very limited evidence suggests that mirtazapine has a faster onset of action than fluoxetine, paroxetine, and sertraline.
3. Nefazodone leads to increased quality of sleep compared to fluoxetine.
4. There is insufficient evidence to determine a comparative difference in efficacy among the studied agents for dysthymia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder and late luteal phase dysphoric disorder.
5. Depression in children is not as well studied as in adults.
 - a. Citalopram and fluoxetine are the only two agents studied shown to be better than placebo.
 - b. Sertraline, venlafaxine, and paroxetine were shown to be no better than placebo.

Conclusions- Safety and Adverse events:

1. Recent evidence from a systematic review of published and unpublished data suggests that only fluoxetine has a favorable risk/benefit profile in pediatric populations.
2. There is insufficient evidence to determine a clinically significant comparative difference between agents in this class for discontinuation rates, suicidality, seizures, hyponatremia, hepatotoxicity or cardiovascular events.
 - a. Nefazodone does carry an FDA “black box” warning of possible life threatening liver failure and further states: “Patients with active liver disease or with high levels on liver function tests should not take nefazodone.”
3. Fair quality evidence suggests that bupropion and nefazodone have a lower incidence of sexual side effects compared to other drugs in this class. (For the comparison of bupropion vs. sertraline NNT=7)
4. Fair quality evidence suggests that paroxetine, sertraline and mirtazapine have a higher incidence of sexual side effects than other drugs in this class.
5. Multiple fair quality studies demonstrate a comparatively greater weight gain in patients taking mirtazapine and paroxetine than those taking sertraline and fluoxetine.

Conclusions- Subgroups:

1. There is insufficient evidence to determine a comparative difference among agents in this class based on subpopulations of age, comorbidities, ethnicity or gender.
2. In a large meta-analysis of paroxetine vs. placebo evidence suggests that the response rate is lower in Hispanic and Asian populations compared to White and Black populations for major depressive disorders in adults, anxiety disorders, and PMDD.
 - a. Of interest, among responders Asian populations showed the highest rate of complete response.
3. In patients with panic disorder treated with sertraline; females showed a higher response rate than males on 2 of 5 outcome measures. (Frequency of attacks [p=0.02] and time spent worrying [p=0.01]).

Supporting Evidence

Key Question 1: For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders, do second-generation antidepressants differ in efficacy or effectiveness?

I. For adult outpatients with depressive disorder (major depressive disorder and dysthymia subtypes) and pediatric outpatients with major depressive disorder, do second-generation antidepressants differ in efficacy?

A. Major Depressive Disorder (MDD) in Adults

At the time of this review the following drugs are currently approved by the FDA for the treatment of depressive disorders in adults: citalopram, escitalopram, fluoxetine, paroxetine, sertraline, mirtazapine, duloxetine, venlafaxine, bupropion, and nefazodone. A comparative effectiveness review of the pharmacological treatment of adult depression, conducted for AHRQ (Agency for Healthcare Research and Quality), employed statistical methods to evaluate the comparative efficacy for each possible comparison among second-generation antidepressants.¹⁵ Authors used meta-regression and network meta-analyses to conduct indirect comparisons of the response rates of drugs with insufficient direct head-to-head evidence. Their conclusion was that results from direct and indirect comparisons indicate that no substantial differences exist among second-generation antidepressants. A fair meta-analysis comparing paroxetine with some second-generation antidepressants,¹⁶ a meta-analysis comparing venlafaxine to selective serotonin reuptake inhibitors¹⁷ and a systematic review conducting indirect comparisons of escitalopram with venlafaxine XR¹⁸ provide consistent results.

Since the publication of the AHRQ report 14 new head-to-head trials have been published.¹⁹⁻³² Results of these studies are consistent with the findings from the AHRQ report and it appears very unlikely that this new evidence would have led to changes in the statistical results.

Seven systematic reviews and 72 randomized controlled trials compared the effectiveness or efficacy of one second generation antidepressant to another for treating patients with MDD. All included studies compared equivalent doses of the compared drugs. We did not find any head-to-head studies conducted in a population with dysthymia, but we included three studies with active or placebo controls conducted in a dysthymic population. Most studies received a *fair* rating for internal validity. The generalizability of the results was hard to determine and might often be limited. Most trials (65 %) were of short (6 to 8 weeks) or medium (9 to 11 weeks) duration; 35 percent reported a follow-up of 12 weeks or more. Two European trials^{5,6} and one US trial⁷ in primary care settings, with less stringent eligibility criteria, could be viewed as effectiveness trials. These studies also had long periods of followup.^{6,7} Drug equivalency was present in all included studies. Trial reporting was often incomplete. Most articles did not report the method of randomization or allocation concealment. Although last-observation-carried-forward methods (or LOCF analysis, which means that the last observed measurement serves as the substitute for missing values because of the drop out of patients at different time points) were a frequent method of intention to- treat analysis, few authors reported the overall number of patients lost to follow-up from randomization to the end of the trial.

The percentage of imputed measurements, a potential source of bias, was sometimes hard to assess. Many studies did not report the ethnic backgrounds of participants.

Loss to follow-up (number of patients randomized who did not proceed to endpoint), a potential source of bias, was a frequent problem of internal validity. Only 21 trials (43%) reported a loss to follow-up of less than 20 percent. This high drop-out rate may be attributable to specific characteristics of a psychiatric outpatient population and a relatively high rate of adverse events in the examined drug class.

SSRIs compared to SSRIs in adult outpatients with MDD

Citalopram vs. escitalopram

Five published trials³⁶⁻⁴⁰ and one unpublished⁴¹ trial all of fair quality, compared the efficacy of escitalopram and citalopram. Two studies reported statistically significantly higher response rates for escitalopram than for citalopram treated patients (76.1% vs. 61.3%, $p < 0.05$ and 63.7% vs. 52.6%; $p = 0.021$).^{8,9}

In both studies escitaloprom also led to higher remission rates than escitalopram. One trial was a fair-rated European/Canadian flexible dose study that compared the efficacy and tolerability of citalopram (20-40mg/d) to escitalopram (10-20mg/d) and placebo in 471 depressed outpatients attending primary care centers.¹⁰ Loss to follow-up was 7 percent. Intention-to-treat results showed that the escitalopram group had significantly more responders ($\geq 50\%$ improvement on MADRS; 63.7% vs. 52.6%; $p = 0.021$) and remitters (MADRS < 12 ; 52.1% vs. 42.8%; $p < 0.036$) than the citalopram group. Escitalopram was numerically better at all time points on all three efficacy scales (MADRS, CGI-I, CGI-S). The study did not assess health outcomes. The fourth study was a fair fixed dose trial (escitalopram 10mg/d, citalopram 20mg/d) in 357 European primary care patients over 24 weeks.¹¹ Escitalopram patients had significantly higher response rates at week 8 (63% vs. 55%; $p < 0.05$) but not at week 24 (80% vs. 78%; $p = \text{NR}$). Escitalopram had a significantly lower CGI-S scores (1.75 vs. 2.00) and significantly fewer withdrawals (12.7% vs. 22.4%) than citalopram at week 24. A pooled analysis of data from three RCTs concluded that escitalopram significantly improved sleep disturbance compared to citalopram.¹² It may be significant, however, that both citalopram and escitalopram are produced by the same manufacturer who funded all four available studies. Generic brands of citalopram are available in the US, while escitalopram is still patented.

An unpublished, flexible-dose study, derived from the FDA-CDER database, did not find any statistically significant differences in efficacy outcomes between escitalopram and citalopram.⁴¹

The EPC conducted two meta-analyses of these studies comparing the effects of citalopram to escitalopram on MADRS scores at week 8. The outcome of the first meta-analysis was the relative risk of being a responder on the MADRS scale at week 8. A “response” was defined as an improvement of 50 percent or more on the MADRS scale. Pooled results included 1,769 patients and yielded a statistically significant additional treatment effect for escitalopram. The relative risk that a patient would respond was 1.15 (95% CI 1.08 to 1.22) for escitalopram relative to citalopram. Both random effects and fixed effects models presented similar, statistically significant results. The NNT to gain one additional responder based on the pooled risk difference is 12 (95% CI 7 to 32).

The second meta-analysis was an effect size meta-analysis assessing the pooled difference of points on the MADRS scale. The weighted mean difference (WMD) presented an additional treatment effect of a 1.51 point reduction (95% CI 0.58 to 2.45; $P=0.01$) for escitalopram compared to citalopram. Although statistically significant, the clinical significance of the actual difference in effect sizes may be questionable. A 1.3 point change on the MADRS represents about one-fifth to one-quarter of a standard deviation. A recent methods study concluded that, in general, a change of about one-half of a standard deviation on a health-related scale reflects a minimally important difference for a patient.

Citalopram vs. fluoxetine

In a fair-rated trial from France, 397 outpatients with MDD attending general practices were randomly assigned to citalopram (20mg/d) or fluoxetine (20mg/d) over 8 weeks.¹³ Loss to follow-up was 12.6 percent. No intention-to-treat analysis was conducted for efficacy measures. Citalopram had a faster onset of efficacy with significantly more patients rated as responding on the MADRS scale ($p = 0.048$) or completely recovered on MADRS and HAM-D scales ($p = 0.034$, $p = 0.025$) after 2 weeks. By 8 weeks, however, MADRS or HAM-D scores showed no statistically significant differences.

Citalopram vs. sertraline

A good-quality Swedish study assessed the effectiveness of citalopram (20-60mg/d) and sertraline (50-150mg/d) in 400 patients in general practice during 24 weeks of treatment.⁵ The majority of patients suffered recurrent depression (sertraline, 56%; citalopram, 65%) and used other medications for medical illnesses (sertraline, 55%; citalopram, 44.5%). Loss to follow-up was 18 percent. The investigators found no significant differences between treatment groups in any measures of depression severity at any point in time (MADRS, Clinical Global Impressions Severity Scale [CGI-S]), Clinical Global Impressions Improvement Scale [CGI-I]). Also, in a subgroup analysis of patients with recurrent depression, they did not report any differences in effectiveness between drugs. Response rates were similar at week 24 (sertraline, 75.5%. citalopram, 81.0%). This study was one of only a few trials that had not been funded by the pharmaceutical industry.

Escitalopram compared with fluoxetine

A fair, 8-week fixed dose trial evaluated the comparative efficacy of escitalopram (10 mg/d), fluoxetine (20 mg/d), and placebo in depressed patients 65 years or older.⁴⁵ At study endpoint neither active drug was more efficacious than placebo. MADRS response rates were 46 percent, 37 percent, and 47 percent for patients on escitalopram, fluoxetine, and placebo, respectively. Withdrawal rates were significantly higher among patients on fluoxetine than on escitalopram (17% compared with 26%; $P<0.05$).

Escitalopram compared with paroxetine

Two fair studies evaluated the comparative effectiveness and safety of escitalopram and paroxetine.^{27, 28} An 8-week flexible dose study (escitalopram : 10-20 mg/d; paroxetine 20-40 mg/d) did not identify any statistically significant differences in efficacy between the two treatment groups (MADRS) after 8 weeks of treatment.²⁸ Response (68% compared with 72%) and remission (56% compared with 65%) were similar between

patients on escitalopram and paroxetine. The second study, a 24-week fixed-dose trial reported similar findings, however, higher remission rates of patients on escitalopram than on paroxetine reached statistical significance after 24 weeks (75% compared with 67%; $P < 0.05$).²⁷ In both trials patients taking paroxetine had higher discontinuation rates than those on escitalopram. In the fixed dose study, this difference reached statistical significance (32% compared with 19%; $P < 0.01$).²⁷

Escitalopram compared with sertraline

A fair, 8-week trial, funded by the producers of escitalopram, compared fixed-dose escitalopram (10 mg/d) with flexible-dose sertraline (50-200 mg/d) in 212 outpatients with major depressive disorder.²⁰ At study endpoint, no differences in efficacy could be detected between the two treatment groups. Seventy-two percent of patients on escitalopram and 69 percent of patients on sertraline achieved HAM-D treatment response, 49% and 53% achieved remission. Other efficacy outcomes (HAM-A, CGI-I, CGI-S, CES-D) were also similar between treatment groups.

Fluoxetine vs. fluvoxamine

Two fair studies evaluated the comparative effectiveness and safety of fluoxetine and fluvoxamine in outpatients with MDD. A 7-week flexible dose study (fluoxetine: 20-80mg/d; fluvoxamine 100-150mg/d) did not identify any statistically significant differences in efficacy between the two treatment groups (HAM-D, HAM-A, CGI-S, Raskin-Covi Scale, Hopkins Symptoms Checklist).¹⁴ Both treatment regimens significantly improved scores on assessment scales. The second study was a 6-week fixed dose European trial (fluoxetine 20mg/d; fluvoxamine 100mg/d) in 184 outpatients with MDD.²⁷ Results are consistent with those of the flexible-dose study; the primary outcome measure (HAM-D) was not significantly different at any time. The drugs were equally effective for secondary outcome measures (CGI, Clinical Anxiety Scale [CAS], the Irritability, Depression, and Anxiety Scale [IDAS], Beck's Scale for Suicide Ideation [Beck's SSI]) such as suicidal ideation, sleep, anxiety, and severity of illness at endpoint. Fluvoxamine had significantly more responders on CGI-S (29% vs. 16%; $p < 0.05$) and a greater reduction of CGI-S scores ($p < 0.05$) at week 2 but not at weeks 4 or 6.

Fluoxetine vs. paroxetine

Seven fair-rated studies compared fluoxetine to paroxetine. Two RCTs were conducted in a population older than 60 years. The best trial was an Italian study lasting 1 year that enrolled 242 patients to compare the effects of fluoxetine (20-60mg/d) and paroxetine (20-40mg/d) on mood and cognitive function in depressed, nondemented persons (65 years or older).¹⁵ Paroxetine had a faster onset of action and a significantly greater improvement of HAM-D scores during the first 6 weeks (week 3: $p < 0.05$; week 6: $p < 0.002$). For up to a year paroxetine was effective in a higher percentage of patients than fluoxetine ($p < 0.002$ by Kaplan-Meier analysis). Treatment groups did not differ significantly in CGI scores. Fluoxetine had more severe adverse events than paroxetine (22 versus 9; $p < 0.002$).

The other six studies lasted 6 to 12 weeks. Loss to follow-up was between 20 and 36 percent. Two studies supported a faster onset of action of paroxetine than fluoxetine, four trials did not. Five studies did not find differences in the improvement of anxiety in patients with depression.

The EPC conducted a meta-analysis of six of these studies comparing the effects of fluoxetine to paroxetine on HAM-D scores at the end of follow-up. A “response” was defined as an improvement of 50 percent or more on the HAM-D scale. The seventh study could not be included because the article did not provide the necessary data.¹⁵ The statistical analysis included 795 patients. Results show that the response rate did not differ significantly between fluoxetine and paroxetine (RR: 1.09; 95% CI 0.97 – 1.21) for the random effects model, and the fixed effects model was similarly nonsignificant. Tests for heterogeneity were not significant. Funnel plot, Kendell’s test, and L’Abbe plot did not indicate major biases. However, given the small number of component studies, results of these tests must be viewed cautiously.

Fluoxetine vs. sertraline

Six studies compared fluoxetine to sertraline. The top-level evidence consisted of two effectiveness trials^{6,7} and one efficacy trial¹⁶ with long periods of follow-up. Two fair-rated, multicenter trials from France were conducted in office settings (private psychiatrists and general physicians [GPs]).^{6,16} The psychiatrists’ study randomized 238 patients for 24 weeks and the GP study 242 patients for nearly 26 weeks (180 days) to fluoxetine (20-60mg/d) or sertraline (50-150mg/d). The majority of patients had concomitant medical conditions. Both studies assessed quality of life as a secondary outcome measure (Sickness Impact Profile [SIP], Functional Status Questionnaire [FSQ]). Exclusion criteria were less stringent in the GP trial than the psychiatrist trial. Loss to follow-up was 4.5 percent in the GP trial and 29.8 percent in the psychiatrist trial. In the GP trial, researchers conducted outcome assessments only at day 120 and day 180, but patients could choose to consult the physician at any time. Intention-to-treat analyses in both studies did not reveal any statistically significant differences in any primary (MADRS, HAM-D, CGI) or secondary (Covi Anxiety Scale, HAD, SIP, Leeds Sleep Evaluation) efficacy measures.

The ARTIST trial was an open-label RCT designed as an effectiveness study and carried out in a primary care setting (primary care physicians) over 9 months.⁷ Treatments were randomly allocated. This study enrolled 601 patients at 76 primary care sites. Initial diagnosis for enrollment was not based on diagnostic criteria but rather on the judgment of the treating physician. Criteria-based evaluation classified 74 percent of patients as having MDD, 18 percent dysthymia, and 8 percent minor depression. Patients’ treatments could be switched among study drugs or to other antidepressive medications as needed. Intention-to-treat analysis maintained the original randomization. Outcome measures assessing changes in depression and health related quality of life measures (work, social and physical functioning, concentration and memory, sexual functioning) were administered over the telephone by a blinded third party. Range of dosage and loss to follow-up were incompletely reported. Results did not reveal any significant differences among drugs in any outcome measures at either 3 or 9 months. All treatment groups significantly improved during the study compared to baseline.

Three additional fair-rated trials did not find any significant differences in primary outcome measures (HAM-D, MADRS, CGI-S). Treatment durations varied from 6 to 16 weeks.

The EPC conducted a meta-analysis of five of these studies comparing the effects of fluoxetine to sertraline on HAM-D scores at study endpoint. All studies except one were

financially supported by the manufacturer of sertraline. Our outcome measure was the relative risk of being a responder on HAM-D or MADRS scales at study endpoint. A “response” was defined as an improvement of 50% or more on the HAM-D scale. Pooled results included 1,190 patients and yielded a modest additional treatment effect for sertraline just reaching statistical significance. The relative risk of being a responder at study endpoint was 1.10 (95% CI 1.01-1.22) for sertraline relative to fluoxetine. Both random effects and fixed effects models presented similar, statistically significant results. The NNT to gain one additional responder based on the pooled risk difference is 17. A meta-analysis of responders based only on the HAM-D scale did not yield different results. However, all included studies were of fair quality, with some having a loss to follow-up of more than 30 percent. Tests for heterogeneity were not significant. Funnel plot, Kendall’s test and L’Abbe plot did not indicate major biases. However, given the small number of component studies results of these tests must be viewed cautiously.

Paroxetine vs. fluvoxamine

Two RCTs one flexible-dose⁶⁰(old report) and one fixed-dose,⁶¹ compared the efficacy and safety of paroxetine (20-50mg/d) and fluvoxamine (50-150mg/d) in 60 outpatients with MDD.⁴⁰old report Loss to follow-up was 30 percent. Results presented no statistically significant differences on HAM-D, Ham-A, CGI, and SCL-56.

The fixed-dose trial provided consistent findings.⁶¹

Paroxetine vs. sertraline

One fair-rated Swedish RCT compared paroxetine (20-40mg/d) to sertraline (50-150mg/d) in a 24-week study.¹⁷ A total of 353 patients participated. Outcome measures included MADRS, CGI, and Battelle Quality of Life Measure (BQOL). Loss to follow-up was 35.4 percent. LOCF analysis yielded no significant differences in primary outcome measures (MADRS, CGI) at any point in time. Treatment groups did not differ significantly on BQOL factors.

Sertraline vs. fluvoxamine

A fair-rated, 7-week study compared the depression scores and tolerability of sertraline (50-200mg/d) and fluvoxamine (50-150 mg/d) in 97 depressed patients.¹⁸ Loss to follow-up was 30.9 percent. Efficacy did not differ significantly between treatment groups. A fair-rated, small Italian RCT (n = 64) randomly assigned asymptomatic patients with a history of unipolar depression and at least one episode within the past 28 months to prophylactic sertraline (100-200mg/d) or fluvoxamine (200-300mg/d) treatment for 24 months. Patients who remained without recurrence (n = 47) prolonged their treatment for another 24 months in an open-label manner. Primary outcome measures were monthly HAM-D assessments. There was no loss to follow-up. Recurrence during the first 2 years of prophylactic treatment did not differ significantly between treatment groups (single recurrence: 21.9% of sertraline-treated patients vs. 18.7% of fluvoxamine patients; z = 0.14, p = 0.88). At the 4-year follow-up, no significant differences in recurrences were apparent (sertraline, 13.6%; fluvoxamine, 20%).

Other second-generation antidepressants compared to SSRIs in adult outpatients with MDD.

Duloxetine vs. fluoxetine

A fair 8-week RCT assigned 173 patients to duloxetine (40-120mg/d), fluoxetine (20mg/d), or placebo.¹⁹ Overall loss to follow-up was 35 percent. Results revealed no statistically significant differences between duloxetine and fluoxetine in response (49% vs. 45%) and remission (43% vs. 30%). However, the fixed-dose design for fluoxetine but not for duloxetine reduces the validity of this direct comparison.

Duloxetine compared with escitalopram

Three fair, fixed-dose studies compared duloxetine (60 mg/d) to escitalopram (10-20 mg/d).^{19, 24, 25} The longest study (N=295) lasted 24 weeks.²⁴ An 8-week non-inferiority trial (N=684) did not detect any differences in onset of action or efficacy outcomes (HAM-D) between duloxetine and escitalopram.¹⁹ Likewise, after 24 weeks response (73% compared with 77%) and remission (70% compared with 73%) rates were similar between duloxetine and escitalopram. No differences in efficacy could be detected on the HAM-A and CGI-I scales after 24 weeks. In two trials patients on duloxetine had statistically significantly higher discontinuation rates due to adverse events than patients on escitalopram (17% compared with 9%; P<0.05).^{24, 25}

Duloxetine vs. paroxetine

Three fair, 8-week, fixed-dose trials assessed the comparative efficacy of duloxetine (80mg/d), duloxetine (120mg/d), paroxetine (20mg/d), and placebo.^{20, 23} In all three trials efficacy outcomes were similar among duloxetine and paroxetine regimens. In the largest study, 60 percent of patients on duloxetine achieved response and 49 percent remission compared with 65 percent and 50 percent of patients on paroxetine.²² Important to note is that these trials compared a low to medium dose of paroxetine (20 mg) to a medium (80 mg) and high dose (120 mg) of duloxetine.

Mirtazapine vs. fluoxetine

A Taiwanese study compared mirtazapine (30-45mg/d) to fluoxetine (20-40mg/d) over 6 weeks in 133 moderately depressed Chinese patients.⁴⁷ Overall loss to follow-up was 39.4 percent; the drop-out rate was higher in the mirtazapine than the fluoxetine group (45.5% vs. 33.3%; p = NR). LOCF analysis showed no significant differences in any primary outcome measures. More mirtazapine-treated patients than fluoxetine-treated patients reached response and remission at all time points of the study, but none of these differences was statistically significant.

Mirtazapine vs. paroxetine

Two trials assessed the efficacy of mirtazapine (15-45mg/d) and paroxetine (20-40mg/d). The German study enrolled 275 patients in a 6-week trial.²¹ The US trial randomized 255 participants for 8 weeks.²² Loss to follow-up was 23 percent and 27 percent, respectively. In both trials, mirtazapine and paroxetine were equally effective in reducing HAM-D scores at the endpoint. Mirtazapine led to a faster response in both trials. In the German study, 23.2 percent of mirtazapine-treated patients and 8.9 percent of paroxetine-treated patients responded to the treatment at week 1 (p < 0.002). A Kaplan-Meier analysis in the US trial showed a significantly faster time to response for mirtazapine than for paroxetine

(mean 26 days versus mean 40 days; $p = 0.016$). No significant difference in response rates on the CGI scale was noted. The NNT to yield one additional responder at weeks 1 or 2 is 7.

Mirtazapine vs. sertraline

One fair-rated, recent multinational European study examined the onset of efficacy of mirtazapine (30-45mg/d) compared to that of sertraline (50-150mg/d) in 346 outpatients.²³ Loss to follow-up was 20.8 percent. Onset of action was faster for the mirtazapine group. The mean change of HAM-D scores was significantly greater during the first 2 weeks for mirtazapine than for sertraline ($p < 0.05$); after 2 weeks the difference remained greater but lacked statistical significance. CGI scores did not show significant differences, but MADRS score were significantly greater at week 1 in the mirtazapine group.

Venlafaxine vs. citalopram

A fair European 6-month study compared venlafaxine ER (37.5-150mg/d) to citalopram (10-30mg/d) for the treatment of depression in elderly outpatients (mean age 73 years). No statistical differences in any outcome measures (MADRS, CGI-S, CGI-I) could be detected at study endpoint. The remission rates were 19 percent for venlafaxine and 23 percent for citalopram. Both treatment groups reached a 93 percent response rate.

Venlafaxine vs. escitalopram

Two fair 8-week studies assessed the comparative effectiveness of venlafaxine XR and escitalopram. A fair European, multinational study assigned 293 patients to escitalopram (10-20mg/d) or venlafaxine XR (75-150mg/d).²⁴ Results presented no statistically significant differences in response (Venlafaxine XR: 79.6%; escitalopram: 77.4%) and remission (Venlafaxine XR: 69.7%; escitalopram: 69.9%). Survival analysis of the intention-to-treat population indicated that escitalopram-treated patients achieved sustained remission 6.6 days earlier than patients on venlafaxine XR ($p < 0.01$). The second trial reported similar results. No statistically significant differences were apparent between venlafaxine XR and escitalopram in response (48% vs. 58.8%) and remission rates.

Venlafaxine vs. fluoxetine

A South American multicenter study with a good quality rating randomized 382 patients to venlafaxine (75-150mg/d) or fluoxetine (20-40mg/d) for 8 weeks²⁵. Patients were predominantly female and moderately to severely ill. The majority had a previous history of depression (venlafaxine, 79.6%; fluoxetine, 77.4%). Loss to follow-up was 12.3 percent. LOCF analysis yielded no significant differences between study groups in any primary efficacy measures (HAM-D, MADRS, CGI, Hopkins Symptom Checklist). Both treatment groups showed significant decreases of HAM-D and MADRS scores from baseline ($p < 0.05$). Response rates were similar in both treatment groups (venlafaxine, 80.6%; fluoxetine, 83.9%).

Three fair-rated studies reported mixed results about the efficacy of venlafaxine and fluoxetine in comorbid patients with high anxiety or GAD. Only one study reported significantly greater response rates on HAM-D (71.9% vs. 49.3%; $p = 0.008$) and MADRS (75.0% vs. 49.3%; $p = 0.001$) for venlafaxine than for fluoxetine.²⁶ At the end

of the trial, 59.4 percent of venlafaxine-treated patients and 40.3 percent of fluoxetine-treated patients were in remission ($p = 0.028$). All three studies presented greater improvements on anxiety scales (HAM-A, Covi Anxiety Scale) in patients treated with venlafaxine than with fluoxetine. However, differences were only statistically significant in one trial (Covi Anxiety scale: $p = 0.0004$).²⁶ Seven additional trials also provided inconsistent evidence on the efficacy of venlafaxine compared to fluoxetine. One study reported a significantly higher response rate of venlafaxine than fluoxetine (72% vs. 60%; $p = 0.023$).

The EPC conducted a meta-analysis of eight studies comparing venlafaxine to fluoxetine. All studies were financially supported by the manufacturer of venlafaxine. Three studies were excluded because of missing data.^{25, 32, 75} The main outcome measure was the response to treatment on HAM-D at study endpoint. Results, based on 2593 patients, show no statistical difference between venlafaxine and fluoxetine (relative risk 0.04; 95% CI -1.20E-04 – 0.080). Tests for heterogeneity were not significant. Funnel plot, Kendall's test, and L'Abbe plot did not indicate major biases. However, given the small number of component studies results of these tests must be viewed cautiously. The NNT based on the pooled risk difference is 34. However, most included studies were of fair quality, with some having a loss to follow-up of more than 30 percent. These findings are similar to results of a meta-analysis recently reported by Smith et al. (2002).²⁷

Venlafaxine showed a modest but statistically significantly greater standardized effect size (-0.14; 95% CI -0.22 to -0.06) and a significantly greater odds ratio (OR) for remission (OR 1.42; 95% CI 1.17 to 1.73) compared to fluoxetine. The OR for response was numerically greater for venlafaxine but did not reach statistical significance (OR: 1.17; 95% CI 0.99 to 1.38). This study included inpatients and therefore did not meet the eligibility criteria for this report.

Venlafaxine vs. paroxetine

Two fair studies compared venlafaxine to paroxetine. A Spanish study compared venlafaxine (75-150mg/d) to paroxetine (20-40mg/d) in outpatients ($n = 84$) with either MDD or dysthymia over 24 weeks.²⁸ The majority (88%) of patients were female. The percentage of dysthymic patients was not reported, and the authors did not differentiate between dysthymia and mild or moderate depression. Loss to follow-up was 32 percent, with a substantially higher loss to follow-up in the venlafaxine group (39% vs. 26%). Intention-to-treat analysis yielded no significant differences between treatment groups on any primary outcome measures (HAM-D, MADRS, CGI) at 24 weeks. However, sample size for this study was small, and it was underpowered because it had been designed as a pilot study.

A 12-week, British fixed-dose trial randomized 361 mainly moderately ill patients (based on CGI severity score) treated in 43 general practices to either venlafaxine XR (75mg/d) or paroxetine (20mg/d).²⁹ Loss to follow-up was 27.4 percent. Results revealed no significant differences in efficacy measures or quality of life scores between study groups.

Venlafaxine vs. sertraline

Two good trials and one fair trial²¹ compared the efficacy of sertraline to venlafaxine. A good quality Scandinavian trial compared venlafaxine (75-150mg/d) to sertraline (50-100mg/d) in 147 patients who were mainly moderately to markedly ill.³⁰ Study duration

was 8 weeks; loss to follow-up was 19 percent. Both treatment groups showed statistically significant reductions in MADRS, HAM-D, and CGI scores. Response rates on the HAM-D scale were higher for venlafaxine at the endpoint (83% vs. 68%; $p = 0.05$), as were remission rates (68% vs. 45%; $p = 0.008$). No significant differences were noted for response or remission rates on MADRS and CGI scales.

By contrast, the other two studies did not find any differences in efficacy between sertraline(50-150mg/d) and venlafaxine XR (75-225mg/d).

Bupropion vs. SSRIs

A recent, fair-rated meta-analysis compared the benefits and risks of bupropion to SSRIs as a class in 1,332 adult outpatients with MDD.³¹ The age of the participants ranged from 36 to 70 years. The analysis included five double-blinded, head-to-head RCTs with study durations from 6 to 16 weeks. Three trials assessed the efficacy and safety of bupropion versus sertraline, one assessed bupropion versus paroxetine, and one assessed bupropion versus fluoxetine. The weighted mean differences of CGI-S and HAM-A scores did not differ significantly between bupropion and SSRIs. However, the authors could not pool data on HAM-D and CGI-S because of lack of data.

Bupropion compared with escitalopram

A fair pooled data analysis of two identically designed randomized controlled trials assessed the comparative efficacy of bupropion XL (300-450 mg/d), escitalopram (10-20 mg/d), and placebo.²⁶ Both studies lasted 8 weeks and enrolled a total of 830 patients. No differences in efficacy could be detected between the two active treatments (HAM-D, CGI-I, CGI-S, HAD). After 8 weeks, 43 percent of patients on bupropion XL, 45 percent on escitalopram, and 34 percent on placebo achieved remission. Response rates were 62 percent, 65 percent, and 52 percent, respectively.

Bupropion vs. fluoxetine

A fair, 6-week study compared the efficacy of bupropion (225-450mg/d) and fluoxetine (20-80 mg/d) in 123 patients with moderate to severe depression.³² Loss to follow-up was 27.6 percent but similar in the two treatment groups. Results presented no significant differences in efficacy measures (changes of HAM-D, HAM-A, CGI-S, CGI-I scores). Response rates were similar for both drugs (bupropion, 62.7%; fluoxetine, 58.3%).

Another fair, 8-week RCT compared efficacy and sexual side effects of bupropion SR (150-400mg/d), fluoxetine (20-60mg/d), and placebo in 456 outpatients with MDD.⁶⁹ Loss to followup was 36 percent. Results showed no statistically significant differences in efficacy.

Bupropion vs. paroxetine

One fair RCT examined the efficacy of bupropion SR (100-300 mg/d) and paroxetine (10-40mg/d) in 100 outpatients ages 60 years or older (range 60-88 years) over 6 weeks. The majority of patients were white (bupropion SR: 98%, paroxetine: 90%) and female (bupropion SR: 54%, paroxetine: 60%) and had not used antidepressants for the current episode before enrollment (bupropion SR 83%; paroxetine 88%). The overall loss to follow-up was 16 percent with no significant difference between treatment groups. Statistical LOCF analysis showed that efficacy in any outcome measure did not differ

significantly between treatment groups. Response rates ($\geq 50\%$ reduction in HAM-D scores) were similar in both groups (bupropion SR 71%; paroxetine 77%). Both treatment groups improved significantly in quality-of-life scales (Quality-of-Life in Depression Scale [QLDS], Short Form-36 Health Survey [SF-36]) between baseline and endpoint ($p < 0.0001$), but the treatment groups did not differ significantly.^{33,34}

Bupropion vs. sertraline

A fair, 16-week trial assessed efficacy and tolerability of bupropion SR (100-300mg/d) and sertraline (50-200mg/d) in outpatients ($n = 248$) with moderate to severe depression. Intention-to-treat analysis with a LOCF method was used to assess main outcome measures. Loss to follow-up was 31.5 percent but similar in the two treatment groups. Efficacy measures (changes of scores on HAM-D, HAM-A, CGI-S, CGI-I) did not differ significantly by treatment group.

Nefazodone vs. fluoxetine

Three studies with identical protocols examined the effects of antidepressive treatment with either nefazodone or fluoxetine on sleep in outpatients with MDD. Data from these trials were pooled into one analysis.³⁵ A total of 125 patients with MDD and sleep disturbance were enrolled for 8 weeks. Loss to follow-up was 17 percent. Effects on sleep were measured by the Hamilton Depression Rating Scale (HADR) Sleep Disturbance Factor, Inventory for Depressive Symptomatology-Clinician Related (IDS-C), Inventory for Depressive Symptomatology – Self-Rated (IDS-SR), and EEG measurements. Nefazodone significantly improved sleep quality as assessed by clinician ratings and self reported evaluations ($p < 0.01$). Nefazodone and fluoxetine were equally effective in reducing depressive symptoms (changes in HAM-D scores). Response rates for depression were 47 percent for nefazodone and 45 percent for fluoxetine.

Nefazodone vs. paroxetine

Another fair, multi-national study enrolled 206 moderately depressed patients to an 8-week, acute-phase trial comparing nefazodone (200-600mg/d) to paroxetine (20-40mg/d). Patients who responded to acute treatment were enrolled in an open-label continuation phase ($n = 108$) from week 8 to month 6.³⁶ Overall loss to follow-up was 27.2 percent during the acute trial and 32.4 percent during the continuation phase. Both groups showed significant improvements from baseline HAM-A, HAM-D, and MADRS scores in the acute phase without significant differences between study groups. Clinical improvement was either maintained or improved during the open-label continuation phase without significant differences between groups.

Nefazodone vs. sertraline

A fair, multicenter European study assessed the efficacy and tolerability of nefazodone (100-600mg/d) and sertraline.³⁷ One hundred-sixty outpatients with moderate to severe depression were enrolled in this 6-week trial. Loss to follow-up was 24.4 percent. Intention-to-treat results did not show significant differences in efficacy between treatment groups. Response rates were similar (nefazodone 59%, sertraline 57%).

B. Dysthymia in Adults

The following drugs are currently approved by the FDA for the treatment of dysthymia in adults: citalopram, escitalopram, fluoxetine, sertraline, mirtazapine, bupropion, and nefazodone. We did not find any head-to-head trials among patients with dysthymia. Five placebo-controlled studies assessed efficacy and tolerability of fluoxetine, paroxetine, and sertraline in a population with dysthymia.

SSRIs compared to placebo in adults with dysthymia

Fluoxetine vs. placebo

A good RCT determined the efficacy and safety of fluoxetine (10-60mg/d) in elderly patients with dysthymia over 12 weeks.³⁸ ITT results of this NIMH-funded study indicated that fluoxetine had limited efficacy. Response rates on HAM-D did not differ significantly between fluoxetine and placebo (27.3% vs. 19.6%; $p = 0.4$). Likewise, no difference in quality of life could be detected. Statistically significant differences were limited to treatment group – time interactions which presented greater improvements over time on HAM-D and the Cornell Dysthymia Rating Scale (CDRS) for fluoxetine than for placebo.

A second study conducted in patients 18 years or older (mean 43 years) found that fluoxetine had significantly more responders (53.8% vs. 35.9%; $p = 0.03$) than placebo.³⁹ Remission rates favored fluoxetine but did not reach statistical significance (44.4% vs. 25.6%; $p = 0.07$).

In the older subgroup, paroxetine-treated patients showed a greater change in Hopkins Symptom Checklist (HSCL-D 20) scores than placebo-treated patients ($p = 0.004$) but not more change than patients on behavioral therapy ($p = 0.17$). For older dysthymia patients with high or intermediate baseline functioning scores, paroxetine improved mental health functioning significantly compared to placebo. Overall, however, improvements for paroxetine-treated dysthymia patients were not statistically significantly different from those on placebo. The younger subgroup did not show statistically significant differences between treatment groups on the HSCL-D scale. For dysthymia only, the remission rate was significantly higher in the paroxetine group than in the placebo group (80% vs. 40%; $p = 0.008$).

Sertraline vs. imipramine vs. placebo

One RCT compared sertraline (50-200mg/d) to imipramine (50-300mg/d) and placebo in 416 patients who had had the diagnosis of dysthymia for more than 5 years. Study duration was 12 weeks; loss to follow-up was 24.3 percent. Outcomes included quality of life and other measures of functional capacity. Both imipramine (64.0%) and sertraline (59.0%) had significantly more responders (CGI 1 or 2) than placebo (44.3%), but the two therapeutic groups did not differ significantly. Quality of life and overall psychosocial functioning improved significantly in both active treatment groups compared to the placebo group.

Sertraline vs. placebo

A multinational study enrolled 310 dysthymic patients for 12 weeks to compare sertraline (50-200mg/d) to placebo.⁴⁰ Loss to follow-up was 24.2 percent. Patients in the sertraline group had significantly greater reductions in most efficacy measures (MADRS, CGI, HAD-A, HAD-D, Structured Interview Guide for the Hamilton Depression Rating Scale,

Seasonal Affective Disorders Version [SIGH-SAD]), than did those in the placebo group. The rates of responders and remitters were also significantly higher in the sertraline group (Hamilton Rating Scale for Anxiety (HAM-A): $p = 0.001$; CGI-I: $p < 0.001$). The quality of life scale (BQLS) showed significantly greater improvements in eight of nine domains in the sertraline group.

C. Subsyndromal Depressive Disorders in Adults

Citalopram compared with sertraline

The only head-to-head evidence that we found was a nonrandomized, single-blinded trial (N=138) lasting 1 year which assessed the comparative efficacy and safety of citalopram and sertraline in patients with late-life minor depression or other subsyndromal depressive disorders.¹¹⁵ This study did not meet our formal eligibility criteria. Because it is the only available head-to-head evidence, we are briefly summarizing its results. Overall, both treatments improved depressive symptoms. No significant differences in efficacy could be detected at any time point. At the end of the study, remission was achieved by 53 percent of patients on citalopram and 42 percent on sertraline ($P=0.25$). Likewise, no differences in psychosocial functioning emerged.

Fluoxetine compared with placebo

A 12-week trial (N = 162) evaluated the efficacy of fluoxetine in patients with minor depression.¹¹⁶ Improvements on depression scales (HAM-D, Beck Depression Inventory [BDI], IDS-C) were statistically significantly greater for patients receiving fluoxetine than for those receiving placebo. Likewise, the overall severity of illness (CGI-S) improved statistically significantly more in the fluoxetine than in the placebo group ($P=0.002$). No significant differences could be detected in psychosocial outcomes.

Paroxetine compared with placebo

A large primary-care-based effectiveness study randomized 656 patients with dysthymia or minor depression to 11 weeks of paroxetine (10-40 mg/day), placebo, or behavioral therapy.^{111, 112} Participants were stratified into patients 60 years and older (N=415) and patients younger than 60 years (N=241) for ITT analysis. In the 60 or older subgroup, patients receiving paroxetine showed a greater change in HSCL-D-20 scores than those receiving placebo ($P=0.004$), but those on paroxetine did not demonstrate more change than patients on behavioral therapy ($P=0.17$).¹¹² Effects were similar for patients with dysthymia and minor depression. Paroxetine was not more efficacious than placebo in patients with minor depression in the younger subgroup.¹¹¹

D. Seasonal Affective Disorder in Adults

Currently, only bupropion has Food and Drug Administration-approval for the treatment of seasonal affective disorder. As in other chapters, we view Food and Drug Administration-approval as evidence for general efficacy, and therefore do not review placebo-controlled trials on drugs that have been Food and Drug Administration-approved.

We found three publications that met our eligibility criteria. These describe two studies assessing selective serotonin reuptake inhibitors, one placebo controlled trial of sertraline,

and one head-to-head randomized controlled trial comparing fluoxetine to light therapy.¹¹⁷⁻¹¹⁹

Sertraline compared with placebo

One fair study randomized 187 outpatients with DSM-III-R criteria for either major depression, depressive disorder NOS, bipolar disorder depressed or bipolar disorder NOS with a seasonal pattern to 8 weeks of sertraline (50-200 mg/d) or placebo.¹¹⁷ Sertraline was better than placebo at endpoint in the ITT population for all of the outcomes measured, including both physician (HAM-D-29, HAMD-21, HAM-D-17, HAM-D item 1, CGI-S, HAM-A) and patient assessed (HAD-D, HAD-A) measures of depression and anxiety. 62.4 percent of patients in the sertraline group achieved a CGI-I response (rating of one or two), compared with 46.2 percent in the placebo group, $P=0.04$. The mean final dose of sertraline was 111.3 ± 44.9 mg/d.

Fluoxetine compared with placebo

One fair study randomized 68 patients to treatment with either fluoxetine (20 mg/d) or placebo.¹²¹ The study duration of 5 weeks did not meet our eligibility criteria, however we mention it here due to lack of evidence. Clinical response, defined as a greater than 50 percent reduction in HAM-D-29 over the five weeks, was achieved by 59 percent of the fluoxetine group compared to 34 percent of the placebo group, a statistically significant result ($P<0.05$).

Fluoxetine compared with light therapy

One good randomized controlled trial compared fluoxetine 20 mg/d to light therapy (10 000 lux, 30 minutes/day between 7:00am and 8:00 am) in 96 patients with DSM-IV criteria for major depressive episodes with a seasonal pattern over 8 weeks.¹¹⁸ Primary outcomes measured were clinical response and remission, based on a reduction in HAM-D-24 of greater than fifty percent (response), plus a score of eight or less at endpoint (remission). Both fluoxetine and light therapy were shown to be effective over time, but there were no differences in clinical response rate (both 67%) or remission (54% and 50%, respectively). A subgroup analysis of severely depressed patients, defined as a HAM-D-24 of at least 30, also revealed comparable response (73% compared with 70%) and remission (50% compared with 48%) rates.

An additional fair randomized controlled trial comparing 5 weeks of fluoxetine 20 mg/d to light therapy (3000 lux, 2h/d, morning or evening) in 40 patients did not meet our eligibility criteria because of its short duration.¹²⁰ Results, however, were consistent with findings reported in the trial above. Seventy percent of patients treated with light therapy and 65 percent of the fluoxetine group achieved a response to treatment. Numerically more patients on light therapy than on fluoxetine achieved remission (50% compared with 25%; $P=0.10$).

Major Depressive Disorder in Children and Adolescents

Currently, fluoxetine is the only second-generation antidepressant approved by the FDA for treating MDD in children (2 to 12 years) and adolescents (13 to 18 years). Published evidence is based on controlled clinical trials of children and adolescents 7 to 18 years of

age. Fluvoxamine and sertraline are approved for the treatment of OCD in pediatric patients, although they are not approved for treating MDD.

A thorough review of published and unpublished studies for citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline, venlafaxine, and mirtazapine was conducted by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA).⁴¹ Based on analyses conducted by the Expert Working Group of the Committee on Safety of Medicines (CSM) of the MHRA, the agency concluded that only fluoxetine has been shown to have a favorable risk benefit profile. Conclusions were based on the fact that, with the exception of fluoxetine, clinical trial data failed to demonstrate efficacy in a pediatric population. In addition, an increased risk of suicidal thoughts and self-harm was observed consistently across drugs.

SSRIs compared to placebo in pediatric outpatients with major depressive disorder

Citalopram vs. placebo

One 8-week study randomized 174 children (7 to 11 years) and adolescents (12 to 17 years) with MDD to citalopram (20-40 mg/d) or placebo.⁴² Diagnosis was established with the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL). Overall loss to follow-up was 22 percent. The primary outcome was the mean change from baseline to endpoint in the CDRS-R. Secondary outcome measures included the CGI-I and CGI-S. At 8 weeks, intention-to-treat analysis confirmed significantly greater reduction in the CDRS-R for citalopram-treated patients than for placebo-treated patients ($p < 0.05$). Significant differences were not reported for secondary outcome measures.

Fluoxetine vs. placebo

Although we did not review placebo-controlled evidence for fluoxetine because the FDA has already established its general efficacy and tolerability, we did review the Treatment for Adolescents with Depression Study (TADS) because it specifically compared fluoxetine, fluoxetine plus CBT, CBT alone, and placebo.⁴³ In this good, 12-week, US-based multicenter study of 439 adolescents (12 to 17 years), placebo and flexible-dose fluoxetine (10-40 mg/d) were administered double-blind; CBT alone and CBT with fluoxetine were administered unblinded. Primary outcome measures included the CDRS-R and CGI-I. Overall loss to followup was 18 percent. Compared to fluoxetine alone ($p = 0.02$) and CBT alone ($p = 0.01$), treatment with fluoxetine plus CBT was superior on the CDRS-R. Both fluoxetine alone ($p < 0.001$) and fluoxetine plus CBT ($p < 0.001$) demonstrated significantly greater improvement on the CGI-I compared to placebo. The trial was subsequently extended to 36 weeks in an open label manner. 128 327 patients completed the trial, which did not include a placebo arm, and demonstrated equivalent effectiveness between fluoxetine, CBT and combination therapy (response rates 81% compared with 81% compared with 86%, respectively). Suicidal events were more common in the fluoxetine only group compared to the CBT only and combination groups across the 36 weeks of treatment (14.7% compared with 6.3% compared with 8.4%, respectively).

Paroxetine compared with placebo

Three multicenter, double-blinded, randomized-controlled trials compared flexible-dose paroxetine to placebo. 129-131 One 8-week study conducted in 12 centers in the US and

Canada randomized 275 adolescents (12 to 18 years) to double-blind treatment with paroxetine (20-40 mg/d), imipramine (200-300 mg/d), or placebo.¹²⁹ One fair international study based in South Africa randomized 286 patients aged 13-18 to 12 weeks of paroxetine 20-40 mg/day or placebo,¹³⁰ and one fair US based trial randomized 206 patients aged 7-17 to 8 weeks of paroxetine 10-50 mg/day or placebo.¹³¹ All patients met DSM-IV criteria for major depressive disorder. Patients were generally excluded if they had another psychiatric condition or posed a serious suicide risk. The primary outcomes were HAM-D, CDRS-R, MADRS and K-SADS-L depression subscale score. Secondary measures included CGI-I, CGI-S, BDI, MFQ. All three studies reported similar response rates between patients treated with paroxetine and placebo. For example in the South African study, in 13-18 year old patients a reduction in MADRS of greater than 50 percent was achieved in 60.5 percent of the paroxetine group and 58.2 percent of the placebo group.¹³⁰ A post hoc sub-group analysis of patients 16 or younger demonstrated a numerical advantage for placebo over paroxetine in MADRS response (placebo 64.9% compared with paroxetine 55.1%). Similarly, the US study of 7-17 year olds demonstrated no difference between paroxetine and placebo in any outcome (change in CDRS score, CGI-I or CGI-S). The post hoc sub-group analysis of 7-11 year old children also revealed a trend for better outcome with placebo over paroxetine (change in CDRS 5.3 points in favor of placebo, $P=0.054$).

Sertraline vs. placebo

One published multinational (US, India, Canada, Costa Rica, and Mexico) study pooled data from two double-blind RCTs conducted in 53 centers.⁴⁴ These identically designed, concurrently conducted 10-week trials randomized 376 children and adolescents (6 to 17 years) to flexible-dose sertraline (50-200 mg/d) or placebo. Significantly more sertraline-treated patients were female ($p = 0.02$). Twenty percent of randomized participants did not complete the study. The primary efficacy measure was mean change from baseline score on the CDRS-R. In the intention-to-treat analysis, sertraline-treated patients had a significantly greater mean change in CDRS-R score ($p < 0.01$). Significant differences were observed as early as week 3. Secondary efficacy measures included treatment response ($\geq 40\%$ decrease in CDRS-R or CGI-I score of 2 or lower), symptoms of anxiety (Multidimensional Anxiety Scale for Children [MASC]), patient's social functioning [CGAS], and quality of life [PQ-LES-Q]). Significantly more sertraline-treated patients were defined as treatment responders ($p < 0.05$). Statistically significant differences were not observed for measures of anxiety, social functioning, or quality of life. Of note for this study is the fact that only pooled data from the two independent trials were published. Before this pooling, neither trial had demonstrated a consistent advantage for sertraline over placebo (data available at <http://medicines.mhra.gov.uk>). One trial reported significantly more sertraline-treated CDRS-R responders ($p = 0.033$ compared to placebo).

Escitalopram compared with placebo

One fair 8 week trial randomized 268 children aged 6-17 years to either flexible dose escitalopram 10-20 mg/day or placebo.¹³³ The primary outcome measure was change in baseline score on the CDRS-R. Escitalopram showed no advantage over placebo in either the primary outcome or any of the secondary outcomes measured (CGI-S, CGI-I, CGAS) for children aged 6-17. A post hoc analysis of children aged 6-11 years and adolescents

aged 12-17 years demonstrated a statistically significant advantage for escitalopram in CGI-S, CGI-I and CGAS, but not CDRS-R for adolescents only. The results in the 6-11 year old subgroup remained equivocal.

SNRIs compared to placebo in pediatric outpatients with major depressive disorder

Venlafaxine vs. placebo

One 6-week trial randomized 40 children and adolescents (8 to 18 years) to treatment with venlafaxine and psychotherapy or placebo and psychotherapy.⁴⁵ Of participants randomized to active treatment, children (8 to 12 years) received venlafaxine in fixed doses of 37.5 mg/d and adolescents (13 to 18 years) received fixed doses of 75 mg/d. An intention-to-treat analysis was not conducted, thereby excluding 17.5 percent of participants randomized to venlafaxine or placebo (15% and 20%, respectively). Efficacy measures evaluated mean change from baseline on two clinician-rated depression scales (HAM-D and CDRS-R), a patient-rated symptoms scale (CDI), and a parent-rated measure of behavioral functioning (CBCL). Compared to placebo, statistically significant differences from baseline were not reported for any of the efficacy measures.

Systematic review of published and unpublished data comparing SSRIs and SNRIs to placebo in pediatric outpatients with major depressive disorder

Three systematic reviews evaluated published and unpublished studies comparing a SSRI or SNRI to placebo in children and adolescents.⁴⁶ [123-125](#)

The largest report reviewed studies comparing citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine to placebo were reviewed, including data for 2,145 randomized participants (5 to 18 years). The authors abstracted data on remission and response (where appropriate criteria were used), and mean depression score. Scales and responder definitions were different for each study. Risks were assessed by abstracting data on suicide-related behaviors and discontinuation of treatment due to adverse events. Risk-benefit profiles were evaluated for each drug. Fluoxetine was the only second-generation reported to have a favorable risk-benefit profile. Data from two unpublished citalopram trials supported a negative risk/benefit profile, although evidence of efficacy was stated to be limited. Published and unpublished data combined for paroxetine demonstrated no improvement in depressive symptoms and little effect on response; additionally, an increased risk of serious adverse events was reported. Unpublished data on sertraline indicated that it may be even less effective than reported in published trials. Combined, published and unpublished data on venlafaxine suggested a negative risk-benefit profile. This review highlights distinctions between published and unpublished studies, revealing the potential for publication bias. In this study that reviewed more comprehensive evidence than published studies alone, the authors concluded that fluoxetine is the only second-generation antidepressant to demonstrate a favorable risk-benefit profile for the treatment of pediatric outpatients with MDD.

II. For adult outpatients with anxiety disorders (generalized anxiety disorder, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder), do second-generation antidepressants differ in efficacy?

Generalized Anxiety Disorder (GAD)

Currently, two SSRIs; escitalopram and paroxetine, are approved by the FDA for the treatment of GAD. In addition, one SNRI; venlafaxine and one selective serotonin and norepinephrine reuptake inhibitor (duloxetine) is approved for the treatment of GAD. Two head-to-head trials compared one second-generation antidepressant to another for the treatment of GAD, although one was excluded from this review because of high loss to follow-up.¹⁰⁵ FDA-approved evidence supports the general efficacy of escitalopram, paroxetine, and venlafaxine and duloxetine for treating GAD. Additional placebo-controlled evidence supporting the general efficacy these drugs was not reviewed. . We included four placebo-controlled trials (eight publications) of escitalopram, paroxetine, and venlafaxine that included measures of quality of life, functional capacity, or somatic symptoms. Additionally, we identified one trial (two publications) that assessed efficacy and tolerability of sertraline; an SSRI currently not FDA-approved for GAD. Included placebo-controlled escitalopram, paroxetine, and venlafaxine trials addressed a range of health outcomes not commonly addressed in FDA approval. Two RCTs comparing paroxetine to placebo and one RCT comparing venlafaxine to placebo evaluated measures of functional capacity; the paroxetine studies utilized the Sheehan Disability Scale (SDS) to assess health-related disability, and the venlafaxine trial used the Social Adjustment rating Scale-Self Report (SAS-SR). One escitalopram trial assessed quality of life with the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). A secondary analysis of pooled data from placebo-controlled venlafaxine XR trials reported on somatic and psychic symptoms.

SSRIs compared to SSRIs in adult outpatients with GAD

Escitalopram compared with paroxetine

A fair rated randomized controlled trial compared escitalopram to paroxetine (and placebo) in 681 patients over a 12 week duration.¹³⁵ All active arms were found to improve the symptoms of generalized anxiety disorder compared to placebo. Escitalopram 10 mg was shown to be more effective than paroxetine 20 mg. In the case of CGI-I, escitalopram 10 mg was significantly superior to paroxetine 20 mg at week 12, $P < 0.05$ (Data = NR) and the difference in the HAM-A at 12 weeks was -2.06 (95% CI -3.90 to -0.21, $P < 0.05$).

Paroxetine compared with sertraline

One fair rated RCT compared paroxetine (10-40mg/d) to sertraline (25-100mg/d) in 55 patients with GAD.⁴⁷ Study duration was 8 weeks. At study endpoint no statistically significant differences in any outcome measures were apparent. Both treatment groups experienced significant reductions in HAM-A scores with similar response (paroxetine 68%, sertraline 61%) and remission rates (paroxetine 40%, sertraline 46%). Likewise no differences could be detected in quality of life outcome measures.

Selective serotonin reuptake inhibitors compared to serotonin and norepinephrine reuptake inhibitors in adult outpatients with generalized anxiety disorder

Paroxetine compared with venlafaxine

A poor quality study compared venlafaxine and paroxetine.¹³⁶ This small study with 46 participants and a high drop-out rate of 30 percent found no difference between the two

treatments. The rates of response (> 50% reduction in the HAM-A) were 90.5 percent for venlafaxine compared with 92 percent for paroxetine ($P=0.855$).

Serotonin and norepinephrine reuptake inhibitors compared to selective serotonin and norepinephrine reuptake inhibitor in adult outpatients with generalized anxiety disorder

Venlafaxine compared with duloxetine

A comparison of venlafaxine and duloxetine found no differences between the two treatments in a large ($N = 487$), poor quality study (attrition > 40%).¹³⁸ The mean decrease in the HAM-A total scores was 11.8 for duloxetine and 12.4 for venlafaxine. Treatment response was similar with > 50 percent reduction in the HAM-A in 47 percent of duloxetine- and 54 percent of venlafaxine-treated patients.

SSRIs compared to placebo in adult outpatients with GAD

Sertraline vs. placebo

Currently, sertraline is not FDA-approved for the treatment of GAD. We identified two placebo controlled trials that assessed the efficacy and tolerability of sertraline in GAD.⁴⁸ ¹³⁹⁻¹⁴¹ Overall these studies found that sertraline could result in better efficacy than placebo in the treatment of generalized anxiety disorder.

A 12-week, multicenter, multicountry trial randomized 378 outpatients with a primary diagnosis of DSM-IV- defined anxiety disorder to sertraline 50-150 mg/d or placebo. Patients with a history of other psychiatric disorders, including MAD, were excluded. The primary efficacy measure was the HAM-A; secondary assessments included the CGI-I, CGI-S, MADRS, HADS, Q-LESQ, the Endicott Work Productivity Scale, and the HAM-A psychic and somatic anxiety factors. At endpoint, the mean reduction in HAM-A total score was -11.7 for the sertraline group and -8.0 for the placebo ($p < 0.0001$). Additionally, sertraline was significantly better than placebo on all secondary assessments, including the quality-of-life and work productivity measures. A 10-week, multicenter, multinational trial randomized 326 outpatients with a primary diagnosis of DSM-IV- defined anxiety disorder to sertraline 50-200 mg/d or placebo. The inclusion/exclusion criteria were similar to those above as were the outcomes. At endpoint, the mean reduction in HAM-A total score was -12.71 for the sertraline group and -11.15 for the placebo ($P=0.032$). Additionally, sertraline was significantly better than placebo on secondary assessments, including the quality-of-life and CGI measures.

Obsessive-Compulsive Disorder

The FDA has approved the following SSRIs for the treatment of OCD: fluoxetine, sertraline, paroxetine, and fluvoxamine.

SSRIs compared to SSRIs in adult outpatients with OCD

Sertraline vs. fluoxetine

A multicenter Canadian study evaluated the use of sertraline (50-200 mg/d) and fluoxetine (20- 80 mg/d) in 150 patients over a 24-week period.⁴⁹ More than 79 percent of patients had a duration of illness of 10 years or more. Loss to follow-up was 29

percent, with no differential between fluoxetine- and sertraline-treated groups. At 24 weeks, mean response (Y-BOCS) did not differ significantly between the groups, although sertraline-treated patients had shown statistically greater improvement in mean change from baseline (Y-BOCS) at weeks 4, 8, and 12. Remission rates were greater for sertraline-treated patients at week 12 but not at week 24. Both sertraline and fluoxetine showed equivalent efficacy in improving secondary symptoms of depression (HAM-D) and generalized anxiety (CAS).

Other second-generation antidepressants compared to SSRIs in adult outpatients with OCD

Venlafaxine vs. paroxetine

A 12-week Dutch study evaluated the use of venlafaxine XR (75-300 mg/d) and paroxetine (15- 60 mg/d) in 150 patients.⁵⁰ Loss to follow-up was 33%. At 12 weeks, efficacy as reported by the mean reduction in Y-BOCS total score did not differ significantly between the two groups. Analysis of Y-BOCS obsessions and compulsions subscales revealed an equally high treatment effect over time. Also, response rates (full response \geq 50% reduction in Y-BOCS; partial response \geq 35% reduction in Y-BOCS) did not differ at the end of the trial. Quality of life was assessed using the Lancashire Quality of Life Profile: extended Dutch version (LqoLP). Both groups improved on all domains following treatment without showing a significant difference.

In one head-to-head trial, after a 4-week tapering phase the investigators switched 43 nonresponders to 12 weeks of therapy with the alternate treatment.⁵¹ At the end of 12 weeks, intention-to-treat analysis demonstrated a mean decrease on the Y-BOCS of 1.8 in the venlafaxine group and 6.5 in the paroxetine group. Responder rates (Y-BOCS) were 56 percent for paroxetine and 19 percent for venlafaxine; 42 percent of the nonresponders benefited from the crossover.

Escitalopram compared with paroxetine

A 24-week multinational study compared escitalopram (10 or 20 mg/day), paroxetine (40 mg/day and placebo in 466 patients.¹⁵¹ Attrition was 29 percent. At 12 (primary outcome) or 24 weeks, efficacy as reported by the mean reduction in Y-BOCS total score did not differ significantly between the two active groups, nor did the response rates (either CGI-I = 1 or 2 or $>$ 25% Y-BOCS decrease) differ between paroxetine or escitalopram groups.

SSRIs augmentation compared to SSRI alone in adult outpatients with OCD

A 12-week trial assessed the additional benefits of augmenting treatment with citalopram (40- 80mg/d) with mirtazapine (15-30 mg/d) in 49 outpatients with OCD.⁵² Patients were randomized to citalopram plus placebo or citalopram plus mirtazapine. Obsessive-compulsive symptoms were measured with the Y-BOCS; secondary outcome measures included the HAM-D and CGI-I. Loss to follow-up was 8 percent. At endpoint, no significant differences were reported between the two treatment groups. Patients augmented with mirtazapine had a significantly greater reduction in Y-BOCS total score beginning at week 2, although this difference persisted only through week 6 of the study.

SSRIs compared to placebo in adult outpatients with OCD

Meta-analyses

Four meta-analyses reviewed available evidence from placebo-controlled studies; we rated three analyses as fair quality one as good quality 148. One study pooled results from 10 trials that compared SSRIs *as a class* with placebo.⁵³ Data representing 1,076 patients were pooled to define the SSRI group, which consisted of fluvoxamine (five studies), fluoxetine (two studies), and sertraline (three studies). Several studies incorporated multiple dosing arms in the study design. For these trials, only the highest dosing arm was incorporated in the meta-analytic results.

As a class⁶⁰, SSRIs were found to be superior to placebo. For obsessive-compulsive symptoms considered together, an effect size of 0.47 (95% Confidence Interval [CI], 0.33, 0.61) was observed for SSRIs compared to placebo. Effect sizes generally were consistent for each of the SSRIs when compared to placebo.

A second meta-analysis evaluated placebo-controlled trials of fluvoxamine, fluoxetine, sertraline, and paroxetine.⁵⁴ Specifically, this study used meta-regression to identify sources of heterogeneity in these trials (and clomipramine trials). They identified 12 trials published before 2000 that compared SSRIs to placebo. Only studies that assessed efficacy with Y-BOCS were incorporated in the meta-regression. Effect sizes were estimated as the difference in improvement (decrease in Y-BOCS) between active drug and placebo. Four fluvoxamine studies showed a net improvement of -4.84 (95% CI, -7.78, -1.83). For the three fluoxetine studies, net improvement was -1.61 (95% CI -2.18, -1.04); for four sertraline studies, the pooled difference in Y-BOCS was calculated to be -2.47 (95% CI, -6.13, 1.20). Only one paroxetine study was included; the difference in improvement was estimated as -3.00 (95% CI, -4.91, -1.09).

A third meta-analysis assessed medication effect sizes in six published placebo-controlled trials;⁵⁵ two fluvoxamine studies; two sertraline studies; and two fluoxetine studies. Compared to placebo, effect sizes did not differ significantly between the three SSRIs evaluated.

A fourth meta-analysis included 17 studies and 3097 participants. 148 All consisted of placebo comparisons compared with; five used sertraline, five fluvoxamine, three compared fluoxetine, three paroxetine and one used citalopram. Overall, the drugs evaluated provided greater efficacy than placebo, however, there were differences in the incidence of adverse events, in particular nausea. Citalopram, fluvoxamine and paroxetine all had a greater rate of nausea compared to placebo and fluoxetine and sertraline did not.

Citalopram vs. placebo

A fair multicenter study conducted in Europe and South Africa compared various fixed-doses of citalopram to placebo in 401 outpatients with OCD characterized as stable for more than 6 months.⁵⁶ Loss to follow-up was 16 percent, with small differences between groups. All three doses of citalopram produced significantly more responders ($\geq 25\%$ improvement in Y-BOCS) than placebo ($p < 0.01$). The high-dose citalopram (60mg) response reached statistical significance at week 3, whereas the lower doses (20mg and 40mg) reached statistical significance at week 7. On the patient-rated Sheehan Disability Scale, the citalopram-treated patients showed significant improvements for most items.

Panic Disorder

Only fluoxetine, paroxetine, sertraline, and venlafaxine are currently approved by the FDA for the treatment of panic disorder. We viewed FDA approval as evidence for general efficacy and did not review placebo-controlled trials of fluoxetine, paroxetine, sertraline, and venlafaxine if no additional health outcomes were assessed.

SSRIs compared to SSRIs in adult outpatients with Panic Disorder

Four fair double-blinded RCTs compared the efficacy and tolerability of one SSRI to another.

Citalopram vs. escitalopram

One multicenter study randomized 366 patients with panic disorder to citalopram (10-40mg/d), escitalopram (5-20mg/d), or placebo.⁵⁷ Study duration was 10 weeks. Patients with and without concomitant agoraphobia were included. Quality of life and health-related functional capacity were additional outcome measures. Loss to follow-up was 32 percent. The frequency of panic attacks was significantly reduced for escitalopram compared to placebo ($p = 0.04$) but not for citalopram compared to placebo. Both treatments significantly improved quality of life, panic disorder symptoms, and severity of the disease ($p < 0.05$) compared to placebo. The article does not report a direct comparison of citalopram to escitalopram.

Sertraline vs. paroxetine

A German RCT randomized 225 patients with panic disorder to paroxetine (40 – 60 mg/d) or sertraline (50 – 150 mg/d).⁵⁸ Study duration was 12 weeks. Patients with and without concomitant agoraphobia were included. Quality of life was assessed as a secondary outcome measure. Results revealed no statistically significant differences in PAS (Panic and Agoraphobia Scale) scores between treatment groups ($p = 0.589$). Furthermore, no statistical differences in secondary outcome measures (PAS subscales, CGI-S, HAM-A, Sertraline-Quality of Life Battery) could be detected.

Venlafaxine ER compared with paroxetine

Two multi-national fixed-dose randomized controlled trials compared two different doses of venlafaxine ER to paroxetine (venlafaxine ER 75 mg/d or 150 mg/d compared with paroxetine 40 mg/d and venlafaxine ER 75 mg/d or 225 mg/d compared with paroxetine 40 mg/d).^{169, 170} Both studies received a fair rating for internal validity. Loss to follow up was reported as 20.8 percent and 20.1 percent, respectively. Results provided mixed findings. The study conducted in Europe (N=664) demonstrated no statistically significant difference in efficacy between venlafaxine ER 75 mg/d or 150 mg/d and paroxetine 40 mg/d (patients free from full-symptom panic attacks at 12 weeks: 54.4% compared with 59.7% compared with 60.9%).¹⁶⁹ In the second trial (N=653), the venlafaxine ER 225 mg/d group had a significantly greater percentage of patients free of full-symptom panic attacks at the 12 week endpoint compared to the paroxetine 40 mg/d group (70.0% compared with 58.3%; $P < 0.05$) and also had a significantly lower PDSS score (4.78 compared with 6.26; $P < 0.05$).¹⁷⁰ However, this study compared a high dose of venlafaxine ER to a medium dose of paroxetine.

SSRIs compared to placebo in adult outpatients with Panic Disorder

Fluvoxamine vs. placebo

Three fair-rated studies, all lasting 8 weeks, compared fluvoxamine (50-300mg/d) to placebo. The first study enrolled 75 patients to fluvoxamine (50-300mg/d), placebo, or cognitive therapy.⁵⁹ Loss to follow-up was 20 percent. Outcome measures included functional capacity (Sheehan Disability Scale). Statistical analysis did not fulfill accepted criteria for intention-to-treat analysis (only subjects who completed 3 weeks of medication were analyzed). Fluvoxamine showed significantly greater improvements in all primary (Panic Attack Severity Score, Clinical Anxiety Score [CAS], CGI, MADRS) and secondary (Sheehan Disability Scale) efficacy measures compared to placebo. The second study randomized 50 patients to fluvoxamine (50-300mg/d) or placebo.⁶⁰ Loss to follow-up was 28 percent, and no intention-to-treat analysis was done. The fluvoxamine group reported significantly fewer major panic attacks starting at week 4 until the endpoint ($p < 0.05$); they also had significantly lower scores on CAS and MADRS ($p < 0.05$). By contrast, active drug and placebo groups did not differ significantly in terms of minor panic attacks and Sheehan disability scores. The third trial enrolled 188 participants. Loss to follow-up was about 35 percent. Results were consistent with the other studies. Fluvoxamine showed a significantly greater efficacy in most primary (Daily Panic Attack Inventory) and secondary (MADRS, CGI-I, CGI-S, CAS, Sheehan Disability Scale) outcome measures compared to placebo.

Post-Traumatic Stress Disorder (PTSD)

For PTSD, we found two head-to-head studies; one comparing citalopram to sertraline, and one comparing nefazodone to sertraline. No other second-generation antidepressants were compared to one another. Currently only sertraline and paroxetine are FDA-approved for treating PTSD. We viewed FDA approval as evidence for general efficacy and did not review placebo controlled trials of sertraline and paroxetine if no additional health outcomes were assessed.

SSRIs compared to other second-generation antidepressants in adult outpatients with PTSD

Sertraline vs. Citalopram

A fair study randomized 59 outpatients with PTSD to 10 weeks of citalopram (20-50 mg/d), sertraline (50-200 mg/d), or placebo.⁶¹ Primary outcomes measures (CAPS, BDI) did not indicate any statistically significant differences in efficacy between citalopram and sertraline and between the active treatments and placebo.

Sertraline vs. Nefazodone

A fair-rated RCT randomized 37 patients with PTSD to 12 weeks of sertraline (50-200mg/d) or nefazodone (100-600mg/d).⁶² Sertraline- and nefazodone-treated patients did not differ significantly on primary (CAPS2, CGI) and secondary outcome measures (DTS, MADRS, PSQI, SDS, HAM-A). Both treatment groups had statistically significant improvements within group from baseline to endpoint on all outcome measures. Loss to follow-up was 38 percent; the rate of post-randomization exclusion because of lack of data was 28 percent. However, treatment groups of analyzed participants did not differ in baseline characteristics.

Results of this study were consistent with findings from an open-label trial in Turkish earthquake survivors.¹⁷⁸ This study met our formal eligibility criteria; however we determined it to be of poor quality (completers analysis only). Because of the lack of head-to-head evidence we are including its findings. Sixty earthquake survivors received sertraline or nefazodone in a non-randomized manner, based on availability. No differences in efficacy outcomes (Posttraumatic Stress Diagnostic Scale [PDS], Posttraumatic Stress Disorder Scale [TOP-8], CGI) could be detected between patients on sertraline or nefazodone after 6 months of treatment.

Sertraline compared with venlafaxine

A fair 12-week, placebo-controlled randomized controlled trial (N=538) evaluated the comparative efficacy and safety of sertraline (25-200 mg/d) and venlafaxine ER (37.5-300 mg/d).¹⁷⁹ At study endpoint, 30.2 percent on venlafaxine ER and 24.3 percent on sertraline achieved remission. In other primary outcome measures the efficacy of sertraline and venlafaxine ER was similar (CAPS, CGI-S, Assessment of Functioning [GAF], Vulnerability to the Effects of Stress Scale [SVS]). Both treatment groups had statistically significant improvements on all outcome measures compared with placebo.

SSRIs compared to placebo in adult outpatients with PTSD

Fluoxetine vs. placebo

Three placebo-controlled randomized controlled trials provide conflicting results on the general efficacy of fluoxetine for the treatment of post-traumatic stress disorder.

A small fair-rated study enrolled 54 patients to 12 weeks of fluoxetine (10-60mg) or placebo.⁶³ Loss to follow-up was 31.5 percent. Using the Duke Global Rating for PTSD cut-off score of 1 (no symptoms) to define responders, the fluoxetine group had significantly more responders than the placebo group (59% vs. 19%; $p < 0.005$).

According to Duke Global Rating for PTSD cut-off scores of 1 (no symptoms) or 2 (minimal symptoms) to define responders, a nonstatistically significant trend toward fluoxetine was observed ($p = 0.06$). Health-related secondary outcome measures (SIP, disability and stress subscales) showed significantly greater improvements for fluoxetine ($p < 0.005$). A Kaplan-Meier analysis reported a significantly faster onset of efficacy for fluoxetine ($p < 0.005$) than for placebo.

Two additional, fair studies did not detect any statistically significant differences between fluoxetine and placebo for the treatment of post-traumatic stress disorder. One study was a 12-week, fixed-dose (fluoxetine 20 or 40 mg/d) trial (N=411) that enrolled primarily women (71%) with post-traumatic stress disorder.¹⁸¹ At study endpoint both primary outcome measures (TOP-8, CAPS) showed similar efficacy outcomes between fluoxetine and placebo. The other trial (N=88) was an 8-week flexible-dose randomized controlled trial that compared fluoxetine (20-60 mg/d) to placebo, psychotherapy, or eye movement desensitization and reprocessing.¹⁸² No significant difference in CAPS scores were detected at endpoint between fluoxetine- and placebo-treated patients.

Venlafaxine compared with placebo

A fair, 6-month, placebo-controlled randomized controlled trial assessed the efficacy of venlafaxine ER (37.5-300 mg/d) in 329 patients with post-traumatic stress disorder.¹⁸³ Overall improvements were significantly greater for patients on venlafaxine ER than on placebo (CAPS, CGI-S, HAM-D). After 6 months, 51 percent of patients on venlafaxine

ER achieved remission compared with 38 percent on placebo ($P=0.01$). Patients on venlafaxine ER had also greater improvements than the placebo group with respect to quality of life and functional capacity. Withdrawal rates were similar between groups.

Social Anxiety Disorder

Currently, three SSRIs ; fluvoxamine CR, paroxetine and sertraline, are approved by the FDA for the treatment of social anxiety disorder. In addition, the extended release formulation of one SNRI; venlafaxine, is approved for the treatment of social anxiety disorder.

SSRIs compared to SSRIs in adult outpatients with social anxiety disorder

One fair-rated double-blinded RCT compared the efficacy and tolerability of one SSRI to another.

Escitalopram vs. paroxetine

One multinational study randomized 839 patients with social anxiety disorder to fixed doses of escitalopram (5, 10, or 20 mg/d), paroxetine 20 mg/d, or placebo.⁶⁴ Eligible patients had a baseline LSAS score of 70 or higher with a score of 5 or higher on one or more of the SDS subscales. Overall loss to follow-up in this 24-week trial was 29 percent. The primary outcome measure was mean change from baseline to week 12 in the LSAS total score; secondary outcome measures included the LSAS subscales, CGI-I, CGI-S, and SDS. No significant differences in LSAS total score were observed between any escitalopram treatment group and the paroxetine group in the intention-to-treat analysis. The authors did not report any intention-to-treat results for secondary outcome measures. In the observed-cases-analysis at 24 weeks, escitalopram 20 mg/d was superior to paroxetine 20 mg/d on the CGI-S. Significant differences (favoring escitalopram 20 mg/d) were noted on the SDS at weeks 16 and 20, but differences between escitalopram and paroxetine were not significantly different at week 24.

Other second-generation antidepressants compared to SSRIs in adult outpatients with social anxiety disorder

One fair double-blinded RCT compared the efficacy and tolerability of one second-generation antidepressant to an SSRI.

Venlafaxine vs. paroxetine

Two 12-week multicenter trials compared venlafaxine ER to paroxetine and placebo. A European trial randomized 436 patients with social anxiety disorder⁶⁵ and an American trial randomized 440 patients with social anxiety disorder⁶⁶ to venlafaxine ER (75-225 mg/d), paroxetine (20-50 mg/d), or placebo. At 12 weeks, no significant differences in any outcome measure were observed between venlafaxine ER and paroxetine in either trial. Both venlafaxine ER and paroxetine were significantly better than placebo for all primary and secondary outcome measures ($p < 0.05$), including the measures of functional capacity (SDI) and work productivity (WPAI).

SSRIs compared to placebo in adult outpatients with social anxiety disorder

One meta-analysis one systematic review and five placebo-controlled trials provide additional evidence.

One systematic review evaluated the efficacy of selective serotonin reuptake inhibitors compared with placebo in the treatment of social anxiety disorder in adults.¹⁸⁸ This

review included placebo-controlled trials of selective serotonin reuptake inhibitors ranging in duration from 10-24 weeks and converted treatment effects to standardized effect sizes. Authors concluded that, in general, selective serotonin reuptake inhibitors are more effective than placebo in treating social anxiety disorder.

Fluvoxamine, paroxetine, and sertraline vs. placebo

One fair meta-analysis evaluated published and unpublished evidence comparing SSRIs with placebo in the treatment of social anxiety disorder. Eight studies of unreported quality were included in the review. Primary treatment outcomes included global improvement (CGI-I) and mean change in LSAS. Odds ratios for SSRI-treatment response compared to placebo varied between 2.1 and 26.2, favoring the SSRIs. Overall, evidence is inconclusive about differences in efficacy between fluvoxamine, sertraline, and paroxetine.

Escitalopram vs. placebo

One fair 12-week study compared flexible doses of escitalopram to placebo.⁶⁷ This trial randomized 358 participants meeting DSM-IV criteria for social anxiety disorder with a score of at least 70 on the LSAS to escitalopram (10-20 mg/d) or placebo. Overall loss to follow-up was 19 percent (18% for placebo and 20% for escitalopram). The primary efficacy measure was the LSAS total score; secondary outcome measures included the LSAS subscales, CGI-S, CGI-I, SDS, and MADRS. At endpoint, escitalopram was significantly better than placebo as assessed by the LSAS total score ($p < 0.01$). One fair relapse prevention study openly treated 517 patients with generalized social anxiety disorder with escitalopram (10-20mg/d) for 12 weeks.⁶⁸ Responders (CGI-I score of 1 or 2) were randomized to 24 weeks of double-blind treatment with escitalopram or placebo. The primary efficacy parameter was time to relapse, defined as ≥ 10 point increase in LSAS total score from randomization. Of 372 randomized patients, 198 escitalopram-treated patients (65%) and 75 placebo-treated patients (41%) completed the 24-week study. In the escitalopram group, 42 patients relapsed (22%), while 91 patients (50%) relapsed in the placebo group. The median time to relapse was 407 days for escitalopram-treated patients and 144 days for placebo-treated patients ($p < 0.001$).

Fluoxetine vs. placebo

Two fair study compared flexible doses of fluoxetine to placebo.⁶⁹ This trial randomized 60 participants meeting DSM-IV criteria for social anxiety disorder for at least 6 months to 14 weeks of fluoxetine (20-60 mg/d) or placebo. Loss to follow-up was 20 percent with a higher rate in the placebo control group than the active fluoxetine group (23% vs. 16%, respectively). The primary efficacy measure was the LSAS. Significant improvements in LSAS scores were reported for fluoxetine and placebo, with no statistically significant differences between groups ($p = 0.901$). Overall, no statistically significant differences were reported on secondary efficacy measures.

Fluvoxamine vs. placebo

Two 12-week trials compared fluvoxamine to placebo. One study randomized 92 participants with a primary diagnosis of social anxiety disorder and a score of 20 or greater on the BSPS to flexible doses of immediate release fluvoxamine (50-300 mg/d) or placebo.⁷⁰ Another trial randomized 300 participants with generalized social anxiety

disorder to controlled release fluvoxamine (100-300 mg/d) or placebo.⁷¹ Although loss to follow-up was not reported explicitly in the trial of immediate release fluvoxamine, 25 percent of fluvoxamine-treated patients and 9.1 percent of placebo-treated patients withdrew from the study because of adverse events. Likewise in the trial of controlled-release fluvoxamine, overall loss to follow-up was 32 percent; 26 percent of fluvoxamine-treated patients and 5% of placebo-treated patients withdrew from the study because of adverse events. Outcome measures included the LSAS, CGI-S, CGI-I, and SDS. LSAS scores were significantly more improved for fluvoxamine-treated patients compared to placebo-treated patients in both trials ($p < 0.05$). Significantly more immediate release fluvoxamine-treated patients were rated as CGI-I responders ($p < 0.05$); the number of responders was not statistically different in the comparison of controlled release fluvoxamine and placebo ($p = 0.078$). Both dosage forms of fluvoxamine were significantly better than placebo on all other anxiety scales and two of the three subscales of the Sheehan Disability Scale (work and family functioning). The second trial¹⁹² randomized 117 patients meeting DSM-IV criteria for social anxiety disorder (no minimum time of illness) to fluoxetine (10-60 mg/d) or placebo for 14 weeks. (In total, 295 patients were randomized in this study to arms that included comprehensive cognitive behavioral therapy. However, we included only two arms—the fluoxetine arm and the placebo arm.) The attrition rate was 36 percent with a higher rate in the placebo group than the fluoxetine group (40% compared with 32%); however, the differential rate was not considered high. Primary efficacy measures were the CGI-I, CGI-S and BPS. CGI-I response rates were significantly higher in fluoxetine treated patients (51% compared with 32%). Fluoxetine-treated patients also showed a significantly greater improvement in CGI-S score from baseline ($P < 0.05$) and in Social Phobia and Anxiety Inventory (SPAI) score ($P < 0.05$).

Mirtazapine vs. placebo

One fair 10-week trial compared mirtazapine to placebo in 114 women with social phobia.⁷² The primary outcome measure was the change in SPIN score; LSAS and SF-36 scores also were assessed. After 10 weeks, mirtazapine-treated patients were significantly more improved than placebo-treated patients on the SPIN (difference in change = -8.1; $p < 0.001$), LSAS (difference in change -20.2; $p < 0.001$), and the SF-36 domains of general health perception, vitality, social functioning, role-emotional, and mental health ($p < 0.001$ for all). Statistically significant differences were not noted in physical functioning ($p = 0.91$), role-physical ($p = 0.77$), and bodily pain ($p = 0.53$).

Other second-generation antidepressants compared with placebo

Nefazodone compared with placebo

One fair trial compared nefazodone to placebo in adults meeting the DSM-IV criteria for general social phobia for at least 1 year.¹⁹⁴ 105 patients were randomized to nefazodone (100-600 mg/d) or placebo for 14 weeks. The primary outcome measures were percentage of CGI-I responders (1 or 2) at endpoint and the mean change from baseline in LSAS total score. Secondary efficacy measures included CGI-S, Social Phobia Inventory, SPS, and Social Interaction Anxiety Scale. More nefazodone- than placebo-treated patients were CGI-I responders, but the difference was not significant (31.4%

compared with 23.5%, $P=0.38$). With the exception of the Social Phobia Scale, there were no significant differences between groups in measures of social phobia. Nefazodone-treated patients had significantly higher incidences of some adverse events: dizziness ($P<0.01$), nausea/vomiting (23.5% compared with 7.8%, $P=0.03$), and dry mouth (23.5% compared with 2.0%, $P<0.01$).

III. For adult outpatients with premenstrual dysphoric disorder or late luteal phase dysphoric disorder, do SSRIs or second generation antidepressants differ in efficacy?

The FDA has approved fluoxetine, sertraline, and paroxetine for the treatment of PMDD and LLPDD. We did not find any head-to-head studies comparing SSRIs or other second-generation antidepressants to each other.

SSRIs compared to placebo in adult outpatients with premenstrual or late luteal phase dysphoric disorders

SSRIs vs. placebo

Only one study reported on efficacy outcomes of non-FDA-approved SSRIs.⁷³ This good-quality meta-analysis pooled data from 15 trials comparing various SSRIs to placebo; seven used fluoxetine, five used sertraline, one used citalopram, one used paroxetine, and one used fluvoxamine. The investigators converted data from each trial to standardized mean differences (SMDs) for the proportion of patients who showed improvement in overall premenstrual symptoms; they used a random effects model to estimate pooled efficacy. The pooled SMD favoring SSRI over placebo was -1.066 (95% CI, -1.381, -0.750) equivalent to an odds ratio of 6.91 (95% CI, 3.90, 12.2). However, this meta-analysis also included cross-over studies. In the more conservative analysis, which excluded five studies with a cross-over design, the authors estimated a smaller SMD of -0.75 (95% CI, -0.98, -0.51).

Other second-generation antidepressants compared to placebo in adult outpatients with premenstrual dysphoric disorder or late luteal phase dysphoric disorder

Venlafaxine vs. placebo

One fair RCT compared an SNRI, specifically a continuous daily dose of venlafaxine (50-200 mg/d), to placebo over four menstrual cycles.⁷⁴ It reported 36 percent of subjects as lost to follow-up. Venlafaxine-treated subjects had significantly lower premenstrual daily symptom report scores and 21-item HAM-D scores than placebo subjects. Sixty percent of venlafaxine-treated subjects were considered responders (e.g., had more than a 50% reduction in baseline symptom report score), whereas only 35 percent of placebo-treated subjects were characterized as responders.

Nefazodone vs. placebo

One fair RCT compared a second-generation antidepressant, specifically both a continuous and intermittent daily dose of nefazodone (100-400 mg/d), to placebo over two menstrual cycles.⁷⁵ This trial did not, however, compare intermittent and continuous therapy to each other. Twenty-two percent of subjects were reported as lost to follow-up in this trial. For both dosing methods, no significant differences were seen between nefazodone and placebo in either patient self-rated global improvement or any of the

individual symptoms assessed (irritability, depressed mood, affect lability, tension, breast tenderness, bloating, and food craving).

KEY QUESTION 2. Adverse Events

For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorder, do second-generation antidepressants differ in safety, tolerability, or adverse events?

Most of the studies that examined the efficacy of one drug relative to another also determined differences in tolerability. Methods of adverse events assessment differed greatly. Only six studies used objective scales such as the UKU-SES (Utvvalg for Kliniske Undersogelser Side Effect Scale) or the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often it was hard to determine whether assessment methods were unbiased and adequate. Rarely were adverse events prespecified and defined. Short study durations and small sample sizes additionally limited the validity of adverse events assessment in many trials. Few RCTs were designed to assess adverse events as primary outcomes. Most published studies were post hoc analyses or retrospective reviews of databases. We included observational studies if the sample size was larger than 100 and the study duration was at least 1 year

A. Tolerability and Discontinuation Rates

Nausea, headache, diarrhea, fatigue, dizziness, sweating, sexual side effects, tremor, dry mouth, and weight gain were the commonly reported adverse events.

Discontinuation rates because of adverse events were generally not statistically significantly different, except in five trials. One study reported that significantly more patients on fluvoxamine than on sertraline discontinued treatment;¹⁸ another showed a higher rate of discontinuations in citalopram than in escitalopram-treated patients;¹¹ another trial had significantly more patients on venlafaxine than on escitalopram drop out because of adverse events;⁷⁶ the other two trials provided conflicting evidence on the discontinuation rates of mirtazapine and paroxetine.^{21,22}

Venlafaxine had a consistently higher rate of nausea and vomiting than SSRIs. In six studies, the difference reached statistical significance. In six additional trials, the higher rates of nausea or vomiting for venlafaxine were not statistically significant. A pooled analysis of published and unpublished trials of duloxetine did not find significant differences in nausea between duloxetine (40-120mg/d) and paroxetine (20mg/d) or between duloxetine (120mg/d) and fluoxetine (20mg/d).⁷⁷

Three trials reported a significantly higher rate of dizziness in the venlafaxine group than in the fluoxetine group. Three other studies reported significantly higher rates of diarrhea in sertraline-treated patients than in comparison drugs.^{17, 23} In another trial conducted in patients 65 years and older, patients using fluoxetine had significantly more severe adverse events than patients treated with paroxetine.¹⁵

A British study pooled data from Prescription-Event-Monitoring (PEM) of general practitioners 6 months to 1 year after they had issued prescriptions.⁷⁸ Included drugs were fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, and nefazodone. The final cohort exceeded 10,000 patients for each drug. Demographics and indications were comparable among study groups. Nausea and vomiting were the two most frequent clinical reasons for withdrawal in the first month of treatment for all drugs. Venlafaxine

had the highest rate of nausea and vomiting per 1000 patient months. Like patients using paroxetine, venlafaxine patients also most frequently reported male sexual dysfunction. However, sweating, impotence, and ejaculation failure were significantly higher in the paroxetine group than in the other groups ($p = 0.004$; $p < 0.001$). In addition, patients using paroxetine and those using nefazodone most frequently reported drowsiness and sedation. Sertraline and fluoxetine had significantly lower rate ratios of agitation and anxiety. However, there were more reports of mania during 90 days with fluoxetine than with any other drug. The death and suicide rates did not differ significantly among study groups. Among SSRIs only, drowsiness and sedation were significantly higher in the fluvoxamine and paroxetine group than in the fluoxetine and sertraline group. Suicide rates did not differ significantly among study groups. Adverse events were reported by physicians rather than patients; the nonresponse rate was 40 percent. Therefore, measurement bias, selection bias, and potential confounding may compromise these results.

Three RCTs were powered primarily to detect differences in adverse events between fluvoxamine and citalopram and fluvoxamine and paroxetine, and fluvoxamine and fluoxetine. A Dutch multicenter trial was designed to assess between-group comparisons of gastrointestinal side effects between citalopram (20-40mg/d) and fluvoxamine (100-200mg/d).⁷⁹ A total of 217 patients were enrolled for 6 weeks. Overall, 57 percent of patients reported adverse events. Significantly more patients in the fluvoxamine group had an excess incidence of diarrhea (+13%; $p = 0.026$) or nausea (+16%; $p = 0.017$). However, the authors did not provide a baseline comparison of gastrointestinal illnesses between groups. Differences at baseline could bias results.

The second study enrolled 60 patients to fluvoxamine (50-150mg/d) or paroxetine (20-50mg/d) for 7 weeks.⁸⁰ Sweating was the only significantly higher adverse event: 30 percent in paroxetine patients vs. 10 percent in fluvoxamine patients ($p = 0.028$).

The third trial assessed differences in adverse events between fluvoxamine (100-150mg/d) and fluoxetine (20-80mg/d) in 100 patients over 7 weeks.¹⁴ Fluoxetine-treated patients suffered from nausea significantly more often than fluvoxamine patients (42.5% vs. NR; $p = 0.03$) A meta-analysis of 15 RCTs did not find any statistically significant differences in discontinuation rates because of adverse events between fluoxetine and other SSRIs as a class.

A fair-rated, Dutch prospective observational study followed 1,251 patients for up to 12 months to assess adverse events of sertraline ($n = 659$) compared to other SSRIs (fluoxetine, fluvoxamine, paroxetine).⁸¹ No exclusion criteria were applied. Psychiatrists recorded adverse events at each patient visit. The WHO adverse reaction terminology was used for outcome assessment. Significantly more sertraline patients had the diagnosis of depressive disorder at baseline ($p < 0.001$). Overall, 74.1 percent of patients reported at least one adverse event. Diarrhea occurred more frequently in the sertraline group than in the other SSRI groups ($p < 0.05$). However, abdominal pain was reported more frequently by other SSRI users than sertraline users ($p < 0.05$). No other adverse event differed significantly across groups.

The EPC conducted meta-analyses to assess differences in the the overall loss to follow-up, the discontinuation rates because of adverse events, and the discontinuation rates because of lack of efficacy of SSRIs as a class compared to some other second-generation antidepressants (bupropion, mirtazapine, and venlafaxine) in adult outpatients with MDD.

The only statistically significant difference in pooled estimates was a higher discontinuation rate because of adverse events for venlafaxine-treated patients than for patients on SSRIs (relative risk, 1.36; 95% CI 1.09 to 1.69). Overall, this finding was balanced by lower discontinuation rates because of lack of efficacy for venlafaxine (relative risk, 0.73; 95% CI 0.52 to 1.02). Overall discontinuation rates did not differ significantly between venlafaxine and SSRIs (RR: 1.06; 95% CI 0.93-1.22). No significant differences could be detected between SSRIs and mirtazapine or between SSRIs and bupropion.

B. Specific Adverse Events

Suicidality

In 2004 an Expert Working Group of the UK Committee on Safety in Medicines (CSM) investigated ongoing safety concerns about suicidal behavior with some second-generation antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, venlafaxine) in patients with MDD.⁹⁴ The Expert Working Group studied data from 477 published and unpublished randomized controlled trials on more than 40,000 individuals. However, these data were limited to studies funded by the pharmaceutical industry.

In summary, the Expert Group advised that the balance of risks and benefits for the treatment of depression in children less than 18 years is unfavorable for citalopram, escitalopram, mirtazapine, paroxetine, sertraline, and venlafaxine. Only fluoxetine appeared to have a favorable risk-benefit ratio. Fluvoxamine could not be assessed for pediatric use because of lack of data. Conclusions were based on the fact that, with the exception of fluoxetine, clinical trial data failed to demonstrate efficacy in a pediatric population. In addition, an increased risk of suicidal thoughts and self-harm was observed consistently across drugs.

For adults, clinical trial data consistently showed that the risk of suicide-related events in patients receiving second-generation antidepressants is higher than in patients on placebo. However, none of the pooled estimates for individual drugs reached statistical significance. The risk of suicide-related events was similar between second-generation antidepressants and active comparators.

In addition, the Expert Group commissioned an observational study (a nested case-control study) using the General Practice Research Database (GPRD) to investigate the association between antidepressants and self-harm based on data on more than 146,000 patients with a first prescription of an antidepressant for depression.⁸² This study did not find any evidence that the risk of suicide (OR 0.57; 95% CI 0.26 to 1.25) or self-harm (OR 0.99; 95% CI 0.86 to 1.14) is greater in patients on second-generation antidepressants than in patients on TCAs. *In patients younger than 18 years, however, the risk of self-harm was significantly greater in patients on SSRIs than on TCAs (OR 1.59; 95% CI 1.01 to 2.50).* Although no statistically significant differences among SSRIs were detected, the greatest risk of self-harm was among paroxetine users.

A recent, good meta-analysis of published data on more than 87,000 patients in SSRI trials for various conditions reported a significantly higher risk of suicide attempts for SSRI patients than for placebo-treated patients (2.25; 95% CI 1.14 to 4.55).⁸³

Furthermore, an increase in the odds ratio of suicide attempts was observed for SSRIs compared to interventions other than TCAs (OR 1.94; 95% CI 1.06 to 3.57). No

significant difference existed in the pooled analysis of SSRIs compared to TCAs (OR 0.88; 95% CI 0.54 to 1.42).

An analysis of Food and Drug Administration data reported consistent results.²²³ The use of antidepressant drugs in pediatric patients was associated with statistically significant increase in suicidality (relative risk 1.66; 95% CI 1.02 to 2.68). Findings of other studies are mixed.

Sexual dysfunction

A subgroup analysis of a good Swedish RCT examined the incidence of sexual side effects from citalopram (20-60mg/d) compared to those from sertraline (50-150 mg/d)^{5,84} in 308 study completers with MDD. Outcome assessment was conducted at baseline and at week 24. Citalopram and sertraline did not differ significantly in the magnitude and frequency of sexual side effects.

A good meta-analysis including data on 1,332 patients reported a significantly higher rate of sexual satisfaction in bupropion- than in SSRI-treated patients with MDD (RR 1.28; 95% CI 1.16-1.41).³¹

Two fair-rated RCTs compared the incidence of sexual dysfunction in 360 and 364 patients with MDD during 8 weeks of treatment with bupropion (150-400mg/d), sertraline (50-200mg/d), or placebo. Outcome measures were efficacy (HAM-D, CGI) and sexual dysfunction as assessed by investigators using DSM-IV definitions for sexual dysfunction disorders. Intention-to-treat analyses yielded no significant differences between bupropion and sertraline in any efficacy measures at trial endpoints. During the studies, sertraline showed more sexual adverse events than bupropion at various time points. However, in one trial overall satisfaction with sexual function did not differ significantly between the bupropion and the sertraline group at endpoint.⁸⁵ In the other study, beginning at day 21 until the end of the study, the overall satisfaction with sexual function was significantly higher in the bupropion group than in the sertraline group ($p < 0.05$).⁸⁶

The third RCT assessed the sexual side effects of bupropion SR (150-400mg/d) and sertraline (100- 300mg/d) in 248 depressed outpatients.⁸⁷ Study duration was 16 weeks; loss to follow-up was 31.5 percent. Sexual dysfunction was determined by investigator interviews and patient-completed questionnaires. Treatment groups were comparable at baseline. Intention-to-treat analysis showed that, beginning at day 7, significantly fewer bupropion-treated patients than sertraline-treated patients reported sexual dysfunction ($p < 0.001$) throughout the study. These findings were significant for males ($p < 0.05$) and for females ($p < 0.01$). Significantly more patients in the sertraline group developed sexual arousal disorder, orgasm dysfunction, or ejaculation disorder (men: 63% vs. 15%; $p < 0.001$; women: 41% vs. 7%; $p < 0.001$).

The combined NNT to yield one additional person who is satisfied with the overall sexual function is 7.

A fair, 8-week RCT compared efficacy and sexual side effects of bupropion (150-400mg/d), fluoxetine (20-60mg/d), and placebo in 456 outpatients with MDD.⁸⁸ Loss to follow-up was 36 percent. Efficacy did not differ significantly. Bupropion had more remitters than fluoxetine (47% vs. 40%) at endpoint. Bupropion also showed significantly fewer sexual side effects than fluoxetine throughout the study. Beginning at week 1 until endpoint, significantly more fluoxetine-treated patients were dissatisfied with their overall sexual function than bupropion-treated patients ($p < 0.05$).

Similarly, a fair 8-week randomized controlled trial comparing bupropion with paroxetine reported significantly lower rates of sexual dysfunction for bupropion than for paroxetine (Sex Effects Scale, $P < 0.05$).²³⁰ Subgroup analysis revealed that a significant difference in anti-depressant related sexual dysfunction was detected in men but not in women.

The largest observational study was a Spanish open-label, prospective study using the Psychotropic- Related Sexual Dysfunction Questionnaire (PRSexDQ) in 1,022 outpatients treated with various antidepressants.⁸⁹ All patients had normal sexual functioning at study onset. Overall, 59 percent of patients experienced some type of sexual dysfunction. Among second-generation antidepressants, citalopram, paroxetine, and venlafaxine had the highest incidence of sexual dysfunction (73 percent, 71 percent, and 67 percent, respectively); mirtazapine and nefazodone had the lowest (24 percent and 8 percent, respectively). This study did not include data on bupropion, escitalopram, and trazodone.

In one trial, significantly more patients on sertraline withdrew because of sexual side effects than did patients on bupropion (3.3% vs. 13.5%; $p = 0.004$).⁹⁰

In another study patients on duloxetine reported statistically significantly lower rates of sexual dysfunction than patients on escitalopram (33% compared with 49%; $P = 0.01$).²³³

Changes in weight

A 32-week acute and continuation trial assessed differences in weight changes among patients treated with fluoxetine, paroxetine, and sertraline.⁹¹ Paroxetine patients showed a significantly greater mean weight change (+3.6%) than did those taking fluoxetine (-0.2%; $p = 0.015$) and sertraline (+1.0%; $p < 0.001$). Significantly more patients in the paroxetine group (25.5%) had a weight gain of more than 7 percent than in the fluoxetine (6.8%; $p = 0.016$) and sertraline groups (4.2%; $p = 0.003$). A 1-year, placebo-controlled continuation trial of fluoxetine reported similar findings. Initially, fluoxetine treatment led to a modest weight loss; from week 12 to week 50, however, a significant weight gain compared to placebo was reported (+3.1kg; $p < 0.001$).

A double-blinded placebo-controlled 52-week acute and continuation trial assessed weight changes during bupropion treatment.⁹² Bupropion-treated patients showed a modest but nevertheless significant decrease of body weight from baseline (-1.15 kg; $p < 0.001$). The magnitude of weight change was closely related to the body mass index (BMI). Patients with a higher BMI experienced greater weight loss.

Two RCTs assessing the efficacies of mirtazapine and paroxetine reported significantly greater weight gains in the mirtazapine group than in the paroxetine group.^{21,22}

Seizures

Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of seizures in patients taking any of the reviewed drugs, including bupropion.

An analysis of Food and Drug Administration data derived from approval reports indicated a higher risk of seizures for bupropion compared with other antidepressants.²³⁶

Overall, 0.6 percent of patients treated with bupropion experienced seizures. The standardized incidence ratio compared with placebo was 1.58 (1.03, 2.32).

Cardiovascular adverse events

A post hoc analysis examined pooled data from 3,744 patients participating in venlafaxine trials.⁹³ At 6 weeks, 11.5 percent of venlafaxine patients had a supine diastolic blood pressure (DBP) greater than 90 mm Hg (imipramine: 7.9%, placebo: 5.7%; $p < 0.001$). During continuation treatment (up to 12 months), significantly more venlafaxine subjects with normal supine DBPs developed elevated readings ($p = 0.05$). A randomized controlled trial comparing sertraline to venlafaxine detected an increase of supine diastolic blood pressure of 3.1 mm Hg for venlafaxine compared to a decrease of 1.4 mm Hg for sertraline after 8 weeks ($p = 0.004$).⁹⁴

A post-hoc analysis of six RCTs (published and unpublished) comparing duloxetine to fluoxetine and paroxetine did not find any statistically significant differences in supine systolic or diastolic blood pressure.²⁰⁷ Duloxetine treated patients had a greater mean change in heart rates than fluoxetine-(+2.8beats/min. vs. -1.0 beat/min.) and paroxetine-treated patients (+1.0 beats/min. vs. -1.4 beats/min.). One randomized controlled trial of 311 elderly patients with major depressive disorder did not detect any differences in supine blood pressure between duloxetine and placebo.²⁴⁰

A case-control study including 916 cases of intracerebral or subarachnoid hemorrhage did not detect any association between hemorrhage stroke and selective serotonin reuptake inhibitors (OR 1.1 < 95% CI 0.7 to 1.8).²⁴¹

Hyponatremia

Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of hyponatremia in patients treated with SSRIs. However, the methods of our report did not include case reports and case series. The published literature includes numerous case reports of hyponatremia and inappropriate secretion of antidiuretic hormone as rare side effects. Even if this evidence is considered weak, it could be important in the absence of studies with the methodological strength to account for rare adverse events.

Hepatotoxicity

Evidence from controlled trials and observational studies is also insufficient to conclude for or against an increased risk of liver toxicity during nefazodone treatment. Nevertheless, numerous case reports not included in this report contain low-level quality but potentially important evidence citing an increased risk of liver toxicity during nefazodone treatment.⁹⁵

KEY QUESTION 3. Subgroups

Are there subgroups of patients based on demographics (age, racial groups, sex), other medications, or co-morbidities for which one second-generation antidepressant is more effective or associated with fewer adverse events?

Demographics

Age

SSRIs as a class

A pooled data data-analysis of trials comparing venlafaxine to SSRIs reported that older women responded poorer to SSRI-treatment than younger women. This difference could not be observed in men.⁹⁶

Citalopram compared with sertraline

One randomized trial evaluated citalopram and sertraline in the treatment of 138 non-demented elderly patients with minor depressive disorder and subsyndromal symptomatology.¹¹⁵ Although this trial does not meet our eligibility criteria because of the study design (nonrandomized trial), we are briefly summarizing it because it is the only evidence pertaining to a comparison of these two selective serotonin reuptake inhibitors. Both treatments improved depressive symptoms (as measured by the HAM-D scale); HAM-D remission rates were similar for citalopram and sertraline at the end of the study (53% and 42%, $P=0.25$). Similar improvements were seen in Global Assessment of Function (GAF) and cognitive scores.

Escitalopram compared with fluoxetine

One 8-week study compared escitalopram, fluoxetine, and placebo in 518 participants older than 65 years of age (mean age in each treatment group, 75 years).⁴⁵ Outcome measures included the MADRS and the CGI-S. Patients on escitalopram experienced greater improvement than those on fluoxetine in MADRS score (using LOCF analysis) at week 8 ($P<0.01$); however, the patients treated with escitalopram and with placebo did not differ significantly. Escitalopram, placebo, and fluoxetine MADRS response rates were similar (46%, 47%, and 37%, respectively, P =not significant). In addition, MADRS remission rates were similar for escitalopram and placebo (40% and 42%), but for fluoxetine compared with placebo, the difference was statistically significant (30% compared with 42%, $P=0.05$). Escitalopram- and fluoxetine-treated patients experienced significantly more nausea than placebo-treated patients ($P<0.01$).

Fluoxetine vs. paroxetine

Two RCTs were conducted in a population older than 60 years. The first trial was an Italian study lasting 1 year that enrolled 242 patients to determine the effects of fluoxetine (20-60mg/d) and paroxetine (20-40mg/d) on mood and cognitive function in depressed, nondemented persons (65 years or older). Both groups significantly improved on their HAM-D scores and cognitive performance. Paroxetine showed a faster onset of action and a significantly greater improvement of HAM-D scores during the first 6 weeks (Week 3: $p < 0.05$; Week 6: $p < 0.002$). A Kaplan-Meier analysis evaluating the percentage of responders over time revealed a significant difference in favor of paroxetine ($p < 0.002$). Treatment groups did not differ significantly in CGI scores. Fluoxetine had a significantly greater number of patients with severe adverse events than paroxetine (22 versus 9; $p < 0.002$). However, loss to follow-up in this study was 39.3 percent, so the validity of the results should be viewed cautiously.¹⁵

The second trial conducted in an elderly population enrolled 108 patients with major depression in Austria and Germany for 6 weeks using the same dosage as the Italian study.⁹⁷ Loss to follow-up was not reported. An intention-to-treat analysis revealed no differences between the treatment groups in changes of scores on MADRS and HAM-D; the paroxetine group had significantly more responders at 6 weeks on MADRS and HAM-D scales (37.5% vs. 17.5%; $p = 0.04$). Patients on paroxetine also had significantly better MMSE and SCAG scores assessing cognitive function at Week 3 than did those on fluoxetine. No statistically significant differences in adverse events were reported. A post hoc analysis of two placebo controlled trials of duloxetine reported that no differences in efficacy could be detected in women across different age groups.⁹⁸

Fluoxetine vs. sertraline

One fair, 12-week study comparing fluoxetine to sertraline was conducted in 236 participants older than 60 years.⁹⁹ Loss to follow-up was 32.2%. In this study, outcome measures also included quality of life (Q-LES-Q) and cognitive assessments (SLT, MMSE, Digital Symbol Substitution Test). Fluoxetine- and sertraline-treated patients did not differ significantly on primary outcome measures (MADRS, HAM-D). Response rates (fluoxetine, 71%; sertraline, 73%) and remission rates (46% vs. 45%) were similar. Quality of life and other patient-rated secondary efficacy measures were similar for both treatment groups at endpoint. Sertraline treated patients showed a greater cognitive improvement on the Digit Symbol Substitution Test at endpoint ($p = 0.037$). A subgroup analysis of 75 patients 70 years of age or older showed a greater response rate for sertraline-treated patients ($p = 0.027$).

A subgroup analysis of a long-term effectiveness trial comparing fluoxetine, paroxetine, and sertraline reports similar response and remission rates for patients older than 65 years and the general study population.⁷

Paroxetine vs. placebo vs. behavioral therapy

A large, fair, primary-care-based study randomized 656 patients with dysthymia or minor depression to eleven weeks of paroxetine (10-40mg), placebo, or behavioral therapy.¹⁰⁰ Participants were stratified into patients 60 years and older ($n = 415$) and patients younger than 60 years ($n = 241$) for intention-to-treat analysis. Loss to follow-up was not reported for either subgroup. In the older subgroup, paroxetine-treated patients showed a greater change in HSCLD 20 (Hopkins Symptom Checklist) scores than placebo-treated patients ($p = 0.004$) but not more than patients on behavioral therapy ($p = 0.17$). For older dysthymia patients with high or intermediate baseline functioning scores, paroxetine improved mental health functioning significantly compared to placebo. Overall, however, improvements for paroxetine-treated dysthymia patients were not statistically significant different from those on placebo. The younger subgroup did not show statistically significant differences between treatment groups on the HSCL-D scale. For dysthymia only, the remission rate was significantly higher in the paroxetine group than in the placebo group (80% vs. 40%; $p = 0.008$).

Another fair trial randomized 323 patients older than 60 years with MDD to paroxetine IR, paroxetine CR, or placebo.¹⁰¹ No significant differences between paroxetine IR and paroxetine CR were apparent for any primary outcomes measures (HAM-D, CGI-I) or adverse events.

Mirtazapine vs. paroxetine

A fair trial randomized 255 elderly participants for eight weeks.²¹ Loss to follow-up was 27 percent. Mirtazapine and paroxetine were equally effective in reducing HAM-D scores at the endpoint, but mirtazapine lead to a faster response. A Kaplan-Meier analysis showed a significantly faster time to response for mirtazapine (mean 26 days versus mean 40 days for paroxetine; $p = 0.016$). No significant difference in response rates on the CGI scale was noted. Significantly more mirtazapine-treated patients reported weight gain ($p < 0.05$). Paroxetine treated patients reported a significantly higher rate of nausea, tremor, and flatulence ($p < 0.05$).

Venlafaxine versus citalopram

A fair European 6-month study compared venlafaxine ER (37.5-150mg/d) to citalopram (10-30mg/d) for the treatment of depression in elderly outpatients (mean age 73 years).¹⁰² No statistical differences in any outcome measures (MADRS< CGI-S, CGI-I) could be detected at study endpoint.

Venlafaxine compared with fluoxetine

One fair trial compared venlafaxine IR (37.5 – 225 mg/d) to fluoxetine (20 – 60 mg/d) for the treatment of unipolar depression in elderly patients (mean age 71 years).³⁰ Both treatment groups experienced a significant reduction in HAM-D total scores at 8 weeks; however, there were no significant differences between groups in HAM-D, MADRS, or CGI scores at endpoint. Remission rates at 8 weeks were 27 percent for venlafaxine and 20 percent for fluoxetine. Venlafaxine-treated patients experienced significantly higher rates of nausea (45% compared with 23%), dry mouth (23% compared with 6%) and constipation (22% compared with 10%); $P < 0.01$ for all three comparisons.

Venlafaxine versus sertraline

One study determined efficacy and safety of venlafaxine (25-100mg/d) compared to sertraline (18.5-150mg/d) in 52 frail nursing home residents. Loss to follow-up was 44.2 percent; therefore, we deemed the efficacy analysis not to be valid. However, venlafaxine-treated patients had a significantly higher rate of severe adverse events ($p = 0.022$) and withdrawal because of severe adverse events or side effects ($p = 0.005$) than did the sertraline-treated patients.

Bupropion vs. paroxetine

One fair RCT examined the efficacy of bupropion SR (100-300 mg/d) and paroxetine (10- 40mg/d) in 100 outpatients ages 60 years or older (range 60-88 years) over 6 weeks.^{33, 34} The majority of patients were white (bupropion SR, 98%; paroxetine, 90%), female (bupropion SR, 54%; paroxetine, 60%), and did not use antidepressants for the current episode before enrollment (bupropion SR, 83%; paroxetine, 88%). Statistical analysis used a LOCF method. The overall loss to follow-up was 16 percent with no significant difference between treatment groups. Efficacy according to any outcome measure did not differ significantly between treatment groups.

A meta-analysis combined original data from eight comparable, double-blind, active-controlled, randomized trials.¹⁰³ A primary objective of this meta-analysis was to determine differences in response and remission based on sex and age. Analysis of the pooled data showed that neither age nor sex influenced the efficacy measures ($p > 0.05$); no significant interaction terms emerged for age by treatment, sex by treatment, or age by sex by treatment (all p values > 0.1).

We did not identify any head-to-head trials that compare one second-generation antidepressant to another in children and adolescents. There is FDA-approved evidence for the efficacy of fluoxetine and fair evidence from a pooled analysis of two placebo-controlled trials for the efficacy of sertraline.⁴⁵ Existing evidence does not support the efficacy of other second generation antidepressants. Additional evidence suggests that sertraline may not be as efficacious as reported in previous reports. Based on a systematic review of published and unpublished studies comparing second-generation antidepressant

to placebo, only fluoxetine was shown to be safe and effective in the treatment of MDD in children and adolescents.⁴⁷ This review reported an increased risk of suicidal thoughts and behavior for citalopram, paroxetine, sertraline, and venlafaxine, but not for fluoxetine.

Ethnicity

Duloxetine compared with placebo

Two pooled analyses of seven placebo-controlled duloxetine trials assessed the efficacy and tolerability of duloxetine in Hispanic²⁵³ and African American patients²⁵⁴ compared to Caucasian patients. The first analysis included 1342 Caucasians and 120 Hispanics and found no difference in efficacy outcomes for Hispanics and Caucasians.²⁵³ There were no significant differences between groups in discontinuation rates due to adverse events in the types or occurrence of specific adverse events. The second analysis of 1300 Caucasians and 123 African Americans also found no evidence for a differential effect of duloxetine in African-American and Caucasian patients in efficacy or safety outcomes.²⁵⁴

Paroxetine versus placebo

A pooled analysis of 104 paroxetine trials (14,875 patients) detected slightly lower response rates for Hispanics and Asians than for Blacks and Whites.¹⁰⁴

Fluoxetine versus placebo

An RCT examined ethnic differences in response to antidepressant treatment among depressed HIV-positive patients.¹⁰⁵ A total of 118 patients were randomized to either fluoxetine (20-80mg/d) or placebo for 8 weeks. Of all participants, 67 percent were white, 19 percent black, and 14 percent Latino; only 1.1 percent (n = 2) were female. Loss to follow-up was significantly greater among Latinos (53%) than among blacks (14%) and whites (28%; p < 0.05). Ethnicity was not associated with the total number of treatment emergent side effects or dosage. Among completers within the active-treatment group, whites were more likely to respond to treatment than the other two groups (84% vs. 50% in blacks and 67% in Latinos). Among completers in the placebo group, Latinos were more likely to show treatment response (80%) than were blacks (36%) or whites (43%). However, a statistical analysis of these findings was not possible because of the low number of Latinos who completed the study.

Citalopram

One study that did not meet our inclusion criteria performed a secondary analysis of data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study to compare remission and response rates among Blacks, Whites, and Hispanics with nonpsychotic major depressive disorder.²⁵⁷ We briefly describe it here because of the paucity of evidence on this topic. STAR*D included outpatients in 23 psychiatric and 18 primary care centers. Participants received flexible doses of citalopram for up to 14 weeks. There were significant differences in baseline characteristics among ethnic groups. Prior to adjustment for such differences, Black participants had lower HRSD17 remission rates (18.6%) than white (30.1%) or Hispanic participants (24.2%). After adjustments, there were no significant differences in HRSD remission rates among

groups; however, remission rates were still lower for Blacks compared to whites based on the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR). In general, Black and Hispanic participants had poorer responses to citalopram compared to White participants.

Gender

A meta-analysis described above¹²⁰ and a pooled data analysis of venlafaxine RCTs¹¹³ did not find any significant associations between sex and outcomes or sex and treatment of MDD. A pooled analysis of data from four sertraline-RCTs conducted in populations with panic disorder, however, reported better responses of female patients on some outcome measures (panic attack frequency, time spent worrying).¹⁰⁶ No differences were apparent in quality of life measures.

A pooled data analysis of four placebo-controlled duloxetine trials assessed safety and tolerability of duloxetine for the treatment of major depressive disorder in 560 men and 1062 women.²⁵⁹ This analysis showed no significant differential sex effects for pulse, blood pressure or weight. Withdrawals due to adverse events were similar between men and women. The only significant difference was in the occurrence of nausea; the nausea rate among placebo-treated patients was significantly greater in females than in males (10.7% compared with 3.7%, $P < 0.008$).

One fair study randomized patients to bupropion (150-300 mg/d) or paroxetine (20-40 mg/d).²³⁰ Subgroup analysis revealed that a significant difference in anti-depressant related sexual dysfunction was detected in men but not in women. There were no significant drug differences between bupropion- and paroxetine-treated women in sexual function. However, paroxetine-treated men reported a worsening of sexual function while bupropion-treated men had no significant change in sexual function (Sex FX total, $P < 0.002$).

In a study comparing fluvoxamine (50 mg/d) and paroxetine (20 mg/d), there was a significant difference in the decrease in hot flashes in menopausal women favoring paroxetine (-81.1 compared with -66.8, $P < 0.01$).⁶¹ However, there were no statistically significant differences in depression symptoms.

Other Medications-Drug Interaction

The evidence for drug-drug interactions is limited. Based on our review criteria, head-to-head trials specifically evaluating drug-drug interactions were not identified.

One larger study nonsystematically pooled data from fluoxetine trials to evaluate efficacy, agitation, and suicidal ideation. Based on this study, the clinical efficacy and safety of fluoxetine was not confounded by concomitant use of anxiolytics, sedatives, or antipsychotics.¹⁰⁷

One review evaluated the evidence for drug-drug interactions between SSRIs and other CNS drugs. It concluded that the SSRIs are not equivalent in their potential for drug interactions and that each combination must be assessed individually. The authors also noted a general trend in which, compared to other antidepressants, citalopram and sertraline appeared to have less propensity for important interactions.¹⁰⁸

Because only limited evidence supports drug interactions among the second-generation antidepressants, our review focuses on the potential for drug interactions. Information compiled in this search does not follow a systematic process but is provided as a

summary of the evidence for drug interactions. Appendix D of the DERP report summarizes second-generation antidepressant pharmacokinetic properties known to be related to drug interactions. Some interactions are inferred based on reports of enzyme induction or inhibition. Clinical significance of the interactions are referenced as contraindicated, requires monitoring, or no significant interaction.

Comorbidities

Alcohol/substance abuse

Fluoxetine versus placebo

A fair study of 51 depressed alcoholics assessed the efficacy of fluoxetine (20-40mg/d) in a 12-week, placebo-controlled, acute-phase trial and a subsequent 1-year follow-up period with a naturalistic treatment by physicians unrelated to this study (n = 31).

Outcome measures included changes on HAM-D and BDI and in alcohol consumption. Results of the acute phase trial showed significantly greater improvements of depressive symptoms for fluoxetine-treated patients ($p < 0.05$) on HAM-D but not on BDI. During the 1-year open-label follow-up, HAM-D scores remained significantly lower for the fluoxetine group than for the placebo group. However, no additional improvement during the follow-up treatment was reported. A subgroup analysis showed that depressed alcoholics who were cocaine abusers (n = 17) had a significantly worse outcome than depressed alcoholics who were not (n = 34). Cocaine abusers showed significantly worse outcomes on both the HAM-D ($p = 0.17$) and the BDI ($p = 0.001$).

Another fair placebo-controlled study investigated the efficacy of fluoxetine (40mg/d) in 68 cocaine-dependent patients with MDD.²³¹ Results showed no difference in efficacy between fluoxetine and placebo at the end of this 12-week study.

A fair placebo-controlled trial lasting 8 weeks determined the efficacy of fluoxetine (dosage range not reported) in 120 depressed patients with HIV and AIDS.¹⁰⁹ The majority of patients were male (97.3%) and white (65%). Loss to follow-up was 27.5 percent. The main outcome measures were response to treatment defined as a 50 percent improvement on the HAM-D scale, a score lower than 8, and a CGI score of 1 or 2. According to these criteria, the rate of response did not differ significantly between treatment groups (fluoxetine 57%, placebo 41%). Using the HAM-D scale alone as a criterion, the investigators reported a significantly greater response rate for fluoxetine-treated patients (79% vs. 57%; $p = 0.03$). The treatment groups did not differ significantly in adverse events.

A fair, small RCT assessed the efficacy and tolerability of fluoxetine treatment (20-60mg/d) compared to placebo in 44 methadone-maintained opioid addicts.¹¹⁰ Study duration was 3 months; loss to follow-up was 15.9 percent. Both groups had significantly decreased scores on BDI and HADRS ($z = 2.37$; $p = 0.01$). Efficacy did not differ significantly between placebo and fluoxetine treatment. However, the sample size was small and the study is likely to be underpowered (no power calculations were reported).

A poor quality study investigated the efficacy of fluoxetine (40 mg/d) in 68 cocaine-dependent patients with major depressive disorder.²⁶⁸ The trial was rated poor for efficacy due to its high attrition rate (53%), but we included it here because of the dearth of evidence on this topic. Results showed no difference in efficacy between fluoxetine and placebo at the end of this 12-week study.

One fair 16-week randomized controlled trial assessed the efficacy and tolerability of fluoxetine (20 mg/d) plus cognitive behavior therapy compared with placebo plus cognitive behavior therapy in 126 adolescents (mean age 17.2 years) with major depressive disorder and comorbid substance abuse disorder and conduct disorder.²⁶⁹ Decreases in Childhood Depression Rating Scale-Revised (CDRS-S) scores were greater in fluoxetine- than placebo-treated patients (-22.5 compared with -16.6). Fluoxetine-treated patients showed a greater CGI-I response than placebo patients, but the difference was not statistically significant (76.3% compared with 66.7%, relative risk = 1.14). There were no differences between groups in substance abuse disorder, conduct disorder or urine drug screen. In addition, there were no differences between groups in the incidence of adverse events.

Nefazodone compared with placebo

One randomized trial compared nefazodone and placebo in the treatment of depressed patients with depression and comorbid alcohol dependence over a 10-week period.²⁷⁰ HAM-D scores at endpoint showed no significant difference between treatment groups in depressive symptoms ($P=0.51$). Nefazodone-treated subjects averaged 0.8 fewer heavy drinking days per week than placebo-treated subjects ($P=0.01$). More nefazodone-treated patients were abstinent during treatment; however, the difference did not reach statistical significance ($P=0.17$).

Paroxetine compared with placebo

A fair study randomized 42 subjects with social anxiety disorder and a co-occurring alcohol use disorder to paroxetine (10-60 mg/d) or placebo for 16 weeks.²⁷¹ Decreases in total LSAS scores were significantly greater for paroxetine- compared to placebo-treated patients (53% compared with 32%, $P=0.02$). A higher percentage of paroxetine-treated patients were CGI responders (defined as improvement score of 1 or 2) compared to placebo-treated patients (55% compared with 27%). The mean reductions in Social Phobia Inventory (SPIN) results were greater in the paroxetine group but did not reach statistical significance (46% compared with 31%, $P=0.15$). Three specific adverse events occurred significantly more frequently in paroxetine-treated patients: tremor (45% compared with 14%, $P=0.03$), myoclonus (35% compared with 5%, $P=0.01$) and anorgasmia/delayed ejaculation (55% compared with 18%, $P=0.01$).

Sertraline compared with placebo

Three fair randomized controlled trials compared sertraline and placebo in the treatment of patients with depression and co-occurring alcohol dependence.²⁷²⁻²⁷⁴ A 24-week study compared sertraline (50-150 mg/d) with placebo in recently detoxified alcohol-dependent patients with current depressive symptoms.²⁷² Response (> 50% decrease in MADRS score) was slightly higher in sertraline- than placebo-treated patients (44% compared with 39%). Both groups experienced significant improvements in HAM-D and MADRS scores during the study, but the two groups did not differ significantly. Relapse rates were higher in sertraline- than placebo-treated patients (31.8% compared with 23.1%) but the difference was not statistically significant ($P=0.37$). Adverse event rates were similar for both treatment groups. The overall attrition rate was greater than 40

percent; however, there was not a significant difference in withdrawal between groups (sertraline, 45% compared with placebo, 44%).

A 12-week trial showed similar results.²⁷³ In this fair study, 82 currently depressed, actively drinking alcohol-dependent subjects were randomized to sertraline (50-200 mg/d) or placebo. There was no significant difference between groups in depression symptoms. However, in women, treatment with sertraline was associated with less depression at the end of treatment than those receiving placebo based on HAM-D scores ($P=0.04$) and BDI scores ($P=0.005$). There was no treatment group difference for men. There was no difference between groups in time to first heavy drinking day ($P=0.661$) or days abstinent or heavy drinking days per week. Sertraline-treated subjects had fewer drinks per drinking day compared to placebo-treated subjects; the difference was significant ($P=0.27$). Less drinking during the study was associated with improved depression outcomes. Serious adverse events occurred in four subjects: three treated with sertraline and one treated with placebo. Loss to follow-up was twice as high in the placebo group (33%) compared to the sertraline group (16%); however, details were not reported on withdrawals due to tolerability or lack of efficacy.

The third study was structured differently but produced similar results.²⁷⁴ This study randomized 328 patients with co-occurring major depressive disorder and alcohol dependence to sertraline (50-200 mg/d) or placebo for 10 weeks. After the run-in period, two groups of patients were randomized separately based on HAM-D scores: Group A scores were > 17 while Group B scores were < 16 . Mean reduction in HAM-D scores did not differ significantly between all sertraline-treated (-10.8) and placebo-treated (-9.6) patients ($P=0.14$). There were significant differences in HAM-D response rates by group stratification. In Group A, sertraline led to significantly higher response rate than placebo (64% compared with 47%, $P=0.022$). However, in Group B, sertraline patients had a significantly lower response rate than placebo patients (58% compared with 77%, $P=0.018$). There were no significant differences between medication groups in the reduction in BDI score from baseline to endpoint nor within Group A or Group B. No significant differences were detected between medication groups in drinking measures. Overall, the incidence of adverse events was similar between medication groups; however, significantly more sertraline-treated patients discontinued due to adverse events than placebo-treated patients ($P<0.05$).

Alzheimer's disease/dementia

Citalopram compared with placebo

One poor-quality randomized trial compared citalopram and placebo for patients 65 years of age and older with depression and comorbid mild to moderate dementia.²⁷⁵ We rated this trial poor because it appeared to be a completer-analysis only and had high attrition. In the efficacy analysis, which includes only those patients who completed the trial, the mean HAM-D score at endpoint ($P<0.05$) and the improvement in HAM-D total score at endpoint ($P<0.01$) were statistically significantly better for citalopram- compared to placebo-treated patients. CGI-S results were similar; the percentage of patients achieving CGI improvement (defined as a score of 1 or 2) was significantly higher for citalopram-treated patients compared to placebo-treated patients (60% compared with 24%, $P<0.001$).

Sertraline compared with placebo

Two randomized trials compared sertraline and placebo for patients with depression and comorbid Alzheimer's disease,^{276, 277} but only one of these trials met our inclusion criteria.²⁷⁶ The first,²⁷⁶ a fair 12-week trial, demonstrated that sertraline was statistically significantly superior to placebo as measured by both the Cornell Score for Depression in Dementia (CSDD) and the HDRS (P=0.01). More patients treated with sertraline responded to treatment (full responders, 38%; partial responders, 46%) than did patients treated with placebo (full responders, 20%; partial responders, 15%) (P=0.007). The second trial²⁷⁷ failed to satisfy our eligibility criteria due to its small sample size (N = 31). We mention it here because of the limited evidence on this topic. This 8-week trial of late-stage Alzheimer's disease did not detect a statistically significant difference between sertraline and placebo; 47 percent and 36 percent, respectively, achieved at least a 50 percent improvement in the CSDD, and 35 percent and 50 percent, respectively, achieved at least a 50 percent improvement in the Gestalt Depression Scale. However, this study may not have been powered to detect statistically significant differences.

Arthritis

Our searches yielded only one trial that evaluated the efficacy of an antidepressant in depressed patients with comorbid arthritis.²⁷⁸ This study is a subgroup analysis of a larger placebo-controlled trial in elderly patients randomized to duloxetine (60 mg/d) or placebo.²⁷⁹ The subgroup analysis analyzed 233 subjects with major depressive disorder and co-occurring arthritis, diabetes and/or vascular disease; 55 percent of patients had diabetes. There were no statistically significant treatment-by-comorbidity interactions for any comorbidity (P=0.266) in HAM-D, GDS, or SF-36 scores or in response or remission rates. Results must be interpreted with caution as this was the only study addressing this topic.

Cancer

Fluoxetine vs. placebo

A fair placebo-controlled European trial lasting 5 weeks studied the efficacy of fluoxetine in 91 cancer patients with depression or adjustment disorder.¹¹¹ The majority of the patients were female; 13% in the fluoxetine group and 5% in the placebo group had metastatic disease. Outcome measures included quality of life. Loss to follow-up was 24.2 percent. Efficacy according to the main, observer-rated outcome measures (HADS, MADRS, HAS) did not differ significantly between the active drug and placebo groups. Improvements were generally greater in the fluoxetine group but statistically significant only for the SCL90-R (33% vs. 15%; p = 0.04), which measures global psychological adjustment. No statistically significant difference in quality of life was reported. However, study duration was short and a substantially greater percentage of patients in the fluoxetine group had a more advanced stage of cancer at baseline. Fluoxetine-treated patients had a significantly greater drop-out rate than placebo-treated patients (33% vs. 15%; p = 0.04).

Paroxetine compared with placebo

A 6-week randomized trial compared paroxetine (20 mg/d) and placebo in depressed breast cancer patients who were receiving at least four cycles of chemotherapy to evaluate whether the use of an antidepressant can alleviate symptoms of depression and reduce fatigue.²⁸¹ Although this study was rated poor because of lack of ITT analysis and inadequate description of study duration, we included it because it was the only study conducted in cancer patients that satisfied our inclusion criteria. Paroxetine was more effective in reducing depression during chemotherapy, as measured by the Center for Epidemiological Studies of Depression (CES-D) ($P=0.006$). No differences between treatment groups were apparent with respect to fatigue.

Diabetes

Our searches yielded two trials that evaluated the efficacy of an antidepressant in depressed patients with comorbid diabetes. The details of the first study²⁷⁸ are described above (in the KQ3 arthritis section). Only 15 percent of patients had comorbid diabetes mellitus. There were no statistically significant treatment-by-comorbidity interactions for any comorbidity ($P=0.266$) in HAM-D, GDS, or SF-36 scores or in response or remission rates. Results must be interpreted with caution based on the small percentage of patients in this study who had comorbid diabetes in this study.

The second study²⁸², a poor-quality 6-month randomized trial, evaluated paroxetine (20 mg/d) compared with placebo for treating mildly depressed patients with co-occurring type 2 diabetes. We rated the study poor quality due to the high differential (39.8%) in attrition rates for paroxetine (4.2%) compared to placebo (44%). Five placebo patients and one paroxetine patient withdrew consent before starting study medication. Six additional patients withdrew during treatment (all placebo-treated). We included this study here because it is the only study on this particular topic (mild depression and diabetes). Both groups showed improvement in quality of life and decreases in anxiety and depressive symptoms. However, at 6 months, differences between groups were not statistically significant, perhaps because the study was underpowered. Results must be interpreted cautiously because of that possibility together with the high differential loss to follow-up.

HIV/AIDS

Two studies compared the efficacy and tolerability of fluoxetine and placebo in the treatment of patients with depression and comorbid HIV/AIDS.^{255, 283}

A fair placebo-controlled trial lasting 8 weeks determined the efficacy of fluoxetine (dosage range not reported) in 120 depressed patients with HIV and AIDS.²⁸³ The majority of patients were male (97.3%) and white (65%). Loss to follow-up was 27.5 percent. The main outcome measures were response to treatment defined as a 50 percent improvement on the HAM-D scale, a score lower than 8, and a CGI score of 1 or 2. According to these criteria, the rate of response did not differ significantly between treatment groups (fluoxetine 57%, placebo 41%). Using the HAM-D scale alone as a criterion, the investigators reported a significantly greater response rate for fluoxetine-treated patients (79% compared with 57%; $P=0.03$). The treatment groups did not differ significantly in adverse events.

The second trial²⁵⁵ (described above for ethnicity) evaluated the efficacy and tolerability of fluoxetine (20-80 mg/day) and placebo in depressed patients with comorbid

HIV/AIDS. This study was rated poor because it had no ITT analysis; however, we included it here because of the very limited evidence on this topic. Response rates among subjects who completed the study were higher in the fluoxetine group than in the placebo group; however, the differences were not significant.

Multiple sclerosis

We detected only one study assessing the efficacy and tolerability of antidepressants for depression with comorbid multiple sclerosis (MS).²⁸⁴ Forty-two MS patients diagnosed with major depressive disorder and/or dysthymia were randomized to paroxetine (10-40 mg/d) or placebo for 12 weeks. Although more paroxetine-treated patients achieved at least a 50 percent reduction in HAM-D scores (57%) compared to placebo-treated patients (40%), the difference was not statistically significant ($P=0.354$). Paroxetine- and placebo-treated patients showed improvement in secondary measures (CES-D, MFIS, SF-36), but there were no significant differences between treatment groups. Paroxetine patients reported higher rates of nausea, headache, dry mouth and sexual dysfunction.

Somatizing depression

Fluoxetine versus paroxetine

A retrospective evaluation of 89 patients from two trials comparing fluoxetine (20-80mg/d) to paroxetine (20-50mg/d) determined whether depressed, somatizing patients with a gastrointestinal (GI) component have a higher degree of GI side effects than nonsomatizing depressed participants.¹¹² Participants with baseline complaints of nausea, upset stomach, GI somatic symptoms, or weight loss were not statistically more likely to develop additional GI side effects than those without such complaints at the start of the trials.

Stroke

Citalopram compared with placebo

One fair 6-week randomized trial evaluated the efficacy of citalopram (10-40 mg/d) and placebo in the treatment of 66 patients with poststroke depression.²⁸⁶ Citalopram was associated with significantly greater improvements in depression compared to placebo on the HAM-D; mean (SD) improvements for citalopram compared with placebo were 8.0 (6.0) and 7.2 (5.8), respectively.

Sertraline compared with placebo

A fair 26-week trial evaluated the efficacy and tolerability of sertraline (60-100 mg/d) compared with placebo in the treatment of minor depression and less severe depression in 123 stroke patients.²⁸⁷ Sertraline and placebo patients improved substantially but did not differ significantly in HAM-D response rates (76% compared with 78%) or in MADRS remission rates (81% compared with 87%). However, at week 26, sertraline was associated with greater improvements in quality of life than placebo (effect size not reported, $P<0.05$). Sertraline-treated patients experienced higher rates of three adverse events compared to placebo-treated patients: dry mouth (23.6% compared with 7.4%,

$P < 0.05$), diarrhea (23.6% compared with 9.3%, $P < 0.05$), and emotional indifference (9.1% compared with 0%, $P < 0.05$).

Chronic heart failure

We detected one study evaluating comorbid chronic heart failure in depressed patients.²⁹⁴ However, this study did not meet our inclusion criteria due to its small sample size. We discuss it here because of the paucity of evidence on this topic. In this study, 28 patients with symptomatic congestive heart failure and major depressive disorder were randomized to paroxetine CR (25 mg/d) or placebo for 12 weeks. Paroxetine resulted in significantly more remission of depression (BDI < 10) than placebo (69% compared with 23%, $P = 0.018$). Paroxetine was superior to placebo in quality of life changes based on overall SF-36 scores ($P < 0.05$). Reductions in SF-36 scores did not correlate with improvements in physical quality of life measures ($P > 0.10$). There were no differences in adverse events. Valid conclusions cannot be drawn, however, because of the small sample size in this study.

Coronary artery disease

One fair 12-week Canadian study assessed the efficacy and tolerability of citalopram (20-40 mg/d) and placebo in reducing depressive symptoms in patients with co-occurring coronary artery disease (CAD).²⁸⁸ Improvements in depressive symptoms were greater for citalopram than placebo. Mean HAM-D24 scores at endpoint showed significantly greater improvement in citalopram-treated patients compared to placebo-treated patients (14.9 compared with 11.6, $P = 0.005$); between group difference was 3.33 (95% CI 0.80 to 5.85). Citalopram-treated patients also demonstrated significantly greater decrease in mean BDI-II scores at endpoint ($P < 0.05$); between group difference was 3.61 (95% CI 0.58 to 6.64). Incidences of six adverse events were significantly greater in citalopram-treated patients: dizziness (48.6% compared with 30.3%, $P = 0.002$), diarrhea (49.3% compared with 23.9%, $P < 0.001$), somnolence (43.7% compared with 25.4%, $P = 0.001$), sweating (39.4% compared with 23.9%, $P = 0.005$), palpitations (25.4% compared with 14.8%, $P = 0.003$), and decreased libido or sexual difficulties (21.1% compared with 7.0%, $P = 0.001$). The citalopram group had a lower overall withdrawal rate (13% compared with 30%, $P = \text{NR}$); however, withdrawals due to adverse events were similar between treatment groups.

Post-myocardial infarction

Three placebo-controlled trials and one systematic review evaluating second-generation antidepressants in the treatment of comorbid post-myocardial infarction. A fair quality systematic review sponsored by AHRQ examined the role of depression in post-myocardial infarction.²⁹³ One section of this review addressed selective serotonin reuptake inhibitor treatment for post-myocardial infarction depression and included 11 studies. The authors concluded that selective serotonin reuptake inhibitors improve depression in post-myocardial infarction patients and some surrogate markers of cardiac risk. However, the authors also found that none of the studies was powered to show whether treatment improves survival. The authors did not address the tolerability of selective serotonin reuptake inhibitors in their review.

A 24-week trial randomized 369 patients with major depressive disorder and acute myocardial infarction or unstable angina to sertraline (50-200 mg/d) or placebo.²⁹¹ Sertraline was associated with a significantly greater percent of CGI-I responders compared to placebo (67% compared with 53%, $P=0.01$). However, there was not a significant difference between groups in mean change in HAM-D score ($P=0.14$). The incidence of severe cardiovascular adverse events was lower in sertraline patients (15% compared with 22%), but the difference was not significant. Both nausea and diarrhea were significantly more common in sertraline patients ($P=NR$).

The second, a good quality trial randomized 54 depressed patients after a first myocardial infarction to fluoxetine (20-60 mg/d) or placebo for 25 weeks (9 weeks of acute treatment and an additional 16 week continuation phase).^{289, 295} Significantly more sertraline-treated patients were HAM-D responders compared to placebo-treated patients after 25 weeks (48% compared with 26%, $P=0.05$). In addition, sertraline patients showed a greater mean decrease in SCL-90 hostility scores (-2.44 compared with -0.07, $P=0.02$). Percent of HAM-D remitters and mean decreases in HAM-D score also favored sertraline; however, differences did not reach statistical significance. One sertraline- and six placebo-treated patients were rehospitalized for a cardiac event during the study ($P=0.13$).

The third study randomized 91 patients to mirtazapine (30-45 mg/d) or placebo for 8 weeks of acute treatment (and a 16-week continuation phase).²⁹⁰ After 8 weeks of treatment, mirtazapine was superior to placebo based on BDI and CGI scales but not HAM-D. The difference between treatment groups in mean decrease in HAM-D score was not significant at 8 weeks (standardized effect size [SES] 1.30 compared with 0.96). Based on change in HAM-D score at 8 weeks, more mirtazapine-treated patients were responders (57% compared with 40%), but the difference was not significant ($P=0.18$). Mirtazapine-treated patients showed a significantly greater decrease in BDI score at 8 weeks (-4.6 compared with -1.72, $P=0.02$). Decrease in CGI score was greater in mirtazapine-treated patients but the difference was not statistically significant ($P=0.06$). The differences between groups in decrease in HAM-D scores and BDI scores over 24 weeks was not statistically significant ($P=0.36$ and $P=0.07$). The difference in CGI-scores over 24 weeks favored mirtazapine; the difference was significant ($P=0.05$). Mirtazapine patients experienced significantly more fatigue ($P=0.02$) and changes in appetite ($P=0.02$) over 24 weeks.

Vascular disease

We detected two trials addressing the efficacy of depressed patients with comorbid vascular disease.^{278, 292} One trial that evaluated the efficacy of duloxetine (60 mg/d) and placebo in elderly patients.²⁷⁸ The details of this study are described above (in the KQ3 arthritis section). In this study, 75 percent of the patients had comorbid vascular disease. There were no statistically significant treatment-by-comorbidity interactions for any comorbidity ($P=0.266$) in HAM-D, GDS, or SF-36 scores or in response or remission rates. Results must be interpreted with caution based on the small percentage of patients in this study who had comorbid diabetes in this study.

A fair, retrospective analysis of pooled data of two RCTs determined the safety and efficacy of sertraline (50-150mg/d) in elderly patients with comorbid vascular disease.¹¹³ [Same as 292 in update 4] Vascular comorbidity was not associated with an increase of severity of

adverse events or premature discontinuation. However, these findings were not based on an unbiased literature search and the validity must be viewed cautiously.

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