Drug Class Review

Second Generation Antidepressants

Final Report Update 4

October 2008

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Gerald Gartlehner, M.D., M.P.H.
Laura C. Morgan, MA
Patricia Thieda, MA
Kylie Thaler, M.D.
Richard A. Hansen, Ph.D.
Bradley Gaynes, M.D., M.P.H
Kathleen N. Lohr, Ph.D.
Timothy S. Carey, M.D., M.P.H.

Produced by
RTI-UNC Evidence-based Practice Center
Cecil G. Sheps Center for Health Services Research
University of North Carolina at Chapel Hill
725 Martin Luther King Jr. Blvd, CB# 7590
Chapel Hill, NC 27599-7590
Tim Carey, M.D., M.P.H., Director

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

CECIL G. sheps CENTER
FOR HEALTH SERVICES RESEARCH
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

TABLE OF CONTENTS

EXHIBITS

FIGURES

APPENDIXES

EVIDENCE TABLES – Provided in a separate document.

Suggested Citation for this Report:

Gartlehner G, Morgan LC, Thieda P, Thaler K, Hansen RA, Gaynes B, Lohr KN, Carey TS. Drug class review: Second generation antidepressants. Update 2. http://www.ohsu.edu/drugeffectiveness/reports/final.cfm

Funding:

The Drug Effectiveness Review Project, made up of 15 organizations including 14 state Medicaid agencies, commissioned and funded this report. These organizations selected the topic of the report and had input into its Key Questions. Content and conclusions of the report were determined entirely by researchers at the Evidence-based Practice Center. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in the report.

INTRODUCTION

A. 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 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.[3] 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 and monoamine oxidase inhibitors (with the exception of premenstrual disorder, which historically was untreated). Tricyclic antidepressants and monoamine oxidase inhibitors 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., tricyclic antidepressants tend to cause anticholinergic effects including dry mouth and eyes, urinary hesitancy, and sometimes retention and constipation and monoamine oxidase inhibitors 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, serotonin and norepinephrine reuptake inhibitors, 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 approved the first selective serotonin reuptake inhibitor, fluoxetine. Since then, five other selective serotonin reuptake inhibitors have been introduced: sertraline (1991), paroxetine (1992), citalopram (1999), fluvoxamine (2000), and escitalopram (2002). The serotonin and norepinephrine reuptake inhibitors were first introduced to the market in 1993 with the approval of venlafaxine. In 1994, nefazodone, which is essentially a selective serotonin reuptake inhibitor with additional 5-hydroxytryptamine-2 (5-HT2) and 5-hydroxytryptamine-3 (5-HT3) antagonist properties, was Food and Drug Administration-approved. Mirtazapine, a drug that acts centrally on adrenergic autoreceptors, was added to the therapeutic arsenal in 1996.[4] Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (selective serotonin and norepinephrine reuptake inhibitor), was approved for the treatment of major depressive disorder 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 selective serotonin reuptake inhibitors (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 serotonin and norepinephrine reuptake inhibitors (venlafaxine) are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Mirtazapine, sometimes characterized as a serotonin and norepinephrine reuptake inhibitor, 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, all of the other second-generation antidepressants are approved for the treatment of major depressive disorder. Table 1 summarizes the newer products that are available in the US by mechanism of action.

Since their introduction, the second-generation antidepressants have established a prominent role in the US pharmaceutical market. To illustrate their importance, the top 10 drug therapy classes accounted for 35.1 percent of US prescription sales in 2003. The antidepressant class, including selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors, ranked third among this group, accounting for $10.9 billion in US prescription sales.[5] The serotonergic class dominates this market, accounting for 57.6 percent of market share in 2002.[5] Prescription drug spending for these products is not anticipated to decline until 2009, when the leading brands will suffer patent expirations.

Compared to the first-generation antidepressants, the selective serotonin reuptake inhibitors and other second-generation antidepressant have comparable efficacy and comparable or better side effect profiles.[6, 7] 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 selective serotonin reuptake inhibitors 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. 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 (major depressive disorder, dysthymic disorder, subsyndromal depression, and seasonal affective disorder), generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, 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 (known as late luteal phase dysphoric disorder in the DSM, version III revised [III-R]) among adult outpatient populations. Technically, premenstrual dysphoric disorder 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 late luteal phase dysphoric disorder in DSM III-R except for the addition of one item. Of note, as of 1999, the Food and Drug Administration Neuropharmacology Advisory Committee supported the concept of premenstrual dysphoric disorder as a distinct clinical entity.

Finally, we examine the role of these agents in treating major depressive disorder in pediatric outpatient populations. Tables 1 and 2 show included drugs, dosage forms and recommended doses, and Food and Drug Administration-approved (labeled) uses.

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

Class	Generic name	US trade name[a]	Dosage forms	Labeled uses
Selective Serotonin Reuptake Inhibitors (SSRI)	Fluoxetine[b]	Prozac®; Prozac Weekly®; Sarafem®	10, 20, 40 mg 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[b]	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[c]
	Citalopram	Celexa®	10, 20, 40 mg tabs; 1, 2 mg/ml solution	MDD
	Fluvoxamine[b]	Luvox®	25, 50, 100 mg tabs	OCD (peds ≥ 8 years of age/adults)
	Escitalopram	Lexapro®[e]	10, 20 mg tabs 1 mg/ml solution	MDD; GAD
Selective Serotonin and Norepinephrine Reuptake Inhibitor (SSNRI)	Duloxetine	Cymbalta®	20, 30, 60 mg caps	MDD DPNP GAD Fibromyalgia
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	MDD; GAD[d]; Panic disorder; Social anxiety disorder[d]
Other second-generation antidepressants	Bupropion[b]	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[b]	Remeron®	15, 30, 45 mg tabs; 15, 30, 45 mg orally disintegrating tabs	MDD
	Nefazodone[b]	Serzone®	50, 100, 150, 200, 250 mg tabs	MDD

Abbreviations: DPNP, diabetic peripheral neuropathic pain; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; PMDD, premenstrual dysphoric disorder; SSRI, selective serotonin reuptake inhibitor.
[a] CR, SR, XL, and XR are registered trademarks referring to controlled, sustained, or extended-release dosage forms.
[b] Generic available for some dosage forms.
[c] Only Paxil CR® (not Paxil®) is approved for the treatment of PMDD.
[d] Only Effexor XR® is approved for the treatment of GAD and social anxiety disorder.
[e] Lexapro was denied approval for social anxiety disorder 3/30/2005.

Table 2. Usual dosing range and frequency of administration (adults)

Generic Name	US Trade Name[a]	Usual Daily Dosing Range	Frequency
Fluoxetine	Prozac®	10-80 mg	Once or twice daily
	Prozac Weekly®	90 mg (weekly)	Once weekly
	Sarafem®	20 mg	Once daily (continuous or intermittent)
Sertraline	Zoloft®	25-200 mg	Once daily
Paroxetine	Paxil®	10-60 mg	Once daily
	Paxil CR®	12.5-75 mg	Once daily
Citalopram	Celexa®	20-60 mg	Once daily
Fluvoxamine	Luvox®	50-300 mg	Once or twice daily
Escitalopram	Lexapro®	10-20 mg	Once daily
Duloxetine	Cymbalta®	40-60 mg[b]	Once or twice daily
Venlafaxine	Effexor®	75-375 mg	Two to three times daily
	Effexor XR®	75-225 mg	Once daily
Mirtazapine	Remeron®	15-45 mg	Once daily
Bupropion	Wellbutrin®	100-450 mg	Three times daily
	Wellbutrin SR®	150-400 mg	Twice daily
	Wellbutrin XL®	150-450 mg	Once daily
	Zyban®	150-300 mg	N/A (aid to smoking cessation)
Nefazodone[c]	Serzone®	200-600 mg	Twice daily

[a] CR, SR, XL, and XR are registered trademarks referring to controlled, sustained, or extended-release dosage forms.
[b] Food and Drug Administration labeling information states that there is no evidence that doses greater than 50 mg/day confer any additional benefit" for the treatment of MDD.
[c] withdrawn from the US market effective June 14, 2004.

B. Scope and Key Questions

The purpose of this review is to compare the efficacy, effectiveness, and tolerability (adverse events) of second-generation antidepressant medications. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. 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 Drug Effectiveness Review Project 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?

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.[8] The results of effectiveness studies are more applicable to the average patient than results from highly selected populations in efficacy studies.

For each of the three key questions, we evaluated specific outcome measures (where appropriate), as reported in Table 3. For efficacy and effectiveness, we focused on head-to-head trials comparing one second-generation antidepressant to another. When sufficient head-to-head evidence was not available, we evaluated placebo-controlled evidence of efficacy for medications not already approved by the Food and Drug Administration for the stated disorder. Observational studies were included to assess safety and tolerability. Studies were organized by disease state; we generalize efficacy, safety, and tolerability only to the disease state for which it was studied.

Table 3. Outcome measures and study eligibility criteria

Outcome	Outcome Measures	Study Eligibility Criteria
Efficacy/ Effectiveness	• Response • Remission • Speed of response/remission • Relapse • Quality of life • Functional capacity • Hospitalization	• Head-to-head randomized controlled clinical trials or meta-analyses evaluating: - One second-generation antidepressant compared with another • When sufficient evidence was not available for head-to-head trials within a specific diagnostic group, we evaluated: - Placebo-controlled trials
Safety/ Tolerability	• Overall adverse effect reports • Withdrawals because of adverse effects • Serious adverse event reports • Specific adverse events or withdrawals because of specific adverse events, including: - *hyponatremia* - *seizures* - *suicide* - *hepatoxicity* - *weight gain* - *gastrointestinal symptoms* - *loss of libido* - *others*	• Head-to-head randomized controlled clinical trials or meta-analyses evaluating: - One second-generation antidepressant compared with another • When sufficient evidence was not available for head-to-head trials within a specific diagnostic group, we evaluated - Placebo-controlled trials - Observational studies

METHODS

A. Literature Search

To identify articles relevant to each key question we searched MEDLINE, Embase, The Cochrane Library, PsychLit, and the International Pharmaceutical Abstracts. We used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (major depressive disorder, dysthymia, subsyndromal depression, seasonal affective disorder, general anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, premenstrual dysphoric disorder), drug interactions, and adverse events with a list of 11 specific second-generation antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, mirtazapine, duloxetine, venlafaxine, bupropion, and nefazodone). We limited the electronic searches to "human" and "English language." Sources were searched from 1980 to 2008 (April) to capture literature relevant to the scope of our topic. See Appendix A for complete search strategy.

We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials, and meta-analyses. We also manually searched reference lists of pertinent and relevant review articles and letters to the editor. All citations were imported into an electronic database (Endnote® v. X.02). Additionally, we hand searched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the Food and Drug Administration.

Furthermore the Center for Evidence-based Policy at the Oregon Health and Science University (OHSU) contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy (http://www.ohsu.edu/drugeffectiveness/pharma/Final_Submission_Protocol_Ver1_1.pdf). We received dossiers from six pharmaceutical companies.

Our searches found 3015 citations, unduplicated across databases. Additionally we detected 198 articles from manually reviewing the reference lists of pertinent review articles. Forty references stemmed from pharmaceutical dossiers and 6 from public comments. The total number of citations included in the database was 3259.

B. Study Selection

Two persons independently reviewed abstracts. If both reviewers agreed that the trial did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles. Records were considered for exclusion if they did not meet pre-established eligibility criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons to antidepressant medications outside our scope of interest.

For this review, results from well-conducted, valid head-to-head trials provide the strongest evidence to compare drugs with respect to effectiveness, efficacy, and adverse events. randomized controlled trials of at least 6 weeks' duration and an outpatient study population with a sample size greater than 40 participants were eligible for inclusion. We defined head-to-head trials as those comparing one second-generation antidepressant with another.

We did not examine placebo-controlled trials in detail if head-to-head trials were available. We viewed Food and Drug Administration approval as evidence for general efficacy;

therefore, we did not review placebo-controlled trials for Food and Drug Administration-approved indications except when outcome measures assessed quality of life or other health outcomes that are not generally required for Food and Drug Administration approval.

If no head-to-head evidence was published, we reviewed placebo-controlled trials for indications of interest that had not already been approved by the Food and Drug Administration. We reviewed all placebo-controlled trials for indications without Food and Drug Administration approval to provide an overview of efficacy without taking drug equivalency into account. In other words, we did not evaluate the dosage of one drug relative to the dosage of an alternative drug in a different trial. High dosages may yield greater treatment effects compared to placebo than do low or medium dosages. Comparisons of treatment effects across trials must, therefore, be made cautiously.

For adverse events we included both experimental and observational studies. For observational studies, we included those with large sample sizes (≥ 100 patients), lasting at least 1 year that reported an included outcome.

Initially, we reviewed studies with health outcomes as primary outcome measures. Outcomes for efficacy or effectiveness were response, remission, speed of response, relapse, functional capacity, and hospitalization. If no study measuring health outcomes was available for a particular indication or population subgroup, we included intermediate outcomes (e.g., changes in depression scores). Safety outcomes included overall and specific adverse events (e.g., suicide, sexual side effects, hyponatremia, weight change, seizures, gastrointestinal symptoms), withdrawals attributable to adverse events, serious adverse events, and drug interactions.

We included meta-analyses in our evidence report if we found them to be relevant for a key question and of good or fair methodological quality.[9] We did not review individual studies if they were included in a high-quality meta-analysis. We excluded meta-analyses that were not based on a comprehensive systematic literature search or did not maintain the units of the studies in their statistical analyses. We checked our database to guarantee that our literature search had detected trials included in any meta-analyses that we discarded, and we then obtained any missing articles.

Overall, we included 1083 articles on an abstract level and retrieved 789 of those as full text articles for background information or to be reviewed for inclusion into the evidence report. Studies included as abstracts but not retrieved as full text articles were mainly placebo-controlled trials with respect to key questions or indications for which sufficient evidence from head-to-head trials was available (see Appendix E).

C. Data Abstraction

We designed and used a structured data abstraction form to ensure consistency of appraisal for each study. Trained reviewers abstracted data from each study and assigned an initial quality rating. A senior reviewer read each abstracted article, evaluated the completeness of the data abstraction, and confirmed the quality rating. We abstracted the following data from included trials: study design, eligibility criteria, intervention (drugs, dose, duration), additional medications allowed, methods of outcome assessment, population characteristics, sample size, loss to follow-up, withdrawals due to adverse events, results, and adverse events reported. We recorded intention-to-treat results if available.

D. Quality Assessment

We assessed the internal validity (quality) of trials based on predefined criteria (Appendix B). These criteria are based on those developed by the US Preventive Services Task Force (ratings: good-fair-poor)[10] and the National Health Service Centre for Reviews and Dissemination.[11] External validity (generalizability) was assessed and reported but did not influence quality ratings.

Two independent reviewers assigned quality ratings; they resolved any disagreements by discussion and consensus or by consulting a third, independent party. Elements of internal validity assessment included, among others, randomization and allocation concealment, similarity of compared groups at baseline, use of intention-to-treat analysis, and overall and differential loss to follow-up.

Loss to follow-up was defined as the number of persons randomized who did not reach the endpoint of the study,[12] independent of the reason and the use of intention-to-treat analysis. We adopted a cut-off point of 20 percent loss to follow-up as a limit beyond which bias was likely to be introduced because of missing endpoint assessments. Trials with more than 20 percent but less than 40 percent loss to follow-up were eligible for a quality rating of fair (but not good). Studies with more than 40 percent overall loss to follow-up or more than 15 percentage points differential loss to follow-up between study groups were rated as poor. These cut-off points took into consideration that loss to follow-up appears to be higher in psychiatric populations than in other study populations.

Trials that had a fatal flaw in one or more categories were rated poor quality and not included in the analysis of the evidence report (Appendix C) unless the evidence was severely lacking for an indication. Trials that met all criteria were rated good quality. The majority of trials received a quality rating of fair. This includes studies that presumably fulfilled all quality criteria but did not report their methodologies to an extent that answered all our questions. Thus, the "fair quality" category includes trials with quite different strengths and weaknesses. The results of some fair quality studies are *likely* to be valid; others are *probably* valid. From 311 eligible articles (218 studies) we excluded 61 (58 studies) on the grounds of poor methodological quality (Appendix C). Of the included studies, 9 were of poor quality (1 in post-traumatic stress disorder, 2 in generalized anxiety disorder, and 6 in KQ3—subgroups); we included these studies because of limited available evidence.

E. Data Synthesis

We conducted meta-analyses of data for head-to-head comparisons for trials that were fairly homogenous in study populations and outcome assessments. Our outcome measure of choice was the relative risk of being a responder on the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS) (more than 50 percent improvement from baseline) at study endpoint. We chose this outcome measure because response to treatment can be viewed as a close proxy to health outcomes. Therefore, such an outcome measure has more clinical significance than a comparison of mean changes of scores on rating scales.

For each meta-analysis, we conducted a test of heterogeneity and applied both a random and a fixed effects model. We report the random effects model results because, in all three meta-analyses, the results from random and fixed effects models were very similar. If the relative risk

was statistically significant, we then conducted a meta-analysis of the risk differences to calculate the number needed to treat on the pooled risk difference.

We assessed publication bias using funnel plots and Kendell's tests. However, given the small number of component studies in our meta-analyses results of these tests must be viewed cautiously. All statistical analyses were conducted using StatsDirect, version 2.3.8.

RESULTS

Overview

We identified 3213 citations from searches and reviews of reference lists. We identified an additional 40 citations from dossiers submitted by pharmaceutical companies and 6 from public comments. Some citations from the dossiers were reported in abstract form only and were subsequently excluded.

In all, we included 218 studies: 157 randomized controlled trials, 27 meta-analyses, 24 observational studies, and 10 studies of other design. Furthermore, we retrieved 92 articles for background information. Two studies of interest could not be retrieved after multiple attempts.[13, 14] Figure 1 (QUORUM Tree) documents the disposition of the 789 articles for these studies.

Reasons for exclusions were based on eligibility criteria or methodological criteria (Figure 1, QUORUM Tree). Fifty-eight studies (61 articles) that met the eligibility criteria were later rated as poor quality for internal validity and excluded from the analysis (Appendix C). The two main reasons for a poor quality rating among randomized controlled trials were high loss to follow-up (more than 40%) and lack of double-blinding. Among meta-analyses, lack of a systematic literature search was the main reason for exclusions. A lack of systematic literature search leads to a selected spectrum of trials and subsequently to biased results.[12]

Of 218 included studies, 63 percent were financially supported by pharmaceutical companies; 21 percent were funded by governmental agencies or independent funds. For 16 percent of included studies, we could not determine funding source.

Studies reviewed for this report employed a notable array of diagnostic scales and health status or quality of life instruments. Most were pertinent to depressive and other disorders considered in this report, but some are considered more generic instruments to assess, e.g., health-related quality of life. Table 4 lists diagnostic scales and health status or quality-of-life instruments encountered in this literature and used in this report.

Table 4. Abbreviations and full names of diagnostic scales and other instruments

Abbreviation	Full name of instrument
BDI II	Beck Depression Inventory II
BQOL	Battelle Quality of Life Measure
Beck's SSI	Scale for Suicide Ideation
CAS	Clinical Anxiety Scale
CAPS	Clinician Administered PTSD Scale
CCEI	Crown Crisp Experiential Index
CDRS	Cornell Dysthymia Rating Scale
CGI	Clinical Global Impressions
CGI –I	Clinical Global Impressions Improvement Scale
CGI – S	Clinical Global Impressions Severity Scale
CIS	Clinical Interview Schedule
DSM – IV	Diagnostic and Statistical Manual of Mental Disorders, version IV
ESRS	Extrapyramidal Symptom Rating Scale
FSQ	Functional Status Questionnaire
GHQ	General Health Questionnaire
HAD	Hospital Anxiety and Depression Rating Scale
HADRS	Hamilton Depression Rating Scale
HAM – A	Hamilton Rating Scale for Anxiety
HAM – D	Hamilton Rating Scale for Depression
IDAS	Irritability, depression, and anxiety scale
IDS C	Inventory for Depressive Symptomatology – Clinician Rated
IDS SR	Inventory for Depressive Symptomatology – Self Rated
MADRS	Montgomery Asberg Depression Rating Scale
MMSE	Mini Mental State Examination
MOCI	Maudsley Obsessive Compulsive Inventory
PAS	Panic and Agoraphobia Scale
PRIME MD	Primary Care Evaluation of Mental Disorder
PSE	Present State Examination
PGIS	Patient Global Improvement Scale
QLDS	Quality of Life in Depression Scale
QLSQ	Quality of Life Enjoyment and Satisfaction Questionnaire
RCIS	Revised Clinical Interview Schedule—Shona Version
SADS	Schedule for Affective Disorders and Schizophrenia
SCAG	Sandoz Clinical Assessment Geriatric Scale
SF-36	Medical Outcomes Study Health Survey - Short Form 36
SIGH SAD	Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version
SIP	Sickness Impact Profile
SCID	Structured Clinical Interview for DSM III Revised
SCL 25	Hopkins Symptom Checklist 25 item version
SLT	Shopping List Task
SDS	Sheehan Disability Scale
SDS	Self rating Depression Scale
SSQ	Shona Symptom Questionnaire
Y-BOCS	Yale Brown Obsessive Compulsive Scale

Key Question 1.

For outpatients with depressive, anxiety, adjustment, and/or premenstrual dysphoric disorder, do second-generation antidepressants differ in efficacy?

We included 125 randomized controlled trials, 18 meta-analyses, and 1 study of other design. Of the randomized controlled trials, 91 were head-to-head trials; 34 were placebo-controlled trials.

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 in Adults

The following drugs are currently approved by the Food and Drug Administration 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 inhibitors[17] and a systematic review conducting indirect comparisons of escitalopram with venlafaxine XR[18] 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. We have added information on these new studies to Table 6 and describe them in more detail in the chapter on the respective comparisons if they have added new, relevant information.

Seven systematic reviews and 72 randomized controlled trials compared the effectiveness or efficacy of one second-generation antidepressant to another for treating patients with major depressive disorder (Table 6).

Most subjects were younger than 60 years. Inclusion was generally determined on a criteria-based diagnosis (DSM-III-R, DSM-IV]) of major depressive disorder and a predefined cut-off point of a universally used depression scale (e.g., HAM-D: 18 or MADRS: 19). Most patients had moderate to severe depression as measured by a variety of scales. Most studies excluded patients who had additional Axis I disorders, high suicidal risk, or progressive medical diseases or who used psychotherapy, electroconvulsive therapy, or psychotropic medications.

Most trials used one or more of the following outcome measures:

- response rate, e.g., more than 50 percent improvement of symptoms on a depression symptoms rating scale, or much or very much improved as assessed by a global assessment method;
- rate of remission; or

- changes in scores on depression scales

Quality of life and functional capacity were rarely assessed, and if they were, they were considered only as a secondary outcome. Most studies employed both physician-rated scales (e.g., HAM-D, MADRS, Clinical Global Impressions Scale [CGI]) and patient-rated scales (e.g., Hospital Anxiety and Depression Rating Scale [HAD-A], Battelle Quality of Life Scale). All studies used physician-rated scales to assess the main outcome measures.

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

Most studies received a *fair* rating for internal validity. The 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[33, 34] and one US trial[35] in primary care settings, with less stringent eligibility criteria, could be viewed as effectiveness trials. These studies also had long periods of follow-up.[34, 35] 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. High drop-out rates may be attributable to specific characteristics of a psychiatric outpatient population and a relatively high rate of adverse events in the examined drug class.

Selective serotonin reuptake inhibitors compared to selective serotonin reuptake inhibitors in adult outpatients with major depressive disorder

Citalopram compared with escitalopram

Five published trials[36-40]and one unpublished[41] trial all of fair quality, compared the efficacy of escitalopram and citalopram. Four studies were conducted over 8 weeks, two of them as fixed dose trials[36, 37, 39] (escitalopram 10 mg/d and 20 mg/d to citalopram 20 mg/d and 40 mg/d). Overall, results favored escitalopram over citalopram. Three studies reported statistically significantly higher response and remission rates for escitalopram than for citalopram. One trial was a fair-rated European/Canadian flexible dose study that compared the efficacy and tolerability of citalopram (20-40 mg/d) to escitalopram (10-20 mg/d) and placebo in 471 depressed outpatients attending primary care centers.[36] Loss to follow-up was 7 percent. Intention-to-treat results showed that the escitalopram group had significantly more responders

(≥ 50% improvement on MADRS; 63.7% compared with 52.6%; *P*=0.021) and remitters (MADRS < 12; 52.1% compared with 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.

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]

A pooled analysis of data from three randomized controlled trials concluded that escitalopram significantly improved sleep disturbance compared to citalopram.[42]

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.

Table 5. Characteristics and effect sizes of studies comparing citalopram to escitalopram

Study	N	Duration	Dosage Esc. – Cit. mg/d	Response(%)	Remission(%)	Quality Rating
Burke et al. 2002[37]	491	8 weeks	20 compared with 40	51.2 compared with 45.6 *P*=NR (NS)	NR	Fair
			10 compared with 40	50 compared with 45.6 *P*=NR (NS)	NR	
Colonna et al. 2005[38]	357	8 weeks	10 compared with 20	63 compared with 55 *P*<0.05	NR	Fair
		24 weeks	10 compared with 20	80 compared with 78 *P*=NR (NS)	NR	
Lepola et al. 2003[36]	471	8 weeks	10-20 compared with 20-40	63.7 compared with 52.6 *P*=0.021	52.1 compared with 42.8 *P*=0.036	Fair
Moore et al. 2005[39]	280	8 weeks	20 compared with 40	76.1 compared with 61.5 *P*=0.009	56.1 compared with 43.6 *P*=0.04	Fair
SCT-MD-02 (unpublished)[41]	243	8 weeks	10-20 compared with 20-40	46 compared with 51 *P*=NR	NR	Fair
Yevtushenko et al. 2007[40]	330	6 weeks	10 compared with 10 compared with 20	95.4 compared with 44.3 compared with 83.3 *P*<0.001	89.8 compared with 25.5 compared with 50.9	Fair

We conducted two meta-analyses of these studies comparing the effects of citalopram to escitalopram on MADRS scores at weeks 6 to 8. The outcome of the first meta-analysis was the relative risk of being a responder on the MADRS scale (Exhibit 1). A "response" was defined as

an improvement of 50 percent or more on the MADRS scale. Pooled results included 1759 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 number needed to treat 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 (Exhibit 2). 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.[43]

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

Citalopram compared with fluoxetine

In a fair-rated trial from France, 397 outpatients with major depressive disorder attending general practices were randomly assigned to citalopram (20 mg/d) or fluoxetine (20 mg/d) over 8 weeks.[44] 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 compared with sertraline

A good-quality Swedish study assessed the effectiveness of citalopram (20-60 mg/d) and sertraline (50-150 mg/d) in 400 patients in general practice during 24 weeks of treatment.[33] 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%). Treatment groups did not differ significantly in adverse events. 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 compared with fluvoxamine

Two fair studies evaluated the comparative effectiveness and safety of fluoxetine and fluvoxamine in outpatients with major depressive disorder.[46, 47] A 7-week flexible dose study (fluoxetine: 20-80 mg/d; fluvoxamine 100-150 mg/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).[47] Both treatment regimens significantly improved scores on assessment scales. The second study was a 6-week fixed dose European trial (fluoxetine 20 mg/d; fluvoxamine 100 mg/d) in 184 outpatients with major depressive disorder.[46] 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% compared with 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 compared with paroxetine

Seven fair-rated studies compared fluoxetine to paroxetine.[48-54] Two randomized controlled trials were conducted in a population older then 60 years.[48, 51] The best trial was an Italian study lasting 1 year that enrolled 242 patients to compare the effects of fluoxetine (20-60 mg/d) and paroxetine (20-40 mg/d) on mood and cognitive function in depressed, nondemented persons (65 years or older).[48] 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 compared with 9; $P<0.002$).

The other six studies[49-54] 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,[50, 51] four trials did not.[49, 52-54] In one study paroxetine-treated patients older than 60 years had a significantly greater response rate on HAM-D and MADRS scales (37.5% compared with 17.5%; P=0.04) than fluoxetine-treated patients. Patients on paroxetine had significantly better Mini Mental State Examination (MMSE) and Sandoz Clinical Assessment Geriatric Scale (SCAG) scores assessing cognitive function at week 3 than did those on fluoxetine. Five studies did not find differences in the improvement of anxiety in patients with depression.[48, 49, 52-54] A Canadian randomized controlled trial assessed anxiolytic activity and akathisia as secondary outcome measures and could not detect any significant differences between treatment groups.[49] However, study groups in this trial were not similar at baseline with respect to recurrent depression (paroxetine 76.5% compared with fluoxetine 59.5%), the validity of results might be limited.[49]

We 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.[49-54] 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.[48] The statistical analysis included 795 patients. Results (Exhibit 3) show that the response rate did not differ significantly between fluoxetine and paroxetine (relative risk 1.09; 95% CI 0.97 to 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 compared with sertraline

Six studies compared fluoxetine to sertraline.[34, 35, 53, 55-57] The top-level evidence consisted of two effectiveness trials[34, 35] and one efficacy trial[58] with long periods of follow-up.

Two fair-rated, multicenter trials from France were conducted in office settings (private psychiatrists and general physicians [GPs]).[34, 58] The psychiatrists' study randomized 238 patients for 24 weeks and the GP study 242 patients for nearly 26 weeks (180 days) to fluoxetine (20-60 mg/d) or sertraline (50-150 mg/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 or in the incidence of adverse events.

The ARTIST trial was an open-label randomized controlled trial designed as an effectiveness study and carried out in a primary care setting (primary care physicians) over 9 months.[35] 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 major depressive disorder, 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. Subgroup analyses did not show different effectiveness for patients with major depressive disorder or for those older than 60 years.

Three additional fair-rated trials did not find any significant differences in primary outcome measures (HAM-D, MADRS, CGI-S).[53, 55, 57, 59] Treatment durations varied from 6 to 16 weeks. One study was conducted in 236 participants older than 60 years.[57, 59] In this randomized controlled trial, outcome measures also included quality of life (Q-LES-Q) and cognitive assessments (Shopping List Task [SLT], MMSE, Digital Symbol Substitution Test). Results on these health outcome measures were similar for both drugs. A subgroup analysis of 75 patients 70 years of age or older showed a greater response rate for sertraline-treated patients (P=0.027).[59]

We conducted a meta-analysis of five of these studies comparing the effects of fluoxetine to sertraline on HAM-D scores at study endpoint.[34, 53, 55-57] All studies except one were financially supported by the manufacturer of sertraline. Results are presented in Exhibit 4. We excluded one study because a different diagnostic scale measured the outcome.[35] 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 percent or more on the HAM-D scale. Pooled results included 1190 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 to 1.22) for sertraline relative to fluoxetine. Both random effects and fixed effects models presented similar, statistically significant results. The number needed to treat 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, 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.

Paroxetine compared with fluvoxamine

Two randomized controlled trials, one flexible-dose[60] and one fixed-dose,[61] compared the efficacy and safety of paroxetine and fluvoxamine. The flexible-dose trial was a fair 7-week randomized controlled trial comparing the efficacy and safety of paroxetine (20-50 mg/d) and fluvoxamine (50-150 mg/d) in 60 outpatients with major depressive disorder.[60] Loss to follow-up was 30 percent. Results presented no statistically significant differences on HAM-D, HAM-A, CGI, and SCL-56. Significantly more paroxetine than fluvoxamine patients suffered from sweating (33% compared with 10%; P=0.028). The fixed-dose trial provided consistent findings.[61]

Paroxetine compared with sertraline

One fair-rated Swedish randomized controlled trial compared paroxetine (20-40 mg/d) to sertraline (50-150 mg/d) in a 24-week study.[62] 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. Clinically significant improvement occurred over

baseline among all quality-of-life factors. Treatment groups did not differ significantly on BQOL factors. Diarrhea was more frequent in the sertraline group (35.2% compared with 15.2%; $P<0.01$). Patients in the paroxetine group had higher rates of fatigue (45.8% compared with 21.0%; $P<0.01$), decreased libido in females (8.8% compared with 1.8%; $P<0.05$), micturition problems (6.2% compared with 0.6%; $P<0.05$), and constipation (16.4% compared with 5.7%; $P<0.01$).

Sertraline compared with fluvoxamine

A fair-rated, 7-week study compared the depression scores and tolerability of sertraline (50-200 mg/d) and fluvoxamine (50-150 mg/d) in 97 depressed patients.[63] Loss to follow-up was 30.9 percent. Efficacy did not differ significantly between treatment groups. Both regimens led to significant improvements in depression scores from baseline (HAM-D, CGI). Significantly more patients withdrew because of adverse events in the fluvoxamine group (N=9) than in the sertraline group (N=1; $P=0.016$). Sertraline-treated patients reported a significantly greater rate of sexual dysfunction (28% compared with 10%; $P=0.047$).

A fair-rated, small Italian randomized controlled trial (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 (100-200 mg/d) or fluvoxamine (200-300 mg/d) treatment for 24 months.[64, 65] 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 compared with 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%). Adverse events did not differ significantly during the first 24 months of prophylactic treatment.

Other second-generation antidepressants compared to selective serotonin reuptake inhibitors in adult outpatients with major depressive disorder

Duloxetine compared with fluoxetine

A fair 8-week randomized controlled trial assigned 173 patients to duloxetine (40-120 mg/d), fluoxetine (20 mg/d), or placebo.[66] Overall loss to follow-up was 35 percent. Results revealed no statistically significant differences between duloxetine and fluoxetine in response (49% compared with 45%) and remission (43% compared with 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 compared with paroxetine

Three fair, 8-week, fixed-dose trial assessed the comparative efficacy of duloxetine (60 mg/d), duloxetine (80 mg/d), duloxetine (120 mg/d), paroxetine (20 mg/d), and placebo.[22, 23, 67] 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 compared with fluoxetine

A Taiwanese study compared mirtazapine (30-45 mg/d) to fluoxetine (20-40 mg/d) over 6 weeks in 133 moderately depressed Chinese patients.[68] Overall loss to follow-up was 39.4 percent; the drop-out rate was higher in the mirtazapine than the fluoxetine group (45.5% compared with 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. No differences in the incidence of adverse events were statistically significant.

Mirtazapine compared with paroxetine

Two trials assessed the efficacy of mirtazapine (15-45 mg/d) and paroxetine (20-40 mg/d).[69, 70] The German study enrolled 275 patients in a 6-week trial.[69] The US trial randomized 255 participants for 8 weeks.[70] 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 compared with mean 40 days; $P=0.016$). No significant difference in response rates on the CGI scale was noted. Both trials reported weight gain in significantly more mirtazapine-treated patients than in paroxetine-treated patients ($P<0.05$). Paroxetine-treated patients in the US study reported significantly higher rates of nausea, tremor, and flatulence ($P<0.05$). The number needed to treat to yield one additional responder at weeks 1 or 2 is 7.

Mirtazapine compared with sertraline

One fair-rated, recent multinational European study examined the onset of efficacy of mirtazapine (30-45 mg/d) compared to that of sertraline (50-150 mg/d) in 346 outpatients.[71] 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. The Changes in Sexual Functioning Questionnaire did not show significant differences although for mirtazapine the trend was positive. A significantly higher number of patients withdrew because of adverse events in the mirtazapine group (12.5% compared with 3%; *P*=NR).

Venlafaxine compared with citalopram

A fair European 6-month study compared venlafaxine ER (37.5-150 mg/d) to citalopram (10-30 mg/d) for the treatment of depression in elderly outpatients (mean age 73 years).[72] 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 compared with escitalopram

Two fair 8-week studies assessed the comparative effectiveness of venlafaxine XR and escitalopram.[73, 74] A fair European, multinational study assigned 293 patients to escitalopram (10-20 mg/d) or venlafaxine XR (75-150 mg/d).[73] 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 ($P<0.01$). Significantly more patients on venlafaxine XR than on escitalopram reported nausea (26% compared with 17%; $P<0.05$), sweating (12.5% compared with 6%; $P<0.05$), and constipation (6% compared with 2%; $P<0.05$).

The second trial reported similar results.[74] No statistically significant differences were apparent between venlafaxine XR and escitalopram in response (48% compared with 58.8%) and remission rates. Significantly more patients in the venlafaxine group withdrew because of adverse events (16% compared with 4%; $P<0.01$) or reported nausea (24% compared with 6%; $P<0.05$).

Venlafaxine compared with fluoxetine

A South American multicenter study with a good quality rating randomized 382 patients to venlafaxine (75-150 mg/d) or fluoxetine (20-40 mg/d) for 8 weeks.[75] 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%). No significant differences in adverse events were observed.

Three fair-rated studies reported mixed results about the efficacy of venlafaxine and fluoxetine in comorbid patients with high anxiety[76, 77] or generalized anxiety disorder.[78, 79] Only one study reported significantly greater response rates on HAM-D (71.9% compared with 49.3%; $P=0.008$) and MADRS (75.0% compared with 49.3%; $P=0.001$) for venlafaxine than for fluoxetine.[76] 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: $P=0.0004$).[76] Two studies reported significantly more dizziness ($P<0.001$) and sweating ($P<0.05$) in the venlafaxine group than in the fluoxetine group.[77-79]

Seven additional trials also provided predominantly consistent evidence on a similar efficacy of venlafaxine and fluoxetine.[29-32, 80-82] Only one study reported a significantly higher response rate of venlafaxine than fluoxetine (72% compared with 60%; $P=0.023$).[81]

We conducted a meta-analysis of eight studies comparing venlafaxine to fluoxetine.[29, 31, 76-78, 80-82] All studies were financially supported by the manufacturer of venlafaxine. Three studies were excluded because of missing data.[30, 32, 75] The main outcome measure was the response to treatment on HAM-D at study endpoint. Results (Exhibit 5), 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, 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.

These findings are similar to results of a meta-analysis recently reported by Smith et al. (2002).[83] Venlafaxine showed a modest but statistically significantly greater standardized effect size (-0.14; 95% CI -0.22 to -0.06) and a significantly greater 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 compared with paroxetine

Two fair studies compared venlafaxine to paroxetine.[84, 85] A Spanish study compared venlafaxine (75-150 mg/d) to paroxetine (20-40 mg/d) in outpatients (N=84) with either major depressive disorder or dysthymia over 24 weeks.[84] 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% compared with 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 (75 mg/d) or paroxetine (20 mg/d).[85] Loss to follow-up was 27.4 percent. Results revealed no significant differences in efficacy measures, quality of life scores, or adverse events between study groups.

Venlafaxine compared with sertraline

Two good trials[86, 87] and one fair[21] trial compared the efficacy of sertraline to venlafaxine. A good quality Scandinavian trial compared venlafaxine (75-150 mg/d) to sertraline (50-100 mg/d) in 147 patients who were mainly moderately to markedly ill.[87] 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% compared with 68%; P=0.05), as were remission rates (68% compared with 45%; P=0.008). No significant differences were noted for response or remission rates on MADRS and CGI scales. No significant differences were observed for adverse events. By contrast, the other two studies did not find any differences in efficacy between sertraline(50-150 mg/d) and venlafaxine XR (75-225 mg/d).[21, 86]

Bupropion compared with selective serotonin reuptake inhibitors

A recent, fair-rated meta-analysis compared the benefits and risks of bupropion to selective serotonin reuptake inhibitors as a class in 1332 adult outpatients with major depressive disorder.[88] The age of the participants ranged from 36 to 70 years. The analysis included five double-blinded, head-to-head randomized controlled trials with study durations from 6 to 16

weeks. Three trials assessed the efficacy and safety of bupropion compared with sertraline, one assessed bupropion compared with paroxetine, and one assessed bupropion compared with fluoxetine. The weighted mean differences of CGI-S and HAM-A scores did not differ significantly between bupropion and selective serotonin reuptake inhibitors. 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 compared with fluoxetine

A fair, 6-week study compared the efficacy of bupropion (225-450 mg/d) and fluoxetine (20-80 mg/d) in 123 patients with moderate to severe depression.[89] 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%). Adverse events did not differ significantly between treatment groups.

Another fair, 8-week randomized controlled trial compared efficacy and sexual side effects of bupropion SR (150-400 mg/d), fluoxetine (20-60 mg/d), and placebo in 456 outpatients with major depressive disorder.[90] Loss to follow-up was 36 percent. Results showed no statistically significant differences in efficacy. At endpoint, bupropion SR had more remitters than fluoxetine (47% compared with 40%). Bupropion SR also showed significantly fewer sexual side effects than fluoxetine throughout the study. Beginning at week 1 until endpoint, significantly more fluoxetine-treated patients than bupropion SR-treated patients ($P<0.05$) were dissatisfied with their overall sexual function.

Bupropion compared with paroxetine

One fair randomized controlled trial examined the efficacy of bupropion SR (100-300 mg/d) and paroxetine (10-40 mg/d) in 100 outpatients ages 60 years or older (range 60-88 years) over 6 weeks.[91, 92] 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 (≥ 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.

Bupropion compared with sertraline

A fair, 16-week trial assessed efficacy and tolerability of bupropion SR (100-300 mg/d) and sertraline (50-200 mg/d) in outpatients (N=248) with moderate to severe depression.[93] 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. The article did not report on response or remission rates. Some adverse events (nausea, diarrhea, somnolence, sweating) were significantly higher among sertraline-treated patients ($P<0.05$). Discontinuation rates because of sexual adverse events were also significantly higher in the sertraline group (13.5% compared with 3.3%, $P=0.004$).

Two fair-rated randomized controlled trials compared the incidence of sexual dysfunction in 360 and 364 patients with major depressive disorder during 8 weeks of treatment with bupropion SR (150-400 mg/d), sertraline (50-200 mg/d), or placebo.[94, 95] 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 reported no significant differences in any efficacy measures between bupropion SR and sertraline at 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.[94] 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 ($P<0.05$).[95]

Nefazodone compared with fluoxetine

Three studies with identical protocols examined the effects of antidepressive treatment with either nefazodone or fluoxetine on sleep in outpatients with major depressive disorder.[96-98] Data from these trials were pooled into one analysis.[98] A total of 125 patients with major depressive disorder 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 (HADRS) 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 compared with paroxetine

Another fair, multi-national study enrolled 206 moderately depressed patients to an 8-week, acute-phase trial comparing nefazodone (200-600 mg/d) to paroxetine (20-40 mg/d).[99, 100] Patients who responded to acute treatment were enrolled in an open-label continuation phase (N=108) from w eek 8 to month 6.[100] 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 compared with sertraline

A fair, multicenter European study assessed the efficacy and tolerability of nefazodone (100-600 mg/d) and sertraline.[101] 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%). Additional outcome measures assessed by questionnaire were sexual function and satisfaction under antidepressant treatment. Overall satisfaction with sexual function was significantly higher in the nefazodone group ($P<0.01$). Among men, 67 percent in the sertraline group and 19 percent in the nefazodone group reported difficulty with ejaculation ($P<0.01$). Other adverse events did not differ significantly between the two groups.

Summary of the evidence

Seventy-two head-to-head trials compared the effectiveness and efficacy of one selective serotonin reuptake inhibitor or other second-generation antidepressant to another. All studies addressed initial use of antidepressants.

Overall, effectiveness and efficacy were similar and the majority of trials did not identify substantial differences among drugs. These findings were also confirmed by indirect comparisons of drugs with little or no direct head-to-head evidence. Discontinuation rates and response and remission rates assessed on multiple diagnostic scales did not differ substantially when taking all the evidence into consideration. We did not find any evidence that one group has a greater benefit from an individual drug than another. Differences among medications exist in speed of response and some aspects of health-related quality of life. For example, mirtazapine presents a faster onset of action than paroxetine and sertraline (Table 7); bupropion has fewer sexual side effects than fluoxetine and sertraline (Table 8); and nefazodone improves sleep quality (Table 9).

Few studies assessed the efficacy of second generation antidepressants in comorbid patients with other psychiatric disorders. Patients with other axis I disorders were generally excluded from study participation. Secondary outcome measures often included anxiety scales. Overall, no substantial differences in improvements on anxiety scales exist. However, mixed results or findings limited to a single trial make the body of evidence inconclusive if any of the second generation antidepressants has a higher efficacy in comorbid patients with high anxiety, recurrent depression, or somatization. A recent systematic review did not detect any differences in efficacy between selective serotonin reuptake inhibitors and other second-generation antidepressants for the treatment of major depressive disorder with anxiety.[102] Generally, high rates of loss to follow-up limit the validity of many studies.

Effectiveness

One good[33] and two fair-rated[34, 35] effectiveness trials provide good to fair evidence that treatment effectiveness does not differ among compared drugs. These comparisons included citalopram to sertraline, fluoxetine to sertraline, and fluoxetine to sertraline and paroxetine. Findings are consistent with evidence from efficacy trials. Two of these trials provide fair evidence that improvement of health-related quality of life (work, social and physical functioning, concentration and memory, sexual functioning) does not differ significantly between fluoxetine, paroxetine, and sertraline.[34, 35] The effectiveness of citalopram and sertraline did not differ significantly in a subgroup analysis of patients with recurrent depression.[33] However, this finding is limited to a single trial.

Efficacy

Twelve studies comparing one selective serotonin reuptake inhibitor to another provide good to fair evidence that no significant differences exist among selective serotonin reuptake inhibitors in improving health-related quality of life or measures of functional capacity (e.g., sleep quality, cognitive function).[20, 34, 37, 46, 51, 58, 60-62, 103]

A pooled analysis of data from three fair-rated trials with identical study protocols comparing nefazodone to fluoxetine reports that improvement of sleep quality is significantly greater in nefazodone-treated patients than in fluoxetine-treated patients.[98] All three studies were financially supported by a manufacturer of nefazodone. Similarly, pooled data indicates greater benefits of escitalopram than citalopram in reducing sleep disturbance.[42]

Several other efficacy studies assessed quality of life and health-related functional capacity in selective serotonin reuptake inhibitors compared to other second-generation antidepressants.[21-25, 31, 71, 92, 101] The body of evidence for these comparisons is either inconsistent or based on a single trial. No firm conclusions can be drawn from their results.

Seventy-two efficacy studies and an evidence report conducting indirect comparisons assessed intermediate outcomes such as changes on HAM-D or MADRS scales. Overall, efficacy was similar and the majority of trials did not identify substantial differences among drugs. Statistically significant differences of pooled response rates of some meta-analyses are likely not clinically significant.

Three studies yielded fair evidence that mirtazapine has a significantly faster onset of action than paroxetine and sertraline.[69-71] The number needed to treat to yield one additional responder at weeks 1 or 2 is 7. A fourth study also reported a faster onset of response for mirtazapine than for fluoxetine but this did not reach statistically significant levels.[68] The overall efficacy did not differ significantly between mirtazapine and selective serotonin reuptake inhibitors.

Seven trials[89-91, 93-95] and one meta-analysis[88] present fair evidence that efficacy is not significantly different between bupropion and escitalopram, fluoxetine, paroxetine, or sertraline. Five trials provide fair evidence that bupropion has fewer sexual side effects than escitalopram, fluoxetine, and sertraline.[26, 90, 93-95]

Table 6. Interventions, numbers of patients, and quality ratings of studies in adults with major depressive disorder

Author, Year	Interventions	N	Results	Quality rating
Second-generation antidepressants compared with second-generation antidepressants				
Gartlehner et al. 2007[15]	All second-generation antidepressants (SR)	NR	No differences	Good
Selective serotonin reuptake inhibitors compared with selective serotonin reuptake inhibitors				
Burke et al. 2002[37]	Citalopram compared with escitalopram	491	No differences	Fair
Colonna et al. 2005[38]	Citalopram compared with escitalopram	357	Significantly more responders and remitters in the escitalopram group at 8 weeks but not at 24 weeks	Fair

Author, Year	Interventions	N	Results	Quality rating
Lader et al. 2005[42]	Citalopram compared with escitalopram (pooled data)	1321	Greater efficacy of escitalopram in reducing sleep disturbance	Fair
Lepola et al. 2003, 2004[36, 104]	Citalopram compared with escitalopram	471	Significantly more responders and remitters in the escitalopram group	Fair
Moore et al. 2005[39]	Citalopram compared with escitalopram	280	Significantly more responders and remitters in the escitalopram group	Fair
SCT-MD-02, 2001 (unpublished)[41]	Citalopram compared with escitalopram	243	No differences	Fair
Yevtushenko et al. 2007[40]	Citalopram compared with escitalopram	330	Significantly more responders and remitters in the escitalopram group	Fair
Patris et al. 1996[44]	Citalopram compared with fluoxetine	357	Faster onset of citalopram	Fair
Ekselius et al. 1997[33]	Citalopram compared with sertraline	400	No differences	Good
Kasper et al. 2005[45]	Escitalopram compared with fluoxetine	518	No differences	Fair
Boulenger et al. 2006[27]	Escitalopram compared with paroxetine	454	Higher remission rates of escitalopram after 24 weeks	Fair
Baldwin et al. 2006[28]	Escitalopram compared with paroxetine	323	No difference	Fair
Ventura et al. 2007[20]	Escitalopram compared with sertraline	212	No difference	Fair
Dalery et al. 2003[46]	Fluoxetine compared with fluvoxamine	184	Faster onset of fluvoxamine	Fair
Rapaport et al. 1996[47]	Fluoxetine compared with fluvoxamine	100	No differences	Fair
Cassano et al. 2002[48]	Fluoxetine compared with paroxetine	242	Faster onset of paroxetine	Fair
Chouinard et al. 1999[49]	Fluoxetine compared with paroxetine	203	No differences	Fair
De Wilde et al. 1993[50]	Fluoxetine compared with paroxetine	100	Faster onset of paroxetine	Fair
Gagiano et al. 1993[54]	Fluoxetine compared with paroxetine	90	No differences	Fair
Schone et al. 1993[51]	Fluoxetine compared with paroxetine	108	Faster onset of paroxetine	Fair
Fava et al. 1998[52]	Fluoxetine compared with paroxetine	128	No differences	Fair
Bennie et al. 1995[55]	Fluoxetine compared with sertraline	286	No differences	Fair
Boyer et al. 1998[58]	Fluoxetine compared with sertraline	242	No differences	Fair
Fava et al. 2002[53]	Fluoxetine compared with sertraline compared with paroxetine	284	No differences	Fair
Finkel et al. 1999[59]	Fluoxetine compared with sertraline	75	Faster onset of sertraline	Fair
Sechter et al. 1999[34]	Fluoxetine compared with sertraline	238	No differences	Fair

Author, Year	Interventions	N	Results	Quality rating
Newhouse et al. 2000[57]	Fluoxetine compared with sertraline	236	No differences	Fair
Kroenke et al. 2001[35]	Fluoxetine compared with sertraline compared with paroxetine	601	No differences	Fair
Katzman et al. 2007[16]	Paroxetine compared with other antidepressants	NR	No differences	Good
Aberg-Wistedt et al. 2000[62]	Paroxetine compared with sertraline	353	No differences	Fair
Kiev et al. 1997[60]	Paroxetine compared with fluvoxamine	60	No differences	Fair
Ushiroyama et al. 2004[61]	Paroxetine compared with fluvoxamine	105	No differences	Fair
Nemeroff et al. 1995[63]	Sertraline compared with fluvoxamine	97	No differences	Fair
Franchini et al. 1997, 2000[64, 65]	Sertraline compared with fluvoxamine	64	No differences	Fair
Serotonin and norepinephrine reuptake inhibitors compared with selective serotonin reuptake inhibitors				
Nierenberg et al. 2007[19]	Duloxetine compared with escitalopram	684	No differences	Fair
Khan et al. 2007[25]	Duloxetine compared with escitalopram	278	Higher response and remission rates for escitalopram	Fair
Wade et al. 2007[24]	Duloxetine compared with escitalopram	295	Higher response and remission rates for escitalopram after 8 weeks; no differences after 24 weeks	Fair
Detke et al. 2004[67]	Duloxetine compared with paroxetine	367	No difference	Fair
Lee et al. 2007[22]	Duloxetine compared with paroxetine	478	No difference	Fair
Perahia et al. 2006[23]	Duloxetine compared with paroxetine	392	No difference	Fair
Goldstein et al. 2002[66]	Duloxetine compared with paroxetine	173	No difference	Fair
Hong et al. 2003[68]	Mirtazapine compared with fluoxetine	133	No differences	Fair
Schatzberg et al. 2002[69]	Mirtazapine compared with paroxetine	255	Faster onset of mirtazapine	Fair
Benkert et al. 2000[70]	Mirtazapine compared with paroxetine	275	Faster onset of mirtazapine	Fair
Behnke et al. 2003[71]	Mirtazapine compared with sertraline	346	Faster onset of mirtazapine	Fair
Weinmann et al. 2008[17]	Venlafaxine compared with SSRIs (SR)	3142	No difference	Good
Bielski et al. 2004[74]	Venlafaxine compared with escitalopram	198	No differences	Fair
Eckert et al. 2006[18]	Venlafaxine compared with escitalopram	3212	No differences	Fair
Montgomery et al. 2004[105]	Venlafaxine compared with escitalopram	293	No differences	Fair
Allard et al. 2004[72]	Venlafaxine compared with citalopram	151	No differences	Fair
Costa e Silva et al. 1998[75]	Venlafaxine compared with fluoxetine	382	No differences	Fair

Author, Year	Interventions	N	Results	Quality rating
Alves et al. 1999[80]	Venlafaxine compared with fluoxetine	87	Faster onset of venlafaxine	Fair
Corya et al. 2006[32]	Venlafaxine compared with fluoxetine	119	No differences	Fair
Dierick et al. 1996[81]	Venlafaxine compared with fluoxetine	314	Significantly higher response rate for venlafaxine	Fair
De Nayer et al. 2002[76]	Venlafaxine compared with fluoxetine	146	Significantly greater improvement for venlafaxine	Fair
Keller et al. 2007[29]	Venlafaxine ER compared with fluoxetine	1096	No differences	Fair
Nemeroff et al. 2007[31]	Venlafaxine compared with fluoxetine	308	No differences	Fair
Schatzberg et al. 2006[30]	Venlafaxine compared with fluoxetine	300	No differences	Fair
Tylee et al. 1997[82]	Venlafaxine compared with fluoxetine	341	No differences	Fair
Rudolph et al. 1999[77]	Venlafaxine XR compared with fluoxetine	301	No differences	Fair
Silverstone et al. 1999[78, 79]	Venlafaxine XR compared with fluoxetine	368	No differences	Fair
Ballus et al. 2000[84]	Venlafaxine compared with paroxetine	84	No differences	Fair
McPartlin et al. 1998[85]	Venlafaxine XR compared with paroxetine	361	No differences	Fair
Mehtonen et al. 2000[87]	Venlafaxine compared with sertraline	147	Significantly higher response rate for venlafaxine	Good
Shelton et al. 2006[21]	Venlafaxine XR compared with sertraline	160	No differences	Fair
Sir et al. 2005[86]	Venlafaxine XR compared with sertraline	163	No differences	Good
Other second-generation antidepressants (DopRi, 5-HT$_2$) compared with selective serotonin reuptake inhibitors				
Nieuwstraten et al. 2001[88]	Bupropion compared with SSRIs (SR)	1332	No differences	Good
Panzer et al. 2005[102]	SSRIs compared with other second-generation antidepressants (SR)	NR	No differences in patients with comorbid anxiety	Fair
Clayton et al. 2006[26]	Bupropion compared with escitalopram	830	No differences	Fair
Feighner et al. 1991[89]	Bupropion compared with fluoxetine	123	No differences	Fair
Coleman et al. 2001[90]	Bupropion compared with fluoxetine	456	No differences	Fair
Weihs et al. 2000[91, 92]	Bupropion SR compared with paroxetine	100	No differences	Fair
Coleman et al. 1999[95]	Bupropion compared with sertraline	364	No differences	Fair
Croft et al. 1999[94]	Bupropion compared with sertraline	360	No differences	Fair
Kavoussi et al. 1997[93]	Bupropion compared with sertraline	248	No differences	Fair
Rush et al. 1998[98]	Nefazodone compared with fluoxetine	125	No differences	Fair
Baldwin et al. 1996, 2001[99, 100]	Nefazodone compared with paroxetine	206	No differences	Fair

Author, Year	Interventions	N	Results	Quality rating
Feiger et al. 1996[101]	Nefazodone compared with sertraline	160	No differences	Fair

Abbreviations: SR, Systematic review; SSRI, selective serotonin reuptake inhibitor.

Table 7. Study characteristics and effect sizes of trials indicating a faster onset of mirtazapine than fluoxetine, paroxetine, and sertraline

Study	Sample size	Comparison	Effect size	p-value	Comments
Faster onset of mirtazapine					
Behnke et al. 2003[71]	346	Sertraline	Significantly higher response rates at days 7, 10, and 14 with mirtazapine (rates not reported)	Day 7: *P*<0.05 Day 10: *P*<0.01 Day 14: *P*<0.05	No statistically significant differences in response and remission at endpoint (day 56)
Benkert et al. 2000[70]	275	Paroxetine	Significantly more responders (23.2% compared with 8.9%) and remitters (8.8% compared with 2.4%) at day 7 with mirtazapine. response: remission: RRR: 0.15 0.07 RD: 0.14 0.07 NNT: 8 15	response: *P*=0.002 remission: *P*=0.03	More responders and remitters in the mirtazapine group throughout the study. No statistically significant difference at endpoint (response: 58.3% compared with 53.7%; remission: 40.9% compared with 34.8%)
Hong et al. 2003[68]	133	Fluoxetine	At day 28 significantly more responders with mirtazapine (53,3% compared with 39.0%) RRR: 0.23 RD: 0.14 NNT: 7	Difference does not reach statistical significance. No p-values reported	No statistically significant differences in overall response rate at week 6; more responders in the mirtazapine group (58% compared with 51%)
Schatzberg et al. 2002[69]	255	Paroxetine	Significantly more responders at day 14 with mirtazapine (27.8% compared with 13.3%); RRR: 0.17 RD: 0.14 NNT: 7 significantly greater decrease of HAM-D scores from day 7 to day 21with mirtazapine; median time to response: Mirtazapine: 26 days Paroxetine: 40 days	*P*=0.005 *P*<0.01 (day 7, 14) *P*=0.024 (day 21) Kaplan-Mayer: *P*=0.016	No statistically significant differences in overall response rate at week 8; more responders in the mirtazapine group (58% compared with 51%) at endpoint.

Abbreviations: RRR, relative risk reduction; RD, risk difference; NNT, number needed to treat.

Table 8. Study characteristics and effect sizes of trials indicating fewer sexual adverse events for bupropion than escitalopram, fluoxetine, paroxetine, and sertraline

Study	Sample size	Comparison	Effect measure	*P* value	Comments
Lower rate of sexual side effects with bupropion SR					
Clayton et al. 2006[26]	830	Escitalopram	Incidence of worsened sexual functioning was significantly lower in patients on bupropion XL than on escitalopram	*P*<0.05	DSM-IV criteria for sexual dysfunction disorders No statistically significant differences in efficacy outcome measures at endpoint (week 8)
Coleman et al. 2001[90]	456	Fluoxetine, placebo	Significantly more bupropion SR patients were satisfied with overall sexual functioning (analysis only for patients satisfied at baseline; no rates reported)	*P*<0.05	DSM-IV criteria for sexual dysfunction disorders No statistically significant differences in efficacy outcome measures at endpoint (week 8)
Coleman et al. 1999[95]	364	Sertraline	Beginning at day 21 significantly more patients on bupropion SR were satisfied with their sexual functioning (endpoint: 85% compared with 62%) Endpoint: RRR: 0.59 RD: 0.22 NNT: 5	*P*<0.05	DSM-IV criteria for sexual dysfunction disorders No statistically significant differences in efficacy outcome measures at endpoint (week 8)
Croft et al. 1999[94]	360	Sertraline placebo	Beginning at day 7 through day 42 significantly more bupropion SR patients were satisfied with overall sexual functioning; difference was not statistically significant at endpoint (75% compared with 65%) endpoint: RRR: 0.29 RD: 0.10 NNT: 10	*P*<0.05	Assessment of sexual function in an investigator-conducted structured interview No statistically significant differences in efficacy outcome measures at endpoint (week 8)

Study	Sample size	Comparison	Effect measure	p-value	Comments
Kavoussi et al. 1997[93, 106]	248	Sertraline,	Significantly more patients on sertraline experienced orgasm delays and/or failure	*P*<0.01	Assessment of sexual function in an investigator-conducted structured interview ;
			Women : 41% compared with 7% RRR : 0.85 RD : 0.38 NNT : 3		No statistically significant differences in efficacy outcome measures at endpoint (week 16)
			Men : 61% compared with 10% RRR : 0.84 RD : 0.51 NNT : 2		
			Higher overall satisfaction with sexual functioning with bupropion SR at endpoint (79% compared with 58%)	*P*<0.001	
			RRR : 0.50 RD : 0.21 NNT : 5		
Feighner et al. 1991[89]	61	Fluoxetine	NR	NR	Bupropion IR ; study does not report on differences in sexual adverse events

Abbreviations: RRR, relative risk reduction; RD, risk difference; NNT, number needed to treat.

Table 9. Study characteristics and effect sizes of trials indicating a better sleep profile with nefazodone than fluoxetine

Study	Sample size	Comparison	Effect measure	p-value	Comments
Better sleep profile with nefazodone					
Rush et al. 1998[98]	125	Fluoxetine	Significantly greater improvements from baseline for nefazodone on HDRS Sleep Disturbance Factors, IDS-C, and IDSR Total Sleep factors	*P*<0.05	Pooled analysis of 3 identical studies assessing sleep quality

Abbreviations: RRR, relative risk reduction; RD, risk difference; NNT, number needed to treat.

B. Dysthymia in Adults

The following drugs are currently approved by the Food and Drug Administration 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 (Table 10) assessed efficacy and tolerability of fluoxetine, paroxetine, and sertraline in a population with dysthymia.[107-114]

1. Selective serotonin reuptake inhibitors compared to placebo in adults with dysthymia

Fluoxetine compared with placebo

A good randomized controlled trial determined the efficacy and safety of fluoxetine (10-60 mg/d) in elderly patients with dysthymia over 12 weeks.[113] 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% compared with 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% compared with 35.9%; P=0.03) than placebo.[114] Remission rates favored fluoxetine but did not reach statistical significance (44.4% compared with 25.6%; P=0.07).

Paroxetine compared with placebo compared with behavioral therapy

A large, fair-rated, primary-care-based study randomized 656 patients with dysthymia or minor depression to 11 weeks of paroxetine (10-40 mg/d), 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 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 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% compared with 40%; P=0.008).

Sertraline compared with imipramine compared with placebo

One randomized controlled trial compared sertraline (50-200 mg/d) to imipramine (50-300 mg/d) and placebo in 416 patients who had had the diagnosis of dysthymia for more than 5 years.[107-109] 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. The number of patients who discontinued therapy because of adverse events was significantly higher for imipramine than for sertraline (18.4% compared with 6.0%; $P=0.001$).

Sertraline compared with placebo

A multinational study enrolled 310 dysthymic patients for 12 weeks to compare sertraline (50-200 mg/d) to placebo.[110] 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.

2. Summary of the evidence

We identified no head-to head trials. In other trials, significant differences in population characteristics make this evidence insufficient to identify differences between treatments.

Effectiveness

One fair study, based in a primary care setting, provides mixed evidence on the effectiveness of paroxetine compared to placebo. A subgroup of patients older than 60 years showed a significantly greater improvement than those on placebo; a subgroup of patients younger than 60 years did not show any difference in effectiveness between paroxetine and placebo.[110, 112]

Efficacy

Evidence from one good study indicates that fluoxetine has only limited efficacy in elderly patients with dysthymia.[113] Fair evidence from two studies indicates that sertraline has a significantly greater efficacy in the treatment of dysthymia than placebo.[107-110] In both trials, sertraline treatment led to a significantly greater improvement of quality of life and psychosocial functioning than placebo.

Table 10. Interventions, numbers of patients, and quality ratings in controlled trials of adults with dysthymia

Author, Year	Interventions	N	Results	Quality rating
Selective serotonin reuptake inhibitors compared with placebo				
Barrett et al. 2001[111] Williams et al. 2000[112]	Paroxetine compared with placebo compared with Behavioral therapy	656	Significantly more responders for paroxetine in patients older than 60 years	Fair
Devanand et al. 2005[113]	Fluoxetine compared with placebo	90	No differences in response rates and quality of life	Good
Thase et al. 1996[107-109]	Sertraline compared with Imipramine compared with placebo	412	Significantly more responders for sertraline than placebo	Fair
Ravindran et al. 2000[110]	Sertraline compared with placebo	310	Significantly more responders and remitters for sertraline	Fair
Vanelle et al. 1997[114]	Fluoxetine compared with placebo	111	Significantly more responders for fluoxetine	Fair

C. Subsyndromal Depressive Disorders in Adults

1. Head-to-head evidence

We did not find any head-to-head randomized controlled trials.

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.

2. Placebo-controlled evidence.

Two studies were conducted in populations with minor depression.

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]

3. Summary of the evidence

We identified no head-to head randomized controlled trial. The only available head-to-head evidence was a nonrandomized, open-label trial comparing citalopram with sertraline.

Effectiveness

In one effectiveness study, effectiveness did not differ significantly between paroxetine and placebo for the treatment of minor depression.[111, 112]

Efficacy

A nonrandomized open-label trial did not detect any differences in efficacy between citalopram and sertraline.[115] In placebo-controlled trials, significant differences in population characteristics make the evidence insufficient to identify differences between treatments.[111, 112, 116]

Table 11. Interventions, numbers of patients, and quality ratings in controlled trials of adults with subsyndromal depression

Author, Year	Interventions	N	Results	Quality rating
Selective serotonin reuptake inhibitors compared with placebo				
Barrett et al. 2001[111] Williams et al. 2000[112]	Paroxetine compared with placebo compared with Behavioral therapy	656	Significantly more responders for paroxetine in patients older than 60 years	Fair
Judd et al. 2004[116]	Fluoxetine compared with placebo	162	Greater improvements on depression scales for fluoxetine than for placebo; no difference in psychosocial outcomes	Fair

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] We excluded two studies because they had a study duration of 5 weeks, which did not meet our eligibility criteria. Nevertheless, we briefly summarize them in the following paragraphs due to lack of evidence for this indication.[120, 121] No second-generation antidepressants were compared to one another.

Inclusion of patients was determined by a criteria-based (DSM-III-R, DSM-IV) diagnosis of major depressive episodes with a seasonal pattern,[118] or more broadly, major depression, depressive disorder NOS, bipolar disorder depressed, or bipolar disorder NOS with a seasonal pattern.[117] Both studies also used seasonal affective disorder specific evaluation tools, either the Hamilton depression scale HAM-D-24, consisting of the HAMD-17 plus 7 addition seasonal affective disorder specific criteria, or the SIGH-SAD (Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version). In addition, all patients were enrolled during winter.

1. Selective serotonin reuptake inhibitors compared to placebo in adult outpatients with seasonal affective disorder

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 ($P<0.05$).

2. Selective serotonin reuptake inhibitors compared to light therapy in adult outpatients with Seasonal Affective Disorder

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).

3. Summary of the Evidence

No head-to-head evidence was available. We identified two trials, one comparing sertraline to placebo, and one comparing fluoxetine to light therapy.

Effectiveness

We did not identify any study with a high degree of generalizability.

Efficacy

One placebo controlled randomized controlled trial offers statistically significant evidence for the efficacy of sertraline in seasonal effective disorder.[117] One good randomized controlled trial of fluoxetine compared with light therapy demonstrated no difference in efficacy between the two therapies.[118]

Table 12. Interventions, numbers of patients, and quality ratings of controlled trials in adults with seasonal affective disorder

Author, Year	Interventions	N	Results	Quality rating
Selective serotonin reuptake inhibitors compared with placebo				
Moscovitch et al. 2004[117]	Sertraline compared with placebo	187	Significantly greater efficacy of sertraline	Fair
Selective serotonin reuptake inhibitors compared with light therapy				
Lam et al. 2006[118]	Fluoxetine compared with light therapy	96	No difference in efficacy between fluoxetine and light therapy	Good

E. Major Depressive Disorder in Children and Adolescents

Currently, fluoxetine is the only second-generation antidepressant approved by the Food and Drug Administration for treating major depressive disorder 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 obsessive-compulsive disorder in pediatric patients, although they are not approved for treating major depressive disorder.

In September 2004, the Food and Drug Administration completed a review of existing data for the risk of both suicidal ideation and suicide attempts in children taking antidepressant drugs for major depressive disorder. Based on this review, the Food and Drug Administration instructed the manufacturers of all antidepressants included in this review to revise the labeling for their products to include a boxed warning and expanded warning statements that alert health care providers to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents. The Food and Drug Administration's analysis was based on pooled data from short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (selective serotonin reuptake inhibitors and others). This analysis revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. Although no suicides occurred in these trials, the average risk of such events was 4 percent in patients taking antidepressants—twice the placebo risk of 2 percent.

Recent media reports revealed that drug manufacturers may have deliberately under reported or misclassified serious adverse events such as suicidality. We tried to minimize publication bias by requesting unpublished data submitted to the Food and Drug Administration and searching the CDER archives to identify unpublished trials. However, we were unable to obtain further information not already publicly available.

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).[122] 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.

In the published literature, we did not identify any head-to-head trials comparing one second-generation antidepressant to another for treating major depressive disorder in children and adolescents. We found seven fair controlled trials comparing a non-Food and Drug Administration-approved selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor to placebo (Table 13). Additionally, one good-rated trial compared fluoxetine, cognitive-behavioral therapy (CBT), and fluoxetine plus CBT to placebo.

In addition, three systematic reviews evaluated placebo-controlled evidence for the use of selective serotonin reuptake inhibitors and a serotonin and norepinephrine reuptake inhibitor.[123-125] Two reviews highlighted placebo-controlled evidence already included in this discussion,[124, 125] so we do not comment on them further here. One review, however analyzed published and

unpublished data for citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine.[123] We cite the evidence reported in this article because of its contrast with other published evidence.

Of the primary studies evaluated, patient populations generally were between the ages of 6 and 18 years. In general, inclusion was determined by a combination of several factors, often including a criteria-based diagnosis for major depressive disorder (DSM-III, DSM-IV) in addition to a predefined severity of disease (HAM-D ≥ 12; CDRS-R > 40; Children's Global Assessment Scale < 60, Montgomery-Åsberg Depression Rating Scale [MADRS] ≥ 16). Several studies used different inclusion cut-off points when defining severity of disease. All studies lasted between 6 and 12 weeks. Patients were excluded if they were suicidal, had a current or past failure on a study drug, had a seizure disorder, or had a current or past history of bipolar disorder, panic disorder, schizoaffective disorder, obsessive-compulsive disorder, or other significant mental illness.

Primary outcome measures included mean change in score on a standardized depression rating scale (Children's Depression Rating Scale Revised [CDRS-R]), HAM-D, MADRS, or the Children's Depression Inventory [CDI]), response (≥ 40%-50% reduction in depression score), or remission (≤ 8 on the HAM-D). Secondary efficacy measures included additional measures of improvement, depression, or anxiety (CGI-I, 9-item subscale of the Kiddie Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version [K-SADS-L], MADRS, HAM-A, Mood and Feelings Questionnaire [MFQ]), and multiple domains of functioning, general health, behavior, and quality of life (Autonomous Function Checklist for parents, Self-Perception Profile, Sickness Impact Profile, Global Assessment of Functioning [GAF] Scale, Child Behavior Checklist [CBCL], Children's Global Assessment Scale [CGAS], Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire [PQ-LES-Q]).

1. Selective serotonin reuptake inhibitors compared to placebo in pediatric outpatients with major depressive disorder

Citalopram compared with placebo

One 8-week study randomized 174 children (7 to11 years) and adolescents (12 to 17 years) with major depressive disorder to citalopram (20-40 mg/d) or placebo.[126] 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 then for placebo-treated patients ($P<0.05$). Significant differences were not reported for secondary outcome measures. More than 10 percent of citalopram-treated patients experienced rhinitis, nausea, and abdominal pain (P=NR for comparison with placebo).

Fluoxetine compared with placebo

Although we did not review placebo-controlled evidence for fluoxetine because the Food and Drug Administration 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.[127] 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 follow-up 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. Differences in harm-related adverse events were not significant across treatment groups (P=0.15). 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). Vomiting, dizziness, sweating and suicide-related adverse events were more frequent in the paroxetine group.

Sertraline compared with placebo

One published multinational (US, India, Canada, Costa Rica, and Mexico) study pooled data from two double-blind randomized controlled trials conducted in 53 centers.[132] 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 (≥ 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. Sertraline-treated patients reported a higher incidence of insomnia, diarrhea, vomiting, anorexia, and agitation.

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. There was a similar incidence of side effects in both groups, including suicide related events.

2. Serotonin and norepinephrine reuptake inhibitors compared to placebo in pediatric outpatients with major depressive disorder

Venlafaxine compared with placebo

One 6-week trial randomized 40 children and adolescents (8 to 18 years) to treatment with venlafaxine and psychotherapy or placebo and psychotherapy.[134] 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. A higher percentage of patients experienced side effects in the venlafaxine group than in the placebo group at almost every treatment week.

3. Systematic reviews of published and unpublished data comparing selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors to placebo in pediatric outpatients with major depressive disorder

Three systematic reviews evaluated published and unpublished studies comparing a selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor to placebo in children and adolescents.[123-125] The largest report reviewed placebo-controlled studies on citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine, including data for 2145 randomized participants (5 to 18 years).[123] 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 major depressive disorder.

4. Summary of the evidence

We did not identify any head-to-head trials. Published evidence is insufficient to compare one second-generation antidepressant to another in pediatric outpatients with major depressive disorder. Recent evidence from a systematic review of published and unpublished data suggests that only fluoxetine has a favorable risk-benefit profile in pediatric populations.

Effectiveness

We did not identify any study with a high degree of generalizability.

Efficacy

The existing evidence, summarized in three systematic reviews of published and unpublished randomized controlled trials, provides fair evidence that efficacy to improve health outcomes does not differ between placebo and citalopram, escitalopram, sertraline, paroxetine, and venlafaxine.[123-125] These studies support a greater efficacy for fluoxetine compared to placebo. No evidence exists for duloxetine, fluvoxamine, mirtazapine, bupropion, and nefazodone.

Table 13. Interventions, numbers of patients, and quality ratings of studies in children and adolescents with major depressive disorder

Author, Year	Interventions	N	Results	Quality rating
Systematic reviews				
Whittington et al. 2004[123] (SR))	Citalopram compared with placebo Fluoxetine compared with placebo Paroxetine compared with placebo Sertraline compared with placebo Venlafaxine compared with placebo	2145	Only fluoxetine had favorable risk-benefit profile	Fair
Usala et al. 2008[124] (SR)	Citalopram compared with placebo	2530	Only fluoxetine had favorable risk-benefit profile	Fair

Author, Year	Interventions	N	Results	Quality rating
	Escitalopram compared with placebo Fluoxetine compared with placebo Paroxetine compared with placebo Sertraline compared with placebo			
Hetrick et al. 2007[125] (SR)	Citalopram compared with placebo Fluoxetine compared with placebo Paroxetine compared with placebo Sertraline compared with placebo	1972	Only fluoxetine had favorable risk-benefit profile	Good
Selective serotonin reuptake inhibitors compared with placebo				
Wagner et al. 2004[126]	Citalopram compared with placebo	174	Significantly greater efficacy for citalopram	Fair
March et al. 2004[127] March et al. 2007[128]	Fluoxetine plus CBT compared with Fluoxetine compared with CBT compared with placebo	439	Greater improvement on the CDRS-R for fluoxetine plus CBT compared to fluoxetine alone, CBT alone, or placebo. Results after 36 weeks equivocal.	Good
Keller et al. 2001[129]	Paroxetine compared with Imipramine compared with placebo	275	No differences	Fair
Wagner et al. 2003[132]	Sertraline compared with placebo	376	Significantly greater efficacy for sertraline	Fair
Wagner et al. 2006[133]	Escitalopram compared with placebo	268	No differences	Fair
Emslie et al. 2006[131]	Paroxetine compared with placebo	206	No differences	Fair
Berard et al. 2006[130]	Paroxetine compared with placebo	286	No differences	Fair
Serotonin and norepinephrine reuptake inhibitors compared with placebo				
Mandoki et al. 1997[134]	Venlafaxine compared with placebo	40	No differences	Fair

Abbreviations: SR, systematic review.

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?

A. Generalized Anxiety Disorder

Currently, two selective serotonin reuptake inhibitors, escitalopram and paroxetine, are approved by the Food and Drug Administration for the treatment of generalized anxiety disorder. In addition, one serotonin and norepinephrine reuptake inhibitor (venlafaxine) and one selective serotonin and norepinephrine reuptake inhibitor (duloxetine), are approved for the treatment of generalized anxiety disorder.

Four head-to-head trials compared one second-generation antidepressant to another for the treatment of generalized anxiety disorder.[135-138] Two are rated fair[135, 137] and two rated poor.[136, 138] Food and Drug Administration-approved evidence supports the general efficacy of duloxetine, escitalopram, paroxetine, and venlafaxine for treating generalized anxiety disorder. Additional placebo-controlled evidence supporting the general efficacy these drugs was not reviewed. Additionally, we identified two trials (three publications) that assessed efficacy and tolerability of sertraline,[139-141] a selective serotonin reuptake inhibitor currently not Food and Drug Administration-approved for generalized anxiety disorder.

Across reviewed studies that assessed health outcomes, the populations examined were 18 to 80 years of age. Inclusion was based on a criteria-based diagnosis (DSM-IV) of generalized anxiety disorder with a minimum score of 18 or 20 on the HAM-A and a score of two or higher on the anxious mood and tension items of the HAM-A. Patients were excluded if they were considered to have major depressive disorder, generally defined by a score of 16-17 or higher on the MADRS.

1. Selective serotonin reuptake inhibitors compared to selective serotonin reuptake inhibitors in adult outpatients with generalized anxiety disorder

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 small randomized controlled trial compared paroxetine (10-40 mg/d) to sertraline (25-100 mg/d) in 55 patients with generalized anxiety disorder.[137] 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.

2. 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).

3. 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.

4. Selective serotonin reuptake inhibitors compared to placebo in adult outpatients with generalized anxiety disorder

Sertraline compared with placebo

Currently, sertraline is not Food and Drug Administration-approved for the treatment of generalized anxiety disorder. We identified two placebo-controlled trials that assessed the efficacy and tolerability of sertraline in generalized anxiety disorder.[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, multinational 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-LES-Q, 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 50-2000 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.

4. Summary of the evidence

Overall, evidence is insufficient to compare one second-generation antidepressant to another for treating generalized anxiety disorder. However, in the case of escitalopram compared with paroxetine there appears to be trend supporting the use of escitalopram compared with paroxetine.[135] The other available comparisons showed no difference in the outcomes based on active treatment.[136-138, 142]

Effectiveness

We did not identify any study with a high degree of generalizability.

Efficacy

One poor-rated small head-to-head trial did not detect any significant differences in efficacy between paroxetine and venlafaxine.[136] One head-to-head trial did not detect any significant differences in efficacy between paroxetine and sertraline.[137] And finally one poor-rated head-to-head trial did not detect any significant differences in efficacy between duloxetine and venlafaxine.[138]

Food and Drug Administration-approved evidence shows the general efficacy of duloxetine, escitalopram, paroxetine, and venlafaxine for treating generalized anxiety disorder. Additional evidence supports the general efficacy of sertraline.[139, 140] Evidence is insufficient about efficacy of citalopram, fluoxetine, fluvoxamine, mirtazapine, bupropion, and nefazodone for treating generalized anxiety disorder. One trial provides evidence of greater improvement in quality of life and work productivity for sertraline than for placebo.[139]

Table 14. Interventions, numbers of patients, and quality ratings of studies in adults with generalized anxiety disorder

Author, Year	Interventions	N	Results	Quality rating
Selective serotonin reuptake inhibitors compared with selective serotonin reuptake inhibitors				
Baldwin et al. 2006[135]	Escitalopram compared with paroxetine	681	Escitalopram 10 mg/day more efficacious in response then paroxetine 20 mg/day	Fair
Kim et al. 2006[136]	Venlafaxine compared with paroxetine	46	No difference	Poor
Ball et al. 2005[137]	Paroxetine compared with sertraline	55	No difference	Fair
Selective serotonin reuptake inhibitors compared with selective serotonin and norepinephrine reuptake inhibitors				
Hartford et al. 2007[138]	Duloxetine compared with venlafaxine	487	No difference	Poor
Selective serotonin reuptake inhibitors compared with placebo				
Allgulander et al. 2004[139] Dahl et al. 2005[140]	Sertraline compared with placebo	378	Significantly greater improvement in HAM-A total score; HAM-A psychic and somatic factors, QoL, and work productivity	Fair
Brawman-Mintzer et al. 2006[141]	Sertraline compared with placebo	326	Significantly greater improvement in HAM-A total score; HAM-A response and HADS	Fair

Abbreviations: QoL, quality of life.

B. Obsessive-Compulsive Disorder

The Food and Drug Administration has approved the following selective serotonin reuptake inhibitors for the treatment of obsessive-compulsive disorder: fluoxetine, sertraline, paroxetine, and fluvoxamine.

Three head-to-head trials addressing the use of selective serotonin reuptake inhibitors or other second-generation antidepressants met our inclusion criteria for the review of obsessive-compulsive disorder (Table 13). One of these head-to-head trials had a 12-week extension phase in which nonresponders were switched to the alternative treatment.[143] One additional trial compared citalopram plus mirtazapine to citalopram alone.[144] Additionally, one placebo-controlled trial was included because it evaluated a selective serotonin reuptake inhibitor not covered in the reviews or approved by the Food and Drug Administration (Table 15). Four meta-analyses pooled data from studies comparing selective serotonin reuptake inhibitors to placebo. All systematic reviews included comparisons of fluoxetine, fluvoxamine, and sertraline to placebo.[145-147] In addition, two reviews included a comparison of paroxetine to placebo[146] and one included placebo compared with citalopram.[148]

Generally, inclusion was based on a criteria-based diagnosis (DSM-III, DSM-IV) of obsessive-compulsive disorder and a predefined cut-off point on an accepted obsessive-compulsive scale (e.g., Y-BOCS, NIMH-OC). The majority of patients could be labeled as

having moderate or severe disease with mild or no comorbid depression. Multiple studies limited inclusion by duration of current illness of 1 year or more.

Commonly examined outcome measures were response rate (e.g., more than 25% or 35% improvement of symptoms on an obsessive-compulsive rating scale, or much or very much improved as assessed by a global assessment method), rate of remission (e.g., reduction below a predefined cut-off point on an obsessive-compulsive scale), or changes in score on obsessive-compulsive scales. Comorbid depression or anxiety and quality of life occasionally were assessed as secondary outcome measures.

All included trials could be characterized as efficacy studies. In addition to efficacy, one head-to-head trial specifically evaluated quality of life. Drug or dosing equivalency was present across all trials.

1. Selective serotonin reuptake inhibitors compared to selective serotonin reuptake inhibitors in adult outpatients with obsessive-compulsive disorder

Sertraline compared with 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.[149] 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). No significant differences in the incidence of side effects between groups were reported.

2. Other second-generation antidepressants compared to selective serotonin reuptake inhibitors in adult outpatients with obsessive-compulsive disorder

Venlafaxine compared with 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.[150] Loss to follow-up was 33 percent. 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 ≥ 50% reduction in Y-BOCS; partial response ≥ 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. Incidence rates of insomnia and dry mouth in venlafaxine-treated patients were more than double those in paroxetine-treated patients.

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.[143] 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.

3. Selective serotonin reuptake inhibitors augmentation compared to selective serotonin reuptake inhibitor alone in adult outpatients with obsessive-compulsive disorder

A 12-week trial assessed the additional benefits of augmenting treatment with citalopram (40-80 mg/d) with mirtazapine (15-30 mg/d) in 49 outpatients with obsessive-compulsive disorder.[144] 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.

4. Selective serotonin reuptake inhibitors compared to placebo in adult outpatients with obsessive-compulsive disorder

Meta-analyses

Four meta-analyses reviewed available evidence from placebo-controlled studies;[145-148] we rated these analyses as fair quality and one as good quality.[148] One study pooled results from 10 trials that compared selective serotonin reuptake inhibitors *as a class* with placebo.[145] Data representing 1076 patients were pooled to define the selective serotonin reuptake inhibitor group, which consisted of fluvoxamine (five studies), fluoxetine (two studies), and sertraline (three studies). Several studies incorporated multiple dosing arms in the study design.[152, 153] For these trials, only the highest dosing arm was incorporated in the meta-analytic results.

As a class, selective serotonin reuptake inhibitors were found to be superior to placebo. For obsessive-compulsive symptoms considered together, an effect size of 0.47 (95% CI 0.33 to 0.61) was observed for selective serotonin reuptake inhibitors compared to placebo. Considering obsessions and compulsions rated separately, effect sizes were reported as 0.54 (95% CI 0.34 to 0.74) and 0.52 (95% CI 0.34 to 0.70), respectively. Effect sizes generally were consistent for each of the selective serotonin reuptake inhibitors when compared to placebo.

A second meta-analysis evaluated placebo-controlled trials of fluvoxamine, fluoxetine, sertraline, and paroxetine.[146] 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 selective serotonin reuptake inhibitors 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[154-157] showed a net improvement of -4.84 (95% CI -7.78 to -1.83). For the three fluoxetine studies,[158-160] net improvement was -1.61 (95% CI -2.18 to -1.04); for four sertraline studies,[161-164] the pooled difference in Y-BOCS was calculated to be -2.47

(95% CI -6.13 to 1.20). Only one paroxetine study was included; the difference in improvement was estimated as -3.00 (95% CI -4.91 to -1.09).

A third meta-analysis assessed medication effect sizes in six published placebo-controlled trials;[147] two fluvoxamine studies;[154, 155] two sertraline studies;[161, 162] and two fluoxetine studies.[158, 159] Compared to placebo, effect sizes did not differ significantly between the three selective serotonin reuptake inhibitors 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 compared with placebo

A fair multicenter study conducted in Europe and South Africa compared various fixed-doses of citalopram to placebo in 401 outpatients with obsessive-compulsive disorder characterized as stable for more than 6 months.[153] Loss to follow-up was 16 percent, with small differences between groups. All three doses of citalopram produced significantly more responders (≥ 25% improvement in Y-BOCS) than placebo ($P<0.01$). The high-dose citalopram (60 mg) response reached statistical significance at week 3, whereas the lower doses (20 mg and 40 mg) reached statistical significance at week 7. On the patient-rated Sheehan Disability Scale, the citalopram-treated patients showed significant improvements for most items. Adverse events were reported in 71 percent of subjects in the active treatment groups. The number of adverse events reported by persons on different citalopram doses did not differ significantly. Ejaculation failure was significantly different from placebo only in the 40 mg citalopram group.

5. Summary of the evidence

Three fair head-to-head studies provide evidence that there is no difference in efficacy between fluoxetine and sertraline or venlafaxine and paroxetine or escitalopram and paroxetine. Other evidence is insufficient to draw conclusions about comparative efficacy between one second-generation antidepressant and another.

Effectiveness

We did not identify any study with a high degree of generalizability.

Efficacy

Three head-to-head trials[149, 150, 151] and four meta-analyses[145, 146, 147, 148] provide fair evidence that no difference in efficacy among evaluated second-generation antidepressants exists. Two head-to-head trials provide fair evidence that the efficacy of venlafaxine XR and paroxetine does not differ in improving health outcomes;[150, 151, 165] in a follow-up study, 42 percent of nonresponders who switched to the alternative treatment achieved a response.[143] One fair placebo-controlled study showed a significantly greater improvement in disability for citalopram compared to placebo.[153] In a second study, citalopram-treated patients augmented with mirtazapine had a faster response than patients treated with citalopram alone, although differences did not persist past 6 weeks.[144]

One study provides fair evidence that sertraline has a faster onset of action than fluoxetine[149] in the treatment of obsessive-compulsive disorder. Another fair-rated study reported a faster response for venlafaxine XR compared to paroxetine.[150] A fair-rated study showed no difference between escitalopram and paroxetine throughout 24 weeks of treatment.[151]

Food and Drug Administration-approved evidence exists for the general efficacy of fluoxetine, sertraline, paroxetine, and fluvoxamine for treating obsessive-compulsive disorder. Evidence is insufficient about the efficacy of mirtazapine, bupropion, and nefazodone for treating obsessive-compulsive disorder. Additionally, one study provides fair evidence supporting a greater efficacy of citalopram than placebo.[153]

Table 15. Interventions, numbers of patients, and quality ratings of studies in adults with obsessive-compulsive disorder

Author, Year	Interventions	N	Results	Quality rating
Selective serotonin reuptake inhibitors compared with selective serotonin reuptake inhibitors				
Stein et al. 2007[151]	Escitalopram compared with paroxetine	466	No differences at 12 or 24 weeks	Fair
Bergeron et al. 2002[149]	Fluoxetine compared with sertraline	150	No differences	Fair
Other second-generation antidepressants compared with selective serotonin reuptake inhibitors				
Denys et al. 2003[143, 150, 165]	Venlafaxine compared with paroxetine	150	No differences	Fair
Selective serotonin reuptake inhibitor compared with selective serotonin reuptake inhibitor plus another second-generation antidepressant				
Pallanti et al. 2004[144]	Citalopram compared with citalopram plus mirtazapine	49	No differences at 12 weeks	Fair
Selective serotonin reuptake inhibitors compared with placebo				
Piccinelli et al. 1995[145]	SSRIs compared with placebo (SR)	1076	Significantly greater efficacy of SSRIs	Fair
Ackerman et al. 2002[146]	SSRIs compared with placebo (SR)	530	No differences among SSRIs	Fair
Stein et al. 1995[147]	SSRIs compared with placebo (SR)	516	No differences among SSRIs	Fair
Soomro et al. 2008[148]	SSRIs compared with placebo (SR)	3097	No differences among SSRIs	Good
Montgomery et al. 2001[153]	Citalopram compared with placebo	401	Significantly greater efficacy of citalopram	Fair

Abbreviations: SR, systematic review; SSRI, selective serotonin reuptake inhibitor.

C. Panic Disorder

Only fluoxetine, paroxetine, sertraline, and venlafaxine are currently approved by the Food and Drug Administration for the treatment of panic disorder. We viewed Food and Drug Administration approval as evidence for general efficacy and did not review placebo-controlled trials of fluoxetine, paroxetine, sertraline, and venlafaxine.

For panic disorder, we identified four head-to-head trials of fair quality comparing one selective serotonin reuptake inhibitor, or other second-generation antidepressant to another.[166-170] We excluded one study – a single-blinded randomized controlled trial with a poor quality rating for internal validity[167]– from our findings, but we discuss it here briefly because of the minimal

amount of published research on this topic. Furthermore, we identified three placebo-controlled trials assessing the efficacy and tolerability of fluvoxamine.[171-173]

Inclusion was generally determined by a criteria-based (DSM-III-R, DSM-IV) diagnosis of panic disorder in addition to a predefined frequency of weekly panic attacks. Patients with at least one to four panic attacks per week or eight in total over the past 4 weeks were eligible for inclusion. Both patients with and without agoraphobia were included in these trials. Common exclusion criteria were additional Axis I disorders, high suicidal risk, a history of alcohol or drug dependence or abuse, use of other psychotropic medications, and progressive medical disease.

The primary outcome measure in all trials was the frequency of panic attacks as assessed with various scales (e.g., Panic and Agoraphobia Scale, Modified Panic and Anticipatory Anxiety Scale [PAAS], Panic Associated Symptoms Scale [PASS]). Secondary outcome measures included changes from baseline in the Panic Disorder Severity Score (PDSS), quality of life and health-related functional capacity (Sheehan Disability Scale [SDS], Fear Questionnaire [FQ]), the Phobia Scale, anxiety-related subscales of the MADRS and HAM-D, and global assessment methods (e.g., CGI, Q-LES-Q).

1. Selective serotonin reuptake inhibitors compared to selective serotonin reuptake inhibitors in adult outpatients with Panic Disorder

Four fair double-blinded randomized controlled trials compared the efficacy and tolerability of one selective serotonin reuptake inhibitor to another.

Citalopram compared with escitalopram

One multicenter study randomized 366 patients with panic disorder to citalopram (10-40 mg/d), escitalopram (5-20 mg/d), or placebo.[166] 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; presumably the two active treatment groups did not differ significantly on efficacy measures.

Sertraline compared with paroxetine

A German randomized controlled trial randomized 225 patients with panic disorder to paroxetine (40-60 mg/d) or sertraline (50-150 mg/d).[168] 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.

Citalopram compared with paroxetine

A small Italian trial enrolled 58 patients to citalopram (20-50 mg/d) and paroxetine (20-50 mg/d) for 60 days.[167] Patients and care providers were not blinded to treatment allocation; therefore, this study received a poor quality rating for internal validity. Loss to follow-up was 10 percent.

Results reported no statistically significant differences between citalopram and paroxetine in any efficacy measures. However, results may be biased because of lack of double blinding.

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.

2. Selective serotonin reuptake inhibitors compared to placebo in adult outpatients with panic disorder

Fluvoxamine compared with placebo

Three fair-rated studies, all lasting 8 weeks, compared fluvoxamine (50-300 mg/d) to placebo.[171-173] The first study enrolled 75 patients to fluvoxamine (50-300 mg/d), placebo, or cognitive therapy.[171] 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 (50-300 mg/d) or placebo.[172] 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.[173] 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.

3. Summary of the evidence

Two fair fixed-dose trials provide inconclusive evidence on the comparative efficacy of venlafaxine ER and paroxetine. One fair head-to-head study provides evidence that efficacy does not differ between citalopram and escitalopram. In other trials, significant differences in study

design and outcome selection make this evidence insufficient to identify differences between treatments.

Effectiveness

We did not identify any study with a high degree of generalizability.

Efficacy

While one fair randomized controlled trial showed venlafaxine ER 225 mg/d to be superior to paroxetine 40 mg/d in reducing full-symptom panic attacks and in PDSS score,[170] the same effect was not seen when comparing venlafaxine ER 150 mg/d or 75 mg/d and paroxetine 40 mg/d.[169, 170]Two fair randomized controlled trials provide evidence that the efficacy of reducing panic attacks and improving quality of life does not differ significantly between citalopram and escitalopram[166] or between paroxetine and sertraline[168] in outpatients with panic disorder. Fair evidence exists from three placebo-controlled trials of significantly greater efficacy and improvement of health outcomes and functional capacity for fluvoxamine compared to placebo.[172-175] Food and Drug Administration-approved evidence supports the general efficacy of fluoxetine, paroxetine, venlafaxine and sertraline for the treatment of panic disorder. Evidence is insufficient about the efficacy of duloxetine, mirtazapine, bupropion, and nefazodone for treating panic disorder.

Table 16. Interventions, numbers of patients, and quality ratings of controlled trials in adults with panic disorder

Author, Year	Interventions	N	Results	Quality rating
Selective serotonin reuptake inhibitors compared with selective serotonin reuptake inhibitors				
Bandelow et al. 2004[168]	Paroxetine compared with Sertraline	225	No difference	Fair
Stahl et al. 2003[166]	Citalopram compared with escitalopram compared with placebo	366	No difference	Fair
Pollack et al. 2007[169]	Venlafaxine ER compared with paroxetine	664	No difference	Fair
Pollack et al. 2007[170]	Venlafaxine ER compared with paroxetine	653	Significantly greater efficacy of venlafaxine ER 225 mg/d compared to paroxetine 40 mg/d	Fair
Selective serotonin reuptake inhibitors compared with placebo				
Asnis et al. 2001[173]	Fluvoxamine compared with placebo	188	Significantly greater efficacy of fluvoxamine	Fair
Black et al. 1993[174]	Fluvoxamine compared with placebo	75	Significantly greater efficacy of fluvoxamine	Fair
Hoehn-Saric et al. 1993[172]	Fluvoxamine compared with placebo	50	Significantly greater efficacy of fluvoxamine	Fair

D. Post-Traumatic Stress Disorder

Currently, only paroxetine and sertraline have been Food and Drug Administration-approved for the treatment of post-traumatic stress 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.

For post-traumatic stress disorder, we found four head-to-head studies: one comparing citalopram to sertraline,[176] two comparing nefazodone to sertraline,[177, 178]and one comparing venlafaxine to sertraline.[179] No other second-generation antidepressants were compared to one another.

In addition we included four placebo-controlled trials assessing the efficacy of fluoxetine and venlafaxine, which are not Food and Drug Administration-approved for the treatment of post-traumatic stress disorder (Table 17).

Inclusion of patients was generally determined by a criteria-based (DSM-III-R, DSM-IV) diagnosis of post-traumatic stress disorder in addition to a predefined threshold on a universally used post-traumatic stress disorder scale (Clinician Administered PTSD Scale [CAPS]). The majority of patients had suffered physical or sexual abuse or had witnessed injury or death of a third person. More than half of the participants had a concomitant diagnosis of major depressive disorder or generalized anxiety disorder or a history of alcohol and substance abuse.

1. Selective serotonin reuptake inhibitors compared to other second-generation antidepressants in adult outpatients with post-traumatic stress disorder

Sertraline compared with citalopram

A fair study randomized 59 outpatients with post-traumatic stress disorder to 10 weeks of citalopram (20-50 mg/d), sertraline (50-200 mg/d), or placebo.[176] 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 compared with nefazodone

A fair-rated randomized controlled trial randomized 37 patients with post-traumatic stress disorder to 12 weeks of sertraline (50-200 mg/d) or nefazodone (100-600 mg/d).[177] 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. 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.

2. Selective serotonin reuptake inhibitors compared to placebo in adult outpatients with post-traumatic stress disorder

Fluoxetine compared with placebo

Three placebo-controlled randomized controlled trials provide conflicting results on the general efficacy of fluoxetine for the treatment of post-traumatic stress disorder.[180, 181] A small fair-rated study enrolled 54 patients to 12 weeks of fluoxetine (10-60 mg) or placebo.[180] Loss to follow-up was 31.5 percent. Using the Duke Global Rating for post-traumatic stress disorder cut-off score of 1 (no symptoms) to define responders, the fluoxetine group had significantly more responders than the placebo group (59% compared with 19%; $P<0.005$). According to Duke Global Rating for post-traumatic stress disorder 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.

3. Summary of the evidence

We identified one head-to-head trial comparing citalopram to sertraline, one study comparing sertraline to nefazodone and one study comparing sertraline to venlafaxine.

Effectiveness
We did not identify any study with a high degree of generalizability.

Efficacy
Three head-to-head trials did not detect any differences in efficacy between citalopram and sertraline,[176] sertraline and nefazodone,[177] and sertraline and venlafaxine ER.[179] Food and Drug Administration-approved evidence exists for the general efficacy of paroxetine and sertraline for treating post-traumatic stress disorder. Placebo-controlled trials report general efficacy of venlafaxine but not of fluoxetine in the treatment of post-traumatic stress disorder. Significant differences in population characteristics make this evidence insufficient to identify differences between treatments based on placebo-controlled evidence.

Table 17. Interventions, numbers of patients, and quality ratings of controlled trials in adults with post-traumatic stress disorder

Author, Year	Interventions	N	Results	Quality rating
Selective serotonin reuptake inhibitors compared with selective serotonin reuptake inhibitors				
Tucker et al. 2005[176]	Citalopram compared with sertraline	59	No difference in efficacy	Fair
Selective serotonin reuptake inhibitors compared with serotonin and norepinephrine reuptake inhibitors				
Davidson et al. 2006[179]	Sertraline compared with venlafaxine ER	352	No difference in efficacy	Fair
Selective serotonin reuptake inhibitors compared with other second-generation antidepressants (DopRi, 5-HT$_2$)				
McRae et al. 2004[177]	Sertraline compared with nefazodone	37	No difference in efficacy	Fair
Saygin et al. 2002[178]	Sertraline compared with nefazodone	60	No differences in efficacy	Poor
Selective serotonin reuptake inhibitors compared with placebo				
Connor et al. 1999[180]	Fluoxetine compared with placebo	54	Significantly greater efficacy of fluoxetine	Fair
Martenyi et al. 2007[181]	Fluoxetine compared with placebo	411	No difference in efficacy	Fair
Van der Kolk et al. 2007[182]	Fluoxetine compared with placebo compared with eye movement desensitization	88	No difference in efficacy between fluoxetine and placebo	Fair
Davidson et al. 2006[183]	Venlafaxine compared with placebo	329	Significantly greater efficacy of venlafaxine	Fair

E. Social Anxiety Disorder

Currently, three selective serotonin reuptake inhibitors – fluvoxamine CR, paroxetine and sertraline – are approved by the Food and Drug Administration for the treatment of social anxiety disorder. In addition, the extended release formulation of one serotonin and norepinephrine reuptake inhibitor, venlafaxine, is approved for the treatment of social anxiety disorder.

Three head-to-head trials (with placebo arms) compared one second-generation antidepressant to another for the treatment of social anxiety disorder.[184-186] Two 12-week trials compared paroxetine to venlafaxine ER;[184, 186] a 24-week trial compared escitalopram to paroxetine.[185] All three trials included measures of functional capacity in addition to efficacy and tolerability.

We reviewed additional evidence from placebo-controlled trials if they assessed a second-generation antidepressant not currently Food and Drug Administration-approved for social anxiety. One meta-analysis compared fluvoxamine, sertraline, and paroxetine to placebo,[187] and one systematic review compared selective serotonin reuptake inhibitors to placebo.[188] In addition, 6 placebo-controlled studies evaluated second-generation antidepressants currently not approved by the Food and Drug Administration for social anxiety disorder: two escitalopram studies,[189, 190] two fluoxetine studies,[191, 192] one mirtazapine study,[193] and one nefazodone study[194] (Table 18).

In general, inclusion was based on a criteria-based diagnosis (DSM-IV) of social anxiety disorder. Several studies required a minimal duration of current illness of 6 months or greater.[184, 186, 191, 194] Additionally, several studies limited eligibility using a predefined cut-off point on a validated anxiety rating scale.[184-186, 190, 191]

The main outcome measures examined were mean change in anxiety as measured by one of several scales, including the Liebowitz Social Anxiety Scale (LSAS), the Brief Social Phobia Scale (BSPS), the HAM-A, and the social phobia subscale of the Marks Fear Questionnaire (MF). Social anxiety global assessment scales such as the Clinical Global Impression-Social Phobia Scale (CGI-SP) also were used. Several studies included patient-rated measures of anxiety using the Social Phobia Scale (SPS) or the Social Phobia Inventory (SPI). Disability; health status, quality of life, and comorbid depression were frequently assessed as secondary outcome measures.

Trial reporting was often incomplete. All trials used an intention-to-treat analysis. Among the included studies, loss to follow-up was between 20 percent and 36 percent. One study had a loss-to-follow-up differential between treatment groups greater than 10 percentage points (13.8 points).[194]

All included trials are characterized as efficacy studies. One study assessed relapse prevention randomizing escitalopram responders (CGI-I score of 1 or 2) to 24 weeks of escitalopram or placebo.[189] This study evaluated the rate of relapse between active treatment and placebo.

1. Selective serotonin reuptake inhibitors compared to selective serotonin reuptake inhibitors in adult outpatients with social anxiety disorder

One fair-rated double-blinded randomized controlled trial compared the efficacy and tolerability of one selective serotonin reuptake inhibitor to another.

Escitalopram compared with 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.[185] 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.

2. Other second-generation antidepressants compared to selective serotonin reuptake inhibitors in adult outpatients with social anxiety disorder

Two fair double-blinded randomized controlled trials compared the efficacy and tolerability of one second-generation antidepressant to a selective serotonin reuptake inhibitor.

Venlafaxine compared with paroxetine

Two 12-week multicenter trials compared venlafaxine ER to paroxetine and placebo.[184, 186] A European trial randomized 436 patients with social anxiety disorder[184] and an American trial randomized 440 patients with social anxiety disorder[186] to venlafaxine ER (75-225 mg/d), paroxetine (20-50 mg/d), or placebo. Eligible patients were 18 years or older who met DSM-IV criteria for social anxiety disorder at least 6 months before enrollment. In the European trial, significantly more females were randomized to placebo than to venlafaxine or paroxetine. The primary outcome measure was the LSAS; secondary outcome measures included the CGI-I, CGI-S, SPI, and SDI. The European trial also included a measure of work productivity WPAI. 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).

3. Selective serotonin reuptake inhibitors compared to placebo in adult outpatients with social anxiety disorder

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

Selective serotonin reuptake inhibitors compared with placebo

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 compared with placebo

One fair meta-analysis evaluated published and unpublished evidence comparing selective serotonin reuptake inhibitors with placebo in the treatment of social anxiety disorder.[187] Eight studies of unreported quality were included in the review: two fluvoxamine studies, two sertraline studies, and four paroxetine studies. Primary treatment outcomes included global improvement (CGI-I) and mean change in LSAS. Odds ratios for selective serotonin reuptake

inhibitor-treatment response compared to placebo varied between 2.1 and 26.2, favoring the selective serotonin reuptake inhibitors. Overall, evidence is inconclusive about differences in efficacy between fluvoxamine, sertraline, and paroxetine.

Escitalopram compared with placebo

One fair 12-week study compared flexible doses of escitalopram to placebo.[190] 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 ($P<0.01$), LSAS subscales ($P<0.05$), CGI-S ($P<0.01$), CGI-I ($P<0.01$), and the work and social domains of the SDS ($P<0.05$). Results were similar to the placebo comparison reported by Lader et al.[185] The most common adverse event reported for escitalopram or placebo was headache (25% in both groups); compared to placebo, more patients randomized to escitalopram reported nausea (12% compared with 22%; P=NR).

One fair relapse prevention study openly treated 517 patients with generalized social anxiety disorder with escitalopram (10-20 mg/d) for 12 weeks.[189] 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 compared with placebo

Two fair studies compared flexible doses of fluoxetine to placebo.[191, 192] The first 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% compared with 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 ($P=0.901$). Secondary efficacy measures included the BSPS, FQ, HAM-A, HAM-D, Global Assessment of Functioning (GAF), and SF-36. Overall, no statistically significant differences were reported on secondary efficacy measures. Compared to placebo, fluoxetine-treated patients had a significant increase in the bodily pain subscale of the SF-36 ($P=0.05$). Significantly more fluoxetine-treated patients had asthenia than placebo-treated patients ($P<0.05$).

The second trial[192] 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 BSPS. 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 compared with placebo

One fair 10-week trial compared mirtazapine to placebo in 114 women with social phobia.[193] 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 ($P=0.53$).

4. 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%, $P<0.01$).

5. Summary of the evidence

Three head-to-head trials compared one second-generation antidepressant to another for the treatment of social anxiety disorder. These trials suggest no differences in efficacy for escitalopram compared with paroxetine and venlafaxine ER compared with paroxetine. Additionally, indirect evidence from a meta-analysis of placebo-controlled trials provides evidence that there is no difference in efficacy between fluvoxamine, paroxetine, and sertraline.

Effectiveness

We did not identify any study with a high degree of generalizability.

Efficacy

One comparative trial provides fair evidence of comparable efficacy between escitalopram and paroxetine for the treatment of social anxiety disorder.[185] Two comparative trials provide fair evidence of comparable efficacy between venlafaxine ER and paroxetine.[184, 186] One meta-analysis of placebo-controlled studies provides fair evidence of comparable efficacies of fluvoxamine, paroxetine, and sertraline for the treatment of social anxiety disorder.[187] Six trials and one systematic review.[188] provide fair evidence that selective serotonin reuptake inhibitors significantly improve health outcomes compared to placebo.[184-186, 190, 192, 193]

Two placebo-controlled trials did not support the efficacy of fluoxetine[191]and nefazodone[194] Evidence from three placebo-controlled trials supports the efficacy of escitalopram,[185, 189, 190] and evidence from one placebo-controlled trial supports the efficacy of mirtazapine in women.[193] Evidence is insufficient about the efficacy of citalopram, duloxetine, mirtazapine, bupropion, and nefazodone for treating social anxiety disorder.

Table 18. Interventions, numbers of patients, and quality ratings of studies in adults with social anxiety disorder

Author, Year	Interventions	N	Results	Quality rating
Selective serotonin reuptake inhibitors compared with selective serotonin reuptake inhibitors				
Lader et al. 2004[185]	Escitalopram compared with paroxetine compared with placebo	839	No difference between active treatments; escitalopram and paroxetine significantly better than placebo	Fair
Other second-generation antidepressants compared with selective serotonin reuptake inhibitors				
Allgulander et al. 2004[184]	Venlafaxine ER compared with paroxetine compared with placebo	436	No difference between active treatments; venlafaxine and paroxetine significantly better than placebo	Fair
Liebowitz et al. 2005[186]	Venlafaxine ER compared with paroxetine compared with placebo	440	No difference between active treatments; venlafaxine and paroxetine significantly better than placebo	Fair
Selective serotonin reuptake inhibitors compared with placebo				
Van der Linden et al. 2000[187]	Fluvoxamine compared with placebo Paroxetine compared with placebo Sertraline compared with placebo (SR)	1482	No differences between active treatments	Fair
Hedges et al. 2007[188]	SSRIs compared with placebo (SR)	3361	SSRIs superior to placebo	Fair
Kasper et al. 2005[190]	Escitalopram compared with placebo	358	Significantly greater efficacy of escitalopram	Fair
Montgomery et al. 2005[189]	Escitalopram compared with placebo	372	Significantly lower risk of relapse for escitalopram	Fair
Davidson et al. 2004[192]	Fluoxetine compared with placebo	295	Significantly greater efficacy of fluoxetine; significantly higher rates of insomnia, headache, nausea, anorgasmia and erectile dysfunction with fluoxetine	Fair
Kobak et al. 2002[191]	Fluoxetine compared with placebo	60	No differences in efficacy	Fair
Muehlbacher et al. 2005[193]	Mirtazapine compared with placebo	66	Significantly greater efficacy of mirtazapine	Fair
Other second generation antidepressants compared with placebo				

Author, Year	Interventions	N	Results	Quality rating
Van Ameringen et al. 2007[194]	Nefazodone compared with placebo	105	No significant difference in efficacy; nefazodone significantly higher incidence in some adverse events	Fair

Abbreviations: SR, systematic review; SSRI, selective serotonin reuptake inhibitors.

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

The Food and Drug Administration has approved fluoxetine, sertraline, and paroxetine for the treatment of premenstrual dysphoric disorder and late luteal phase dysphoric disorder.

We did not find any head-to-head studies comparing selective serotonin reuptake inhibitors or other second-generation antidepressants to each other. One meta-analysis (of 15 randomized controlled trials)[195, 196] and two randomized controlled trials[197, 198] compared other second-generation antidepressants to placebo. These studies are listed in Table 19.

Studies were conducted over two to six menstrual cycles. Of the 15 studies in the meta-analysis, four examined intermittent luteal phase therapy; the others examined continuous therapy. Of the additional two placebo-controlled trials, one trial examined continuous therapy.[197]

Included studies were conducted in women of reproductive age (18 to 45 years) with a clinical diagnosis of premenstrual dysphoric disorder or late luteal phase dysphoric disorder. Women were required to meet DSM criteria in all three trials and in 13 of the 15 studies in the meta-analysis. The detailed interviews required to determine a diagnosis of premenstrual dysphoric disorder in these studies may limit the generalizability of the findings to patients in others settings such a primary care or gynecological offices where a diagnosis of premenstrual dysphoric disorder is often made on less strict criteria. Most studies excluded women with depression or other psychiatric illness, those with irregular menstrual cycles, and those taking hormones (including oral contraceptives).

Both placebo-controlled trials used a patient-assessed daily symptom rating or report in addition to the CGI.[197, 198] Patients monitored their symptoms through the use of diaries, calendars, or visual analog scales. In addition to patient report of symptoms, one trial used the 21-item HAM-D.[197] Studies included in the meta-analysis used similar efficacy outcome measures.

The authors of the meta-analysis have published two versions of their work. Their Cochrane Collaboration report excluded five studies that used a cross-over design during calculation of the main effect and for some of the subanalyses. We present the results of both versions here.

1. Selective serotonin reuptake inhibitors compared to placebo in adult outpatients with premenstrual dysphoric disorder or late luteal phase dysphoric disorder

Selective serotonin reuptake inhibitors compared with placebo

Only one study reported on efficacy outcomes of non-Food and Drug Administration-approved selective serotonin reuptake inhibitors.[195, 196] This good-quality meta-analysis pooled data from 15 trials comparing various selective serotonin reuptake inhibitors 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 selective serotonin reuptake inhibitor over placebo was -1.066 (95% CI -1.381 to -0.750) equivalent to an odds ratio of 6.91 (95% CI 3.90 to 12.2). However, this meta-analysis also included cross-over studies.[196] 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 to -0.51).[195]

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

Venlafaxine compared with placebo

One fair randomized controlled trial compared a serotonin and norepinephrine reuptake inhibitor, specifically a continuous daily dose of venlafaxine (50-200 mg/d), to placebo over four menstrual cycles.[197] 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 compared with placebo

One fair randomized controlled trial 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.[198] 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).

4. Summary of the evidence

We identified no head-to-head trials. Good to fair evidence exists from one meta-analysis that the efficacy of selective serotonin reuptake inhibitors as a class is significantly greater than placebo. One trial provides fair evidence that the efficacy of venlafaxine is significantly greater than the efficacy of placebo. Another study reported no significant treatment effect for nefazodone compared to placebo. Significant differences in study characteristics make this evidence insufficient to identify differences among treatments.

Effectiveness
We did not identify any study with a high degree of generalizability.

Efficacy
One meta-analysis provides good evidence that selective serotonin reuptake inhibitors as a class have a significantly greater efficacy than placebo in the treatment of premenstrual dysphoric disorder and late luteal phase dysphoric disorder.[196] Among selective serotonin reuptake inhibitors that are not Food and Drug Administration approved, this meta-analysis includes data on citalopram and fluvoxamine. One fair randomized controlled trial provides evidence that the efficacy is significantly greater for venlafaxine than for placebo.[197] Lastly, evidence from one fair randomized controlled trial indicates that nefazodone does not have greater efficacy than placebo in the treatment of premenstrual dysphoric disorder or late luteal phase dysphoric disorder.[198] There is Food and Drug Administration-approved evidence of the efficacy of fluoxetine, paroxetine, and sertraline in the treatment of premenstrual dysphoric disorder and late luteal phase dysphoric disorder. We could not identify sufficient evidence on the efficacy of escitalopram, mirtazapine, and bupropion for treating either premenstrual dysphoric disorder or late luteal phase dysphoric disorder.

Continuous therapy as compared to intermittent therapy
A subgroup analysis in a good meta-analysis reported premenstrual dosing did not differ in efficacy from continuous dosing.[196]

Table 19. Interventions, numbers of patients, and quality ratings of studies in adults with premenstrual dysphoric disorder or late luteal phase dysphoric disorder

Author, Year	Interventions	N	Results	Quality rating
Selective serotonin reuptake inhibitors compared with selective serotonin reuptake inhibitors				
Dimmock et al. 2000[196]	5 SSRIs compared with placebo (SR)	904	Significantly greater efficacy of SSRIs	Good
Wyatt et al. 2004[a195]	5 SSRIs compared with placebo (SR)	844	Significantly greater efficacy of SSRIs	Good
Selective serotonin reuptake inhibitors compared with placebo				
Freeman et al. 2001[197]	Venlafaxine compared with placebo	157	Significantly greater efficacy of venlafaxine	Fair
Landen et al. 2001[198]	Nefazadone compared with placebo	69	Significantly greater efficacy of nefazodone	Fair

Abbreviations: SR, systematic review; SSRI, selective serotonin reuptake inhibitors.
[a] This meta-analysis, from the same authors as the Dimmock et al. meta-analysis, represents a more conservative analysis of the same studies; it excluded 5 of the 15 studies from the main effects calculation because of their use of a cross-over design.

Key Question 2.

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. Few studies used objective scales such as the UKU-SES (Utvalg for Kliniske Undersogelser Side Effect Scale) or the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient- reported adverse events with a regular clinical examination by an investigator. 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 randomized controlled trials 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 (Table 21).

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. Table 20 depicts the mean incidence and 95% CI for specific adverse events commonly reported in trials. Statistics are descriptive only and comparisons across different drugs should be made with caution given differences in assessment and reporting of adverse events across trials.

Venlafaxine had a consistently higher rate of nausea and vomiting than selective serotonin reuptake inhibitors. In six studies, the difference reached statistical significance.[73, 74, 77, 81, 82, 84] In six additional trials, the higher rates of nausea or vomiting for venlafaxine were not statistically significant.[75, 76, 78, 80, 85, 87] The rate of patients reporting nausea or vomiting ranged from 25 percent to 36 percent. A pooled analysis of published and unpublished trials of duloxetine did not find significant differences in nausea between duloxetine (40-120 mg/d) and paroxetine (20 mg/d) or between duloxetine (120 mg/d) and fluoxetine (20 mg/d).[199] Three trials reported a significantly higher rate of dizziness in the venlafaxine group than in the fluoxetine group.[77, 78, 82] Three other studies reported significantly higher rates of diarrhea in sertraline-treated patients than in comparison drugs.[53, 62, 71] In another trial conducted in patients 65 years and older, patients using fluoxetine had significantly more severe adverse events than patients treated with paroxetine.[48]

A British study pooled data from Prescription-Event-Monitoring (PEM) of general practitioners 6 months to 1 year after they had issued prescriptions.[200, 201] 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 selective serotonin reuptake inhibitors only, drowsiness and sedation were significantly higher in the fluvoxamine and paroxetine group than in the fluoxetine and sertraline group. Overall, the mean incidence density per 1000 patient months for selective serotonin reuptake inhibitors was highest for fluvoxamine (fluvoxamine 17.6; fluoxetine 7.0; paroxetine 7.6; sertraline 6.2). 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 randomized controlled trials were powered primarily to detect differences in adverse events between fluvoxamine and citalopram[202] and fluvoxamine and paroxetine,[60] and fluvoxamine and fluoxetine.[47] A Dutch multicenter trial was designed to assess between-group comparisons of gastrointestinal side effects between citalopram (20-40 mg/d) and fluvoxamine (100-200 mg/d).[202] 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 (50-150 mg/d) or paroxetine (20-50 mg/d) for 7 weeks.[60] Sweating was the only significantly higher adverse event: 30 percent in paroxetine patients compared with10 percent in fluvoxamine patents ($P=0.028$).

The third trial assessed differences in adverse events between fluvoxamine (100-150 mg/d) and fluoxetine (20-80 mg/d) in 100 patients over 7 weeks.[47] Fluoxetine-treated patients suffered under nausea significantly more often than fluvoxamine patients (42.5% compared with NR; $P=0.03$)

A meta-analysis of 15 randomized controlled trials did not find any statistically significant differences in discontinuation rates because of adverse events between fluoxetine and other selective serotonin reuptake inhibitors as a class.[203]

A fair-rated, Dutch prospective observational study followed 1251 patients for up to 12 months to assess adverse events of sertraline (N=659) compared to other selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine).[204] 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 selective serotonin reuptake inhibitor groups ($P<0.05$). However, abdominal pain was reported more frequently by other selective serotonin reuptake inhibitor users than sertraline users ($P<0.05$). No other adverse event differed significantly across groups.

We pooled data from efficacy trials to assess differences in the overall loss to follow-up, the discontinuation rates because of adverse events, and the discontinuation rates because of lack of efficacy of selective serotonin reuptake inhibitors as a class compared to some other second-generation antidepressants (bupropion, mirtazapine, and venlafaxine) in adult outpatients with major depressive disorder (Exhibit 6). Available data were insufficient to determine results for duloxetine and nefazodone. 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 selective serotonin reuptake inhibitors (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). No significant differences could be detected between selective serotonin reuptake inhibitors and mirtazapine or between selective serotonin reuptake inhibitors and bupropion. Numerical differences in discontinuation rates attributed to adverse events generally favored selective serotonin reuptake inhibitors over mirtazapine and bupropion but did not reach statistical significance.

Table 20. Mean incidence of specific adverse events across comparative trials

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

[a] Mean incidence calculated from head-to-head randomized controlled trials; method and extent of adverse event assessment varied among studies and pooled incidence should be interpreted with caution. Statistics are descriptive only and comparisons across different drugs should be made with caution given differences in assessment and reporting of adverse events across trials.

B. Specific Adverse Events

1. 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 major depressive disorder.[122] 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.

A meta-analysis limited the CSM data to placebo-controlled trials of selective serotonin reuptake inhibitors in adults. Results did not yield any evidence that selective serotonin reuptake inhibitors increase or protect against the risk of suicide (OR 0.85; 95% CI 0.20 to 3.40).[205] However, weak evidence of an increased risk of self-harm was detected (OR 1.57; 95% CI 0.99 to 2.55).

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.[206] 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 tricyclic antidepressants.

Findings of other studies are mixed.[207-218] A good meta-analysis of published data on more than 87 000 patients in selective serotonin reuptake inhibitor trials for various conditions reported a significantly higher risk of suicide attempts for selective serotonin reuptake inhibitor patients than for placebo-treated patients (2.25; 95% CI 1.14 to 4.55).[219] Furthermore, an increase in the odds ratio of suicide attempts was observed for selective serotonin reuptake inhibitors compared to interventions other than tricyclic antidepressants (OR 1.94; 95% CI 1.06 to 3.57). No significant difference existed in the pooled analysis of selective serotonin reuptake inhibitors compared to tricyclic antidepressants (OR 0.88; 95% CI 0.54 to 1.42).

A fair-rated open cohort study using UK data observed 172 598 people to compare the suicide rates of 10 commonly used antidepressants (fluoxetine, dothiepin, amitriptyline, clomipramine, imipramine, flupenthixol, lofepramine, mianserin, doxepin, and trazodone) for 5 years.[213] Suicide was the main outcome measure. Dothiepin was the most commonly prescribed antidepressant and was used as a reference drug. Compared with dothiepin, only fluoxetine

(relative risk 2.1; 95% CI 1.1 to 4.1) and mianserin (relative risk 1.8; 95% CI 1.0 to 3.6) yielded a significantly higher relative risk for suicide. Relative risks did not differ among patients who had no history of being suicidal and had been prescribed only one antidepressant. A recent matched case-control study using data of 159 810 patients in the UK did not support these findings.[220] A total of 555 cases of nonfatal suicidal behavior were matched with 2062 controls. Compared to dothiepin, the risk of suicidal behavior was similar among users of amitriptyline (relative risk 0.83; 95% CI 0.61 to 1.13), fluoxetine (relative risk 1.16; 95% CI 0.90 to1.50), and paroxetine (relative risk 1.29; 95% CI 0.97 to 1.70).

A retrospective review of data in Food and Drug Administration summary reports compared the absolute suicide rate and the suicide rate by patient exposure-years of selective serotonin reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), other antidepressants (nefazodone, mirtazapine, bupropion, maprotiline, trazodone, mianserin, dothiepin, imipramine, amitriptyline, venlafaxine), and placebo.[215] Crude suicide rates and adjusted suicide rates did not differ significantly by patient exposure-years among patients assigned to selective serotonin reuptake inhibitors, other antidepressants, or placebo. A Spanish database review did not find significant differences in suicidal ideation between paroxetine, imipramine, amitriptyline, clomipramine, mianserin, doxepin, maprotiline and placebo.[216] A retrospective cohort and a nested case control study using data from a New Zealand database reported a higher rate of self-harms in selective serotonin reuptake inhibitor- than in tricyclic antidepressant-treated patients (OR: 1.66; 95% CI 1.23 to 2.23) but no differences in suicides.[221] However, no differences in self-harm or suicides were apparent among citalopram-, fluoxetine-, or paroxetine-treated patients. A retrospective analysis of escitalopram trails data found a higher rate of self-harm for escitalopram than for placebo but no differences in suicides.[222]

Findings of the CSM Expert Group on suicidality in children are consistent with results from an earlier NICE (National Institute for Clinical Excellence) report.[123] In patients younger than 18 years the risk of self-harm was significantly greater in patients on selective serotonin reuptake inhibitors than on tricyclic antidepressants (OR 1.59; 95% CI 1.01 to 2.50). Although no statistically significant differences among selective serotonin reuptake inhibitors were detected, the greatest risk of self-harm was among paroxetine users. 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) Results of other studies are mixed.[224-226]

2. Sexual dysfunction

A subgroup analysis of a good Swedish randomized controlled trial examined the incidence of sexual side effects from citalopram (20-60 mg/d) compared to those from sertraline (50-150 mg/d)[33, 227] in 308 study completers with major depressive disorder. 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. Only one patient was lost to follow-up attributable to sexual side effects in this study. Similarly, citalopram did not differ from paroxetine in sexual side effects in a nonrandomized trial.[228]

A good meta-analysis including data on 1332 patients reported a significantly higher rate of sexual satisfaction in bupropion- than in selective serotonin reuptake inhibitor-treated patients with major depressive disorder (relative risk 1.28; 95% CI 1.16 to 1.41).[88]

Multiple studies indicated that bupropion has a lower risk of sexual dysfunction than some selective serotonin reuptake inhibitors.[90, 94, 95, 106, 229] Three studies assessed the incidence of sexual dysfunction in depressed outpatients treated with bupropion or sertraline.[94, 95, 106]

Two fair-rated randomized controlled trials compared the incidence of sexual dysfunction in 360 and 364 patients with major depressive disorder during 8 weeks of treatment with bupropion (150-400 mg/d), sertraline (50-200 mg/d), or placebo.[94, 95] 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.[94] 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 ($P<0.05$).[95]

The third randomized controlled trial assessed the sexual side effects of bupropion SR (150-400 mg/d) and sertraline (100-300 mg/d) in 248 depressed outpatients.[106] 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% compared with 15%; $P<0.001$; women: 41% compared with 7%; $P<0.001$).

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

A fair, 8-week randomized controlled trial compared efficacy and sexual side effects of bupropion (150-400 mg/d), fluoxetine (20-60 mg/d), and placebo in 456 outpatients with major depressive disorder.[90] Loss to follow-up was 36 percent. Efficacy did not differ significantly. Bupropion had more remitters than fluoxetine (47% compared with 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 1022 outpatients treated with various antidepressants.[231] 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 another observational study, findings of a cross-sectional survey of patients on second-generation antidepressants presented similar results.[232] Paroxetine had the highest rate of sexual dysfunction; nefazodone and bupropion had the lowest**.**

Sexual side effects were also commonly reported adverse event for selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors in efficacy trials. Most of these studies did not report the use of targeted questions for sexual side effects. Therefore, patient-reported numbers might not reflect the true incidence. Paroxetine- and sertraline-treated patients frequently reported significantly higher rates of sexual side effects[52, 62, 63, 71, 93, 101] than did patients in the active control groups. In one trial, significantly more patients on sertraline withdrew because of sexual side effects than did patients on bupropion (3.3% compared with 13.5%; P=0.004).[93] 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]

3. Changes in weight

A 32-week acute and continuation trial assessed differences in weight changes among patients treated with fluoxetine, paroxetine, and sertraline.[103] 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.[53] 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). An open-label, nonrandomized, 2.5-year study on obsessive-compulsive disorder patients also reported the lowest increase in weight gain for fluoxetine (+0.5 kg). Other selective serotonin reuptake inhibitors lead to greater weight gains (sertraline +1.0 kg; citalopram +1.5 kg; paroxetine +1.7 kg; fluvoxamine +1.7 kg), however, differences are neither statistically nor clinically significant.[234]

A double-blinded placebo-controlled 52-week acute and continuation trial assessed weight changes during bupropion treatment.[235] 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. Patients with a higher body mass index experienced greater weight loss.

Two randomized controlled trials assessing the efficacies of mirtazapine and paroxetine reported significantly greater weight gains in the mirtazapine group than in the paroxetine group.[69, 70]

4. 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).

A recent chart review of 538 patients with deliberate self-poisoning with antidepressants reported that seizures were more common in patients with venlafaxine overdose than in patients with tricyclic antidepressant or selective serotonin reuptake inhibitor overdose.[237]

5. Cardiovascular adverse events

A post hoc analysis examined pooled data from 3744 patients participating in venlafaxine trials.[238] 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 ($P=0.004$).[86]

A post-hoc analysis of six randomized controlled trials (published and unpublished) comparing duloxetine to fluoxetine and paroxetine did not find any statistically significant differences in supine systolic or diastolic blood pressure.[239] Duloxetine treated patients had a greater mean change in heart rates than fluoxetine-(+2.8 beats/min. compared with -1.0 beat/min.) and paroxetine-treated patients (+1.0 beats/min. compared with -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]

6. Hyponatremia

Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of hyponatremia in patients treated with selective serotonin reuptake inhibitors. 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.[242] 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.

7. 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.[243] One maker of nefazodone has announced that it is withdrawing the drug from the US market by June 2004 because of safety concerns (websource: www.medscape.com/viewarticle/47852; accessed 5-20-2004).

C. Summary of the Evidence

Fair to good evidence from multiple randomized controlled head-to-head trials and retrospective data analyses of prescription event monitoring documents that adverse events profiles are similar among reviewed drugs. Frequencies of some adverse events, however, differ among drugs. Venlafaxine had a significantly higher rate of nausea and vomiting in multiple trials; paroxetine frequently led to higher sexual side effects; mirtazapine to higher weight gains; and sertraline to a higher rate of diarrhea than comparable second-generation antidepressants. A retrospective review of prescription event monitoring data provides fair evidence that, among selective serotonin reuptake inhibitors, fluvoxamine has the highest mean incidence of adverse events.[200]

Pooled estimates from efficacy trials suggest that venlafaxine has a statistically significantly higher rate of discontinuation because of adverse events than do selective serotonin reuptake inhibitors as a class (relative risk 1.36; 95% CI 1.09 to 1.69). However, overall discontinuation rates do not differ significantly between venlafaxine and selective serotonin reuptake inhibitors.

Suicidality

Evidence from controlled trials and observational studies is mixed about a higher risk of suicidality in patients treated with second-generation antidepressants. Data are insufficient to draw conclusions about the comparative risk among second-generation antidepressants.

Sexual dysfunction

Fair evidence from three randomized controlled trials indicates that the rate of sexual side effects is significantly lower for bupropion than for sertraline.[90, 95, 106] The combined number needed to treat to yield one additional person who is satisfied with the overall sexual function is 7. Two additional studies reported fewer sexual side effects in bupropion-treated patients than in patients treated with paroxetine[230]or fluoxetine.[93]

A cross-sectional survey supports this evidence by reporting the lowest rates of sexual side effects for bupropion and nefazodone in patients treated with selective serotonin reuptake inhibitors or other second-generation antidepressants.[232] Multiple trials give fair evidence that paroxetine, sertraline, and mirtazapine tend to have higher rates of sexual side effects than other second-generation antidepressants.[52, 53, 62, 63, 71, 93, 101, 232]

Weight changes

Multiple studies provide fair evidence that mirtazapine and paroxetine lead to a greater weight gain than do fluoxetine and sertraline.[69, 70, 103, 234] Additionally, one fair study presents evidence that bupropion treatment leads to a moderate loss of body weight.[235]

Cardiovascular adverse events

A post hoc analysis of pooled data reports that venlafaxine significantly increases the supine DBP.[238] None of the controlled efficacy trials reported significant changes in heart rates or an increase in arrhythmias during treatment with selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, or other second-generation antidepressants. Another post hoc analysis reports that duloxetine lead to higher heart rates than fluoxetine and paroxetine.[239] One fair randomized controlled trial did not detect any differences in supine blood pressure between duloxetine and placebo.[240]

Other adverse events

A database analysis in the UK on fatal toxicity of second generation antidepressants found venlafaxine to have the highest fatal toxicity rate (13.2/1 000 000 prescription) among second generation antidepressants.[244]

A case-control study did not find an association between selective serotonin reuptake inhibitors and breast cancer.[190] Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the risk of rare but potentially fatal adverse events such as hyponatremia or liver toxicity. However, multiple case reports have indicated that many of the selective serotonin reuptake inhibitors are associated with hyponatremia, especially in older patients.[242] Similarly, reports of liver toxicity with nefazodone have not been confirmed by controlled trials and observational studies.[243] Owing to a lack of studies with the methodological

strength to assess these rare events, conclusions should be made on other grounds such as comorbidities, taking case reports into consideration.

Table 21. Intervention, numbers of patients, and quality ratings of studies assessing adverse events

Author, Year	Interventions	N	Results	Quality rating
Tolerability and discontinuation				
Brambilla et al. 2005[203]	Fluoxetine compared with SSRIs (SR)	NR	No difference in discontinuation rates because of adverse events	Good
Cipriani et al. 2006[245]	Fluoxetine compared with SSRIs (SR)	14 391	No differences in overall discontinuation rates	Good
Greist et al. 2004[199]	Pooled analysis: Duloxetine compared with paroxetine compared with fluoxetine	2345	No differences in nausea between duloxetine and paroxetine, and duloxetine and fluoxetine	Fair
Haffmans et al. 1996[202]	Fluvoxamine compared with paroxetine	217	Significantly more diarrhea and nausea with fluvoxamine	Fair
Kiev et al. 1997[60]	Fluvoxamine compared with paroxetine	60	Significantly more sweating with paroxetine	Fair
Mackay et al. 1997, 1999[200, 201]	Prescription event monitoring	≥ 60 000	Venlafaxine had highest rate of nausea and vomiting; paroxetine highest rate of sexual side effects; among SSRIs, most overall adverse events with fluvoxamine	N/A
Meijer et al. 2002[204]	Sertraline compared with SSRIs (OS)	1251	Significantly more diarrhea with sertraline	Fair
Pigott et al. 2007[246]	Duloxetine compared with escitalopram	296	Over 8 months higher discontinuation rates for duloxetine than for escitalopram	Fair
Rapaport et al. 1996[47]	Fluvoxamine compared with fluoxetine	100	Significantly more nausea with fluoxetine	Fair
Vanderkooy et al. 2002[229]	Bupropion compared with paroxetine compared with sertraline compared with venlafaxine	193	Higher rates of sexual adverse events for paroxetine. Higher rates of gastrointestinal disorders for sertraline	Fair
Suicidality				
Acharya et al. 2006[218]	Duloxetine compared with placebo (pooled data)	2996	No difference in suicide risk	Fair
Aursnes et al. 2005[210]	Paroxetine compared with placebo (pooled data)	1466	Higher risk of suicides in patients on paroxetine	Fair
Bridge et al. 2007[224]	SSRIs (SR)	5310	Higher risk of suicidality for SSRI-treated patients	Good
Didham et al. 2005[221]	SSRIs	57 000	No difference in suicides or self-harm among citalopram, fluoxetine, and paroxetine	Fair
Fergusson et al. 2005[219]	SSRIs compared with placebo (SR)	87 650	Higher risk of suicide attempts for SSRI-treated patients	Good
Gibbons et al. 2007[207]	SSRIs (retrospective cohort study)	226 866	SSRIs have a protective effect	Fair
Gunnell et al. 2005[205]	Second generation antidepressant compared with placebo (SR)	40 000	No differences in adults	Good
Hammad et al. 2006[223]	SSRIs (SR)	4582	Higher risk of suicidality for SSRI-treated patients	Good

Author, Year	Interventions	N	Results	Quality rating
Isacsson et al. 2005[211]	SSRIs (case-control)	41 279	No increased risk	Fair
Jick et al. 2004[214]	SSRIs (case-control; database review)	159 810	No differences	N/A
Jick et al. 1995[213]	Antidepressants (database review)	172 598	Significantly higher risk of suicide with fluoxetine and mianserin compared to dothiepin	N/A
Khan et al. 2003[215]	Antidepressants (database review)	NR	No differences	N/A
Lopez-Ibor 1993[216]	Antidepressants (database review)	4686	No differences	N/A
Martinez et al. 2005[206]	Antidepressants (database review)	146 095	No differences	N/A
Nelson et al. 2007[209]	Sertraline compared with placebo (secondary analysis of RCT data)	752	No difference in suicidal thoughts between sertraline and placebo	Fair
Pedersen et al. 2005[217]	Escitalopram compared with placebo (retrospective cohort study)	4091	Higher rate of self-harm in escitalopram than in placebo	Fair
Tiihonen et al. 2006[212]	Antidepressants (retrospective cohort study)	15 390	Use of antidepressants was associated with an increased risk of attempted suicide	Fair
Valuck et al. 2004[226]	Antidepressants (retrospective cohort study)	24 119	No difference in risk of suicide attempts	Fair
Sexual dysfunction				
Nieuwstraten et al. 2001[88]	Bupropion compared with SSRIs (SR)	1332	Significantly higher rate of sexual satisfaction in bupropion group	Good
Clayton et al. 2002[232]	Cross-sectional survey	6297	Highest risk for paroxetine and mirtazapine; lowest risk for bupropion	N/A
Clayton et al. 2007[233]	Duloxetine compared with escitalopram	114	Significantly more sexual adverse events with escitalopram	Fair
Coleman et al. 2001[90]	Bupropion compared with fluoxetine	456	Significantly more sexual adverse events with fluoxetine	Fair
Coleman et al. 1999[95]	Bupropion compared with sertraline	364	Significantly more sexual adverse events with sertraline	Fair
Croft et al. 1999[94]	Bupropion compared with sertraline	360	No differences	Fair
Ekselius et al. 2001[227]	Citalopram compared with sertraline	308	No differences	Fair
Kennedy et al. 2006[230]	Bupropion compared with paroxetine	141	Significantly more sexual adverse events with paroxetine	Fair
Landen et al. 2005[228]	Citalopram compared with paroxetine	119	No differences	Good
Segraves et al. 2000[106]	Bupropion compared with sertraline	248	Significantly more sexual adverse events with sertraline	Fair
Montejo et al. 2001[231]	Prospective cohort study	1022	Highest incidence of sexual dysfunction for citalopram, paroxetine and venlafaxine; lowest for mirtazapine and nefazodone	Fair
Changes in weight				
Maina et al. 2004[234]	Open-label SSRIs	149	Highest weight gain with paroxetine, fluvoxamine, and citalopram	Fair
Fava et al. 2000[53]	Fluoxetine compared with paroxetine compared with sertraline	284	Highest weight gain with paroxetine	Fair

Author, Year	Interventions	N	Results	Quality rating
Benkert et al. 2000[70]	Mirtazapine compared with paroxetine	275	Significant weight gain with mirtazapine	Fair
Schatzberg et al. 2002[69]	Mirtazapine compared with paroxetine	255	Significant weight gain with mirtazapine	Fair
Cardiovascular events				
Raskin et al. 2008[240]	Duloxetine compared with placebo	311	No difference in supine blood pressure	Fair
Thase et al. 1998[238]	Post hoc analysis	3744	Significantly higher diastolic blood pressure for venlafaxine	N/A
Thase et al. 2005[239]	Post hoc analysis	1873	Greater change in heart rate for duloxetine than for fluoxetine and paroxetine	N/A
Other adverse events				
Alper et al. 2007[236]	Analysis of Food and Drug Administration trials data	33 885	Seizures more common in bupropion than in other antidepressants	Good
Buckley et al. 2005[244]	Database analysis	47 329	Highest rate of fatal toxicity for venlafaxine	N/A
Coogan et al. 2005[247]	Case-control	4996	No association between breast cancer and SSRIs	Fair
Dunner et al. 1998[248]	Prospective observational	3100	Rate of seizures for bupropion within range of other antidepressants	Fair
Johnston et al. 1991[249]	Prospective observational	3341	Rate of seizures for bupropion within range of other antidepressants	Fair
Kharofa et al. 2007[241]	Case-control	916 cases	No increased risk for hemorrhagic stroke for SSRIs	Fair
Whyte et al. 2003[237]	Prospective observational	538	Seizures more common in venlafaxine overdose than TCA or SSRI overdose	Good

Abbreviations: RCT, randomized controlled trial; SR, systematic review; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants.

Key Question 3.

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?

We did not find any studies directly comparing the efficacy and tolerability of second-generation antidepressants between subgroups and the general population. However, multiple studies conducted subgroup analysis or used subgroups as the study population. Results can provide indirect evidence for Key Question 3. Included studies are presented in Table 22.

A. Demographics

1. Age

We did not include any placebo-controlled studies on this topic as there were ample head-to-head trials.

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 compared with paroxetine

Two randomized controlled trials were conducted in a population older then 60 years.[48, 51] The first trial was an Italian study lasting 1 year that enrolled 242 patients to determine the effects of fluoxetine (20-60 mg/d) and paroxetine (20-40 mg/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 compared with 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.

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.[51] 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%compared with 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.

Fluoxetine compared with sertraline

One fair, 12-week study comparing fluoxetine to sertraline was conducted in 236 participants older than 60 years.[57, 59] Loss to follow-up was 32.2 percent. 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% compared with 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 ($P=0.027$).[59]

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.[35]

Mirtazapine compared with paroxetine

A fair trial randomized 255 elderly participants for eight weeks.[69] 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 compared with 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 compared with citalopram

A fair European 6-month study compared venlafaxine ER (37.5-150 mg/d) to citalopram (10-30 mg/d) for the treatment of depression in elderly outpatients (mean age 73 years).[72] 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 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 compared with sertraline

One study determined efficacy and safety of venlafaxine (25-100 mg/d) compared to sertraline (18.5-150 mg/d) in 52 frail nursing home residents (61 to 99 years of age).[250] We graded the quality of this study as poor for efficacy because of high loss to follow-up (44.2%), but we note it here because it is the only study comparing these two agents, and because the high loss to follow-up may be expected in this population (elderly nursing home residents). The investigators reported a significantly higher rate of withdrawal among venlafaxine- than sertraline-treated patients (63% compared with 24%). In addition, 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.

Venlafaxine compared with selective serotonin reuptake inhibitors

A pooled data analysis combined original data from eight comparable, double-blind, active-controlled, randomized trials.[251, 252] A primary objective of this analysis was to determine differences in response and remission based on sex and age. This study was not based on a systematic literature search, so results must be viewed cautiously. For venlafaxine-treated patients, neither age (< 50 or ≥ 50 years of age) nor sex affected remission rates.[252] Among patients treated with selective serotonin reuptake inhibitors, however, a significant interaction was observed between treatment and sex ($P=0.004$); older women had a poorer selective serotonin reuptake inhibitor response (response rate: 28%) than younger women (response rate: 36%), and both older and younger men (response rates: 35% and 36%, respectively). Remission rates for older women treated with venlafaxine (48%) were higher than remission rates for older women treated with selective serotonin reuptake inhibitors (28%, $P=0.0004$). Hormone replacement therapy appeared to eliminate these differences. Additional analyses of age subgroups (≤ 40, 41-54, 55-64, and ≥ 65 years of age) and sex subgroups revealed that no significant age-by-treatment, sex-by-treatment, or age-by-sex-by-treatment interactions occurred. Men and women of different ages within each treatment group had similar rates of remission, response, and absence of depressed mood.[251] Among patients over 40 years of age, the rates of adverse events were similar between the treatment groups, although venlafaxine-treated patients aged 55 to 64 years reported significantly more nausea than placebo ($P<0.003$), and placebo patients aged 41 to 54 years reported a significantly higher frequency of headaches than venlafaxine ($P<0.01$).

Bupropion compared with paroxetine

One fair randomized controlled trial examined the efficacy of bupropion SR (100-300 mg/d) and paroxetine (10-40 mg/d) in 100 outpatients ages 60 years or older (range 60-88 years) over 6 weeks.[91, 92] 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. Response rates (≥ 50% reduction in HAM-D scores) were similar in both groups (bupropion SR, 71%; paroxetine, 77%). Quality-of-life scales (QLDS, SF-36) showed statistically significant improvements in both treatment groups from baseline to endpoint ($P<0.0001$), but they did not differ significantly between treatment groups.

We did not identify any head-to-head trials that compare one second-generation antidepressant to another in children and adolescents. There is Food and Drug Administration-approved evidence for the efficacy of fluoxetine and fair evidence from a pooled analysis of two placebo-controlled trials for the efficacy of sertraline.[132] 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 major depressive disorder in children and adolescents.[123] This review reported an increased risk of suicidal thoughts and behavior for citalopram, paroxetine, sertraline, and venlafaxine, but not for fluoxetine.

2. Ethnicity

Duloxetine compared with placebo

Two pooled analyses of seven placebo-controlled duloxetine trials assessed the efficacy and tolerability of duloxetine in Hispanic[253] and African American patients[254] 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]

Fluoxetine compared with placebo

An randomized controlled trial examined ethnic differences in response to antidepressant treatment among depressed HIV-positive patients.[255] A total of 118 patients were randomized to either fluoxetine (20-80 mg/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% compared with 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.

Paroxetine compared with 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.[256]

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 $HRSD_{17}$ 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.

3. Sex

A pooled data analysis of venlafaxine and selective serotonin reuptake inhibitors described above[251, 252]did not find any significant associations between sex and outcomes or sex and treatment of major depressive disorder. Among patients treated with selective serotonin reuptake inhibitors, however, a significant interaction was observed between treatment and sex (P=0.04); older women had a poorer selective serotonin reuptake inhibitor response (28%) than younger women (36%) and than both older and younger men (35% and 36%, respectively). Additional analyses of the age ($\leq$ 40, 41-54, 55-64, and $\geq$ 65) and sex subgroups revealed no significant sex-by-treatment or age-by-sex interactions; men and women of different ages within each treatment group had similar rates of remission, response, and absence of depressed mood symptoms.[252]

A pooled analysis of data from four sertraline-randomized controlled trials conducted in populations with panic disorder, however, reported better responses of female patients on some outcome measures (panic attack frequency, time spent worrying).[258] 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] There were no clinically meaningful differences between men and women in safety and tolerability with duloxetine treatment. 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.

B. Other Medications-Drug Interaction

The evidence for drug-drug interactions is limited. A 2004 study published in the *Journal of the American Pharmacists Association* reported that very little agreement in reporting clinical significance of drug-drug interactions.[260] In fact, the authors found that only 2.2 percent of major drug interactions were listed in all sources reviewed.

Based on our review criteria, head-to-head trials specifically evaluating drug-drug interactions were not identified. Most drug interaction studies use very small sample populations or a case series design, precluding them from our review. One larger study non systematically 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.[261]

Several reviews summarize the evidence; however, they are not based on systematic searches of the literature and instead simply compile and discuss available evidence. One review explored cytochrome P450 metabolic enzymes (the CYP system) and their interaction with selective serotonin reuptake inhibitors.[262] The authors concluded that the relationship between selective serotonin reuptake inhibitors and P450s does not predict clinically significant interactions but that it can be used as a cue to monitoring, especially among drugs with narrow therapeutic index or in patients taking multiple drugs. Another review evaluated the evidence for drug-drug interactions between selective serotonin reuptake inhibitors and other CNS drugs. It concluded that the selective serotonin reuptake inhibitors 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.[263]

Although drug-drug interactions can be related to a host of different factors, commonly interactions are related to pharmacokinetic properties including metabolism and protein binding. Metabolic enzymes are involved in drug interactions when drugs compete for or inhibit the action of these enzymes. All second-generation antidepressants are metabolized by the liver and have an affinity for drug-metabolizing cytochrome P450 oxidative enzymes. The second-generation antidepressants may be substrates for the enzymes (e.g., the enzyme aids in metabolism of the antidepressant drug) and/or they may alter the activity of the enzyme through inhibition or induction. Protein binding can be involved in drug-drug interactions by altering available quantities of an active drug in the blood stream. When multiple drugs compete for binding to protein, one or more drugs may be displaced. In most cases, this leads to enhanced availability of the drug with lower binding affinity. Many drug-drug interactions are related directly to these underlying properties.

Clinical relevance of drug-drug interactions can be classified in three ways. The most severe type of drug interaction is usually referred to as a contraindication. A *contraindicated* medication should not be given unless required by extreme circumstances. Many drug interactions may be clinically relevant but not preclude combined use of the two medications. Instead, clinicians should acknowledge the interaction, adjust doses appropriately, and *monitor*

for toxic or subtherapeutic effects. A third type of interaction is one that, although it may occur, is *not clinically significant*.

Because only limited evidence supports drug interactions among the second-generation antidepressants, our review focuses on the potential for drug interactions. In addition to published literature cited previously, we reviewed dossiers submitted by pharmaceutical companies, Food and Drug Administration approved labeling, and interactions reported by major reference sources. 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 summarizes second-generation antidepressant pharmacokinetic properties known to be related to drug interactions. Tables in Appendix D report evidence provided in the product labeling (package insert). 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.

C. Comorbidities

1. Alcohol/substance abuse

Fluoxetine compared with placebo

Four randomized placebo-controlled trials assessed the efficacy and tolerability of fluoxetine for the treatment of depression with co-occurring alcoholism[264-266] or co-occurring substance use disorders.[267-269]

One fair study of 51 depressed alcoholics assessed the efficacy of fluoxetine (20-40 mg/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).[264-266] 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 ($P=0.001$).

A fair, small randomized controlled trial assessed the efficacy and tolerability of fluoxetine treatment (20-60 mg/d) compared to placebo for the treatment of major depression in 44 methadone-maintained opioid addicts.[267] 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 ($\geq$ 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 $\geq$ 17 while Group B scores were $\leq$ 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).

2. 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 inclusions 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 trial[277] 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.

3. Arthritis

Our searches yielded only one trial that evaluated the efficacy of an antidepressants 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.

4. Cancer

Fluoxetine compared with placebo

We detected only one trial that studied the efficacy of fluoxetine in cancer patients;[280] however, this placebo-controlled trial failed to meet our inclusion criteria because the duration of the study was less than 6 weeks.. We mention it here because it was the only trial on this topic. This 5-week trial studied the efficacy of fluoxetine in 91 cancer patients with depression or adjustment disorder. The majority of the patients were female; 13 percent in the fluoxetine group and 5 percent 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% compared with 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% compared with 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.

5. Diabetes

Our searches yielded two trials that evaluated the efficacy of an antidepressants in depressed patients with comorbid diabetes.[278, 282] The details of the first study[278] 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 study, 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.

6. 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 trial (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.[255] 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.

7. 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.

8. Somatizing depression

A retrospective evaluation of 89 patients from two trials comparing fluoxetine (20-80 mg/d) to paroxetine (20-50 mg/d) determined whether depressed, somatizing patients with a gastrointestinal (GI) component have a higher degree of GI side effects than non somatizing depressed participants.[285] 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.

9. 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).

10. Vascular disease (cardiovascular, cerebrovascular or peripheral vascular)

We identified six placebo-controlled trials,[278, 288-291] one pooled-data analysis,[292] and one systematic review[293] that addressed depression and co-occurring vascular disease of some type (post-myocardial infarction, vascular disease, coronary artery disease or chronic heart failure. All but one[294] of these studies met our inclusion criteria. The majority of the trials evaluated a different drug (citalopram, duloxetine, fluoxetine, mirtazapine, sertraline, and selective serotonin reuptake inhibitors as a class) with the exception of sertraline—two studies compared sertraline and placebo. Therefore, results are presented here by comorbidity rather than by drug comparison.

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-D_{24} 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=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, ore 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.

The second study, a fair, retrospective analysis of pooled data of two randomized controlled trials determined the safety and efficacy of sertraline (50-150 mg/d) in elderly patients with comorbid vascular disease.[292] 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.

D. Summary of the Evidence

Age

We found no study that directly compared efficacy and safety of treatments in an elderly population compared to a younger population. A fair pooled data analysis did not find significant associations between age and outcomes or age and treatment.[251] However, Findings suggested that older women had a poorer response to selective serotonin reuptake inhibitors than younger women.[251, 252]

Eight studies provide fair to good indirect evidence that efficacy and tolerability for patients older than 60 years and those younger do not differ.[30, 35, 45, 48, 57, 59, 69, 72, 91, 92] Results of these studies, all conducted in patients with major depressive disorder or dysthymia, are generally consistent with results of trials conducted in younger populations. Only one small study reported a higher efficacy of paroxetine than fluoxetine in patients older than 60 years.[51] However, this trial was small and the results are inconsistent with better evidence. Another small study, rated poor for efficacy outcomes, reported a significantly higher loss to follow-up because of adverse events in venlafaxine-treated, frail elderly patients than in sertraline-treated participants.[250]

We did not identify any head-to-head trials that compare one second-generation antidepressant to another in children and adolescents. For major depressive disorder, placebo-controlled evidence supports the efficacy of fluoxetine[296, 297] and sertraline.[132] 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 one systematic review of published and unpublished studies comparing second-generation antidepressants to placebo, only fluoxetine was shown to be safe and effective in the treatment of major depressive disorder in children and adolescents.[123] This review reported an increased risk of suicidal thoughts and behavior for citalopram, paroxetine, sertraline, and venlafaxine, but not for fluoxetine. Two other systematic reviews of confirmed these results finding only fluoxetine had a favorable risk-benefit profile.[124, 125]

Ethnicity

Fair evidence from a pooled data study on paroxetine[256] and a single randomized controlled trial on fluoxetine[255] suggest that response rates, loss to follow-up, and response to placebo treatment might differ between groups of different ethnic background. Hispanics tend to have lower response rates than Blacks and Whites. However, two pooled data analyses (of the same seven placebo-controlled duloxetine trials) found no significant differences between Caucasians and Hispanics[253] or between Caucasians and African Americans.[254]

Sex

A fair trial comparing bupropion and paroxetine showed a significant difference in anti-depressant related sexual dysfunction in men but not in women. Paroxetine-treated men reported a worsening of sexual function while bupropion-treated men had no significant change in sexual function. A fair pooled-data analysis did not find significant associations between sex and outcomes or sex and treatment.[251, 252] Another fair pooled analysis of data from four sertraline-randomized controlled trials conducted in populations with panic disorder reported better responses of female patients on some outcome measures.[258] In a fair randomized controlled trial enrolling menopausal women, paroxetine-treated women showed a significant decrease in hot flashes compared to those treated with fluvoxamine; however, there were no significant differences in depression symptoms between groups.[61]

Concomitant medications

Evidence is insufficient to determine the influence of concomitant medications on the effectiveness of selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, or other second-generation antidepressants.

Comorbidities

No prospective study directly compared the efficacy and tolerability of selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and other second-generation antidepressants in a population with a specific comorbid condition to a population without that same condition. Two retrospective data analyses provide fair evidence that efficacy does not differ between patients with vascular disease and somatizing depressions and patients without these co-morbidities.[285, 292] Various other trials conducted in populations with different comorbidities can provide indirect evidence.[264-267, 280, 281, 283] Four placebo-controlled trials provided fair evidence that treatment effects do not differ between placebo and fluoxetine in methadone-maintained opioid addicts, cocaine abusers, depressed HIV patients or depressed cancer patients.[267, 268, 280, 283] In addition, one fair randomized controlled trial showed no significant difference between fluoxetine and placebo in adolescents with major depressive disorder and comorbid substance abuse and conduct disorder.[269]

Two trials provided fair evidence that treatment effects do not differ between sertraline and placebo in depressed alcoholics.[272, 274] One trial showed greater depression improvement in sertraline-women with co-occurring alcohol disorder compared with placebo; there was no treatment difference for men.[273]

One trial showed sertraline was significantly better than placebo in post –myocardial infarction patients.[291] These findings were confirmed by a systematic review that provided fair evidence that selective serotonin reuptake inhibitors are better as a class than placebo treating depression in post-myocardial infarction patients.[293]

Two separate trials provided fair evidence that there were no difference in duloxetine or paroxetine compared to placebo in the treatment of depressive symptoms in diabetic patients.[278, 282]

One trial reported fair evidence that response rates for fluoxetine-treated alcoholics are significantly higher than for placebo-treated subjects.[264-266] A placebo controlled randomized controlled trial in depressed breast cancer patients reported greater efficacy of paroxetine than placebo in reducing depression but no differences with respect to fatigue.[281]

Table 22. Interventions, numbers of patients, and quality ratings in controlled trials assessing efficacy and effectiveness in subgroups

Author, Year	Interventions	N	Results	Quality rating
Age				
Kasper et al. 2005[45]	Escitalopram compared with fluoxetine compared with placebo	518	No significant difference in response rates; remission rates lower for fluoxetine than escitalopram	Fair
Cassano et al. 2002[48]	Fluoxetine compared with paroxetine	242	Faster onset of paroxetine	Fair
Schone and Ludwig 1993[51]	Fluoxetine compared with paroxetine	108	Faster onset of paroxetine	Fair
Newhouse et al. 2000[57] Finkel et al. 1999[59]	Fluoxetine compared with sertraline	236	No differences	Fair
Kroenke et al. 2001[35]	Fluoxetine compared with sertraline compared with paroxetine	601	No differences	Fair

Author, Year	Interventions	N	Results	Quality rating
Schatzberg et al. 2002[69]	Mirtazapine compared with paroxetine	255	Faster onset of mirtazapine; similar number of CGI responders at end of continuation phase	Fair
Allard et al. 2004[72]	Venlafaxine compared with citalopram XR	151	No differences	Fair
Schatzberg and Roose 2006[30]	Venlafaxine compared with fluoxetine	300	No differences	Fair
Oslin et al. 2003[250]	Venlafaxine compared with sertraline	52	No significant difference in efficacy; tolerability was lower for venlafaxine	Poor
Weihs et al. 2000[91] Doraiswamy et al. 2001[92]	Bupropion SR compared with paroxetine	100	No differences	Fair
Thase et al. 2005[252] Entsuah et al. 2001[251]	Pooled data analysis of venlafaxine (IR and XR) and SSRIs	2045	Venlafaxine response not affected by age or sex; SSRI response poorer in older women; similar efficacy of venlafaxine and SSRIs, except in older women, but HRT appears to eliminate the difference	Fair
Whittington et al. 2004[123]	Meta-analysis	2145	Only fluoxetine had favorable risk-benefit profile	Fair
Ethnicity				
Bailey et al. 2006[254]	Pooled analysis of duloxetine and placebo	1423	No differences between Caucasians and African Americans	Fair
Lewis-Fernandez et al. 2006[253]	Pooled analysis of duloxetine and placebo	1452	No differences in efficacy or tolerability outcomes between Hispanics and Caucasians	Fair
Roy-Byrne et al. 2005[256]	Pooled analysis of paroxetine compared with placebo	14 875	Slightly lower response rates for Hispanics and Asians than for Blacks and Whites	Fair
Wagner et al. 1998[255]	Fluoxetine compared with placebo	118	Ethnicity was not associated with side effects; whites had a higher response rate, Latinos a higher drop-out rate	Poor
Sex				
Kennedy et al. 2006[230]	Bupropion compared with paroxetine	141	No difference between drugs for sexual dysfunction in women	Fair
Ushiroyama et al. 2004[61]	Fluvoxamine compared with paroxetine	105	Significant difference in % change for hot flashes favoring paroxetine	Fair
Stewart et al. 2006[259]	Pooled data analysis of duloxetine compared with placebo	1622	No differences in safety and tolerability	Fair
Clayton et al. 2005[258]	Pooled data analysis of sertraline compared with placebo	673	Better response of female patients on some outcome measures	Fair
Thase et al. 2005[252] Entsuah et al. 2001[251]	Pooled data analysis of: venlafaxine (IR and XR) compared with SSRIs compared with placebo	2045	Venlafaxine response not affected by age or sex; SSRI response poorer in older women; similar efficacy of venlafaxine and SSRIs, except in older women, but HRT appears to eliminate the difference	Fair
Comorbidities				
Alcohol/substance abuse				
Riggs et al. 2007[269]	Fluoxetine compared with placebo	125	No significant differences in adolescents with MDD, SUD and CD	Fair
Schmitz et al. 2001[268]	Fluoxetine compared with placebo	68	No differences in depressed cocaine abusers	Poor
Cornelius et al. 1997, 1998, 2000[264-266]	Fluoxetine compared with placebo	54	Significantly greater efficacy for fluoxetine in depressed alcoholics	Fair

Author, Year	Interventions	N	Results	Quality rating
Petrakis et al. 1998[267]	Fluoxetine compared with placebo	44	No difference in depressed opioid addicts	Fair
Hernandez-Avila et al. 2004[270]	Nefazodone compared with placebo	41	No significant differences	Fair
Book et al. 2007[271]	Paroxetine compared with placebo	42	Significantly greater reduction in LSAS total scores in paroxetine patients	Fair
Kranzler et al. 2006[274]	Sertraline compared with placebo		No differences	Fair
Gual et al. 2003[272]	Sertraline compared with placebo	83	No significant differences	Fair
Moak et al. 2003[273]	Sertraline compared with placebo	82	Greater depression improvement in females treated with sertraline; less drinking associated with greater depression improvement	Fair
Alzheimer's disease/dementia				
Nyth et al. 1992[275]	Citalopram compared with placebo	149	Significantly greater improvement with citalopram	Poor
Lyketsos et al. 2003[276]	Sertraline compared with placebo	44	Sertraline associated with greater response	Fair
Arthritis				
Wise et al. 2007[278]	Duloxetine compared with placebo	233	No significant differences	Fair
Cancer				
Roscoe et al. 2005[281]	Paroxetine compared with placebo	94	Greater efficacy for paroxetine in depressed patients with breast cancer	Poor
Diabetes				
Wise et al. 2007[278]	Duloxetine compared with placebo	233	No significant differences	Fair
Paile-Hyvärinen et al 2007[282]	Paroxetine compared with placebo	49	No differences	Poor
HIV/AIDS				
Rabkin et al 1999[283]	Fluoxetine compared with placebo	120	No difference in depressed HIV/AIDS patients	Fair
Wagner et al. 1998[255]	Fluoxetine compared with placebo	118	Ethnicity was not associated with side effects; whites had a higher response rate, Latinos a higher drop-out rate	Poor
Multiple sclerosis				
Ehde et al. 2008[284]	Paroxetine compared with placebo	42	No significant differences	Fair
Somatizing depression				
Linden et al. 1994[285]	Fluoxetine compared with paroxetine	89	No difference in GI-side effects in somatizing patients	Fair
Stroke				
Andersen et al. 1994[286]	Citalopram compared with placebo	66	Significantly greater improvement in citalopram-treated patients	Fair
Murray et al. 2005[287]	Sertraline compared with placebo	123	No difference in response; greater improvements in QoL with sertraline	Fair
Vascular disease (cardiovascular, cerebrovascular, or peripheral vascular)				
Lesperance et al. 2007[288]	Citalopram compared with placebo	284	Significantly greater improvements in depressive symptoms in citalopram-treated patients	Fair
Wise et al. 2007[278]	Duloxetine compared with placebo	233	No significant differences	Fair
Strik et al. 2000[289, 295]	Fluoxetine compared with placebo	54	Significantly greater response with fluoxetine in post-myocardial infarction patients	Good

Author, Year	Interventions	N	Results	Quality rating
Honig et al. 2007[290]	Mirtazapine compared with placebo	91	Significantly greater CGI improvement with mirtazapine; no significant difference between groups in HAM-D and BDI scores in post-myocardial infarction patients	Fair
Krishnan et al. 2001[292]	Sertraline compared with placebo	220	Vascular comorbidity not associated with more adverse events and premature discontinuation	Fair
Glassman et al. 2002[291]	Sertraline compared with placebo	369	Significantly greater response with sertraline in post-myocardial infarction patients	Fair
Bush et al. 2005[293]	SSRIs (SR)	NR	SSRIs improve depression in post-myocardial infarction patients	Fair

Abbreviations: CD, conduct disorder; CGI, clinical global impressions; HRT, hormone replacement therapy; LSAS, Liebowitz Social Anxiety Scale: MDD, major depressive disorder; QoL, quality of life; SR, systematic review; SSRI, selective serotonin reuptake inhibitor; SUD, substance abuse disorder.

ADDENDUM

On February 29, the Food and Drug Administration approved desvenlafaxine extended-release tablets (*Pristiq*; Wyeth Pharmaceuticals, Inc) for the treatment of major depressive disorder in adult patients. Because this approval took place after finalizing the key questions, we were unable to integrate data on desvenlafaxine in this report.

Desvenlafaxine is a serotonin-norepinephrine reuptake inhibitor and the major active metabolite of venlafaxine XR, which will lose patent protection in 2010. The manufacturer argues that the avoidance of the cytochrome P450 isoenzyme 2D6 could be beneficial in patients requiring concomitant therapy with medications that use this metabolic pathway, such as certain beta-blockers and class I antiarrhythmics. Desvenlafaxine is approved at a once-daily 50 mg dose that does not require titration.

The Food and Drug Administration approval was based on four 8-week placebo controlled randomized controlled trials.[298-301] No head-to-head trials comparing the efficacy and safety of desvenlafaxine to any other second-generation antidepressants appear to be available to date. Like all second-generation antidepressants, desvenlafaxine has a black box warning regarding suicidality.

Exhibit 1. Relative risk meta-analysis of response rates comparing citalopram to escitalopram

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Burke et al. 2002[37]	491	40.1	65%	8 weeks	MADRS
Colonna et al. 2005[38]	357	46	75%	8 weeks	MADRS
Lepola et al. 2003[36]	471	43	72.1%	8 weeks	MADRS
Moore et al. 2005[39]	280	45.2	76.9%	8 weeks	MADRS
SCT-MD-02 (unpublished)[41]	243	41.9	52.6%	8 weeks	MADRS
Yevtushenko et al. 2007[40]	330	34.9	58.4%	6 weeks	MADRS

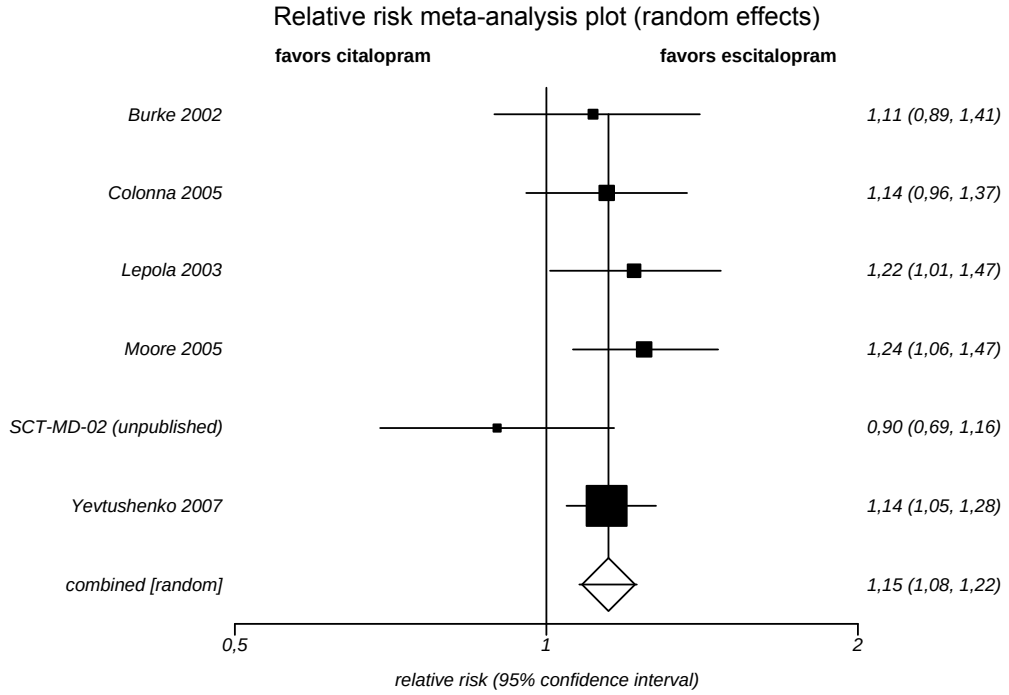


Exhibit 2. Effect size meta-analysis comparing citalopram to escitalopram on the MADRS

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Burke et al. 2002[37]	491	40.1	65%	8 weeks	MADRS
Colonna et al. 2005[38]	357	46	75%	8 weeks	MADRS
Lepola et al. 2003[36]	471	43	72.1%	8 weeks	MADRS
Moore et al. 2005[39]	280	45.2	76.9%	8 weeks	MADRS
SCT-MD-02 (unpublished)[41]	243	41.9	52.6%	8 weeks	MADRS
Yevtushenko et al. 2007[40]	330	34.9	58.4%	6 weeks	MADRS

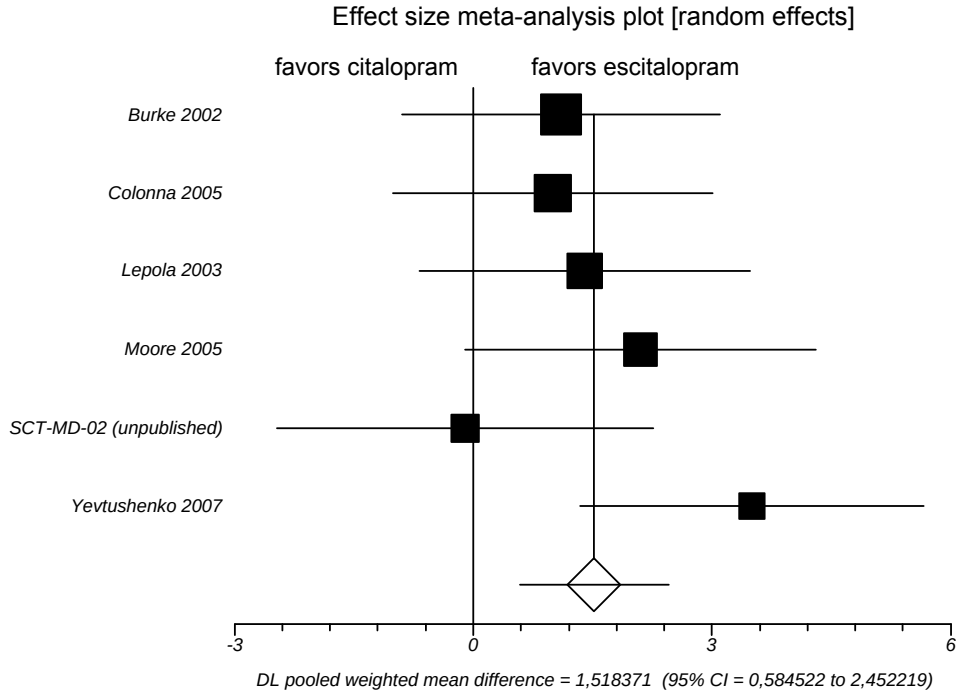


Exhibit 3. Meta-analysis of studies comparing fluoxetine to paroxetine

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Chouinard et al. 1999[49]	203	40.9	61%	12 weeks	HAM-D
De Wilde et al.1993[50]	78	44.0	61%	6 weeks	HAM-D
Fava et al. 1998[52]	128	41.3	51%	10-16 weeks	HAM-D
Fava et al. 2002[53]	188	42.0	65%	10-16 weeks	HAM-D
Gagiano 1993[54]	90	38.7	80%	6 weeks	HAM-D
Schöne et al. 1993[51]	108	74.0	87%	6 weeks	HAM-D

Characteristics of excluded studies

	Sample size	Mean Age	Women	Duration	Scale	Reason for exclusion
Cassano et al. 2002[48]	242	75.3	55%	52 weeks	HAM-D	Missing data

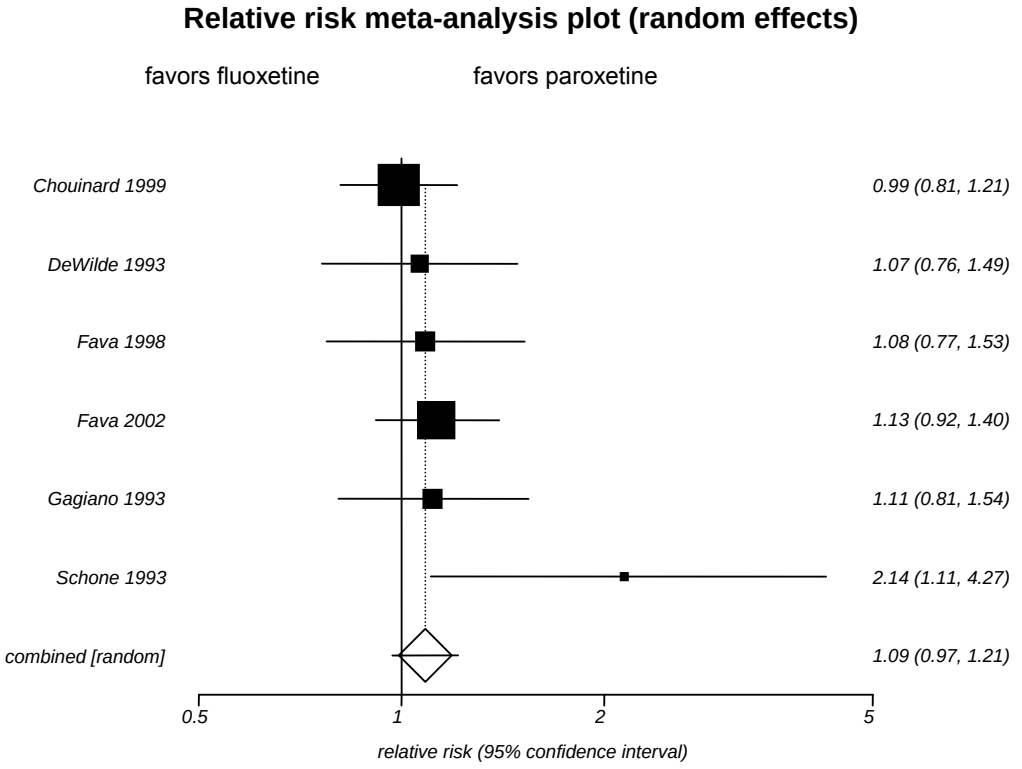


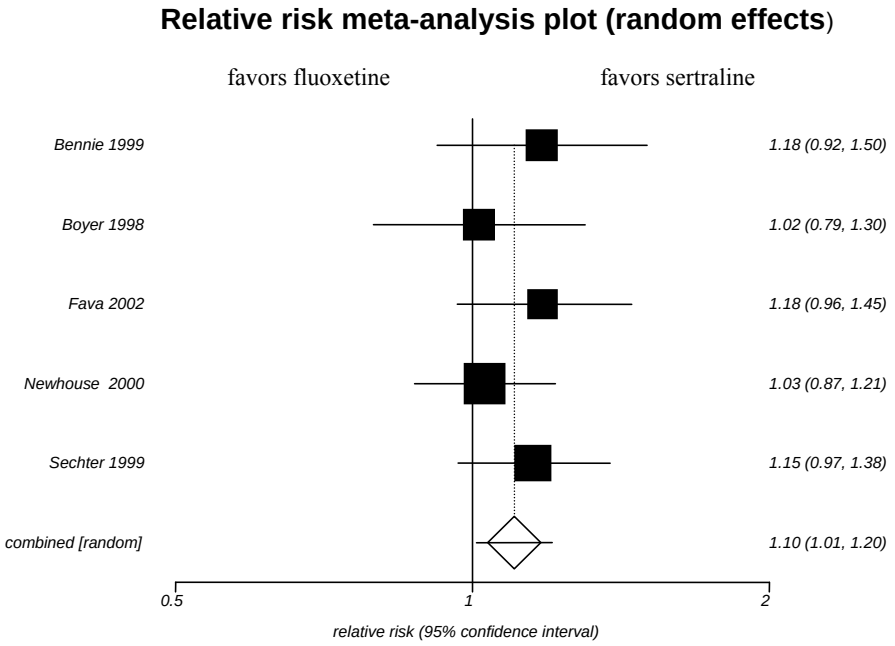
Exhibit 4. Meta-analysis of studies comparing fluoxetine to sertraline

Characteristics of included studies

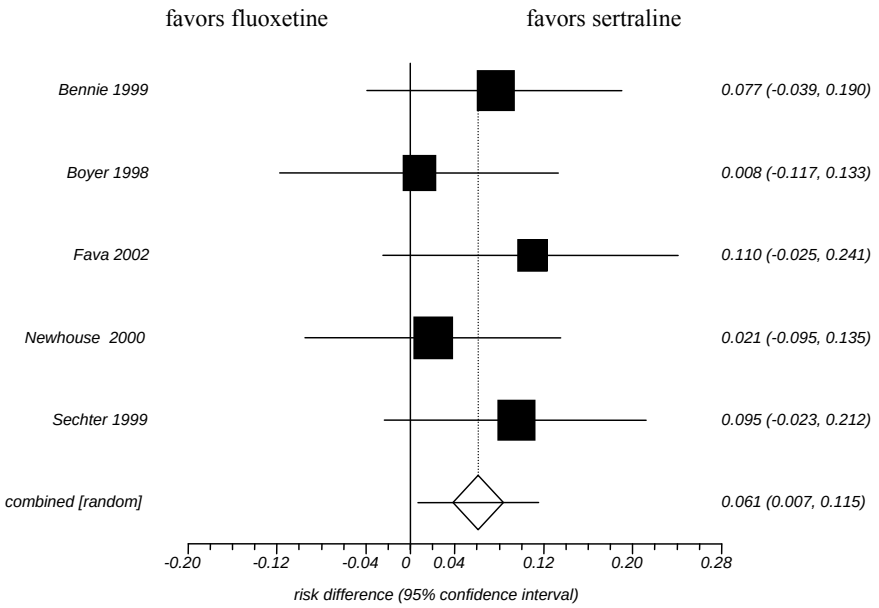
	Sample size	Mean Age	Women	Duration	Scale
Bennie et al. 1999[55]	286	49.9	61%	6 weeks	HAM-D
Boyer et al. 1998[56, 58]	242	43.4	78%	26 weeks	MADRS
Fava et al. 2002[53]	188	42.0	65%	10-16 weeks	HAM-D
Newhouse et al. 2000[57]	236	67.5	57%	12 weeks	HAM-D
Sechter et al. 1999[34]	238	42.8	67%	24 weeks	HAM-D

Characteristics of excluded studies

	Sample size	Mean Age	Women	Duration	Scale	Reason for exclusion
Kroenke et al. 2001[35]	601	46.1	74%	9 months	SF-36	Different outcome measure



Risk difference meta-analysis plot [random effects]



Number needed to treat (empirical results using observed counts only)

Estimates with 95% confidence intervals:

Odds ratio of event in treated cf. controls = 1.288143 (1.013664 to 1.637123)
Relative risk reduction (controls-treated) = -0.105572 (-0.213335 to -0.008186)
Risk difference (controls-treated) = -0.060504 (-0.115759 to -0.004894)
NNT [risk difference] (rounded up) = 17

Exhibit 5. Meta-analysis of studies comparing venlafaxine to fluoxetine

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Alves et al. 1999[80]	87	43.8	92%	12 weeks	HAM-D
De Nayer et al. 2002[76]	146	42.7	68%	12 weeks	MADRS
Dierick et al. 1996[81]	314	43.4	64%	8 weeks	HAM-D
Keller et al. 2007[29]	1096	40.2	61%	10 weeks	HAM-D
Nemeroff et al. 2007[31]	308	39.0	67%	6 weeks	HAM-D
Rudolph et al. 1999[77]	301	40	69%	8 weeks	HAM-D
Silverstone et al. 1999[78]	378	41.9	60%	12 weeks	HAM-D
Tylee et al. 1997[82]	341	44.5	71%	12 weeks	HAM-D

Characteristics of excluded studies

	Sample size	Mean Age	Women	Duration	Scale	Reason for exclusion
Corya et al. 2006[32]	119	45.7	72.5	12 weeks	HAM-D	Missing data
Costa e Silva et al. 1998[75]	382	40.1	53%	8 weeks	HAM-D	Missing data
Schatzberg et al. 2006[30]	300	71	50%	8 weeks	HAM-D	Missing data

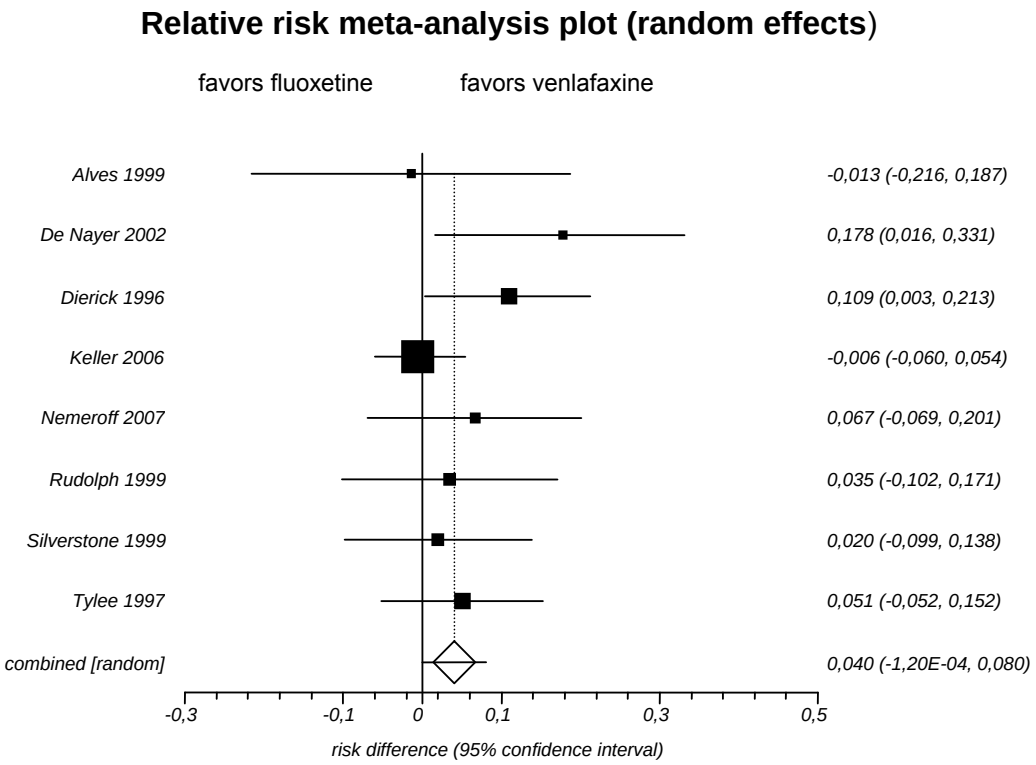

Relative risk meta-analysis plot (random effects)
favors fluoxetine
favors venlafaxine
Alves 1999
De Nayer 2002
Dierick 1996
Keller 2006
Nemeroff 2007
Rudolph 1999
Silverstone 1999
Tylee 1997
combined [random]
-0,013 (-0,216, 0,187)
0,178 (0,016, 0,331)
0,109 (0,003, 0,213)
-0,006 (-0,060, 0,054)
0,067 (-0,069, 0,201)
0,035 (-0,102, 0,171)
0,020 (-0,099, 0,138)
0,051 (-0,052, 0,152)
0,040 (-1,20E-04, 0,080)
-0,3
-0,1
0
0,1
0,3
0,5
risk difference (95% confidence interval)

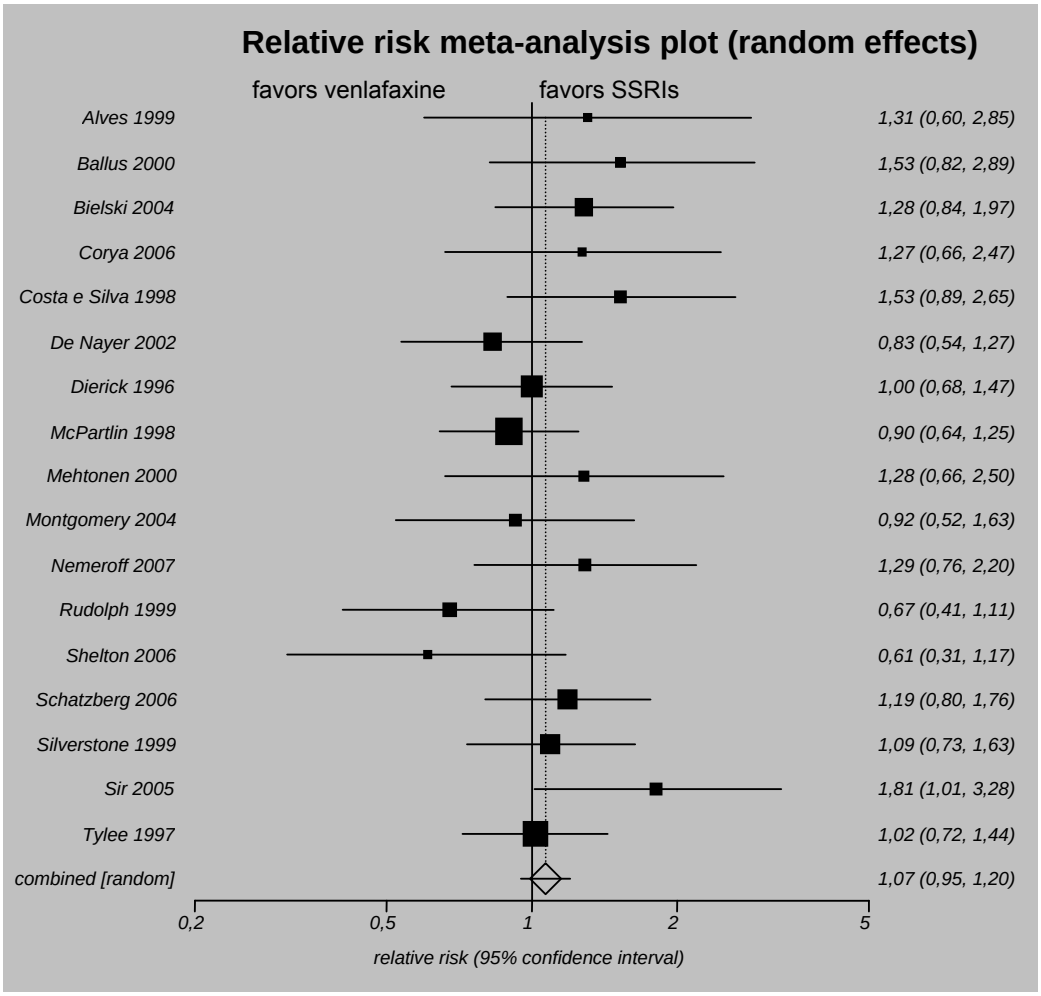
Exhibit 6. Meta-analyses of discontinuation rates

Reasons for treatment discontinuation and overall loss to follow-up of venlafaxine compared to selective serotonin reuptake inhibitors

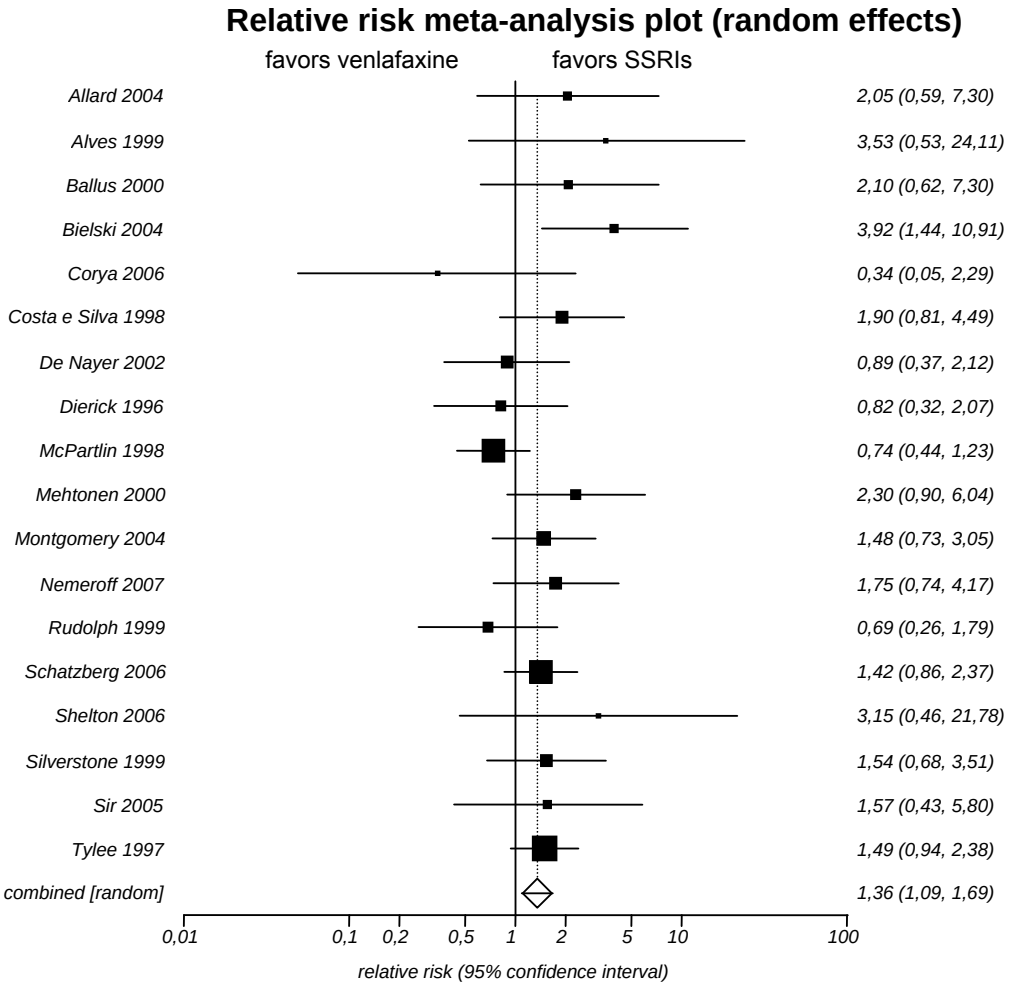
Reason (%)	Venlafaxine (N=1832)	Selective serotonin reuptake inhibitors (N=1825)	*P**
Overall loss to follow-up	449(24.5)	418 (22.9)	0.269
Adverse events	214 (11.2)	155(8.2)	< 0.001
Lack of efficacy	59 (3.7)[1]	82 (5.2)[2]	0.046

* Fisher's exact test; two-sided mid *P* value
[1] based on available data (59/1570)
[2] based on available data (82/1566)

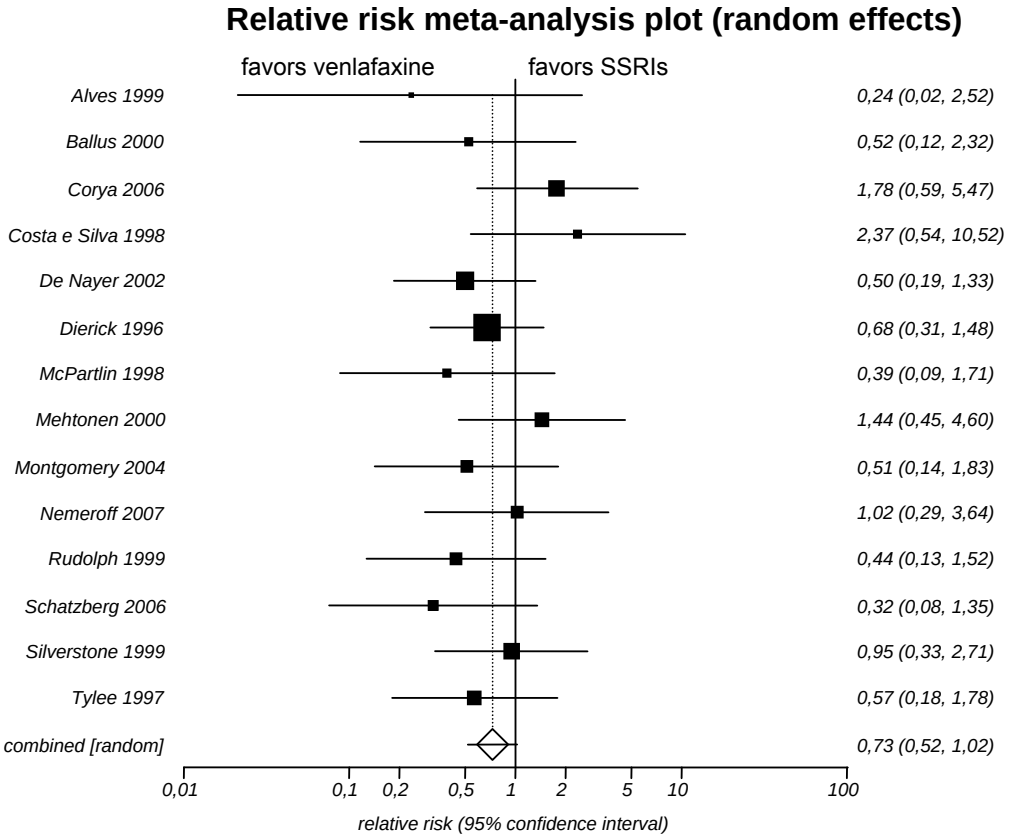
Relative risk meta-analysis of overall loss to follow-up comparing selective serotonin reuptake inhibitors to venlafaxine (random effects)



Relative risk meta-analysis of discontinuation rates due to adverse events comparing selective serotonin reuptake inhibitors to venlafaxine (random effects)



Relative risk meta-analysis of discontinuation rates due to lack of efficacy comparing selective serotonin reuptake inhibitors to venlafaxine (random effects)

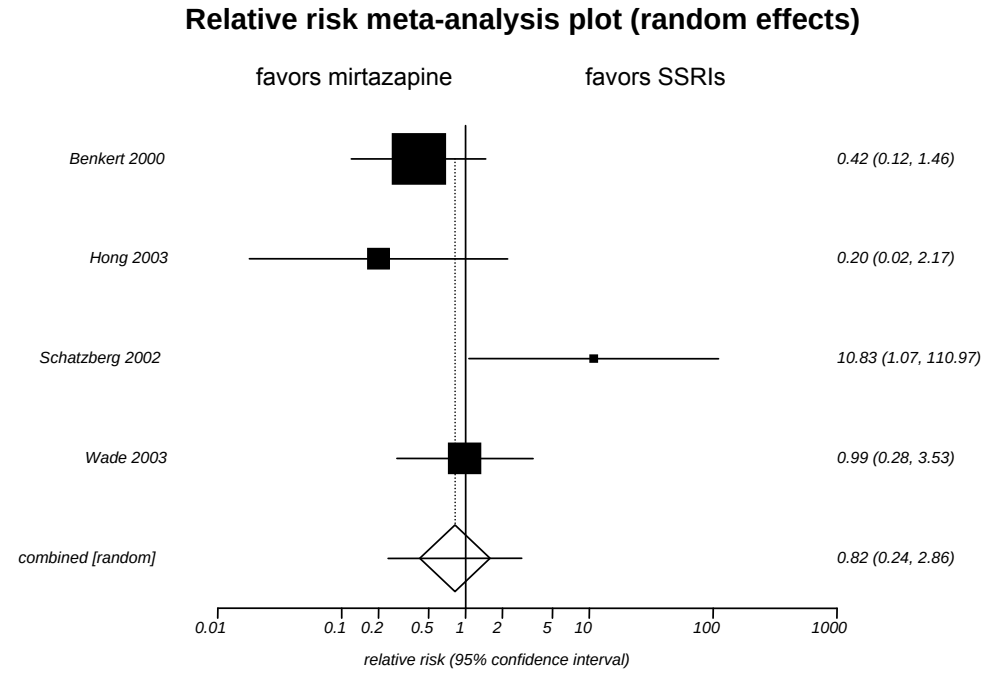


Reasons for treatment discontinuation and overall loss to follow-up of mirtazapine compared to selective serotonin reuptake inhibitors

Reason (%)	Mirtazapine (N= 608)	Selective serotonin reuptake inhibitors (N=596)	*P**
Overall loss to follow-up	182 (29.0)	185 (21.0)	0.677
Adverse events	86 (14.1)	80 (13.4)	0.718
Lack of efficacy	12 (2.0)	13 (2.2)	0.185

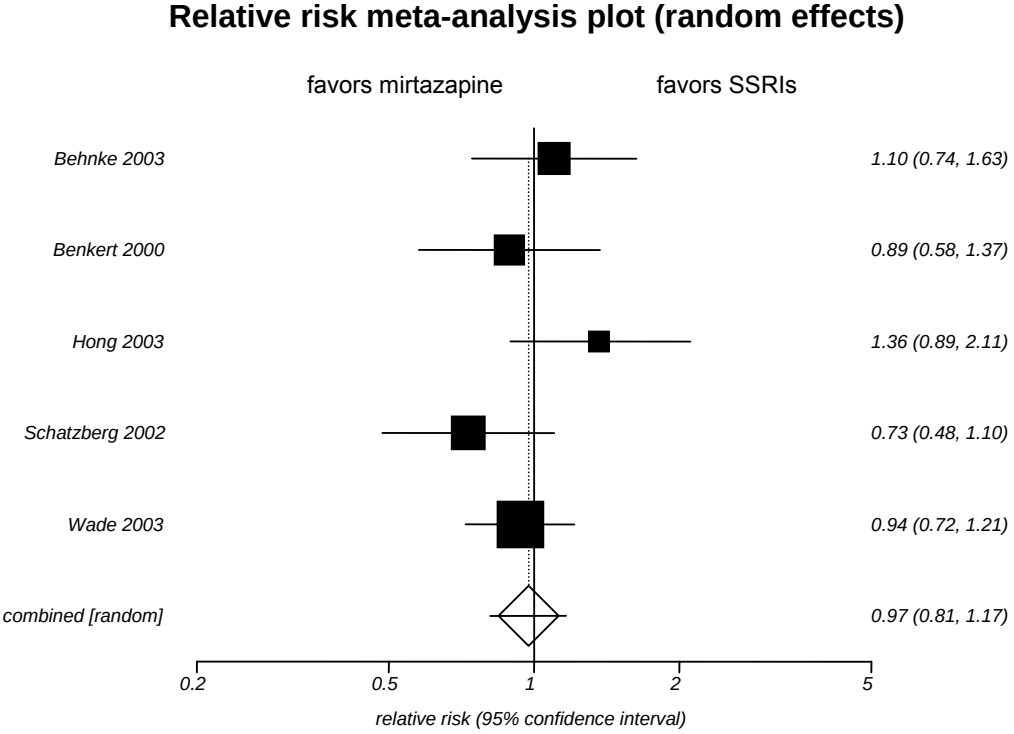
* Fisher's exact test; two-sided mid *P* value

Relative risk meta-analysis of overall loss to follow-up comparing selective serotonin reuptake inhibitors to mirtazapine



.

Relative risk meta-analysis of discontinuation rates due to lack of efficacy comparing selective serotonin reuptake inhibitors to mirtazapine

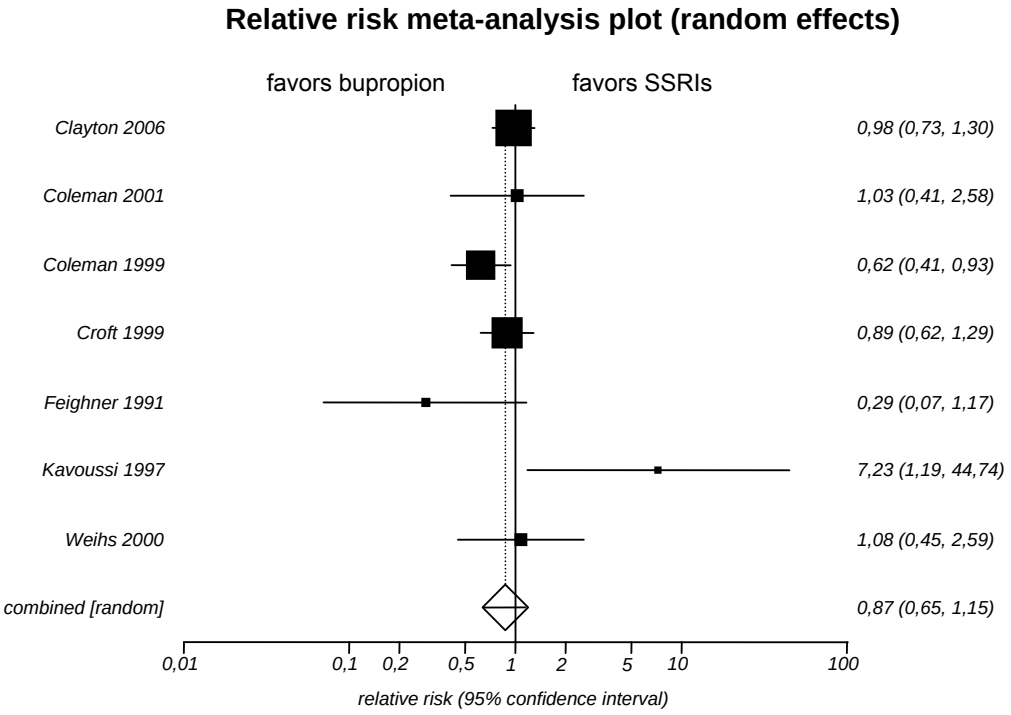


Reasons for treatment discontinuation and overall loss to follow-up of bupropion compared to selective serotonin reuptake inhibitors

Reason (%)	Bupropion (N= 899)	Selective serotonin reuptake inhibitors (N= 912)	*P**
Overall loss to follow-up	156 (17.3)	177 (19.4)	0.260
Adverse events	59 (6.6)	54 (5.9)	0.574
Lack of efficacy	18 (3.1)	24 (4.1)	0.379

* Fisher's exact test; two-sided mid *P* value

Relative risk meta-analysis of overall loss to follow-up comparing selective serotonin reuptake inhibitors to bupropion



Relative risk meta-analysis of discontinuation due to lack of efficacy comparing selective serotonin reuptake inhibitors to bupropion

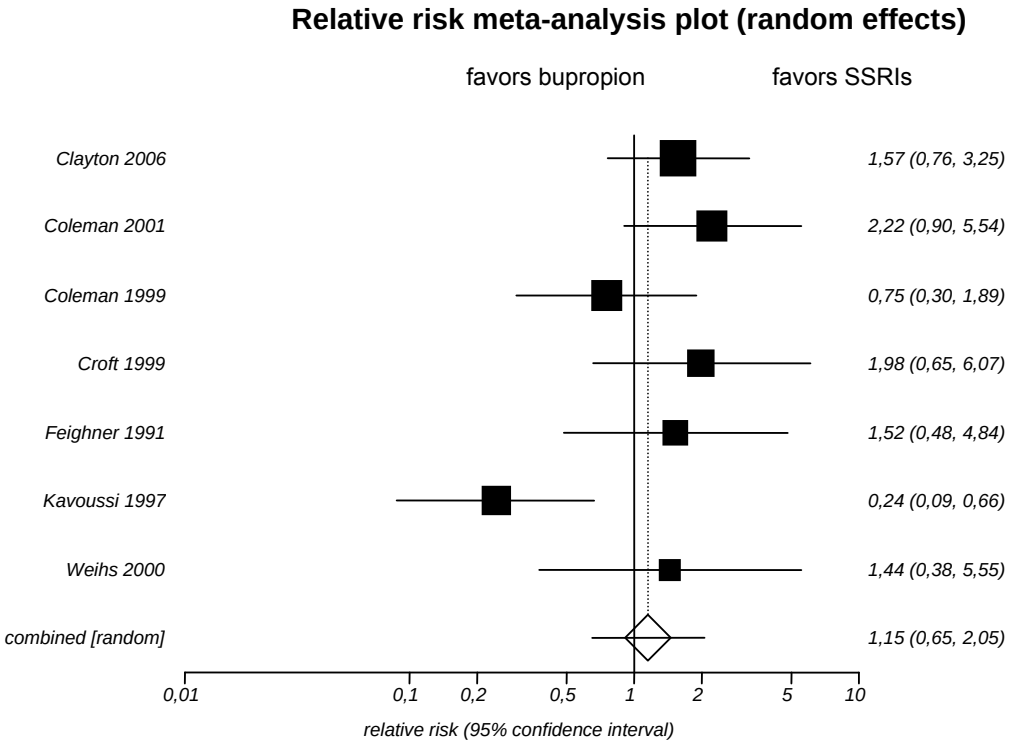
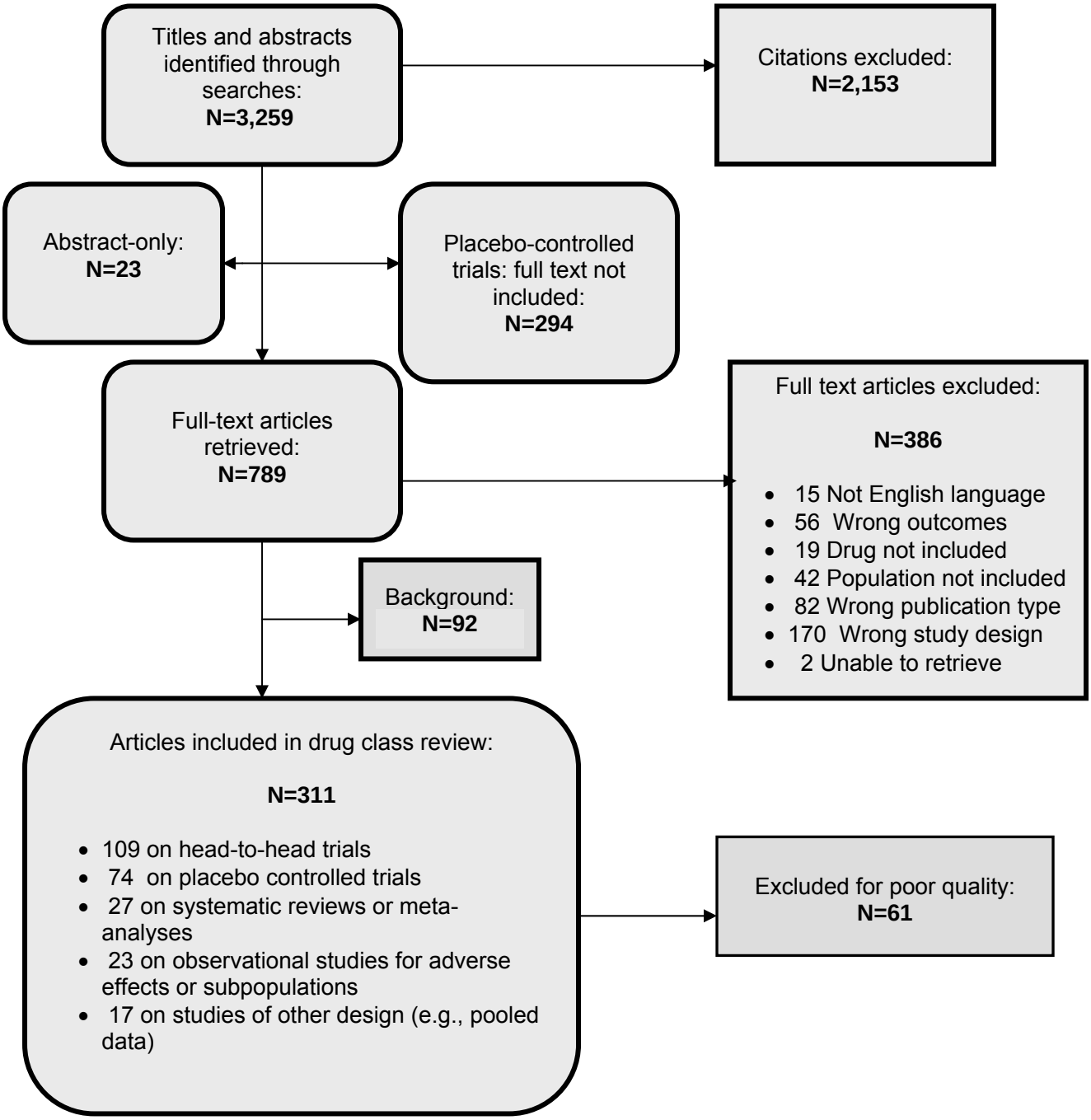


Figure 1. Results of literature search



REFERENCES

1. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994 Jan;51(1):8-19.
2. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003 Jun 18;289(23):3095-105.
3. Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry. 2003 Dec;64(12):1465-75.
4. US Food and Drug Administration. Electronic Orange Book. 2004(http://www.fda.gov/cder/ob/default.htm).
5. IMS Health. Press Release: Growth is sustained by new products despite a difficult year. IMS Reports 2004 February 17, 2004.
6. Williams JW, Mulrow CD, Chiquette E, Noel PH, Augilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Annals Internal Medicine. 2000 May 2;132(9):743-56.
7. Geddes JR, Freemantle N, Mason J, Eccles MP, Boynton J. Selective serotonin reuptake inhibitors (SSRIs) versus other antidepressants for depression. The Cochrane Library (Cochrane Review). 2004 Nov(1).
8. Hoagwood K, Hibbs E, Brent D, Jensen P. Introduction to the special section: efficacy and effectiveness in studies of child and adolescent psychotherapy. J Consult Clin Psychol. 1995 Oct;63(5):683-7.
9. Balk EM, Lau J, Bonis PA. Reading and critically appraising systematic reviews and meta-analyses: a short primer with a focus on hepatology. J Hepatol. 2005;43(4):729-36.
10. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35.
11. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition) 2001.
12. Egger M, Smith GD, Altman DG. Systematic Reviews in Health Care (2nd edition) 2001.
13. Ontiveros A, Garcia-Barriga C. A double-blind, comparative study of paroxetine and fluoxetine in out-patients with depression. British Journal of Clinical Research. 1997 1997:23-32.
14. Colonna L, Reines EH, Andersen HF. Escitalopram is well tolerated and more efficacious than citalopram in long-term treatment of moderately depressed patients. Int J Psychiatry Clin Pract. 2002;6:243-44.
15. Gartlehner G, Hansen RA, Thieda P, DeVeaugh-Geiss AM, Gaynes BN, Krebs EE, et al. Comparative Effectiveness of Second-generation Antidepressants in the Pharmacologic Treatment of Adult Depression. Comparative Effectiveness Review No. 7. (Prepared by RTI-UNC under Contract No. 290-02-0016.) Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. 2007.

16. Katzman MA, Tricco AC, McIntosh D, Filteau MJ, Bleau P, Chokka PR, et al. Paroxetine versus placebo and other agents for depressive disorders: a systematic review and meta-analysis. J Clin Psychiatry. 2007 Dec;68(12):1845-59.
17. Weinmann S, Becker T, Koesters M. Re-evaluation of the efficacy and tolerability of venlafaxine vs SSRI: meta-analysis. Psychopharmacology (Berl). 2008 Mar;196(4):511-20; discussion 21-2.
18. Eckert L, Falissard B. Using meta-regression in performing indirect-comparisons: comparing escitalopram with venlafaxine XR. Curr Med Res Opin. 2006 Nov;22(11):2313-21.
19. Nierenberg AA, Greist JH, Mallinckrodt CH, Prakash A, Sambunaris A, Tollefson GD, et al. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. Curr Med Res Opin. 2007 Feb;23(2):401-16.
20. Ventura D, Armstrong EP, Skrepnek GH, Haim Erder M. Escitalopram versus sertraline in the treatment of major depressive disorder: a randomized clinical trial. Curr Med Res Opin. 2007 Feb;23(2):245-50.
21. Shelton RC, Haman KL, Rapaport MH, Kiev A, Smith WT, Hirschfeld RM, et al. A randomized, double-blind, active-control study of sertraline versus venlafaxine XR in major depressive disorder. J Clin Psychiatry. 2006 Nov;67(11):1674-81.
22. Lee P, Shu L, Xu X, Wang CY, Lee MS, Liu CY, et al. Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil. Psychiatry Clin Neurosci. 2007 Jun;61(3):295-307.
23. Perahia DG, Wang F, Mallinckrodt CH, Walker DJ, Detke MJ. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Psychiatry. 2006 Sep;21(6):367-78.
24. Wade A, Gembert K, Florea I. A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. Curr Med Res Opin. 2007 Jul;23(7):1605-14.
25. Khan A, Bose A, Alexopoulos GS, Gommoll C, Li D, Gandhi C. Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. Clin Drug Investig. 2007;27(7):481-92.
26. Clayton AH, Croft HA, Horrigan JP, Wightman DS, Krishen A, Richard NE, et al. Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. J Clin Psychiatry. 2006 May;67(5):736-46.
27. Boulenger JP, Huusom AK, Florea I, Baekdal T, Sarchiapone M. A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients. Curr Med Res Opin. 2006 Jul;22(7):1331-41.
28. Baldwin DS, Cooper JA, Huusom AK, Hindmarch I. A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder. Int Clin Psychopharmacol. 2006 May;21(3):159-69.
29. Keller MB, Trivedi MH, Thase ME, Shelton RC, Kornstein SG, Nemeroff CB, et al. The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study: outcomes from the acute and continuation phases. Biol Psychiatry. 2007 Dec 15;62(12):1371-9.

30. Schatzberg A, Roose S. A double-blind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depression. Am J Geriatr Psychiatry. 2006 Apr;14(4):361-70.
31. Nemeroff CB, Thase ME, Group ES. A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. Journal of psychiatric research. 2007(3-4):351-9.
32. Corya SA, Williamson D, Sanger TM, Briggs SD, Case M, Tollefson G. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. Depress Anxiety. 2006;23(6):364-72.
33. Ekselius L, von Knorring L, Eberhard G. A double-blind multicenter trial comparing sertraline and citalopram in patients with major depression treated in general practice. Int Clin Psychopharmacol. 1997 Nov;12(6):323-31.
34. Sechter D, Troy S, Paternetti S, Boyer P. A double-blind comparison of sertraline and fluoxetine in the treatment of major depressive episode in outpatients. Eur Psychiatry. 1999 Mar;14(1):41-8.
35. Kroenke K, West SL, Swindle R, Gilsenan A, Eckert GJ, Dolor R, et al. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. JAMA. 2001 Dec 19;286(23):2947-55.
36. Lepola UM, Loft H, Reines EH. Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol. 2003 Jul;18(4):211-7.
37. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. 2002 Apr;63(4):331-6.
38. Colonna L, Andersen HF, Reines EH. A randomized, double-blind, 24-week study of escitalopram (10 mg/day) versus citalopram (20 mg/day) in primary care patients with major depressive disorder. Curr Med Res Opin. 2005 Oct;21(10):1659-68.
39. Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. Int Clin Psychopharmacol. 2005 May;20(3):131-7.
40. Yevtushenko VY, Belous AI, Yevtushenko YG, Gusinin SE, Buzik OJ, Agibalova TV. Efficacy and tolerability of escitalopram versus citalopram in major depressive disorder: a 6-week, multicenter, prospective, randomized, double-blind, active-controlled study in adult outpatients. Clin Ther. 2007 Nov;29(11):2319-32.
41. FDA Center for Drug Evaluation and Research. Statistical Review of NDA 21-323 (Escitalopram Oxalate). http://www.fda.gov/cder/foi/nda/2002/21-323.pdf_Lexapro_Statr.pdf. 2001.
42. Lader M, Andersen HF, Baekdal T. The effect of escitalopram on sleep problems in depressed patients. Hum Psychopharmacol. 2005 Jul;20(5):349-54.
43. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003 May;41(5):582-92.
44. Patris M, Bouchard JM, Bougerol T, Charbonnier JF, Chevalier JF, Clerc G, et al. Citalopram versus fluoxetine: a double-blind, controlled, multicentre, phase III trial in patients with unipolar major depression treated in general practice. Int Clin Psychopharmacol. 1996 Jun;11(2):129-36.
45. Kasper S, de Swart H, Friis Andersen H. Escitalopram in the treatment of depressed elderly patients. Am J Geriatr Psychiatry. 2005 Oct;13(10):884-91.

46. Dalery J, Honig A. Fluvoxamine versus fluoxetine in major depressive episode: a double-blind randomised comparison. Hum Psychopharmacol. 2003 2003 Jul;18(5):379-84.
47. Rapaport M, Coccaro E, Sheline Y, Perse T, Holland P, Fabre L, et al. A comparison of fluvoxamine and fluoxetine in the treatment of major depression. J Clin Psychopharmacol. 1996 Oct;16(5):373-8.
48. Cassano GB, Puca F, Scapicchio PL, Trabucchi M. Paroxetine and fluoxetine effects on mood and cognitive functions in depressed nondemented elderly patients. J Clin Psychiatry. 2002 May;63(5):396-402.
49. Chouinard G, Saxena B, Belanger MC, Ravindran A, Bakish D, Beauclair L, et al. A Canadian multicenter, double-blind study of paroxetine and fluoxetine in major depressive disorder. J Affect Disord. 1999 Jul;54(1-2):39-48.
50. De Wilde J, Spiers R, Mertens C, Bartholome F, Schotte G, Leyman S. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. Acta Psychiatr Scand. 1993 Feb;87(2):141-5.
51. Schone W, Ludwig M. A double-blind study of paroxetine compared with fluoxetine in geriatric patients with major depression. J Clin Psychopharmacol. 1993 Dec;13(6 Suppl 2):34S-9S.
52. Fava M, Amsterdam JD, Deltito JA, Salzman C, Schwaller M, Dunner DL. A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression. Ann Clin Psychiatry. 1998 Dec;10(4):145-50.
53. Fava M, Hoog SL, Judge RA, Kopp JB, Nilsson ME, Gonzales JS. Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia. J Clin Psychopharmacol. 2002 Apr;22(2):137-47.
54. Gagiano CA. A double blind comparison of paroxetine and fluoxetine in patients with major depression. British Journal of Clinical Research. 1993 1993;4:145-52.
55. Bennie EH, Mullin JM, Martindale JJ. A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. J Clin Psychiatry. 1995 Jun;56(6):229-37.
56. Thompson C. Management of depression in real-life settings: knowledge gained from large-scale clinical trials. Int Clin Psychopharmacol. 1994 Jun;9 Suppl 3:21-5.
57. Newhouse PA, Krishnan KR, Doraiswamy PM, Richter EM, Batzar ED, Clary CM. A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. J Clin Psychiatry. 2000 Aug;61(8):559-68.
58. Boyer P, Danion JM, Bisserbe JC, Hotton JM, Troy S. Clinical and economic comparison of sertraline and fluoxetine in the treatment of depression. A 6-month double-blind study in a primary-care setting in France. Pharmacoeconomics. 1998 Jan;13(1 Pt 2):157-69.
59. Finkel SI, Richter EM, Clary CM, Batzar E. Comparative efficacy of sertraline vs. fluoxetine in patients age 70 or over with major depression. Am J Geriatr Psychiatry. 1999 Summer;7(3):221-7.
60. Kiev A, Feiger A. A double-blind comparison of fluvoxamine and paroxetine in the treatment of depressed outpatients. J Clin Psychiatry. 1997 Apr;58(4):146-52.
61. Ushiroyama T, Ikeda A, Ueki M. Evaluation of double-blind comparison of fluvoxamine and paroxetine in the treatment of depressed outpatients in menopause transition. J Med. 2004;35(1-6):151-62.
62. Aberg-Wistedt A, Agren H, Ekselius L, Bengtsson F, Akerblad AC. Sertraline versus paroxetine in major depression: clinical outcome after six months of continuous therapy. J Clin Psychopharmacol. 2000 Dec;20(6):645-52.

63. Nemeroff CB, Ninan PT, Ballenger J, Lydiard RB, Feighner J, Patterson WM, et al. Double-blind multicenter comparison of fluvoxamine versus sertraline in the treatment of depressed outpatients. 1995 1995;3:163-69.
64. Franchini L, Gasperini M, Perez J, Smeraldi E, Zanardi R. A double-blind study of long-term treatment with sertraline or fluvoxamine for prevention of highly recurrent unipolar depression. J Clin Psychiatry. 1997 March;58(3):104-7.
65. Franchini L, Gasperini M, Zanardi R, Smeraldi E. Four-year follow-up study of sertraline and fluvoxamine in long-term treatment of unipolar subjects with high recurrence rate. J Affect Disord. 2000 Jun;58(3):233-6.
66. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. J Clin Psychiatry. 2002 Mar;63(3):225-31.
67. Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Neuropsychopharmacol. 2004 Dec;14(6):457-70.
68. Hong CJ, Hu WH, Chen CC, Hsiao CC, Tsai SJ, Ruwe FJ. A double-blind, randomized, group-comparative study of the tolerability and efficacy of 6 weeks' treatment with mirtazapine or fluoxetine in depressed Chinese patients. J Clin Psychiatry. 2003 Aug;64(8):921-6.
69. Schatzberg AF, Kremer C, Rodrigues HE, Murphy GMJ. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. Am J Geriatr Psychiatry. 2002 Sep-Oct;10(5):541-50.
70. Benkert O, Szegedi A, Kohnen R. Mirtazapine compared with paroxetine in major depression. J Clin Psychiatry. 2000 Sep;61(9):656-63.
71. Behnke K, Sogaard J, Martin S, Bauml J, Ravindran AV, Agren H, et al. Mirtazapine orally disintegrating tablet versus sertraline: a prospective onset of action study. J Clin Psychopharmacol. 2003 Aug;23(4):358-64.
72. Allard P, Gram L, Timdahl K, Behnke K, Hanson M, Sogaard J. Efficacy and tolerability of venlafaxine in geriatric outpatients with major depression: a double-blind, randomised 6-month comparative trial with citalopram. Int J Geriatr Psychiatry. 2004 Dec;19(12):1123-30.
73. Montgomery SA. Comparative efficacy and tolerability of escitalopram oxalate versus venlafaxine XR. Data on file @ Forest Labs. 2004.
74. Bielski RJ, Ventura D, Chang CC. A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. J Clin Psychiatry. 2004 Sep;65(9):1190-6.
75. Costa e Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. J Clin Psychiatry. 1998 Jul;59(7):352-7.
76. De Nayer A, Geerts S, Ruelens L, Schittecatte M, De Bleeker E, Van Eeckhoutte I, et al. Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety. Int J Neuropsychopharmacol. 2002 Jun;5(2):115-20.
77. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J Affect Disord. 1999 Dec;56(2-3):171-81.
78. Silverstone PH, Ravindran A. Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group. J Clin Psychiatry. 1999 Jan;60(1):22-8.

79. Silverstone PH, Salinas E. Efficacy of venlafaxine extended release in patients with major depressive disorder and comorbid generalized anxiety disorder. J Clin Psychiatry. 2001 Jul;62(7):523-9.
80. Alves C, Cachola I, Brandao J. Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. Primary Care Psychiatry. 1999 1999;5(2):57-63.
81. Dierick M, Ravizza L, Realini R, Martin A. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. Prog Neuropsychopharmacol Biol Psychiatry. 1996 Jan;20(1):57-71.
82. Tylee A, Beaumont G, Bowden MW, Reynolds A. A double-blind, randomized, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe depression in general practice. Primary Care Psychiatry. 1997 1997;3:51-8.
83. Smith D, Dempster C, Glanville J, Freemantle N, Anderson I. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. Br J Psychiatry. 2002 2002 May;180:396-404.
84. Ballus C, Quiros G, De Flores T, de la Torre J, Palao D, Rojo L, et al. The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder or dysthymia. Int Clin Psychopharmacol. 2000 Jan;15(1):43-8.
85. McPartlin GM, Reynolds A, Anderson C, Casoy J. A comparison of once-daily venlafaxine XR and paroxetine in depressed outpatients treated in general practice. Primary Care Psychiatry. 1998 1998;4(3):127-32.
86. Sir A, D'Souza RF, Uguz S, George T, Vahip S, Hopwood M, et al. Randomized Trial of Sertraline Versus Venlafaxine XR in Major Depression: Efficacy and Discontinuation Symptoms. J Clin Psychiatry. 2005 Oct;66(10):1312-20.
87. Mehtonen OP, Sogaard J, Roponen P, Behnke K. Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. Venlafaxine 631 Study Group. J Clin Psychiatry. 2000 Feb;61(2):95-100.
88. Nieuwstraten CE, Dolovich LR. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. Ann Pharmacother. 2001 Dec;35(12):1608-13.
89. Feighner JP, Gardner EA, Johnston JA, Batey SR, Khayrallah MA, Ascher JA, et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. J Clin Psychiatry. 1991 Aug;52(8):329-35.
90. Coleman CC, King BR, Bolden-Watson C, Book MJ, Segraves RT, Richard N, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin Ther. 2001 Jul;23(7):1040-58.
91. Weihs KL, Settle ECJ, Batey SR, Houser TL, Donahue RM, Ascher JA. Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. J Clin Psychiatry. 2000 Mar;61(3):196-202.
92. Doraiswamy PM, Khan ZM, Donahue RM, Richard NE. Quality of life in geriatric depression: a comparison of remitters, partial responders, and nonresponders. Am J Geriatr Psychiatry. 2001 Fall;9(4):423-8.
93. Kavoussi RJ, Segraves RT, Hughes AR, Ascher JA, Johnston JA. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. J Clin Psychiatry. 1997 Dec;58(12):532-7.
94. Croft H, Settle EJ, Houser T, Batey SR, Donahue RM, Ascher JA. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clin Ther. 1999 Apr;21(4):643-58.

95. Coleman CC, Cunningham LA, Foster VJ, Batey SR, Donahue RM, Houser TL, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. Ann Clin Psychiatry. 1999 Dec;11(4):205-15.
96. Gillin JC, Rapaport M, Erman MK, Winokur A, Albala BJ. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial. J Clin Psychiatry. 1997 May;58(5):185-92.
97. Armitage R, Yonkers K, Cole D, Rush AJ. A multicenter, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. J Clin Psychopharmacol. 1997 Jun;17(3):161-8.
98. Rush AJ, Armitage R, Gillin JC, Yonkers KA, Winokur A, Moldofsky H, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. Biol Psychiatry. 1998 Jul 1;44(1):3-14.
99. Baldwin DS, Hawley CJ, Abed RT, Maragakis BP, Cox J, Buckingham SA, et al. A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. J Clin Psychiatry. 1996 1996;57 Suppl 2:46-52.
100. Baldwin DS, Hawley CJ, Mellors K. A randomized, double-blind controlled comparison of nefazodone and paroxetine in the treatment of depression: safety, tolerability and efficacy in continuation phase treatment. J Psychopharmacol. 2001 Sep;15(3):161-5.
101. Feiger A, Kiev A, Shrivastava RK, Wisselink PG, Wilcox CX. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry. 1996 1996;57 Suppl 2:53-62.
102. Panzer MJ. Are SSRIs really more effective for anxious depression? Ann Clin Psychiatry. 2005 Jan-Mar;17(1):23-9.
103. Fava M, Judge R, Hoog SL, Nilsson ME, Koke SC. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. J Clin Psychiatry. 2000 2000 Nov;61(11):863-7.
104. Lepola U, Wade A, Andersen HF. Do equivalent doses of escitalopram and citalopram have similar efficacy? A pooled analysis of two positive placebo-controlled studies in major depressive disorder. Int Clin Psychopharmacol. 2004 May;19(3):149-55.
105. Montgomery SA, Huusom AK, Bothmer J. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. Neuropsychobiology. 2004;50(1):57-64.
106. Segraves RT, Kavoussi R, Hughes AR, Batey SR, Johnston JA, Donahue R, et al. Evaluation of sexual functioning in depressed outpatients: a double-blind comparison of sustained-release bupropion and sertraline treatment. J Clin Psychopharmacol. 2000 Apr;20(2):122-8.
107. Thase ME, Fava M, Halbreich U, Kocsis JH, Koran L, Davidson J, et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. Arch Gen Psychiatry. 1996 Sep;53(9):777-84.
108. Kocsis JH, Zisook S, Davidson J, Shelton R, Yonkers K, Hellerstein DJ, et al. Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: psychosocial outcomes. Am J Psychiatry. 1997 Mar;154(3):390-5.

109. Hellerstein DJ, Kocsis JH, Chapman D, Stewart JW, Harrison W. Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: effects on personality. Am J Psychiatry. 2000 Sep;157(9):1436-44.
110. Ravindran AV, Guelfi JD, Lane RM, Cassano GB. Treatment of dysthymia with sertraline: a double-blind, placebo-controlled trial in dysthymic patients without major depression. J Clin Psychiatry. 2000 Nov;61(11):821-7.
111. Barrett JE, Williams JWJ, Oxman TE, Frank E, Katon W, Sullivan M, et al. Treatment of dysthymia and minor depression in primary care: a randomized trial in patients aged 18 to 59 years. J Fam Pract. 2001 May;50(5):405-12.
112. Williams JWJ, Barrett J, Oxman T, Frank E, Katon W, Sullivan M, et al. Treatment of dysthymia and minor depression in primary care: A randomized controlled trial in older adults. JAMA. 2000 Sep 27;284(12):1519-26.
113. Devanand DP, Nobler MS, Cheng J, Turret N, Pelton GH, Roose SP, et al. Randomized, double-blind, placebo-controlled trial of fluoxetine treatment for elderly patients with dysthymic disorder. Am J Geriatr Psychiatry. 2005 Jan;13(1):59-68.
114. Vanelle JM, Attar-Levy D, Poirier MF, Bouhassira M, Blin P, Olie JP. Controlled efficacy study of fluoxetine in dysthymia. Br J Psychiatry. 1997 Apr;170:345-50.
115. Rocca P, Calvarese P, Faggiano F, Marchiaro L, Mathis F, Rivoira E, et al. Citalopram versus sertraline in late-life nonmajor clinically significant depression: a 1-year follow-up clinical trial. J Clin Psychiatry. 2005 Mar;66(3):360-9.
116. Judd LL, Rapaport MH, Yonkers KA, Rush AJ, Frank E, Thase ME, et al. Randomized, placebo-controlled trial of fluoxetine for acute treatment of minor depressive disorder. Am J Psychiatry. 2004 Oct;161(10):1864-71.
117. Moscovitch A, Blashko CA, Eagles JM, Darcourt G, Thompson C, Kasper S, et al. A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. Psychopharmacology (Berl). 2004 Feb;171(4):390-7.
118. Lam RW, Levitt AJ, Levitan RD, Enns MW, Morehouse R, Michalak EE, et al. The Can-SAD study: a randomized controlled trial of the effectiveness of light therapy and fluoxetine in patients with winter seasonal affective disorder. Am J Psychiatry. 2006 May;163(5):805-12.
119. Michalak EE, Murray G, Levitt AJ, Levitan RD, Enns MW, Morehouse R, et al. Quality of life as an outcome indicator in patients with seasonal affective disorder: results from the Can-SAD study. Psychol Med. 2007 May;37(5):727-36.
120. Ruhrmann S, Kasper S, Hawellek B, Martinez B, Hoflich G, Nickelsen T, et al. Effects of fluoxetine versus bright light in the treatment of seasonal affective disorder. Psychol Med. 1998 Jul;28(4):923-33.
121. Lam RW, Gorman CP, Michalon M, Steiner M, Levitt AJ, Corral MR, et al. Multicenter, placebo-controlled study of fluoxetine in seasonal affective disorder. Am J Psychiatry. 1995 Dec;152(12):1765-70.
122. Anonymous. Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants. 2004.
123. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet. 2004 Apr 24;363(9418):1341-5.
124. Usala T, Clavenna A, Zuddas A, Bonati M. Randomised controlled trials of selective serotonin reuptake inhibitors in treating depression in children and adolescents: A systematic review and meta-analysis. European Neuropsychopharmacology. 2008 01;18(1):62-73.

125. Hetrick SE, Merry S, McKenzie J, Sindahl P, Proctor M. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews. 2007(3).
126. Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. Am J Psychiatry. 2004 Jun;161(6):1079-83.
127. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. Jama. 2004 Aug 18;292(7):807-20.
128. March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. The Treatment for Adolescents With Depression Study (TADS): long-term effectiveness and safety outcomes. Arch Gen Psychiatry. 2007 Oct;64(10):1132-43.
129. Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry. 2001 Jul;40(7):762-72.
130. Berard R, Fong R, Carpenter DJ, Thomason C, Wilkinson C. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. J Child Adolesc Psychopharmacol. 2006 Feb-Apr;16(1-2):59-75.
131. Emslie GJ, Wagner KD, Kutcher S, Krulewicz S, Fong R, Carpenter DJ, et al. Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2006 Jun;45(6):709-19.
132. Wagner KD, Ambrosini P, Rynn M, Wohlberg C, Yang R, Greenbaum MS, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. JAMA. 2003 Aug 27;290(8):1033-41.
133. Wagner KD, Jonas J, Findling RL, Ventura D, Saikali K. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. J Am Acad Child Adolesc Psychiatry. 2006 Mar;45(3):280-8.
134. Mandoki MW, Tapia MR, Tapia MA, Sumner GS, Parker JL. Venlafaxine in the treatment of children and adolescents with major depression. Psychopharmacol Bull. 1997 1997;33(1):149-54.
135. Baldwin DS, Huusom AK, Maehlum E. Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, double-blind study. Br J Psychiatry. 2006 Sep;189:264-72.
136. Kim TS, Pae CU, Yoon SJ, Bahk WM, Jun TY, Rhee WI, et al. Comparison of venlafaxine extended release versus paroxetine for treatment of patients with generalized anxiety disorder. Psychiatry Clin Neurosci. 2006 Jun;60(3):347-51.
137. Ball SG, Kuhn A, Wall D, Shekhar A, Goddard AW. Selective serotonin reuptake inhibitor treatment for generalized anxiety disorder: a double-blind, prospective comparison between paroxetine and sertraline. J Clin Psychiatry. 2005 Jan;66(1):94-9.
138. Hartford J, Kornstein S, Liebowitz M, Pigott T, Russell J, Detke M, et al. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. Int Clin Psychopharmacol. 2007 May;22(3):167-74.

139. Allgulander C, Dahl AA, Austin C, Morris PL, Sogaard JA, Fayyad R, et al. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. Am J Psychiatry. 2004 Sep;161(9):1642-9.
140. Dahl AA, Ravindran A, Allgulander C, Kutcher SP, Justin C, Burt T. Sertraline in generalized anxiety disorder: efficacy in treating the psychic and somatic anxiety factors. Acta psychiatrica Scandinavica. 2005;111(6):429-35.
141. Brawman-Mintzer O, Knapp RG, Rynn M, Carter RE, Rickels K. Sertraline treatment for generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2006 Jun;67(6):874-81.
142. Bielski RJ, Bose A, Chang CC. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists. 2005;17(2):65-9.
143. Denys D, van Megen HJ, van der Wee N, Westenberg HG. A doubleblind switch study of paroxetine and venlafaxine in obsessivecompulsive disorder. J Clin Psychiatry. 2004 Jan;65(1):37-43.
144. Pallanti S, Quercioli L, Bruscoli M. Response acceleration with mirtazapine augmentation of citalopram in obsessive-compulsive disorder patients without comorbid depression: a pilot study. J Clin Psychiatry. 2004 Oct;65(10):1394-9.
145. Piccinelli M, Pini S, Bellantuono C, Wilkinson G. Efficacy of drug treatment in obsessive-compulsive disorder. A meta-analytic review. Br J Psychiatry. 1995 Apr;166(4):424-43.
146. Ackerman D, Greenland S. Multivariate meta-analysis of controlled drug studies for obsessive-compulsive disorder. Journal of Clinical Psychopharmacology. 2002 2002;22:309-17.
147. Stein DJ, Spadaccini E, Hollander E. Meta-analysis of pharmacotherapy trials for obsessive-compulsive disorder. International Clin Psychopharm. 1995 1995;10:11-8.
148. Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). Cochrane Database of Systematic Reviews. 2008(1).
149. Bergeron R, Ravindran AV, Chaput Y, Goldner E, Swinson R, van Ameringen MA, et al. Sertraline and fluoxetine treatment of obsessive-compulsive disorder: results of a double-blind, 6-month treatment study. J Clin Psychopharmacol. 2002 Apr;22(2):148-54.
150. Denys D, van der Wee N, van Megen HJ, Westenberg HG. A double blind comparison of venlafaxine and paroxetine in obsessive-compulsive disorder. J Clin Psychopharmacol. 2003 Dec;23(6):568-75.
151. Stein DJ, Andersen EW, Tonnoir B, Fineberg N. Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. Curr Med Res Opin. 2007 Apr;23(4):701-11.
152. Greist JH, Jenike MA, Robinson D, Rasmussen SA. Efficacy of fluvoxamine in obsessive-compulsive disorder: results of multicentre, double blind, placebo-controlled trial. Eur J Clin Res. 1995 1995;7:195-204.
153. Montgomery SA, Kasper S, Stein DJ, Bang Hedegaard K, Lemming OM. Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. Int Clin Psychopharmacol. 2001 Mar;16(2):75-86.
154. Goodman WK, Price LH, Rasmussen SA, Delgado PL, Heninger GR, Charney DS. Efficacy of fluvoxamine in obsessive-compulsive disorder. A double-blind comparison with placebo. Arch Gen Psychiatry. 1989 Jan;46(1):36-44.

155. Jenike MA, Hyman S, Baer L, Holland A, Minichiello WE, Buttolph L, et al. A controlled trial of fluvoxamine in obsessive-compulsive disorder: implications for a serotonergic theory. Am J Psychiatry. 1990 Sep;147(9):1209-15.
156. Mallya GK, K. W, C. W, al. e. Short- and long-term treatment of obsessive-compulsive disorder with fluvoxamine. Ann Clin Psychiatry. 1992 1992;4:77-80.
157. Goodman WK, Kozak MJ, Liebowitz M, White KL. Treatment of obsessive-compulsive disorder with fluvoxamine: a multicentre, double-blind, placebo-controlled trial. Int Clin Psychopharmacol. 1996 Mar;11(1):21-9.
158. Montgomery SA, McIntyre A, Osterheider M, Sarteschi P, Zitterl W, Zohar J, et al. A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. The Lilly European OCD Study Group. Eur Neuropsychopharmacol. 1993 Jun;3(2):143-52.
159. Tollefson GD, Rampey AHJ, Potvin JH, Jenike MA, Rush AJ, kominguez RA, et al. A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry. 1994 Jul;51(7):559-67.
160. Jenike MA, Baer L, Minichiello WE, Rauch SL, Buttolph ML. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. Am J Psychiatry. 1997 Sep;154(9):1261-4.
161. Chouinard G, Goodman W, Greist J, Jenike M, Rasmussen S, White K, et al. Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive disorder. Psychopharmacol Bull. 1990 1990;26(3):279-84.
162. Jenike MA, Baer L, Summergrad P, Minichiello WE, Holland A, Seymour R. Sertraline in obsessive-compulsive disorder: a double-blind comparison with placebo. Am J Psychiatry. 1990 Jul;147(7):923-28.
163. Greist J, Chouinard G, DuBoff E, Halaris A, Kim SW, Koran L, et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry. 1995 Apr;52(4):289-95.
164. Kronig MH, Apter J, Asnis G, Bystritsky A, Curtis G, Ferguson J, et al. Placebo-controlled, multicenter study of sertraline treatment for obsessive-compulsive disorder. J Clin Psychopharmacol. 1999 Apr;19(2):172-6.
165. Tenney NH, Denys DA, van Megen HJ, Glas G, Westenberg HG. Effect of a pharmacological intervention on quality of life in patients with obsessive-compulsive disorder. Int Clin Psychopharmacol. 2003 Jan;18(1):29-33.
166. Stahl SM, Gergel I, Li D. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2003 Nov;64(11):1322-7.
167. Perna G, Bertani A, Caldirola D, Smeraldi E, Bellodi L. A comparison of citalopram and paroxetine in the treatment of panic disorder: a randomized, single-blind study. Pharmacopsychiatry. 2001 May;34(3):85-90.
168. Bandelow B, Behnke K, Lenoir S, Hendriks GJ, Alkin T, Goebel C, et al. Sertraline versus paroxetine in the treatment of panic disorder: an acute, double-blind noninferiority comparison. J Clin Psychiatry. 2004 Mar;65(3):405-13.
169. Pollack MH, Lepola U, Koponen H, Simon NM, Worthington JJ, Emilien G, et al. A double-blind study of the efficacy of venlafaxine extended-release, paroxetine, and placebo in the treatment of panic disorder. Depress Anxiety. 2007;24(1):1-14.

170. Pollack M, Mangano R, Entsuah R, Tzanis E, Simon NM. A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. Psychopharmacology (Berl). 2007 Oct;194(2):233-42.
171. Black DW, Wesner R, Gabel J. The abrupt discontinuation of fluvoxamine in patients with panic disorder. J Clin Psychiatry. 1993 Apr;54(4):146-9.
172. Hoehn-Saric R, McLeod DR, Hipsley PA. Effect of fluvoxamine on panic disorder. J Clin Psychopharmacol. 1993 Oct;13(5):321-6.
173. Asnis GM, Hameedi FA, Goddard AW, Potkin SG, Black D, Jameel M, et al. Fluvoxamine in the treatment of panic disorder: a multi-center, double-blind, placebo-controlled study in outpatients. Psychiatry Res. 2001 Aug 5;103(1):1-14.
174. Black DW, Wesner R, Bowers W, Gabel J. A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder. Arch Gen Psychiatry. 1993 Jan;50(1):44-50.
175. Perahia DG, Pritchett YL, Kajdasz DK, Bauer M, Jain R, Russell JM, et al. A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. J Psychiatr Res. 2008 Jan;42(1):22-34.
176. Tucker P, Potter-Kimball R, Wyatt DB, Parker DE, Burgin C, Jones DE, et al. Can physiologic assessment and side effects tease out differences in PTSD trials? A double-blind comparison of citalopram, sertraline, and placebo. Psychopharmacol Bull. 2003 Summer;37(3):135-49.
177. McRae AL, Brady KT, Mellman TA, Sonne SC, Killeen TK, Timmerman MA, et al. Comparison of nefazodone and sertraline for the treatment of posttraumatic stress disorder. Depress Anxiety. 2004;19(3):190-6.
178. Saygin MZ, Sungur MZ, Sabol EU, C?etinkaya P. Nefazodone versus sertraline in treatment of posttraumatic stress disorder. Klinik Psikofarmakoloji Bulteni. 2002;12(1):1-5.
179. Davidson J, Rothbaum BO, Tucker P, Asnis G, Benattia I, Musgnung JJ. Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. J Clin Psychopharmacol. 2006 Jun;26(3):259-67.
180. Connor KM, Sutherland SM, Tupler LA, Malik ML, Davidson JR. Fluoxetine in post-traumatic stress disorder. Randomised, double-blind study. Br J Psychiatry. 1999 Jul;175:17-22.
181. Martenyi F, Brown EB, Caldwell CD. Failed efficacy of fluoxetine in the treatment of posttraumatic stress disorder: results of a fixed-dose, placebo-controlled study. J Clin Psychopharmacol. 2007 Apr;27(2):166-70.
182. van der Kolk BA, Spinazzola J, Blaustein ME, Hopper JW, Hopper EK, Korn DL, et al. A randomized clinical trial of eye movement desensitization and reprocessing (EMDR), fluoxetine, and pill placebo in the treatment of posttraumatic stress disorder: treatment effects and long-term maintenance. J Clin Psychiatry. 2007 Jan;68(1):37-46.
183. Davidson J, Baldwin D, Stein DJ, Kuper E, Benattia I, Ahmed S, et al. Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. Arch Gen Psychiatry. 2006 Oct;63(10):1158-65.
184. Allgulander C, Mangano R, Zhang J, Dahl AA, Lepola U, Sjodin I, et al. Efficacy of Venlafaxine ER in patients with social anxiety disorder: a double-blind, placebo-controlled, parallel-group comparison with paroxetine. Hum Psychopharmacol. 2004 Aug;19(6):387-96.
185. Lader M, Stender K, Burger V, Nil R. Efficacy and tolerability of escitalopram in 12 and 24week treatment of social anxiety disorder: randomised, doubleblind, placebo-controlled, fixed dose study. Depress Anxiety. 2004 2004;19(4):241-8.

186. Liebowitz MR, Gelenberg AJ, Munjack D. Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. Arch Gen Psychiatry. 2005 Feb;62(2):190-8.
187. van der Linden GJH, Stein DJ, van Balkom A. The efficacy of the selective serotonin reuptake inhibitors for social anxiety disorder (social phobia): a meta-analysis of randomised controlled trials. Int Clin Psychopharm. 2000.
188. Hedges DW, Brown BL, Shwalb DA, Godfrey K, Larcher AM. The efficacy of selective serotonin reuptake inhibitors in adult social anxiety disorder: a meta-analysis of double-blind, placebo-controlled trials. Journal of Psychopharmacology. 2007 Jan 2007;21(02698811):102-11.
189. Montgomery SA, Nil R, Durr-Pal N, Loft H, Boulenger JP. A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder. J Clin Psychiatry. 2005 Oct;66(10):1270-8.
190. Kasper S, Stein DJ, Loft H, Nil R. Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study. Br J Psychiatry. 2005 Mar;186:222-6.
191. Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ. Fluoxetine in social phobia: a double-blind, placebo-controlled pilot study. J Clin Psychopharmacol. 2002 Jun;22(3):257-62.
192. Davidson JR, Foa EB, Huppert JD, Keefe FJ, Franklin ME, Compton JS, et al. Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. Arch Gen Psychiatry. 2004 Oct;61(10):1005-13.
193. Muehlbacher M, Nickel MK, Nickel C, Kettler C, Lahmann C, Pedrosa Gil F, et al. Mirtazapine treatment of social phobia in women: a randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2005 Dec;25(6):580-3.
194. Van Ameringen M, Mancini C, Oakman J, Walker J, Kjernisted K, Chokka P, et al. Nefazodone in the treatment of generalized social phobia: a randomized, placebo-controlled trial. J Clin Psychiatry. 2007 Feb;68(2):288-95.
195. Wyatt KM, Dimmock PW, O'Brien PM. Selective serotonin reuptake inhibitors for premenstrual syndrome. Cochrane Database Syst Rev. 2004(4):CD001396.
196. Dimmock PW, Wyatt KM, Jones PW, O' Brian PMS. Efficacy of selective serotonin inhibitors in premenstrual syndrome: a systematic review. The Lancet. 2000 2000;356:1131-6.
197. Freeman EW, Rickels K, Yonkers KA, Kunz NR, McPherson M, Upton GV. Venlafaxine in the treatment of premenstrual dysphoric disorder. Obstet Gynecol. 2001 Nov;98(5 Pt 1):737-44.
198. Landen M, Eriksson O, Sundblad C, Andersch B, Naessen T, Eriksson E. Compounds with affinity for serotonergic receptors in the treatment of premenstrual dysphoria: a comparison of buspirone, nefazodone and placebo. Psychopharmacology. 2001 2001;155:292-98.
199. Greist J, McNamara RK, Mallinckrodt CH, Rayamajhi JN, Raskin J. Incidence and duration of antidepressant-induced nausea: duloxetine compared with paroxetine and fluoxetine. Clin Ther. 2004 Sep;26(9):1446-55.
200. Mackay FJ, Dunn NR, Wilton LV, Pearce GL, Freemantle SN, Mann RD. A comparison of fluvoxamine, fluoxetine, sertraline and paroxetine examined by observational cohort studies. Pharmacoepid Drug Safety. 1997 1997;6:235-46.
201. Mackay FR, Dunn NR, Martin RM, Pearce GL, Freemantle SN, Mann RD. Newer antidepressants: a comparison of tolerability in general practice. Br J Gen Pract. 1999 Nov;49(448):892-6.
202. Haffmans PM, Timmerman L, Hoogduin CA. Efficacy and tolerability of citalopram in comparison with fluvoxamine in depressed outpatients: a double-blind, multicentre study. The LUCIFER Group. Int Clin Psychopharmacol. 1996 Sep;11(3):157-64.

203. Brambilla P, Cipriani A, Hotopf M, Barbui C. Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. Pharmacopsychiatry. 2005 Mar;38(2):69-77.
204. Meijer WE, Heerdink ER, van Eijk JT, Leufkens HG. Adverse events in users of sertraline: results from an observational study in psychiatric practice in The Netherlands. Pharmacoepidemiol Drug Saf. 2002 Dec;11(8):655-62.
205. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ. 2005 Feb 19;330(7488):385-9.
206. Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. Bmj. 2005 Feb 19;330(7488):389.
207. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ. Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. Am J Psychiatry. 2007 Jul;164(7):1044-9.
208. Schneider LS, Nelson JC, Clary CM, Newhouse P, Krishnan KR, Shiovitz T, et al. An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. Am J Psychiatry. 2003 Jul;160(7):1277-85.
209. Nelson JC, Delucchi K, Schneider L. Suicidal thinking and behavior during treatment with sertraline in late-life depression. Am J Geriatr Psychiatry. 2007 Jul;15(7):573-80.
210. Aursnes I, Tvete IF, Gaasemyr J, Natvig B. Suicide attempts in clinical trials with paroxetine randomised against placebo. BMC Med. 2005 Aug 22;3:14.
211. Isacsson G, Holmgren P, Ahlner J. Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. Acta Psychiatr Scand. 2005 Apr;111(4):286-90.
212. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry. 2006 Dec;63(12):1358-67.
213. Jick SS, Dean AD, Jick H. Antidepressants and suicide. BMJ. 1995 1995 Jan;310:215-8.
214. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. Jama. 2004 Jul 21;292(3):338-43.
215. Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry. 2003 Apr;160(4):790-92.
216. Lopez-Ibor JJ. Reduced suicidality with paroxetine. European Psychiatry. 1993 1993;8(Suppl 1):17S-9S.
217. Pedersen AG. Escitalopram and suicidality in adult depression and anxiety. Int Clin Psychopharmacol. 2005 May;20(3):139-43.
218. Acharya N, Rosen AS, Polzer JP, D'Souza DN, Perahia DG, Cavazzoni PA, et al. Duloxetine: meta-analyses of suicidal behaviors and ideation in clinical trials for major depressive disorder. J Clin Psychopharmacol. 2006 Dec;26(6):587-94.
219. Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. Bmj. 2005 Feb 19;330(7488):396.

220. Jick H, Ulcickas M, Dean A. Comparison of frequencies of suicidal tendencies among patients receiving fluoxetine, lofepramine, mianserin, or trazodone. Pharmacotherapy. 1992 1992;12(6):451-4.
221. Didham RC, McConnell DW, Blair HJ, Reith DM. Suicide and self-harm following prescription of SSRIs and other antidepressants: confounding by indication. Br J Clin Pharmacol. 2005 Nov;60(5):519-25.
222. Kukoyi O, Argo TR, Carnahan RM. Exacerbation of panic disorder with rifampin therapy in a patient receiving citalopram. Pharmacotherapy. 2005 Mar;25(3):435-7.
223. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006 Mar;63(3):332-9.
224. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. Jama. 2007 Apr 18;297(15):1683-96.
225. Emslie G, Kratochvil C, Vitiello B, Silva S, Mayes T, McNulty S, et al. Treatment for Adolescents with Depression Study (TADS): safety results. J Am Acad Child Adolesc Psychiatry. 2006 Dec;45(12):1440-55.
226. Valuck RJ, Libby AM, Sills MR, Giese AA, Allen RR. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. CNS Drugs. 2004;18(15):1119-32.
227. Ekselius L, von Knorring L. Effect on sexual function of long-term treatment with selective serotonin reuptake inhibitors in depressed patients treated in primary care. J Clin Psychopharmacol. 2001 Apr;21(2):154-60.
228. Landen M, Hogberg P, Thase ME. Incidence of sexual side effects in refractory depression during treatment with citalopram or paroxetine. J Clin Psychiatry. 2005 Jan;66(1):100-6.
229. Vanderkooy JD, Kennedy SH, Bagby RM. Antidepressant side effects in depression patients treated in a naturalistic setting: a study of bupropion, moclobemide, paroxetine, sertraline, and venlafaxine. Can J Psychiatry. 2002 Mar;47(2):174-80.
230. Kennedy SH, Fulton KA, Bagby RM, Greene AL, Cohen NL, Rafi-Tari S. Sexual function during bupropion or paroxetine treatment of major depressive disorder. Can J Psychiatry. 2006 Mar;51(4):234-42.
231. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. J Clin Psychiatry. 2001 2001;62 Suppl 3:10-21.
232. Clayton AH, Pradko JF, Croft HA, Montano CB, Leadbetter RA, Bolden-Watson C, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry. 2002 Apr;63(4):357-66.
233. Clayton A, Kornstein S, Prakash A, Mallinckrodt C, Wohlreich M. Changes in sexual functioning associated with duloxetine, escitalopram, and placebo in the treatment of patients with major depressive disorder. J Sex Med. 2007 Jul;4(4 Pt 1):917-29.
234. Maina G, Albert U, Salvi V, Bogetto F. Weight gain during long-term treatment of obsessive-compulsive disorder: a prospective comparison between serotonin reuptake inhibitors. J Clin Psychiatry. 2004 Oct;65(10):1365-71.
235. Croft H, Houser TL, Jamerson BD, Leadbetter R, Bolden-Watson C, Donahue R, et al. Effect on body weight of bupropion sustained-release in patients with major depression treated for 52 weeks. Clin Ther. 2002 Apr;24(4):662-72.

236. Alper K, Schwartz KA, Kolts RL, Khan A. Seizure Incidence in Psychopharmacological Clinical Trials: An Analysis of Food and Drug Administration (FDA) Summary Basis of Approval Reports. Biological Psychiatry. 2007;62(4):345-54.
237. Whyte IM, Dawson AH, Buckley NA. Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. QJM. 2003 May;96(5):369-74.
238. Thase ME. Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. J Clin Psychiatry. 1998 Oct;59(10):502-8.
239. Thase ME, Tran PV, Wiltse C, Pangallo BA, Mallinckrodt C, Detke MJ. Cardiovascular profile of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine. J Clin Psychopharmacol. 2005 Apr;25(2):132-40.
240. Raskin J, Wiltse CG, Dinkel JJ, Walker DJ, Desaiah D, Katona C. Safety and tolerability of duloxetine at 60 mg once daily in elderly patients with major depressive disorder. J Clin Psychopharmacol. 2008 Feb;28(1):32-8.
241. Kharofa J, Sekar P, Haverbusch M, Moomaw C, Woo D. Selective serotonin Reuptake inhibitors and risk of hemorrhagic stroke. Stroke. 2007;38:3049 - 51.
242. Liu BA, Mittmann N, Knowles SR, Shear NH. Hyponatremia and the syndrome of innappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: a review of spontaneous reports. CMAJ. 1996 Sep;155(5):519-27.
243. Stewart DE. Hepatic adverse reactions associated with nefazodone. Can J Psychiatry. 2002 May;47(4):375-7.
244. Buckley NA, McManus PR. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. BMJ. 2002 Dec 7;325(7376):1332-3.
245. Cipriani A, Barbui C, Brambilla P, Furukawa TA, Geddes JR, et al. Are all antidepressants really the same? The case of fluoxetine: A systematic review. Journal of Clinical Psychiatry. 2006 Jun 2006;67(01606689):850-64.
246. Pigott TA, Prakash A, Arnold LM, Aaronson ST, Wohlreich MM, et al. Duloxetine versus escitalopram and placebo: an 8-month, double-blind trial in patients with major depressive disorder. Current Medical Research and Opinion (England). 2007 Jun 2007;23(03007995):1303-18.
247. Coogan PF, Palmer JR, Strom BL, Rosenberg L. Use of selective serotonin reuptake inhibitors and the risk of breast cancer. Am J Epidemiol. 2005 Nov 1;162(9):835-8.
248. Dunner DL, Zisook S, Billow AA, Batey SR, Johnston JA, Ascher JA. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. J Clin Psychiatry. 1998 Jul;59(7):366-73.
249. Johnston JA, Lineberry CG, Ascher JA, Davidson J, Khayrallah MA, Feighner JP, et al. A 102-center prospective study of seizure in association with bupropion. J Clin Psychiatry. 1991 Nov;52(11):450-6.
250. Oslin DW, Ten Have TR, Streim JE, Datto CJ, Weintraub D, DiFilippo S, et al. Probing the safety of medications in the frail elderly: evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents. J Clin Psychiatry. 2003 Aug;64(8):875-82.
251. Entsuah AR, Huang H, Thase ME. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. J Clin Psychiatry. 2001 Nov;62(11):869-77.

252. Thase ME, Entsuah R, Cantillon M, Kornstein SG. Relative antidepressant efficacy of venlafaxine and SSRIs: sex-age interactions. J Womens Health (Larchmt). 2005 Sep;14(7):609-16.
253. Lewis-Fernandez R, Blanco C, Mallinckrodt CH, Wohlreich MM, Watkin JG, Plewes JM. Duloxetine in the treatment of major depressive disorder: comparisons of safety and efficacy in U.S. Hispanic and majority Caucasian patients. J Clin Psychiatry. 2006 Sep;67(9):1379-90.
254. Bailey RK, Mallinckrodt CH, Wohlreich MM, Watkin JG, Plewes JM. Duloxetine in the treatment of major depressive disorder: comparisons of safety and efficacy. J Natl Med Assoc. 2006 Mar;98(3):437-47.
255. Wagner GJ, Maguen S, Rabkin JG. Ethnic differences in response to fluoxetine in a controlled trial with depressed HIV-positive patients. Psychiatr Serv. 1998 Feb;49(2):239-40.
256. Roy-Byrne PP, Perera P, Pitts CD, Christi JA. Paroxetine Response and Tolerability Among Ethnic Minority Patients With Mood or Anxiety Disorders: A Pooled Analysis. J Clin Psychiatry. 2005 Oct;66(10):1228-33.
257. Lesser IM, Castro DB, Gaynes BN, Gonzalez J, Rush AJ, Alpert JE, et al. Ethnicity/race and outcome in the treatment of depression: results from STAR*D. Med Care. 2007 Nov;45(11):1043-51.
258. Clayton AH, Stewart RS, Fayyad R, Clary CM. Sex differences in clinical presentation and response in panic disorder: pooled data from sertraline treatment studies. Arch Women Ment Health. 2005 Nov 15.
259. Stewart DE, Wohlreich MM, Mallinckrodt CH, Watkin JG, Kornstein SG. Duloxetine in the treatment of major depressive disorder: comparisons of safety and tolerability in male and female patients. J Affect Disord. 2006 Aug;94(1-3):183-9.
260. Abarca J, Malone DC, Armstrong EP, Grizzle AJ, Hansten PD, Van Bergen RC, et al. Concordance of severity ratings provided in four drug interaction compendia. J Am Pharm Assoc (Wash DC). 2004 Mar-Apr;44(2):136-41.
261. Wernicke JF, Sayler ME, Koke SC, Pearson DK, Tollefson GD. Fluoxetine and concomitant centrally acting medication use during clinical trials of depression: the absence of an effect related to agitation and suicidal behavior. Depress Anxiety. 1997 1997;6(1):31-9.
262. Harvey AT, Preskorn SH. Cytochrome P450 Enzymes: interpretation of their interactions with selective serotonin reuptake inhibitors. J Clin Psychopharmacol. 1996 Oct;16(5):345-55.
263. Sproule BA, Naranjo CA, Bremner KE, Hassan PC. Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. Clin Pharmacokinet. 1997 Dec;33(6):454-71.
264. Cornelius JR, Salloum IM, Ehler JG, Jarrett PJ, Cornelius MD, Perel JM, et al. Fluoxetine in depressed alcoholics. A double-blind, placebo-controlled trial. Arch Gen Psychiatry. 1997 Aug;54(8):700-5.
265. Cornelius JR, Salloum IM, Thase ME, Haskett RF, Daley DC, Jones-Barlock A, et al. Fluoxetine versus placebo in depressed alcoholic cocaine abusers. Psychopharmacol Bull. 1998 1998;34(1):117-21.
266. Cornelius JR, Salloum IM, Haskett RF, Daley DC, Cornelius MD, Thase ME, et al. Fluoxetine versus placebo in depressed alcoholics: a 1-year follow-up study. Addict Behav. 2000 Mar-Apr;25(2):307-10.
267. Petrakis I, Carroll KM, Nich C, Gordon L, Kosten T, Rounsaville B. Fluoxetine treatment of depressive disorders in methadone-maintained opioid addicts. Drug Alcohol Depend. 1998 May 1;50(3):221-6.

268. Schmitz JM, Averill P, Stotts AL, Moeller FG, Rhoades HM, Grabowski J. Fluoxetine treatment of cocaine-dependent patients with major depressive disorder. Drug Alcohol Depend. 2001 Aug 1;63(3):207-14.
269. Riggs PD, Mikulich-Gilbertson SK, Davies RD, Lohman M, Klein C, Stover SK. A randomized controlled trial of fluoxetine and cognitive behavioral therapy in adolescents with major depression, behavior problems, and substance use disorders. Arch Pediatr Adolesc Med. 2007 Nov;161(11):1026-34.
270. Hernandez-Avila CA, Modesto-Lowe V, Feinn R, Kranzler HR. Nefazodone treatment of comorbid alcohol dependence and major depression. Alcohol Clin Exp Res. 2004 Mar;28(3):433-40.
271. Book SW, Thomas SE, Randall PK, Randall CL. Paroxetine reduces social anxiety in individuals with a co-occurring alcohol use disorder. J Anxiety Disord. 2008;22(2):310-8.
272. Gual A, Balcells M, Torres M, Madrigal M, Diez T, Serrano L. Sertraline for the prevention of relapse in detoxicated alcohol dependent patients with a comorbid depressive disorder: a randomized controlled trial. Alcohol. 2003 Nov-Dec;38(6):619-25.
273. Moak DH, Anton RF, Latham PK, Voronin KE, Waid RL, Durazo-Arvizu R. Sertraline and cognitive behavioral therapy for depressed alcoholics: results of a placebo-controlled trial. J Clin Psychopharmacol. 2003 Dec;23(6):553-62.
274. Kranzler HR, Mueller T, Cornelius J, Pettinati HM, Moak D, Martin PR, et al. Sertraline treatment of co-occurring alcohol dependence and major depression. Journal of clinical psychopharmacology. 2006(1):13-20.
275. Nyth AL, Gottfries CG, Lyby K, Smedegaard-Andersen L, Gylding-Sabroe J, Kristensen M, et al. A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. Acta Psychiatr Scand. 1992 Aug;86(2):138-45.
276. Lyketsos CG, DelCampo L, Steinberg M, Miles Q, Steele CD, Munro C, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. Arch Gen Psychiatry. 2003 Jul;60(7):737-46.
277. Magai C, Kennedy G, Cohen CI, Gomberg D. A controlled clinical trial of sertraline in the treatment of depression in nursing home patients with late-stage Alzheimer's disease. Am J Geriatr Psychiatry. 2000 Winter;8(1):66-74.
278. Wise TN, Wiltse CG, Iosifescu DV, Sheridan M, Xu JY, Raskin J. The safety and tolerability of duloxetine in depressed elderly patients with and without medical comorbidity. Int J Clin Pract. 2007 Aug;61(8):1283-93.
279. Raskin J, Wiltse CG, Siegal A, Sheikh J, Xu J, Dinkel JJ, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. Am J Psychiatry. 2007 Jun;164(6):900-9.
280. Razavi D, Allilaire JF, Smith M, Salimpour A, Verra M, Desclaux B, et al. The effect of fluoxetine on anxiety and depression symptoms in cancer patients. Acta Psychiatr Scand. 1996 Sep;94(3):205-10.
281. Roscoe JA, Morrow GR, Hickok JT, Mustian KM, Griggs JJ, Matteson SE, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat. 2005 Feb;89(3):243-9.
282. Paile-Hyvärinen M, Wahlbeck K, Eriksson JG. Quality of life and metabolic status in mildly depressed patients with type 2 diabetes treated with paroxetine: a double-blind randomised placebo controlled 6-month trial. BMC family practice. 2007:34.

283. Rabkin JG, Wagner GJ, Rabkin R. Fluoxetine treatment for depression in patients with HIV and AIDS: a randomized, placebo-controlled trial. Am J Psychiatry. 1999 Jan;156(1):101-7.
284. Ehde DM, Kraft GH, Chwastiak L, Sullivan MD, Gibbons LE, Bombardier CH, et al. Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis. Gen Hosp Psychiatry. 2008 Jan-Feb;30(1):40-8.
285. Linden RD, Wilcox CS, Heiser JF, Cavanaugh E, Wisselink PG. Are selective serotonin reuptake inhibitors well tolerated in somatizing depressives? Psychopharmacol Bull. 1994 1994;30(2):151-6.
286. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. Stroke. 1994 Jun;25(6):1099-104.
287. Murray V, von Arbin M, Bartfai A, Berggren AL, Landtblom AM, Lundmark J, et al. Double-blind comparison of sertraline and placebo in stroke patients with minor depression and less severe major depression. J Clin Psychiatry. 2005 Jun;66(6):708-16.
288. Lesperance F, Frasure-Smith N, Koszycki D, Laliberte MA, van Zyl LT, Baker B, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. Jama. 2007 Jan 24;297(4):367-79.
289. Strik JJ, Honig A, Klinkenberg E, Dijkstra J, Jolles J. Cognitive performance following fluoxetine treatment in depressed patients post myocardial infarction. Acta Neuropsychiatrica. 2006(1):1-6.
290. Honig A, Kuyper AM, Schene AH, van Melle JP, de Jonge P, Tulner DM, et al. Treatment of post-myocardial infarction depressive disorder: a randomized, placebo-controlled trial with mirtazapine. Psychosom Med. 2007 Sep-Oct;69(7):606-13.
291. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JTJ, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA. 2002 Aug 14;288(6):701-9.
292. Krishnan KR, Doraiswamy PM, Clary CM. Clinical and treatment response characteristics of late-life depression associated with vascular disease: a pooled analysis of two multicenter trials with sertraline. Prog Neuropsychopharmacol Biol Psychiatry. 2001 Feb;25(2):347-61.
293. Bush DE, Ziegelstein RC, Patel UV, Thombs BD, Ford DE, Fauerbach JA, et al. Post-myocardial infarction depression. Evid Rep Technol Assess (Summ). 2005 May(123):1-8.
294. Gottlieb SS, Kop WJ, Thomas SA, Katzen S, Vesely MR, Greenberg N, et al. A double-blind placebo-controlled pilot study of controlled-release paroxetine on depression and quality of life in chronic heart failure. American heart journal. 2007(5):868-73.
295. Strik JJ, Honig A, Lousberg R, Lousberg AH, Cheriex EC, Tuynman-Qua HG, et al. Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind, placebo-controlled trial. Psychosom Med. 2000 Nov-Dec;62(6):783-9.
296. Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry. 1997 Nov;54(11):1031-7.
297. Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry. 2002 Oct;41(10):1205-15.

298. Liebowitz MR, Yeung PP, Entsuah R. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. J Clin Psychiatry. 2007 Nov;68(11):1663-72.
299. Septien-Velez L, Pitrosky B, Padmanabhan SK, Germain JM, Tourian KA. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. Int Clin Psychopharmacol. 2007 Nov;22(6):338-47.
300. DeMartinis NA, Yeung PP, Entsuah R, Manley AL. A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. J Clin Psychiatry. 2007 May;68(5):677-88.
301. Liebowitz MR, Manley AL, Padmanabhan SK, Ganguly R, Tummala R, Tourian KA. Efficacy, safety, and tolerability of desvenlafaxine 50 mg/day and 100 mg/day in outpatients with major depressive disorder. Curr Med Res Opin. 2008 May 27.

Appendix A. Search strategy

#1 Search "Antidepressive Agents, Second-Generation"[MeSH] = 2525

#4 Search Fluoxetine [mh] OR sertraline [mh] OR paroxetine [mh] OR citalopram [mh] OR fluvoxamine [mh] OR bupropion OR nefazodone OR mirtazapine OR venlafaxine OR escitalopram = 10788

#5 Search #1 OR #4 = 11409

#6 Search depressive disorder [mh] OR depression, involutional [mh] or bipolar disorder [mh] or anxiety disorders [mh] OR adjustment disorders [mh] OR premenstrual syndrome [mh] OR Cyclothymic Disorder [mh]= 85151

#7 Search #5 AND #6 = 4565

#8 Search #5 AND #6 Field: All Fields, Limits: All Adult: 19+ years, English, Randomized Controlled Trial, Human = 925

Adverse Events

#10 Search adverse events OR "drug hypersensitivity" [mh] OR "drug toxicity" [mh] OR hyponatremia [mh] OR seizures [mh] OR suicide [mh] OR "weight gain" OR "gastroesophogeal reflux" [mh] OR libido [mh] OR hepatoxicity OR hepatotoxicity Limits: All Adult: 19+ years, English, Human = 27,741

#11 Search #10 AND #7 = 89

Longitudinal Studies

14 Search "Longitudinal Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Case-Control Studies"[MeSH] OR "Comparative Study"[MeSH] OR observational studies = 378,645

#15 Search #14 AND #7 = 185

Drug Interactions

#20 Search "Drug Interactions"[MeSH] = 95,674

#21 Search #7 AND #20 = 292

#22 Search #7 AND #20 Field: All Fields, Limits: All Adult: 19+ years, English, Human = 201

Searches were done in other databases using similar terms, and all searches were compiled into one database. Total unduplicated records are reported below:

PUBMED = 1480
Cochrane = 105 records = 5 new records

EMBASE = 227 records = 14 new records

International Pharmaceutical Abstracts = 78 records = 24 new records

Psychological Abstracts = 55 records = 7 new records

Total unduplicated records across questions and databases = 1530

Searches for literature focused on children were conducted in PUBMED, using the following terms:

#1 Search "Depressive Disorder"[MeSH] OR "Depression, Involutional"[MeSH] = 42,589

#2 Search "Depressive Disorder"[MeSH] OR "Depression, Involutional"[MeSH] Field: All Fields, Limits: All Child: 0-18 years, English, Human = 7934

#3 Search #1 AND #2 Field: All Fields, Limits: All Child: 0-18 years, English, Randomized Controlled Trial, Human = 187

#4 Search #1 AND #2 Field: All Fields Limits: All Child: 0-18 years, English, Meta-Analysis, Human = 9

#5 Search #1 AND #2 Field: All Fields Limits: All Child: 0-18 years, English, Review, Human = 36

#6 Search adverse events OR "drug hypersensitivity" [mh] OR "drug toxicity" [mh] OR hyponatremia [mh] OR seizures [mh] OR suicide [mh] OR "weight gain" OR "gastroesophogeal reflux" [mh] OR libido [mh] OR hepatoxicity OR hepatotoxicity Limits: All Adult: 19+ years, English, Human = 27,741

#7 Search #2 AND #6 = 86

14 Search "Longitudinal Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Case-Control Studies"[MeSH] OR "Comparative Study"[MeSH] OR observational studies = 378,645

15 Search #14 AND #2 = 63

Total unduplicated records for children = 295.

Update 4

#1	Search "Antidepressive Agents, Second-Generation"[MeSH] OR Fluoxetine[mh] OR sertraline[mh] OR paroxetine[mh] OR citalopram[mh] OR fluvoxamine[mh] OR bupropion OR nefazodone OR mirtazapine OR venlafaxine OR escitalopram	16958
#2	Search depressive disorder [mh] OR depression, involutional [mh] OR anxiety disorders [mh] OR premenstrual syndrome [mh] OR "Seasonal Affective Disorder"[Mesh] OR minor depression	96479
#3	Search #1 and #2	6323
#4	Search #1 and #2 Limits: Entrez Date from 2006/04, Humans, English, All Adult: 19+ years	464
#5	Search #1 and #2 Limits: Entrez Date from 2006/04, Humans, Randomized Controlled Trial, English, All Adult: 19+ years	163
#6	Search adverse events OR "drug hypersensitivity" [mh] OR "drug toxicity" [mh] OR hyponatremia [mh] OR seizures [mh] OR suicide [mh] OR "weight gain" OR "gastroesophogeal reflux" [mh] OR libido [mh] OR hepatoxicity OR hepatotoxicity	204622
#7	Search #4 and #6	99
#8	Search "Longitudinal Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Case-Control Studies"[MeSH] OR "Comparative Study"[MeSH] OR observational studies	939733
#9	Search #4 AND #8	94
#10	Search "Drug Interactions"[MeSH]	114401
#11	Search #4 AND #10	15

Cochrane = 7 reviews, All New

EMBASE = 199 = 116 New

IPA = 80 = 51 New

PsycINFO = 31 = 19 New

Total Unduplicated Database = 463

MDD Peds update 4

#3	Search "Depressive Disorder"[Mesh] OR depression, involutional	56420
#4	Search "Depressive Disorder"[Mesh] OR depression, involutional Limits: Entrez Date from 2006/04, Humans, English, All Child: 0-18 years	1276
#5	Search "Depressive Disorder"[Mesh] OR depression, involutional Limits: Entrez Date from 2006/04, Humans, Meta-Analysis, Randomized Controlled Trial, Review, English, All Child: 0-18 years	263
#6	Search "adverse events" [tw] OR "Drug Hypersensitivity"[MeSH] OR "Drug	173943

	Toxicity"[MeSH] OR "Hyponatremia"[MeSH] OR "Seizures"[MeSH] OR "Suicide"[MeSH] OR "Weight Gain"[MeSH] OR "Gastroesophageal Reflux"[MeSH] OR "Libido"[MeSH] OR hepatoxicity [tw]	
#8	Search "Longitudinal Studies"[MeSH] OR ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH]) OR observational studies [tw] OR "Comparative Study"[MeSH]	931306
#10	Search "Drug Interactions"[MeSH]	114272
#12	Search "Antidepressive Agents, Second-Generation"[MeSH] OR "Fluoxetine"[MeSH] OR "Sertraline"[MeSH] OR "Paroxetine"[MeSH] OR "Citalopram"[MeSH] OR "Fluvoxamine"[MeSH] OR "Bupropion"[MeSH] OR "nefazodone"[Substance Name] OR "mirtazapine"[Substance Name] OR "venlafaxine"[Substance Name] OR "Citalopram"[MeSH]	15565
#13	Search #5 AND #12	58
#14	Search #4 AND #6 AND #12	31
#15	Search #4 AND #8 AND #12	20
#16	Search #4 AND #10 AND #12	2

Cochrane = 1 = 0 New

EMBASE = 60 = 23 New

IPA = 14 = 12 New

PsycINFO = 40 = 25 New

Total Unduplicated Database = 134

April 2008 update search

#1	Search "Antidepressive Agents, Second-Generation"[MeSH] OR Fluoxetine[mh] OR sertraline[mh] OR paroxetine[mh] OR citalopram[mh] OR fluvoxamine[mh] OR bupropion OR nefazodone OR mirtazapine OR venlafaxine OR escitalopram	17187
#2	Search depressive disorder [mh] OR depression, involutional [mh] OR anxiety disorders [mh] OR premenstrual syndrome [mh] OR "Seasonal Affective Disorder"[Mesh] OR minor depression	97552
#3	Search #1 AND #2	6386
#4	Search #1 AND #2 Limits: added to PubMed in the last 1 year, Humans, English, All Adult: 19+ years	182
#6	Search ("Randomized Controlled Trial "[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh]) OR single blind method OR double blind method OR random allocation Limits: added to PubMed in the last 1 year, Humans, English, All Adult: 19+ years	9813

#7	Search #4 AND #6 Limits: added to PubMed in the last 1 year, Humans, English, All Adult: 19+ years	76
#8	Search adverse events OR "drug hypersensitivity" [mh] OR "drug toxicity" [mh] OR hyponatremia [mh] OR seizures [mh] OR suicide [mh] OR "weight gain" OR "gastroesophogeal reflux" [mh] OR libido [mh] OR hepatoxicity OR hepatotoxicity Limits: added to PubMed in the last 1 year, Humans, English, All Adult: 19+ years	4545
#9	Search #4 AND #8 Limits: added to PubMed in the last 1 year, Humans, English, All Adult: 19+ years	44
#10	Search "Longitudinal Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Case-Control Studies"[MeSH] OR "Comparative Study"[MeSH] OR observational studies Limits: added to PubMed in the last 1 year, Humans, English, All Adult: 19+ years	34365
#11	Search #4 AND #10 Limits: added to PubMed in the last 1 year, Humans, English, All Adult: 19+ years	44
#12	Search "Drug Interactions"[MeSH] Limits: added to PubMed in the last 1 year, Humans, English, All Adult: 19+ years	484
#13	Search #4 AND #12 Limits: added to PubMed in the last 1 year, Humans, English, All Adult: 19+ years	5

PUBMED = 26

Cochrane = 2 reviews = 1 new

ScienceDirect = 100 = 61 new

IPA = 6 = 6 new

PsycINFO = 26 = 4 New

Total Unduplicated Database = 103

Appendix B. Methods for Drug Class Reviews for Oregon Health Plan Practitioner-Managed Prescription Drug Plan; Oregon Health and Science University Evidence-based Practice Center

Quality Criteria

Assessment of Internal Validity

To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination.

For Controlled Trials

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alteration, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alteration, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
    - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it? (i.e., number assigned to each group, number of subjects who finished in each group, and their results)

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition)

Appendix C. Characteristics of excluded studies for poor quality

Study	Design	Sample size	Intervention	Reason for exclusion
Major depressive disorder				
Aguglia et al. 1993[1]	RCT	108	Sertraline vs. fluoxetine	High loss to follow-up; High differential loss to follow-up
Amini et al. 2005[2]	RCT	36	Mirtazapine vs. fluoxetine	No ITT analysis
Benkert et al. 2006[3]	RCT	242	Mirtazapine vs. venlafaxine	High attrition; no baseline characteristics
Cookson et al. 2006[4]	Pooled analysis	2656	Duloxetine vs. fluoxetine, paroxetine & placebo	No systematic literature search
Davidson et al. 2002[5]	Pooled analysis	1097	Venlafaxine vs. fluoxetine	No systematic literature search
Feiger et al. 2003[6]	Pooled analysis	1088	Sertraline vs. fluoxetine	No systematic literature search
Flament et al. 2001[7]	RCT	286	Sertraline vs. fluoxetine	No ITT analysis
Goldstein et al. 2004[8]	RCT	353	Duloxetine vs. Paroxetine	High loss to follow-up
Gorman et al. 2002[9]	Meta-analysis	1321	Escitalopram vs. citalopram	No systematic literature search
Grigoriadis et al. 2003[10]	Observational	201	Citalopram vs. fluoxetine	No ITT analysis
Lapierre et al. 1987[11]	RCT	63	Fluvoxamine vs. placebo	No ITT analysis
Llorca et al. 2005[12]	Pooled analysis	506	Escitalopram vs. citalopram	No systematic literature search
March et al. 1990[13]	RCT	54	Fluvoxamine vs. placebo	No ITT analysis
Papakostas et al. 2007[14]	Systematic review	988	Trazodone & nefazodone vs. SSRIs	No quality appraisal
Papakostas et al. 2007[15]	Pooled analysis	1672	Bupropion vs. SSRIs	No systematic literature search
Papakostas et al. 2008[16]	Pooled analysis	2890	Bupropion vs. SSRIs	No systematic literature search
Perahia et al. 2008[17]	Pooled analysis	667	Duloxetine vs. venlafaxine	No systematic literature search
Shelton et al. 2005[18]	Pooled analysis	1391	Venlafaxine vs. Fluoxetine and paroxetien	No systematic literature search
Stahl et al. 2000[19]	RCT	323	Citalopram vs. sertraline vs. placebo	High loss to follow-up
Stahl et al. 2002[20]	Pooled analysis	1622	Venlafaxine fluoxetine paroxetine placebo	No systematic literature search
Thase et al.	Pooled	2117	Venlafaxine vs.	No systematic literature

Study	Design	Sample size	Intervention	Reason for exclusion
2001[21]	analysis		SSRI vs. placebo	search
Thase et al, 2005[22]	Meta-analysis	1975	Bupropion vs. SSRI	No systematic literature search
Thase et al. 2006[23]	RCT	348	Bupropion vs. venlafaxine	High loss to follow-up
Wade et al. 2003[24]	RCT	197	Mirtazapine vs. paroxetine	High loss to follow-up
Major depressive disorder-Pediatric				
DeVane et al. 1996[25]	Meta-analysis	61	Fluoxetine vs. placebo	No systematic literature search
Emslie et al. 1997, 1998[26, 27]	RCT	96	Fluoxetine vs. placebo	Loss to follow-up differential > 15 percentage points
Emslie et al. 2002[28]	RCT	219	Fluoxetine vs. placebo	Loss to follow-up differential > 15 percentage points
Mayes et al. 2007[29]	Pooled post hoc analysis	315	Fluoxetine vs. placebo	No systematic literature search
Generalized anxiety disorder				
Bielski et al. 2005[30]	RCT	123	Escitalopram vs. paroxetine	High loss to follow-up
Kelsey et al. 2000[31]	Pooled analysis	2000	Venlafaxine vs. placebo	No systematic literature search
Stahl et al. 2007[32]	Post hoc pooled analysis	1965	Venlafaxine vs. placebo	No systematic literature search
Wan et al. 2006[33]	Pooled analysis	1839	Venlafaxine vs. placebo	No systematic literature search
Obsessive-compulsive disorder				
Cox et al. 1993[34]	Meta-analysis	Not reported	Clomipramine vs. fluoxetine vs. behavior therapy	Lack of information on included studies
Greist et al. 1995[35]	Meta-analysis	1530	Clomipramine vs. fluoxetine vs. fluvoxamine vs. Sertraline	No systematic literature search
Kobak et al. 1998[36]	Meta-analysis	Not reported	Fluoxetine vs. fluvoxamine vs. paroxetine vs. Sertraline	Included uncontrolled trials; lack of information on included studies
Panic				
Nair et al. 1996[37]	RCT	148	Fluvoxamine vs. placebo	High loss to follow-up
Post-traumatic stress disorder				
Chung et al. 2004[38]	Open-label trial	113	Mirtazapine vs. Sertraline	Significant differences in patient characteristics at baseline
Davidson et al. 1998[39]	Open-label trial	15	Fluvoxamine	Open-label, high loss to follow-up
Davidson et al. 1998[40]	Open-label trial	17	Nefazodone	Open-label, high loss to follow-up
De Boer et al. 1992[41]	Open-label trial	24	Fluovoxamine	Open-label, high loss to follow-up

Study	Design	Sample size	Intervention	Reason for exclusion
Martenyi et al. 2002[42, 43]	RCT	301	Fluoxetine vs. placebo	High loss to follow-up
Smajkic et al. 2001[44]	RCT	40	Sertraline vs. paroxetine vs. venlafaxine	Small sample size, no ITT analysis
Tucker et al. 2001[45]	RCT	323	Paroxetine vs. placebo	High loss to follow-up
Social anxiety disorder				
Allgulander et al. 2001[46]	RCT	96	Paroxetine vs. placebo	No ITT analysis, lack of statistical comparisons
Premenstrual dysphoric disorder				
Diegoli et al. 1998[47]	RCT	120	Pyridoxine, alprazolam, fluoxetine, propanolol	Important information about study methodology not reported
Carr et al.2002[48]	Systematic review	NR	fluoxetine	No critical appraisal of study quality; no description of review process
Subgroups				
Beasley et al. 1991[49, 50] and Tollefson et al. 1994[51]	Meta-analysis	3065	Fluoxetine vs. placebo	No systematic literature search
Gülseren et al. 2005[52]	RCT	25	Fluoxetine vs. paroxetine	High rate of post-randomization exclusions
Roy-Byrne et al. 2000[53]	RCT	64	Nefazodone vs. placebo	High loss to follow-up
Adverse events				
Baldwin et al. 2007[54]	Pooled analysis		Escitalopram vs. placebo	No systematic literature search
Croft et al. 2002[55]	RCT	432	Bupropion vs. placebo	High loss to follow-up
Demyttenaere et al. 2005[56]	RCT	85	Escitalopram vs. placebo	No ITT analysis
Ferguson et al. 2001[57]	RCT	72	Nefazodone vs. sertraline	Selection bias
Kennedy et al. 2000[58]	Prospective cohort	174	Paroxetine vs. sertraline vs. venlafaxine	No ITT analysis; high loss to follow-up
Letizia et al. 1996[59]	Systematic review	3828	Fluvoxamine vs. TCA vs. placebo	Search strategy not reported; no critical appraisal of study quality
Thase et al. 2006[23]	RCT	348	Bupropion vs. venlafaxine	High loss to follow-up
Wernicke et al. 1997[60]	Meta-analysis	4016	Fluoxetine, placebo ,TCA	No systematic literature search
Wernicke, 2007[61]	Pooled analysis	14 627	Duloxetine vs. placebo	No systematic literature search

Abbreviations: RCT, randomized controlled trial; TCA, tricyclic antidepressants.

Appendix D. Pharmacokinetic properties and drug interactions

Second-generation antidepressant pharmacokinetic properties related to drug-drug interactions

	Protein Binding	Substrate of		Inhibits	
Citalopram	80%	*Major:* *Minor:*	CYP2C19; CYP3A4 CYP2D6	Weak:	CYP1A2; CYP2B6; CYP2C19; CYP2D6
Escitalopram	56%	*Major:*	CYP2C19; CYP3A4	Weak:	CYP2D6
Fluoxetine	94.5%	*Major:* *Minor:*	CYP2C8/9; CYP2D6 CYP1A2; CYP2B6; CYP2C19; CYP2E1; CYP3A4	*Strong:* *Moderate:* *Weak:*	CYP2D6 CYP1A2 CYP2B6; CYP2C8/9; CYP3A4
Fluvoxamine	80%	*Major:*	CYP1A2; CYP2D6	*Strong:* *Weak:*	CYP1A2; CYP2C19 CYP2B6; CYP3A4; CYP2D6; CYP2C8/9
Paroxetine	95%	*Major:*	CYP2D6	*Strong:* *Moderate:* *Weak:*	CYP2D6 CYP2B6 CYP1A2; CYP2C19; CYP2C8/9; CYP3A4
Sertraline	98%	*Major:* *Minor:*	CYP2C19; CYP2D6 CYP2B6; CYP3A4; CYP2C8/9	*Moderate:* *Weak:*	CYP2C19; CYP2D6; CYP2B6; CYP3A4 CYP1A2; CYP2C8/9
Mirtazapine	85%	*Major:* *Minor:*	CYP1A2; CYP2D6; CYP3A4 CYP2C8/9	*Weak:*	CYP1A2; CYP3A4
Venlafaxine	27%	*Major:* *Minor:*	CYP2D6; CYP3A4 CYP2C8/9; CYP2C19	*Weak:*	CYP2B6; CYP2D6
Bupropion	84%	*Major:* *Minor:*	CYP2C8/9 CYP1A2; CYP2A6; CYP2C8/9; CYP2D6 CYP2E1; CYP3A4	*Weak:*	CYP2D6
Nefazodone	>99%	*Major:*	CYP2D6; CYP3A4	*Strong:* *Weak:*	CYP3A4 CYP1A2; CYP2B6; CYP2D6

*Pharmacokinetic properties abstracted from Lexi-Comp online (licensed by the University)

Clinically Significant Drug Interactions: Selective serotonin reuptake inhibitors

Interacting Drug	Citalopram	Escitalopram	Fluoxetine
Carbamazepine	Monitor (1)[a]	Monitor (2)[a]	Monitor (3)[d]
Cimetidine	Monitor (1)[b]	Monitor (2)[b]	
Clozapine			Monitor (3)[d]
Diazepam			Monitor (3)[d]
Digoxin	No significant interaction (1)	No significant interaction (2)	Monitor (3)[d]
Haloperidol			Monitor (3)[d]
Ketoconazole	Monitor (1)[c]	Monitor (2)[c]	
Lithium	Monitor (1)	Monitor (2)[b]	Monitor (3)
MAOIs	Contraindicated	Contraindicated	Contraindicated
Metoprolol	Monitor (1)[d]	Monitor (2)[d]	
Phenytoin			Monitor (3)[d]
Pimozide			Monitor (3)[d]
Sumatriptan	Monitor (1)	Monitor (2)	Monitor (3)
Ritonavir		No significant interaction (2)	
TCAs	Monitor (1)[d]		
Theophylline	No significant interaction (1)	No significant interaction (2)	
Thioridazine			Contraindicated
Triazolam	No significant interaction (1)	No significant interaction (2)	
Tryptophan			Monitor (3)
Warfarin	Monitor (1)	Monitor (2)	Monitor (3)[d]

Abbreviations: MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressants
[a]Decrease in second generation antidepressant plasma levels
[b]Increase in second generation antidepressant plasma levels
[c] Decrease in plasma levels for the interacting drug or its active metabolite
[d] Increase in plasma levels for the interacting drug or its active metabolite
(1) Citalopram package insert
(2) Escitalopram package insert
(3) Fluoxetine package insert

Clinically Significant Drug Interactions: Selective serotonin reuptake inhibitors

Interacting Drug	Fluvoxamine	Paroxetine	Sertraline
Alprazolam	Monitor (4)[d]		
Atenolol			No significant interaction (6)
Cimetidine		Monitor (5)[b]	Monitor (6)[b]
Diazepam	Monitor (4)[d]	Monitor (5)	Monitor (6)
Digoxin		Monitor (5)[c]	Monitor (6)[d]
Lithium		Monitor (5)	Monitor (6)
Lorazepam	No significant interaction (4)		
MAOIs	Contraindicated (4)	Contraindicated (5)	Contraindicated (6)
Phenobarbital		Monitor (5)	
Phenytoin		Monitor (5)	
Pimozide	Contraindicated (4)		Contraindicated (6)
Procyclidine		Monitor (5)[d]	
Propranolol		No significant interaction (5)	
Triptans		Monitor (5)	Monitor (6)
TCAs		Monitor (5)	Monitor (6)
Temazepam	No significant interaction (4)		
Theophylline	Monitor (4)[d]	Monitor (5)[d]	
Thioridazine	Contraindicated	Contraindicated (5)	
Tolbutamide			Monitor (6)[d]
Tramadol		Monitor (5)[d]	
Triazolam	Monitor (4)[d]		
Tryptophan		Monitor (5)	
Warfarin	Monitor (4)[d]	Monitor (5)[d]	Monitor (6)[d]

Abbreviations: MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant

[a]Decrease in second generation antidepressant plasma levels

[b]Increase in second generation antidepressant plasma levels

[c] Decrease in plasma levels for the interacting drug or its active metabolite

[d] Increase in plasma levels for the interacting drug or its active metabolite

(4) Fluvoxamine package insert
(5) Paroxetine package insert
(6) Sertraline package insert

Clinically Significant Drug Interactions: Mirtazapine, Venlafaxine

Interacting Drug	Mirtazapine	Venlafaxine
Alprazolam	Monitor (7)	
Amiodarone	Monitor (7)[b]	
Carbamazepine	Monitor (7)[a]	
Cimetidine		Monitor (8)[d]
Ciprofloxacin	Monitor (7)[b]	
Diazepam	Monitor (7)	No significant interaction (8)
Erythromycin	Monitor (7)[b]	
Haloperidol		Monitor (8)[d]
Indinavir		Monitor (8)[c]
Ketoconazole	Monitor (7)[b]	
Lithium		No significant interaction (8)
Lorazepam	Monitor (7)	
MAOIs	Contraindicated (7)	Contraindicated (8)
Phenobarbital	Monitor (7)[a]	
Phenytoin	Monitor (7)[a]	
Risperidone		Monitor (8)[d]
TCAs		Monitor (8)[d]
Temazepam	Monitor (7)	
Triazolam	Monitor (7)	

Abbreviations: MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant
[a]Decrease in second generation antidepressant plasma levels
[b]Increase in second generation antidepressant plasma levels
[c] Decrease in plasma levels for the interacting drug or its active metabolite
[d] Increase in plasma levels for the interacting drug or its active metabolite
(7) Mirtazapine package insert
(8) Venlafaxine package insert

Clinically Significant Drug Interactions: Bupropion, Nefazodone

Interacting Drug	Buproprion	Nefazodone
Alprazolam		Monitor (10)[d]
Amantadine	Monitor (9)	
Atenolol	Monitor (9)	
Buspirone		Monitor (10)
Carbamazepine	Monitor (9)	Contraindicated (10)
Cimetidine	Monitor (9)[b]	No significant interaction (10)
Cyclosporine		Monitor (10)[d]
Digoxin		Monitor (10)
Flecainide	Monitor (9)	
Haloperidol	Monitor (9)	Monitor (10)[d]
HMG-CoA Reductase Inhibitors		Monitor (10)[d]
Ketoconazole	Monitor (9)	
Levodopa	Monitor (9)	
Lithium		Monitor (10)
Lorazepam		No significant interaction (10)
MAOIs	Contraindicated (9)	Contraindicated (10)
Metoprolol	Monitor (9)	
Phenobarbital	Monitor (9)	
Phenytoin	Monitor (9)	Monitor (10)
Pimozide		Contraindicated (10)
Propafenone	Monitor (9)	
Propranolol	Monitor (9)	Monitor (10)[b]
Risperidone	Monitor (9)	
Tacrolimus		Monitor (10)[d]
TCAs	Monitor (9)	Monitor (10)
Theophylline	Monitor (9)	Monitor (10)
Thioridazine	Monitor (9)	
Triazolam		Contraindicated (10)

Abbreviations: MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant

[a] Decrease in second-generation antidepressant plasma levels

[b] Increase in second generation antidepressant plasma levels

[c] Decrease in plasma levels for the interacting drug or its active metabolite

[d] Increase in plasma levels for the interacting drug or its active metabolite

(9) Buproprion

(10) Nefazodone

Appendix E. Placebo-controlled trials of second generation antidepressants (not included)

1. Ackerman DL, Greenland S, Bystritsky A, Small GW. Characteristics of fluoxetine versus placebo responders in a randomized trial of geriatric depression. Psychopharmacol Bull 1997;33(4):707-14.
2. Agosti V, McGrath PJ. Comparison of the effects of fluoxetine, imipramine and placebo on personality in atypical depression. J Affect Disord 2002;71(1-3):113-20.
3. Albert R, Ebert D. Full efficacy of SSRI treatment in refractory dysthymia is achieved only after 16 weeks. J Clin Psychiatry 1996;57(4):176.
4. Allgulander C. Paroxetine in social anxiety disorder: a randomized placebo-controlled study. Acta Psychiatr Scand 1999;100(3):193-8.
5. Allgulander C, Hackett D, Salinas E. Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. Br J Psychiatry 2001;179:15-22.
6. Appleby L, Warner R, Whitton A, Faragher B. A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. BMJ 1997;314(7085):932-6.
7. Asakura S, Tajima O, Koyama T. Fluvoxamine treatment of generalized social anxiety disorder in Japan: a randomized double-blind, placebo-controlled study. Int J Neuropsychopharmacol 2007;10(2):263-74.
8. Baldwin D, Bobes J, Stein DJ, Scharwachter I, Faure M. Paroxetine in social phobia/social anxiety disorder. Randomised, double-blind, placebo-controlled study. Paroxetine Study Group. Br J Psychiatry 1999;175:120-6.
9. Ballenger JC, Wheadon DE, Steiner M, Bushnell W, Gergel IP. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry 1998;155(1):36-42.
10. Ballenger JC. Remission rates in patients with anxiety disorders treated with paroxetine. J Clin Psychiatry 2004;65(12):1696-707.
11. Barak Y, Kimhi R, Weizman R. Is selectivity for serotonin uptake associated with a reduced emergence of manic episodes in depressed patients? Int Clin Psychopharmacol 2000;15(1):53-6.
12. Beasley CMJ, Sayler ME, Weiss AM, Potvin JH. Fluoxetine: activating and sedating effects at multiple fixed doses. J Clin Psychopharmacol 1992;12(5):328-33.
13. Beasley CMJ, Potvin JH, Masica DN, et al. Fluoxetine: no association with suicidality in obsessive-compulsive disorder. J Affect Disord 1992;24(1):1-10.
14. Beasley CMJ, Potvin JH. Fluoxetine: activating and sedating effects. Int Clin Psychopharmacol 1993;8(4):271-5.
15. Beasley CMJ, Masica DN, Heiligenstein JH, Wheadon DE, Zerbe RL. Possible monoamine oxidase inhibitor-serotonin uptake inhibitor interaction: fluoxetine clinical data and preclinical findings. J Clin Psychopharmacol 1993;13(5):312-20.
16. Blomhoff S, Haug TT, Hellstrom K, et al. Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. Br J Psychiatry 2001;179:23-30.
17. Boyer P, Mahe V, Hackett D. Social adjustment in generalised anxiety disorder: a long-term placebo-controlled study of venlafaxine extended release. Eur Psychiatry 2004;19(5):272-9.

18. Bradwejn J, Ahokas A, Stein DJ, et al. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. Br J Psychiatry 2005;187:352-9.
19. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA 2000;283(14):1837-44.
20. Brannan SK, Mallinckrodt CH, Brown EB, et al. Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. J Psychiatr Res 2005;39(1):43-53.
21. Brannan SK, Mallinckrodt CH, Detke MJ, Watkin JG, Tollefson GD. Onset of action for duloxetine 60 mg once daily: double-blind, placebo-controlled studies. J Psychiatr Res 2005;39(2):161-72.
22. Brecht S, Courtecuisse C, Debieuvre C, et al. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. J Clin Psychiatry 2007;68(11):1707-16.
23. Brown ES, Vigil L, Khan DA, et al. A randomized trial of citalopram versus placebo in outpatients with asthma and major depressive disorder: a proof of concept study. Biol Psychiatry 2005;58(11):865-70.
24. Burrows AB, Salzman C, Satlin A, et al. A randomized, placebo-controlled trial of paroxetine in nursing home residents with non-major depression. Depress Anxiety 2002;15(3):102-10.
25. Burt VK, Wohlreich MM, Mallinckrodt CH, et al. Duloxetine for the treatment of major depressive disorder in women ages 40 to 55 years. Psychosomatics 2005;46(4):345-54.
26. Byerley WF, Reimherr FW, Wood DR, Grosser BI. Fluoxetine, a selective serotonin uptake inhibitor, for the treatment of outpatients with major depression. J Clin Psychopharmacol 1988;8(2):112-5.
27. Chouinard G, Goodman W, Greist J, et al. Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive disorder. Psychopharmacol Bull 1990;26(3):279-84.
28. Claghorn J. A double-blind comparison of paroxetine and placebo in the treatment of depressed outpatients. Int Clin Psychopharmacol 1992;6 Suppl 4:25-30.
29. Claghorn JL, Kiev A, Rickels K, Smith WT, Dunbar GC. Paroxetine versus placebo: a double-blind comparison in depressed patients. J Clin Psychiatry 1992;53(12):434-8.
30. Claghorn JL. The safety and efficacy of paroxetine compared with placebo in a double-blind trial of depressed outpatients. J Clin Psychiatry 1992;53 Suppl:33-5.
31. Claghorn JL, Earl CQ, Walczak DD, et al. Fluvoxamine maleate in the treatment of depression: a single-center, double-blind, placebo-controlled comparison with imipramine in outpatients. J Clin Psychopharmacol 1996;16(2):113-20.
32. Cohen LS, Miner C, Brown E, et al. Premenstrual daily fluoxetine for premenstrual dysphoric disorder: a placebo-controlled, clinical trial using computerized diaries. Obstet Gynecol 2002;100(3):435-444.
33. Cohen LS, Soares CN, Yonkers KA, et al. Paroxetine controlled release for premenstrual dysphoric disorder: a double-blind, placebo-controlled trial. Psychosom Med 2004;66(5):707-13.
34. Cohn JB, Wilcox C. A comparison of fluoxetine, imipramine, and placebo in patients with major depressive disorder. J Clin Psychiatry 1985;46(3 Pt 2):26-31.
35. Cohn JB, Crowder JE, Wilcox CS, Ryan PJ. A placebo- and imipramine-controlled study of paroxetine. Psychopharmacol Bull 1990;26(2):185-9.

36. Cohn JB, Wilcox CS. Paroxetine in major depression: a double-blind trial with imipramine and placebo. J of Clinical Psychiatry 1992;53 Suppl:52-6.
37. Cohn CK, Robinson DS, Roberts DL, et al. Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. J Clin Psychiatry 1996;57 Suppl 2:15-8.
38. Cooper-Kazaz R, Apter JT, Cohen R, et al. Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial. Arch Gen Psychiatry 2007;64(6):679-88.
39. Corrigan MH, Denahan AQ, Wright CE, Ragual RJ, Evans DL. Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress Anxiety 2000;11(2):58-65.
40. Cunningham LA. Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. Venlafaxine XR 208 Study Group. Ann Clin Psychiatry 1997;9(3):157-64.
41. Davidson JR, DuPont RL, Hedges D, Haskins JT. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry 1999;60(8):528-35.
42. Davidson J, Pearlstein T, Londborg P, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. Am J Psychiatry 2001;158(12):1974-81.
43. Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. Arch Gen Psychiatry 2001;58(5):485-92.
44. Davidson JR, Landerman LR, Farfel GM, Clary CM. Characterizing the effects of sertraline in post-traumatic stress disorder. Psychol Med 2002;32(4):661-70.
45. Davidson JR, Weisler RH, Butterfield MI, et al. Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. Biol Psychiatry 2003;53(2):188-91.
46. Davidson JR, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. Depress Anxiety 2004;19(4):234-40.
47. Davidson J, Yaryura-Tobias J, DuPont R, et al. Fluvoxamine-controlled release formulation for the treatment of generalized social anxiety disorder. J Clin Psychopharmacol 2004;24(2):118-25.
48. Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res 2002;36(6):383-90.
49. Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry 2002;63(4):308-15.
50. Doogan DP, Caillard V. Sertraline in the prevention of depression. Br J Psychiatry 1992;160:217-22.
51. Doogan DP, Langdon CJ. A double-blind, placebo-controlled comparison of sertraline and dothiepin in the treatment of major depression in general practice. Int Clin Psychopharmacol 1994;9(2):95-100.
52. Dubini A, Bosc M, Polin V. Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. J Psychopharmacol 1997;11(4 Suppl):S17-23.

53. Dunbar GC, Cohn JB, Fabre LF, et al. A comparison of paroxetine, imipramine and placebo in depressed out-patients. Br J Psychiatry 1991;159:394-8.
54. Dunbar GC, Claghorn JL, Kiev A, Rickels K, Smith WT. A comparison of paroxetine and placebo in depressed outpatients. Acta Psychiatr Scand 1993;87(5):302-5.
55. Dunlop SR, Dornseif BE, Wernicke JF, Potvin JH. Pattern analysis shows beneficial effect of fluoxetine treatment in mild depression. Psychopharmacol Bull 1990;26(2):173-80.
56. Dunner DL, Goldstein DJ, Mallinckrodt C, Lu Y, Detke MJ. Duloxetine in treatment of anxiety symptoms associated with depression. Depress Anxiety 2003;18(2):53-61.
57. Elliott AJ, Russo J, Roy-Byrne PP. The effect of changes in depression on health related quality of life (HRQoL) in HIV infection. Gen Hosp Psychiatry 2002;24(1):43-7.
58. Entsuah AR, Rudolph RL, Chitra R. Effectiveness of venlafaxine treatment in a broad spectrum of depressed patients: a meta-analysis. Psychopharmacol Bull 1995;31(4):759-66.
59. Entsuah AR, Rudolph RL, Hackett D, Miska S. Efficacy of venlafaxine and placebo during long-term treatment of depression: a pooled analysis of relapse rates. Int Clin Psychopharmacol 1996;11(2):137-45.
60. Entsuah R, Derivan A, Kikta D. Early onset of antidepressant action of venlafaxine: pattern analysis in intent-to-treat patients. Clin Ther 1998;20(3):517-26.
61. Eriksson E, Hedberg MA, Andersch B, Sundblad C. The serotonin reuptake inhibitor paroxetin is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. Neuropsychopharm 1995;12(2):167-176.
62. Evans M, Hammond M, Wilson K, Lye M, Copeland J. Placebo-controlled treatment trial of depression in elderly physically ill patients. Int J Geriatr Psychiatry 1997;12(8):817-24.
63. Fabre LF, Brodie HK, Garver D, Zung WW. A multicenter evaluation of bupropion versus placebo in hospitalized depressed patients. J Clin Psychiatry 1983;44(5 Pt 2):88-94.
64. Fabre LF. A 6-week, double-blind trial of paroxetine, imipramine, and placebo in depressed outpatients. J Clin Psychiatry 1992;53 Suppl:40-3.
65. Fabre LF, Abuzzahab FS, Amin M, et al. Sertraline safety and efficacy in major depression: a double-blind fixed-dose comparison with placebo. Biol Psychiatry 1995;38(9):592-602.
66. Fabre L, Birkhimer LJ, Zaborny BA, Wong LF, Kapik BM. Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. Int Clin Psychopharmacol 1996;11(2):119-27.
67. Fava M, Mulroy R, Alpert J, Nierenberg AA, Rosenbaum JF. Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. Am J Psychiatry 1997;154(12):1760-2.
68. Fava M, Schmidt ME, Zhang S, et al. Treatment approaches to major depressive disorder relapse. Part 2: reinitiation of antidepressant treatment. Psychother Psychosom 2002;71(4):195-9.
69. Fava M, Mallinckrodt CH, Detke MJ, Watkin JG, Wohlreich MM. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates? J Clin Psychiatry 2004;65(4):521-30.
70. Fava M, Alpert J, Nierenberg AA, et al. A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. J Clin Psychopharmacol 2005;25(5):441-7.
71. Fawcett J, Barkin RL. A meta-analysis of eight randomized, double-blind, controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety. J Clin Psychiatry 1998;59(3):123-7.

72. Feiger AD, Bielski RJ, Bremner J, et al. Double-blind, placebo-substitution study of nefazodone in the prevention of relapse during continuation treatment of outpatients with major depression. Int Clin Psychopharmacol 1999;14(1):19-28.
73. Feighner JP, Pambakian R, Fowler RC, Boyer WF, D'Amico MF. A comparison of nefazodone imipramine, and placebo in patients with moderate to severe depression. Psychopharmacol Bull 1989;25(2):219-21.
74. Feighner JP, Boyer WF, Merideth CH, Hendrickson GG. A double-blind comparison of fluoxetine, imipramine and placebo in outpatients with major depression. Int Clin Psychopharmacol 1989;4(2):127-34.
75. Feighner JP. A double-blind comparison of paroxetine, imipramine and placebo in depressed outpatients. Int Clin Psychopharmacol 1992;6 Suppl 4:31-5.
76. Feighner JP, Boyer WF. Paroxetine in the treatment of depression: a comparison with imipramine and placebo. J Clin Psychiatry 1992;53 Suppl:44-7.
77. Feighner JP, Cohn JB, Fabre LFJ, et al. A study comparing paroxetine placebo and imipramine in depressed patients. J Affect Disord 1993;28(2):71-9.
78. Feighner JP, Entsuah AR, McPherson MK. Efficacy of once-daily venlafaxine extended release (XR) for symptoms of anxiety in depressed outpatients. J Affect Disord 1998;47(1-3):55-62.
79. Feighner JP, Overo K. Multicenter, placebo-controlled, fixed-dose study of citalopram in moderate-to-severe depression. J Clin Psychiatry 1999;60(12):824-30.
80. Ferguson JM, Wesnes KA, Schwartz GE. Reboxetine versus paroxetine versus placebo: effects on cognitive functioning in depressed patients. Int Clin Psychopharmacol 2003;18(1):9-14.
81. Fieve RR, Goodnick PJ, Peselow E, Schlegel A. Fluoxetine response: endpoint vs pattern analysis. Int Clin Psychopharmacol 1986;1(4):320-3.
82. Fisch C, Knoebel B. Electrocardiographic findings in sertraline depression trials. Drug Investigation (New Zealand) 1992;4:305-312.
83. Flament MF, Bisserbe JC. Pharmacologic treatment of obsessive-compulsive disorder: comparative studies. J Clin Psychiatry 1997;58 Suppl 12:18-22.
84. Fontaine R, Ontiveros A, Elie R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry 1994;55:234-41.
85. Freeman EW, Rickels K, Sondheimer SJ, Polansky M. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: A randomized controlled trial. Archives-of-General-Psychiatry 1999;56(10):932-939.
86. Freeman EW, Rickels K, Sondheimer SJ, Polansky M, Xiao S. Continuous or intermittent dosing with sertraline for patients with severe premenstrual syndrome or premenstrual dysphoric disorder. Am J Psychiatry 2004;161(2):343-51.
87. Friedman MJ, Marmar CR, Baker DG, Sikes CR, Farfel GM. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. J Clin Psychiatry 2007;68(5):711-20.
88. Gelenberg AJ, Lydiard RB, Rudolph RL, et al. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: A 6-month randomized controlled trial. JAMA 2000;283(23):3082-8.
89. Gelenberg AJ, Trivedi MH, Rush AJ, et al. Randomized, placebo-controlled trial of nefazodone maintenance treatment in preventing recurrence in chronic depression. Biol Psychiatry 2003;54(8):806-17.

90. Golden RN, Nemeroff CB, McSorley P, Pitts CD, Dube EM. Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. 2002;63(7):577-84.
91. Goldstein DJ, Hamilton SH, Masica DN, Beasley CMJ. Fluoxetine in medically stable, depressed geriatric patients: effects on weight. J Clin Psychopharmacol 1997;17(5):365-9.
92. Goldstein DJ, Lu Y, Detke MJ, et al. Effects of duloxetine on painful physical symptoms associated with depression. Psychosomatics 2004;45(1):17-28.
93. Goodman WK, Price LH, Rasmussen SA, et al. Efficacy of fluvoxamine in obsessive-compulsive disorder. A double-blind comparison with placebo. Arch Gen Psychiatry 1989;46(1):36-44.
94. Goodman WK, Kozak MJ, Liebowitz M, White KL. Treatment of obsessive-compulsive disorder with fluvoxamine: a multicentre, double-blind, placebo-controlled trial. Int Clin Psychopharmacol 1996;11(1):21-9.
95. Goodnick PJ, Fieve RR, Peselow ED, Barouche F, Schlegel A. Double-blind treatment of major depression with fluoxetine: use of pattern analysis and relation of HAM-D score to CGI change. Psychopharmacol Bull 1987;23(1):162-3.
96. Green TD, Reynolds CFr, Mulsant BH, et al. Accelerating antidepressant response in geriatric depression: a post hoc comparison of combined sleep deprivation and paroxetine versus monotherapy with paroxetine, nortriptyline, or placebo. J Geriatr Psychiatry Neurol 1999;12(2):67-71.
97. Greenberg RP, Bornstein RF, Zborowski MJ, Fisher S, Greenberg MD. A meta-analysis of fluoxetine outcome in the treatment of depression. J Nerv Ment Dis 1994;182(10):547-51.
98. Greist JH, Jefferson JW, Kobak KA, et al. A 1 year double-blind placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol 1995;10(2):57-65.
99. Greist J, Chouinard G, DuBoff E, et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry 1995;52(4):289-95.
100. Greist JH, Jenike MA, Robinson D, Rasmussen SA. Efficacy of fluvoxamine in obsessive-compulsive disorder: results of multicentre, double blind, placebo-controlled trial. Eur J Clin Res 1995;7:195-204.
101. Halaris AE, Stern WC, Van Wyck Fleet J, Reno RM. Evaluation of the safety and efficacy of bupropion in depression. J Clin Psychiatry 1983;44(5 Pt 2):101-3.
102. Halbreich U, Smoller JW. Intermittent luteal phase sertraline treatment of dysphoric premenstrual syndrome. J Clin Psychiatry 1997;58(9):399-402.
103. Halbreich U, Bergeron R, Yonkers KA, et al. Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. Obstet Gynecol 2002;100(6):1219-29.
104. Halikas JA. Org 3770 (Mirtazapine) versus Trazodone: a placebo controlled trial in depressed elderly patients. Hum Psychopharmacol 1995;10:S125-S133.
105. Heiligenstein JH, Tollefson GD, Faries DE. A double-blind trial of fluoxetine, 20 mg, and placebo in out-patients with DSM-III-R major depression and melancholia. Int Clin Psychopharmacol 1993;8(4):247-51.
106. Heiligenstein JH, Tollefson GD, Faries DE. Response patterns of depressed outpatients with and without melancholia: a double-blind, placebo-controlled trial of fluoxetine versus placebo. J Affect Disord 1994;30(3):163-73.

107. Heiligenstein JH, Ware JEJ, Beusterien KM, et al. Acute effects of fluoxetine versus placebo on functional health and well-being in late-life depression. Int Psychogeriatr 1995;7 Suppl:125-37.
108. Hellerstein DJ, Yanowitch P, Rosenthal J, et al. A randomized double-blind study of fluoxetine versus placebo in the treatment of dysthymia. Am J Psychiatry 1993;150(8):1169-75.
109. Hochstrasser B, Isaksen PM, Koponen H, et al. Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. Br J Psychiatry 2001;178:304-10.
110. Hollander E, Allen A, Steiner M, et al. Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. J Clin Psychiatry 2003;64(9):1113-1121.
111. Hollander E, Koran LM, Goodman WK, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. J Clin Psychiatry 2003;64(6):640-7.
112. Hypericum Depression Trial Study Group. Effect of Hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial. Jama 2002;287(14):1807-14.
113. Jamerson BD, Krishnan KR, Roberts J, Krishen A, Modell JG. Effect of bupropion SR on specific symptom clusters of depression: analysis of the 31-item Hamilton Rating Scale for depression. Psychopharmacol Bull 2003;37(2):67-78.
114. Jefferson JW, Rush AJ, Nelson JC, et al. Extended-release bupropion for patients with major depressive disorder presenting with symptoms of reduced energy, pleasure, and interest: findings from a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2006;67(6):865-73.
115. Jenike MA, Hyman S, Baer L, et al. A controlled trial of fluvoxamine in obsessive-compulsive disorder: implications for a serotonergic theory. Am J Psychiatry 1990;147(9):1209-15.
116. Jenike MA, Baer L, Summergrad P, et al. Sertraline in obsessive-compulsive disorder: a double-blind comparison with placebo. Am J Psychiatry 1990;147(7):923-28.
117. Jenike MA, Baer L, Minichiello WE, Rauch SL, Buttolph ML. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. Am J Psychiatry 1997;154(9):1261-4.
118. Jermain DM, Preece CK, Sykes RL, Kuehl TJ, Sulak PJ. Luteal phase sertraline treatment for premenstrual dysphoric disorder. Results of a double-blind, placebo-controlled, crossover study. Arch Fam Med 1999;8(4):328-32.
119. Judge R, Plewes JM, Kumar V, Koke SC, Kopp JB. Changes in energy during treatment of depression: an analysis of fluoxetine in double-blind, placebo-controlled trials. J Clin Psychopharmacol 2000;20(6):666-72.
120. Kamijima K, Murasaki M, Asai M, et al. Paroxetine in the treatment of obsessive-compulsive disorder: randomized, double-blind, placebo-controlled study in Japanese patients. Psychiatry Clin Neurosci 2004;58(4):427-33.
121. Kampman M, Keijsers GP, Hoogduin CA, Hendriks GJ. A randomized, double-blind, placebo-controlled study of the effects of adjunctive paroxetine in panic disorder patients unsuccessfully treated with cognitive-behavioral therapy alone. J Clin Psychiatry 2002;63(9):772-7.
122. Kane JM, Cole K, Sarantakos S, Howard A, Borenstein M. Safety and efficacy of bupropion in elderly patients: preliminary observations. J Clin Psychiatry 1983;44(5 Pt 2):134-6.

123. Kasper S, Moller HJ, Montgomery SA, Zondag E. Antidepressant efficacy in relation to item analysis and severity of depression: a placebo-controlled trial of fluvoxamine versus imipramine. Int Clin Psychopharmacol 1995;9 Suppl 4:3-12.
124. Katz IR, Reynolds CFr, Alexopoulos GS, Hackett D. Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: pooled analysis of five randomized placebo-controlled clinical trials. J Am Geriatr Soc 2002;50(1):18-25.
125. Katzelnick DJ, Kobak KA, Greist JH, et al. Sertraline for social phobia: a double-blind, placebo-controlled crossover study. Am J Psychiatry 1995;152(9):1368-71.
126. Keller MB, Kocsis JH, Thase ME, et al. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. JAMA 1998;280(19):1665-72.
127. Kerr JS, Fairweather DB, Hindmarch I. Effects of fluoxetine on psychomotor performance, cognitive function and sleep in depressed patients. Int Clin Psychopharmacol 1993;8(4):341-3.
128. Khan A, Fabre LF, Rudolph R. Venlafaxine in depressed outpatients. Psychopharmacol Bull 1991;27(2):141-4.
129. Khan A, Upton GV, Rudolph RL, Entsuah R, Leventer SM. The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-response study. Venlafaxine Investigator Study Group. J Clin Psychopharmacol 1998;18(1):19-25.
130. Klysner R, Bent-Hansen J, Hansen HL, et al. Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. Br J Psychiatry 2002;181:29-35.
131. Kocsis JH, Schatzberg A, Rush AJ, et al. Psychosocial outcomes following long-term, double-blind treatment of chronic depression with sertraline vs placebo. Arch Gen Psychiatry 2002;59(8):723-8.
132. Koponen H, Allgulander C, Erickson J, et al. Efficacy of Duloxetine for the Treatment of Generalized Anxiety Disorder: Implications for Primary Care Physicians. Prim Care Companion J Clin Psychiatry 2007;9(2):100-107.
133. Koran LM, Hackett E, Rubin A, Wolkow R, Robinson D. Efficacy of sertraline in the long-term treatment of obsessive-compulsive disorder. Am J Psychiatry 2002;159(1):88-95.
134. Kronig MH, Apter J, Asnis G, et al. Placebo-controlled, multicenter study of sertraline treatment for obsessive-compulsive disorder. J Clin Psychopharmacol 1999;19(2):172-6.
135. Landen M, Nissbrandt H, Allgulander C, et al. Placebo-controlled trial comparing intermittent and continuous paroxetine in premenstrual dysphoric disorder. Neuropsychopharmacology 2007;32(1):153-61.
136. Lapierre YD. Controlling acute episodes of depression. Int Clin Psychopharmacol 1991;6 Suppl 2:23-35.
137. Lecrubier Y, Bakker A, Dunbar G, Judge R. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. Collaborative Paroxetine Panic Study Investigators. Acta Psychiatr Scand 1997;95(2):145-52.
138. Lecrubier Y, Judge R. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Collaborative Paroxetine Panic Study Investigators. Acta Psychiatr Scand 1997;95(2):153-60.
139. Leinonen E, Lepola U, Koponen H, et al. Citalopram controls phobic symptoms in patients with panic disorder: randomized controlled trial. J Psychiatry Neurosci 2000;25(1):25-32.
140. Lenderking WR, Tennen H, Nackley JF, et al. The effects of venlafaxine on social activity level in depressed outpatients. J Clin Psychiatry 1999;60(3):157-63.

141. Lenox-Smith AJ, Reynolds A. A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care. Br J Gen Pract 2003;53(495):772-7.
142. Lepine JP, Caillard V, Bisserbe JC, et al. A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. Am J Psychiatry 2004;161(5):836-42.
143. Lepola UM, Wade AG, Leinonen EV, et al. A controlled, prospective, 1-year trial of citalopram in the treatment of panic disorder. J Clin Psychiatry 1998;59(10):528-34.
144. Lepola U, Bergtholdt B, St Lambert J, Davy KL, Ruggiero L. Controlled-release paroxetine in the treatment of patients with social anxiety disorder. J Clin Psychiatry 2004;65(2):222-9.
145. Levitan RD, Shen JH, Jindal R, et al. Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects. J Psychiatry Neurosci 2000;25(4):337-46.
146. Liebowitz MR, Stein MB, Tancer M, et al. A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. J Clin Psychiatry 2002;63(1):66-74.
147. Liebowitz MR, DeMartinis NA, Weihs K, et al. Efficacy of sertraline in severe generalized social anxiety disorder: results of a double-blind, placebo-controlled study. J Clin Psychiatry 2003;64(7):785-92.
148. Liebowitz MR, Mangano RM, Bradwejn J, Asnis G. A randomized controlled trial of venlafaxine extended release in generalized social anxiety disorder. J Clin Psychiatry 2005;66(2):238-47.
149. Lineberry CG, Johnston JA, Raymond RN, et al. A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. J Clin Psychiatry 1990;51(5):194-9.
150. Londborg PD, Wolkow R, Smith WT, et al. Sertraline in the treatment of panic disorder. A multi-site, double-blind, placebo-controlled, fixed-dose investigation. Br J Psychiatry 1998;173:54-60.
151. Londborg PD, Hegel MT, Goldstein S, et al. Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. J Clin Psychiatry 2001;62(5):325-31.
152. Lydiard RB, Laird LK, Morton WAJ, et al. Fluvoxamine, imipramine, and placebo in the treatment of depressed outpatients: effects on depression. Psychopharmacol Bull 1989;25(1):68-70.
153. Mallinckrodt CH, Goldstein DJ, Detke MJ, et al. Duloxetine: A New Treatment for the Emotional and Physical Symptoms of Depression. Prim Care Companion J Clin Psychiatry 2003;5(1):19-28.
154. Mallinckrodt CH, Watkin JG, Liu C, Wohlreich MM, Raskin J. Duloxetine in the treatment of Major Depressive Disorder: a comparison of efficacy in patients with and without melancholic features. BMC Psychiatry 2005;5(1):1.
155. Mallya GK, K. W, C. W, al. e. Short- and long-term treatment of obsessive-compulsive disorder with fluvoxamine. Ann Clin Psychiatry 1992;4:77-80.
156. Marcus RN, Mendels J. Nefazodone in the treatment of severe, melancholic, and recurrent depression. J Clin Psychiatry 1996;57 Suppl 2:19-23.
157. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. Am J Psychiatry 2001;158(12):1982-8.

158. Marshall RD, Lewis-Fernandez R, Blanco C, et al. A controlled trial of paroxetine for chronic PTSD, dissociation, and interpersonal problems in mostly minority adults. Depress Anxiety 2007;24(2):77-84.
159. Mendels J, Kiev A, Fabre LF. Double-blind comparison of citalopram and placebo in depressed outpatients with melancholia. Depress Anxiety 1999;9(2):54-60.
160. Menkes DB, Taghavi E, Mason PA, Spears GF, Howard RC. Fluoxetine treatment of severe premenstrual syndrome. BMJ 1992;305(6849):346-7.
161. Menkes DB, Taghavi E, Mason PA, Howard RC. Fluoxetine's spectrum of action in premenstrual syndrome. Int Clin Psychopharmacol 1993;8(2):95-102.
162. Meoni P, Hackett D, Lader M. Pooled analysis of venlafaxine XR efficacy on somatic and psychic symptoms of anxiety in patients with generalized anxiety disorder. Depress Anxiety 2004;19(2):127-32.
163. Mesters P, Cosyns P, Dejaiffe G, et al. Assessment of quality of life in the treatment of major depressive disorder with fluoxetine, 20 mg, in ambulatory patients aged over 60 years. Int Clin Psychopharmacol 1993;8(4):337-40.
164. Michelson D, Lydiard RB, Pollack MH, et al. Outcome assessment and clinical improvement in panic disorder: evidence from a randomized controlled trial of fluoxetine and placebo. The Fluoxetine Panic Disorder Study Group. Am J Psychiatry 1998;155(11):1570-7.
165. Michelson D, Pollack M, Lydiard RB, et al. Continuing treatment of panic disorder after acute response: randomised, placebo-controlled trial with fluoxetine. The Fluoxetine Panic Disorder Study Group. Br J Psychiatry 1999;174:213-8.
166. Michelson D, Allgulander C, Dantendorfer K, et al. Efficacy of usual antidepressant dosing regimens of fluoxetine in panic disorder: randomised, placebo-controlled trial. Br J Psychiatry 2001;179:514-8.
167. Miller SM, Naylor GJ, Murtagh M, Winslow G. A double-blind comparison of paroxetine and placebo in the treatment of depressed patients in a psychiatric outpatient clinic. Acta Psychiatr Scand Suppl 1989;350:143-4.
168. Miner C, Brown E, McCray S, Gonzales J, Wohlreich M. Weekly luteal-phase dosing with enteric-coated fluoxetine 90 mg in premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled clinical trial. Clin Ther 2002;24(3):417-33.
169. Montgomery SA, Rasmussen JG. Citalopram 20 mg, citalopram 40 mg and placebo in the prevention of relapse of major depression. Int Clin Psychopharmacol 1992;6 Suppl 5:71-3.
170. Montgomery SA, Rasmussen JG, Lyby K, Connor P, Tanghoj P. Dose response relationship of citalopram 20 mg, citalopram 40 mg and placebo in the treatment of moderate and severe depression. Int Clin Psychopharmacol 1992;6 Suppl 5:65-70.
171. Montgomery SA, McIntyre A, Osterheider M, et al. A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. The Lilly European OCD Study Group. Eur Neuropsychopharmacol 1993;3(2):143-52.
172. Montgomery SA, Dunbar G. Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. Int Clin Psychopharmacol 1993;8(3):189-95.
173. Montgomery SA, Pedersen V, Tanghoj P, Rasmussen C, Rioux P. The optimal dosing regimen for citalopram--a meta-analysis of nine placebo-controlled studies. Int Clin Psychopharmacol 1994;9 Suppl 1:35-40.
174. Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol 1995;10 Suppl 4:37-45.

175. Montgomery SA. Implications of the severity of social phobia. J Affect Disord 1998;50 Suppl 1:S17-22.
176. Montgomery SA, Sheehan DV, Meoni P, Haudiquet V, Hackett D. Characterization of the longitudinal course of improvement in generalized anxiety disorder during long-term treatment with venlafaxine XR. J Psychiatr Res 2002;36(4):209-17.
177. Montgomery SA, Mahe V, Haudiquet V, Hackett D. Effectiveness of venlafaxine, extended release formulation, in the short-term and long-term treatment of generalized anxiety disorder: results of a survival analysis. J Clin Psychopharmacol 2002;22(6):561-7.
178. Montgomery SA, Tobias K, Zornberg GL, Kasper S, Pande AC. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. J Clin Psychiatry 2006;67(5):771-82.
179. Muijen M, Roy D, Silverstone T, Mehmet A, Christie M. A comparative clinical trial of fluoxetine, mianserin and placebo in depressed outpatients. Acta Psychiatr Scand 1988;78(3):384-90.
180. Narushima K, Kosier JT, Robinson RG. Preventing poststroke depression: a 12-week double-blind randomized treatment trial and 21-month follow-up. J Nerv Ment Dis 2002;190(5):296-303.
181. Nimatoudis I, Zissis NP, Kogeorgos J, et al. Remission rates with venlafaxine extended release in Greek outpatients with generalized anxiety disorder. A double-blind, randomized, placebo controlled study. Int Clin Psychopharmacol 2004;19(6):331-6.
182. Oehrberg S, Christiansen PE, Behnke K, et al. Paroxetine in the treatment of panic disorder. A randomised, double-blind, placebo-controlled study. Br J Psychiatry 1995;167(3):374-9.
183. Olie JP, Gunn KP, Katz E. A double-blind placebo-controlled multicentre study of sertraline in the acute and continuation treatment of major depression. European Psychiatry 1997;12(1):34-41.
184. Ottevanger EA. The efficacy of fluvoxamine in patients with severe depression. Prog Neuropsychopharmacol Biol Psychiatry 1994;18(4):731-40.
185. Oxman TE, Barrett JE, Sengupta A, et al. Status of minor depression or dysthymia in primary care following a randomized controlled treatment. Gen Hosp Psychiatry 2001;23(6):301-10.
186. Ozeren S, Corakci A, Yucesoy I, Mercan R, Erhan G. Fluoxetine in the treatment of premenstrual syndrome. Eur J Obstet Gynecol Reproductive Biol 1997;73:167-70.
187. Pande AC, Sayler ME. Severity of depression and response to fluoxetine. Int Clin Psychopharmacol 1993;8(4):243-5.
188. Pearlstein TB, Halbreich U, Batzar ED, et al. Psychosocial functioning in women with premenstrual dysphoric disorder before and after treatment with sertraline or placebo. J Clin Psychiatry 2000;61(2):101-9.
189. Pearlstein T, Joliat MJ, Brown EB, Miner CM. Recurrence of symptoms of premenstrual dysphoric disorder after the cessation of luteal-phase fluoxetine treatment. Am J Obstet Gynecol 2003;188(4):887-95.
190. Pearlstein TB, Bellew KM, Endicott J, Steiner M. Paroxetine Controlled Release for Premenstrual Dysphoric Disorder: Remission Analysis Following a Randomized, Double-Blind, Placebo-Controlled Trial. Prim Care Companion J Clin Psychiatry 2005;7(2):53-60.

191. Perse TL, Greist JH, Jefferson JW, Rosenfeld R, Dar R. Fluvoxamine treatment of obsessive-compulsive disorder. Am J Psychiatry 1987;144(12):1543-48.
192. Pohl RB, Wolkow RM, Clary CM. Sertraline in the treatment of panic disorder: a double-blind multicenter trial. Am J Psychiatry 1998;155(9):1189-95.
193. Pollack MH, Worthington JJr, Otto MW, et al. Venlafaxine for panic disorder: results from a double-blind, placebo-controlled study. Psychopharmacol Bull 1996;32(4):667-70.
194. Pollack MH, Otto MW, Worthington JJ, Manfro GG, Wolkow R. Sertraline in the treatment of panic disorder: a flexible-dose multicenter trial. Arch Gen Psychiatry 1998;55(11):1010-6.
195. Pollack MH, Zaninelli R, Goddard A, et al. Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001;62(5):350-7.
196. Pols H, Zandergen J, de Loof C, Fernandez I, Griez E. Clinical effects of fluvoxamine on panic symptomatology. Acta Psychiatr Belg 1993;93(3):169-77.
197. Rapaport MH, Wolkow R, Rubin A, et al. Sertraline treatment of panic disorder: results of a long-term study. Acta Psychiatr Scand 2001;104(4):289-98.
198. Rapaport MH, Endicott J, Clary CM. Posttraumatic stress disorder and quality of life: results across 64 weeks of sertraline treatment. J Clin Psychiatry 2002;63(1):59-65.
199. Rapaport MH, Schneider LS, Dunner DL, Davies JT, Pitts CD. Efficacy of controlled-release paroxetine in the treatment of late-life depression. J Clin Psychiatry 2003;64(9):1065-74.
200. Rapaport MH, Bose A, Zheng H. Escitalopram continuation treatment prevents relapse of depressive episodes. J Clin Psychiatry 2004;65(1):44-9.
201. Raskin J, Wiltse CG, Siegal A, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. Am J Psychiatry 2007;164(6):900-9.
202. Rasmussen S, Hackett E, DuBoff E, et al. A 2-year study of sertraline in the treatment of obsessive-compulsive disorder. International Clin Psychopharm 1996;12:309-16.
203. Rasmussen A, Lunde M, Poulsen DL, et al. A double-blind, placebo-controlled study of sertraline in the prevention of depression in stroke patients. Psychosomatics 2003;44(3):216-21.
204. Ravindran AV, Teehan MD, Bakish D, et al. The impact of sertraline, desipramine, and placebo on psychomotor functioning in depression. Hum Psychopharmacol 1995;10(4):273-281.
205. Reimherr FW, Byerley WF, Ward MF, Lebegue BJ, Wender PH. Sertraline, a selective inhibitor of serotonin uptake, for the treatment of outpatients with major depressive disorder. Psychopharmacol Bull 1988;24(1):200-5.
206. Reimherr FW, Chouinard G, Cohn CK, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. J Clin Psychiatry 1990;51 Suppl B:18-27.
207. Reimherr FW, Cunningham LA, Batey SR, Johnston JA, Ascher JA. A multicenter evaluation of the efficacy and safety of 150 and 300 mg/d sustained-release bupropion tablets versus placebo in depressed outpatients. Clin Ther 1998;20(3):505-16.
208. Reimherr FW, Amsterdam JD, Quitkin FM, et al. Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. Am J Psychiatry 1998;155(9):1247-53.
209. Reimherr FW, Strong RE, Marchant BK, Hedges DW, Wender PH. Factors affecting return of symptoms 1 year after treatment in a 62-week controlled study of fluoxetine in major depression. J Clin Psychiatry 2001;62 Suppl 22:16-23.

210. Rickels K, Amsterdam J, Clary C, et al. A placebo-controlled, double-blind, clinical trial of paroxetine in depressed outpatients. Acta Psychiatr Scand Suppl 1989;350:117-23.
211. Rickels K, Amsterdam J, Clary C, et al. The efficacy and safety of paroxetine compared with placebo in outpatients with major depression. J Clin Psychiatry 1992;53 Suppl:30-2.
212. Rickels K, Schweizer E, Clary C, Fox I, Weise C. Nefazodone and imipramine in major depression: a placebo-controlled trial. Br J Psychiatry 1994;164(6):802-5.
213. Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. Am J Psychiatry 2000;157(6):968-74.
214. Rickels K, Zaninelli R, McCafferty J, et al. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. Am J Psychiatry 2003;160(4):749-56.
215. Rickels K, Mangano R, Khan A. A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder. J Clin Psychopharmacol 2004;24(5):488-96.
216. Robert P, Montgomery SA. Citalopram in doses of 20-60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. Int Clin Psychopharmacol 1995;10 Suppl 1:29-35.
217. Romano S, Goodman W, Tamura R, Gonzales J. Long-term treatment of obsessive-compulsive disorder after an acute response: a comparison of fluoxetine versus placebo. J Clin Psychopharmacol 2001;21(1):46-52.
218. Roose SP, Sackeim HA, Krishnan KR, et al. Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. Am J Psychiatry 2004;161(11):2050-9.
219. Roth D, Mattes J, Sheehan KH, Sheehan DV. A double-blind comparison of fluvoxamine, desipramine and placebo in outpatients with depression. Prog Neuropsychopharmacol Biol Psychiatry 1990;14(6):929-39.
220. Rudolph RL, Entsuah R, Chitra R. A meta-analysis of the effects of venlafaxine on anxiety associated with depression. J Clin Psychopharmacol 1998;18(2):136-44.
221. Rudolph RL, Fabre LF, Feighner JP, et al. A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. J Clin Psychiatry 1998;59(3):116-22.
222. Rynn M, Russell J, Erickson J, et al. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. Depress Anxiety 2008;25(3):182-9.
223. Satterlee WG, Faries D. The effects of fluoxetine on symptoms of insomnia in depressed patients. Psychopharmacol Bull 1995;31(2):227-37.
224. Scahill L, Riddle MA, King RA, et al. Fluoxetine has no marked effect on tic symptoms in patients with Tourette's syndrome: a double-blind placebo-controlled study. J Child Adolesc Psychopharmacol 1997;7(2):75-85.
225. Schmidt ME, Fava M, Robinson JM, Judge R. The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. J Clin Psychiatry 2000;61(11):851-7.
226. Schmidt ME, Fava M, Zhang S, et al. Treatment approaches to major depressive disorder relapse. Part 1: dose increase. Psychother Psychosom 2002;71(4):190-4.
227. Schweizer E, Weise C, Clary C, Fox I, Rickels K. Placebo-controlled trial of venlafaxine for the treatment of major depression. J Clin Psychopharmacol 1991;11:233-36.

228. Sharp DM, Power KG, Simpson RJ, Swanson V, Anstee JA. Global measures of outcome in a controlled comparison of pharmacological and psychological treatment of panic disorder and agoraphobia in primary care. Br J Gen Pract 1997;47(416):150-5.
229. Sheehan D, Dunbar GC, Fuell DL. The effect of paroxetine on anxiety and agitation associated with depression. Psychopharmacol Bull 1992;28(2):139-43.
230. Sheehan DV, Burnham DB, Iyengar MK, Perera P. Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. J Clin Psychiatry 2005;66(1):34-40.
231. Sheikh JI, Londborg P, Clary CM, Fayyad R. The efficacy of sertraline in panic disorder: combined results from two fixed-dose studies. Int Clin Psychopharmacol 2000;15(6):335-42.
232. Shrivastava RK, Shrivastava SH, Overweg N, Blumhardt CL. A double-blind comparison of paroxetine, imipramine, and placebo in major depression. J Clin Psychiatry 1992;53 Suppl:48-51.
233. Simeon JG, Dinicola VF, Ferguson HB, Copping W. Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. Prog neuropsychoarmacol Biol Psychiat 1990;14:791-95.
234. Simeon D, Stein DJ, Gross S, et al. A double-blind trial of fluoxetine in pathologic skin picking. J Clin Psychiatry 1997;58(8):341-7.
235. Simon JS, Aguiar LM, Kunz NR, Lei D. Extended release venlafaxine in relapse prevention for patients with major depressive disorder. J Psychiatr Res 2004;38(3):249-57.
236. Small GW, Birkett M, Meyers BS, et al. Impact of physical illness on quality of life and antidepressant response in geriatric major depression. Fluoxetine Collaborative Study Group. J Am Geriatr Soc 1996;44(10):1220-5.
237. Smith WT, Glaudin V, Panagides J, Gilvary E. Mirtazapine vs. amitriptyline vs. placebo in the treatment of major depressive disorder. Psychopharmacol Bull 1990;26(2):191-6.
238. Smith WT, Glaudin V. A placebo-controlled trial of paroxetine in the treatment of major depression. J Clin Psychiatry 1992;53 Suppl:36-9.
239. Stein MB, Chartier MJ, Hazen AL, et al. Paroxetine in the treatment of generalized social phobia: open-label treatment and double-blind placebo-controlled discontinuation. J Clin Psychopharmacol 1996;16(3):218-22.
240. Stein MB, Liebowitz MR, Lydiard RB, et al. Paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial. JAMA 1998;280(8):708-13.
241. Stein DJ, Berk M, Els C, et al. A double-blind placebo-controlled trial of paroxetine in the management of social phobia (social anxiety disorder) in South Africa. S Afr Med J 1999;89(4):402-6.
242. Stein MB, Fyer AJ, Davidson JR, Pollack MH, Wiita B. Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind, placebo-controlled study. Am J Psychiatry 1999;156(5):756-60.
243. Stein DJ, Versiani M, Hair T, Kumar R. Efficacy of paroxetine for relapse prevention in social anxiety disorder: a 24-week study. Arch Gen Psychiatry 2002;59(12):1111-8.
244. Stein MB, Pollack MH, Bystritsky A, Kelsey JE, Mangano RM. Efficacy of low and higher dose extended-release venlafaxine in generalized social anxiety disorder: a 6-month randomized controlled trial. Psychopharmacology (Berl) 2005;177(3):280-8.
245. Stein DJ, van der Kolk BA, Austin C, Fayyad R, Clary C. Efficacy of sertraline in posttraumatic stress disorder secondary to interpersonal trauma or childhood abuse. Ann Clin Psychiatry 2006;18(4):243-9.

246. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group. N Engl J Med 1995;332(23):1529-34.
247. Steiner M, Lamont J, Steinberg S, et al. Effect of fluoxetine on menstrual cycle length in women with premenstrual dysphoria. Obstet Gynecol 1997;90(4 Pt 1):590-5.
248. Steiner M, Romano SJ, Babcock S, et al. The efficacy of fluoxetine in improving physical symptoms associated with premenstrual dysphoric disorder. BJOG 2001;108(5):462-8.
249. Steiner M, Brown E, Trzepacz P, et al. Fluoxetine improves functional work capacity in women with premenstrual dysphoric disorder. Arch Women Ment Health 2003;6(1):71-7.
250. Steiner M, Hirschberg AL, Bergeron R, et al. Luteal phase dosing with paroxetine controlled release (CR) in the treatment of premenstrual dysphoric disorder. Am J Obstet Gynecol 2005;193(2):352-60.
251. Stern WC, Harto-Truax N, Bauer N. Efficacy of bupropion in tricyclic-resistant or intolerant patients. J Clin Psychiatry 1983;44(5 Pt 2):148-52.
252. Stewart JW, Quitkin FM, McGrath PJ, et al. Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo. Arch Gen Psychiatry 1998;55(4):334-43.
253. Stocchi F, Nordera G, Jokinen RH, et al. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. J Clin Psychiatry 2003;64(3):250-8.
254. Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of premenstrual syndrome. Psychopharmacol Bull 1990;26(3):331-5.
255. Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1991;52(7):290-3.
256. Su TP, Schmidt PJ, Danaceau MA, et al. Fluoxetine in the treatment of premenstrual dysphoria. Neuropsychopharmacology 1997;16(5):346-56.
257. Sullivan MD, Katon WJ, Russo JE, et al. Patient beliefs predict response to paroxetine among primary care patients with dysthymia and minor depression. J Am Board Fam Pract 2003;16(1):22-31.
258. Terra JL, Montgomery SA. Fluvoxamine prevents recurrence of depression: results of a long-term, double-blind, placebo-controlled study. Int Clin Psychopharmacol 1998;13(2):55-62.
259. Thase ME. Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. The Venlafaxine XR 209 Study Group. J Clin Psychiatry 1997;58(9):393-8.
260. Thase ME, Nierenberg AA, Keller MB, Panagides J. Efficacy of mirtazapine for prevention of depressive relapse: a placebo-controlled double-blind trial of recently remitted high-risk patients. J Clin Psychiatry 2001;62(10):782-8.
261. Thompson C. Management of depression in real-life settings: knowledge gained from large-scale clinical trials. Int Clin Psychopharmacol 1994;9 Suppl 3:21-5.
262. Tollefson GD, Holman SL. Analysis of the Hamilton Depression Rating Scale factors from a double-blind, placebo-controlled trial of fluoxetine in geriatric major depression. Int Clin Psychopharmacol 1993;8(4):253-9.
263. Tollefson GD, Birkett M, Koran L, Genduso L. Continuation treatment of OCD: double-blind and open-label experience with fluoxetine. J Clin Psychiatry 1994;55 Suppl:69-76; discussion 77-8.

264. Tollefson GD, Holman SL, Sayler ME, Potvin JH. Fluoxetine, placebo, and tricyclic antidepressants in major depression with and without anxious features. J Clin Psychiatry 1994;55(2):50-9.
265. Tollefson GD, Bosomworth JC, Heiligenstein JH, Potvin JH, Holman S. A double-blind, placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. The Fluoxetine Collaborative Study Group. Int Psychogeriatr 1995;7(1):89-104.
266. Trivedi MH, Pigotti TA, Perera P, et al. Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder. J Clin Psychiatry 2004;65(10):1356-64.
267. Turner R. Quality of life: experience with sertraline. Int Clin Psychopharmacol 1994;9 Suppl 3:27-31.
268. Van Ameringen MA, Lane RM, Walker JR, et al. Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. Am J Psychiatry 2001;158(2):275-81.
269. van den Brink RH, van Melle JP, Honig A, et al. Treatment of depression after myocardial infarction and the effects on cardiac prognosis and quality of life: rationale and outline of the Myocardial Infarction and Depression-Intervention Trial (MIND-IT). Am Heart J 2002;144(2):219-25.
270. Vartiainen H, Leinonen E. Double-blind study of mirtazapine and placebo in hospitalized patients with major depression. Eur Neuropsychopharmacol 1994;4(2):145-50.
271. Veeninga AT, Westenberg HGM, Weusten JTN. Fluvoxamine in the treatment of menstrually related mood disorders. Psychopharmacol 1990;102:414-416.
272. Wade AG, Lepola U, Koponen HJ, Pedersen V, Pedersen T. The effect of citalopram in panic disorder. Br J Psychiatry 1997;170:549-53.
273. Wade A, Michael Lemming O, Bang Hedegaard K. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2002;17(3):95-102.
274. Wagstaff AJ, Cheer SM, Matheson AJ, Ormrod D, Goa KL. Spotlight on paroxetine in psychiatric disorders in adults. CNS Drugs 2002;16(6):425-34.
275. Wakelin JS. Fluvoxamine in the treatment of the older depressed patient; double-blind, placebo-controlled data. Int Clin Psychopharmacol 1986;1(3):221-30.
276. Walczak DD, Apter JT, Halikas JA, et al. The oral dose-effect relationship for fluvoxamine: a fixed-dose comparison against placebo in depressed outpatients. Ann Clin Psychiatry 1996;8(3):139-51.
277. Walker JR, Van Ameringen MA, Swinson R, et al. Prevention of relapse in generalized social phobia: results of a 24-week study in responders to 20 weeks of sertraline treatment. J Clin Psychopharmacol 2000;20(6):636-44.
278. Weihs KL, Houser TL, Batey SR, et al. Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. Biol Psychiatry 2002;51(9):753-61.
279. Wenger TL, Stern WC. The cardiovascular profile of bupropion. J Clin Psychiatry 1983;44(5 Pt 2):176-82.
280. Wernicke JF, Dunlop SR, Dornseif BE, Zerbe RL. Fixed-dose fluoxetine therapy for depression. Psychopharmacol Bull 1987;23(1):164-8.
281. Wernicke JF, Dunlop SR, Dornseif BE, Bosomworth JC, Humbert M. Low-dose fluoxetine therapy for depression. Psychopharmacol Bull 1988;24(1):183-8.

282. Westenberg H, Stein D, Yang H, Li D, Barbato L. A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. Journal of clinical psychopharmacology 2004;24(1):49-55.
283. Wikander I, Sundblad C, Andersch B, et al. Citalopram in premenstrual dysphoria: is intermittent treatment during luteal phases more effective than continuous medication throughout the menstrual cycle? J Clin Psychopharmacol 1998;18(5):390-8.
284. Wilson KC, Mottram PG, Ashworth L, Abou-Saleh MT. Older community residents with depression: long-term treatment with sertraline. Randomised, double-blind, placebo-controlled study. Br J Psychiatry 2003;182:492-7.
285. Wood SH, Mortola JF, Chan YF, Moossazadeh F, Yen SS. Treatment of premenstrual syndrome with fluoxetine: a double-blind, placebo-controlled, crossover study. Obstet Gynecol 1992;80(3 Pt 1):339-44.
286. Wood A, Tollefson GD, Birkett M. Pharmacotherapy of obsessive compulsive disorder--experience with fluoxetine. Int Clin Psychopharmacol 1993;8(4):301-6.
287. Yonkers KA, Halbreich U, Freeman E, Brown C, Pearlstein T. Sertraline in the treatment of premenstrual dysphoric disorder. Psychopharmacol Bull 1996;32(1):41-6.
288. Yonkers KA, Halbreich U, Freeman E, et al. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. A randomized controlled trial. Sertraline Premenstrual Dysphoric Collaborative Study Group. JAMA 1997;278(12):983-8.
289. Young SA, Hurt PH, Benedek DM, Howard RS. Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: a randomized, double-blind, placebo-controlled crossover trial. J Clin Psychiatry 1998;59(2):76-80.
290. Zajecka JM. The effect of nefazodone on comorbid anxiety symptoms associated with depression: experience in family practice and psychiatric outpatient settings. J Clin Psychiatry 1996;57 Suppl 2:10-4.
291. Zajecka J, Fawcett J, Amsterdam J, et al. Safety of abrupt discontinuation of fluoxetine: a randomized, placebo-controlled study. J Clin Psychopharmacol 1998;18(3):193-7.
292. Zohar J, Judge R. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. OCD Paroxetine Study Investigators. Br J Psychiatry 1996;169(4):468-74.
293. Zohar J, Amital D, Miodownik C, et al. Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. J Clin Psychopharmacol 2002;22(2):190-5.
294. Zung WW. Review of placebo-controlled trials with bupropion. J Clin Psychiatry 1983;44(5 Pt 2):104-14.

Appendix F. Abstract-only studies (not included)

1. Suicidal ideas with paroxetine or venlafaxine. Prescrire Int. 2004 Feb;13(69):21.
2. Alexopoulos GS, Privitera W, Ventura D, Bose A, Wang Q. Double-blind comparison of escitalopram 10 mg/day and optimally-dosed sertraline 50-200 mg/day in the treatment of major depressive disorder. 2003.
3. Bardenshteyn LM, Ershova AV, Sorokina DO, Bychkova AS. Efficacy of fluoxetine compared to amitriptyline in patients with premenstrual dysphoric disorder. European Psychiatry. 2007;22(Supplement 1):S223-742.
4. Bose A, Gommoll C, Li D, Gandhi C. P.2.c.016 Comparative efficacy of escitalopram and duloxetine in the acute treatment of major depressive disorder. European Neuropsychopharmacology. 2007;17(Supplement 4):S349-S50.
5. Casabona GM, Silenzi V, Guazzelli M. A randomized, double blind, comparison of venlafaxine ER and paroxetine in outpatients with moderate to severe major depression. Eur Neuropsychopharmacol. 2002;12(Suppl 3):S208.
6. Clayton A, Thase ME, Haight BR, Johnson M, Harriett AE, Richard NE. A comparison of bupropion XL with venlafaxine XR for the treatment of MDD: An evaluation of the relative effects on sexual functioning, efficacy, safety, and tolerability. 46th Annual NCDEU (New Clinical Drug Evaluation Unit) Meeting; 2006 June 12 - 15; Boca Raton, FL. 2006:240.
7. Davidson JRT. Escitalopram in the treatment of generalized anxiety disorder: a double-blind, placebo-controlled, flexible dose study. Data on file @ Forest Labs. 2004.
8. de Wilde J, Mertens C, Bartholome F. A double-blind multicentre study comparing paroxetine (20-40 mg) with fluoxetine (20-60 mg) in depressed patients. Biol Psychiatry. 1991 1991;29:255S.
9. Debonnel G, Gobbi G, Turcotte J, Boucher N, Hebert C, De Montigny C, et al. Effects of mirtazapine, paroxetine and their combination: a double-blind study in major depression. Eur Neuropsychopharmacol. 2000 2000;10 (Suppl 3):S252.
10. Ekselius L, von Knorring L, Eberhard G. A double-blind study comparing sertraline and citalopram in patients with major depression treated in general practice. Eur Neuropsychopharmacol. 1997 1997;7 Suppl 2:S147.
11. Emslie GJ. Fluoxetine vs. placebo for continuation treatment of pediatric MDD. 46th Annual NCDEU (New Clinical Drug Evaluation Unit) Meeting; 2006 June 12 - 15; Boca Raton, FL. 2006:44.
12. Figueras G, Perez V, San Martino O, Alverez E, Artigas F. Pretreatment platelet 5-HT concentration predicts the short-term response to paroxetine in major depression. Biol Psychiatry. 1999 1999;40(9):568.
13. Goodman WK, Bose A, Wang Q. Escitalopram 10 mg/day is effective in the treatment of generalized anxiety disorder. Poster presented at: 23rd Annual Conference of the Anxiety Disorders Association of America; March 27-30, 2003; Toronto, Canada. 2003.
14. Gutierrez M. Lack of a pharmacokinetic interaction between escitalopram and the CYP3A4 inhibitor ritonavir. Data on file @ Forest Labs. 2004.
15. Latimer PR, Ravindran AV, Bernatchez JP, Fournier JP, Gojer JA, Barratt K, et al. A six month comparison of toleration and efficacy of sertraline and fluoxetine treatment of major depression. Eur Neuropsychopharm. 1996 1996;6 Suppl 3:124.
16. Lydiard B. Effects of escitalopram on anxiety symptoms in depression. Data on file @ Forest Labs. 2004.

17. McDowell D, Levin FR, Brooks DJ, Carpenter K, Garawi F. Treatment of cannabis-dependent treatment seekers: A double-blind comparison of nefazodone, bupropion and placebo. 68th Annual Scientific Meeting of the College on Problems of Drug Dependence. 2006.
18. Montgomery SA. Comparative efficacy and tolerability of escitalopram oxalate versus venlafaxine XR. Data on file @ Forest Labs. 2004.
19. Ravindran AV, Cameron CJ, Bhatla R, McKay M, Cusi A, Simpson S. Single-center, placebo-controlled, flexible-dose, 12-week study of paroxetine in the treatment of dysthymic disorder without major depression. 46th Annual NCDEU (New Clinical Drug Evaluation Unit) Meeting; 2006 June 12 - 15; Boca Raton, FL. 2006:157.
20. Rudolph R, Entsuah R, Aguiar L, Derivan A. Early onset of antidepressant activity of venlafaxine compared with placebo and fluoxetine in outpatients in a double-blind study. Eur Neuropsychopharm. 1998 1998a;8 Suppl 2:S142.
21. Ruhrman S, Kasper S, Hawellek B, Martinez B, Hoflich G, Nickelsen T, et al. Fluoxetine as a treatment alternative to light therapy in seasonal affective disorder (SAD). Pharmacopsychiatry. 1993;26:193.
22. Salinas E. Once-daily extended release (XR) venlafaxine versus paroxetine in outpatients with major depression. Biol Psychiatry. 1997 1997;42 Suppl 1:244S.
23. Wade AG, Gembert K, Florea I. Comparative study of the efficacy of acute and continuation treatment with Escitalopram versus Duloxetine in patients with major depressive disorder. European Psychiatry. 2008;23(Supplement 2):S268-169.

References

1. Aguglia E, Casacchia M, Cassano GB, et al. Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. Int Clin Psychopharmacol 1993;8(3):197-202.
2. Amini H, Aghayan S, Jalili SA, et al. Comparison of mirtazapine and fluoxetine in the treatment of major depressive disorder: a double-blind, randomized trial. J Clin Pharm Ther 2005;30(2):133-8.
3. Benkert O, Szegedi A, Philipp M, et al. Mirtazapine orally disintegrating tablets versus venlafaxine extended release: a double-blind, randomized multicenter trial comparing the onset of antidepressant response in patients with major depressive disorder. Journal of clinical psychopharmacology 2006(1):75-8.
4. Cookson J, Gilaberte I, Desaiah D, Kajdasz DK. Treatment benefits of duloxetine in major depressive disorder as assessed by number needed to treat. Int Clin Psychopharmacol 2006;21(5):267-73.
5. Davidson JR, Meoni P, Haudiquet V, Cantillon M, Hackett D. Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms. Depress Anxiety 2002;16(1):4-13.
6. Feiger AD, Flament MF, Boyer P, Gillespie JA. Sertraline versus fluoxetine in the treatment of major depression: a combined analysis of five double-blind comparator studies. Int Clin Psychopharmacol 2003;18(4):203-10.
7. Flament MF, Lane R. Acute antidepressant response to fluoxetine and sertraline in psychiatric outpatients with psychomotor agitation. International Journal of Psychiatry in Clinical Practice 2001;5(2):103-109.
8. Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. J Clin Psychopharmacol 2004;24(4):389-99.
9. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: Pooled analysis of placebo-controlled trials. 2002;7(4 Suppl 1):40-44.
10. Grigoriadis S, Kennedy SH, Bagby RM. A comparison of antidepressant response in younger and older women. J Clin Psychopharmacol 2003;23(4):405-7.
11. Lapierre YD, Browne M, Horn E, et al. Treatment of major affective disorder with fluvoxamine. J Clin Psychiatry 1987;48(2):65-8.
12. Llorca PM, Azorin JM, Despiegel N, Verpillat P. Efficacy of escitalopram in patients with severe depression: a pooled analysis. Int J Clin Pract 2005;59(3):268-75.
13. March JS, Kobak KA, Jefferson JW, Mazza J, Greist JH. A double-blind, placebo-controlled trial of fluvoxamine versus imipramine in outpatients with major depression. J Clin Psychiatry 1990;51(5):200-2.
14. Papakostas GI, Fava M. A meta-analysis of clinical trials comparing the serotonin (5HT)-2 receptor antagonists trazodone and nefazodone with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. European Psychiatry 2007;22(7):444-447.
15. Papakostas GI, Montgomery SA, Thase ME, et al. Comparing the rapidity of response during treatment of major depressive disorder with bupropion and the SSRIs: a pooled survival analysis of 7 double-blind, randomized clinical trials. J Clin Psychiatry 2007;68(12):1907-12.
16. Papakostas GI, Trivedi MH, Alpert JE, et al. Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of anxiety symptoms in major depressive disorder:

a meta-analysis of individual patient data from 10 double-blind, randomized clinical trials. J Psychiatr Res 2008;42(2):134-40.
17. Perahia DG, Pritchett YL, Kajdasz DK, et al. A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. J Psychiatr Res 2008;42(1):22-34.
18. Shelton C, Entsuah R, Padmanabhan SK, Vinall PE. Venlafaxine XR demonstrates higher rates of sustained remission compared to fluoxetine, paroxetine or placebo. Int Clin Psychopharmacol 2005;20(4):233-8.
19. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. Biol Psychiatry 2000;48(9):894-901.
20. Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. Biol Psychiatry 2002;52(12):1166-74.
21. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234-41.
22. Thase ME, Haight BR, Richard N, et al. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. J Clin Psychiatry 2005;66(8):974-81.
23. Thase ME, Clayton AH, Haight BR, et al. A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. J Clin Psychopharmacol 2006;26(5):482-8.
24. Wade A, Crawford GM, Angus M, Wilson R, Hamilton L. A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. Int Clin Psychopharmacol 2003;18(3):133-41.
25. DeVane CL, Sallee FR. Serotonin selective reuptake inhibitors in child and adolescent psychopharmacology: a review of published experience. J Clin Psychiatry 1996;57(2):55-66.
26. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997;54(11):1031-7.
27. Emslie GJ, Rush AJ, Weinberg WA, et al. Fluoxetine in child and adolescent depression: acute and maintenance treatment. Depress Anxiety 1998;7(1):32-9.
28. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry 2002;41(10):1205-15.
29. Mayes TL, Tao R, Rintelmann JW, et al. Do children and adolescents have differential response rates in placebo-controlled trials of fluoxetine? CNS Spectr 2007;12(2):147-54.
30. Bielski RJ, Bose A, Chang CC. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists 2005;17(2):65-9.
31. Kelsey JE. Efficacy, safety, and tolerability of venlafaxine XR in generalized anxiety disorder. Depress Anxiety 2000;12 Suppl 1:81-4.
32. Stahl SM, Ahmed S, Haudiquet V. Analysis of the rate of improvement of specific psychic and somatic symptoms of general anxiety disorder during long-term treatment with venlafaxine ER. CNS Spectr 2007;12(9):703-11.
33. Wan GJ, Zhang HF, Tedeschi MA, Hackett D. Estimation of symptom-free days in generalized anxiety disorder. Curr Med Res Opin 2006;22(3):587-91.

34. Cox BJ, Swinson RP, Morrison B, Lee PS. Clomipramine, fluoxetine, and behavior therapy in the treatment of obsessive-compulsive disorder: a meta-analysis. J Behav Ther Exp Psychiatry 1993;24(2):149-53.
35. Greist JH, Jefferson JW, Kobak KA, Katzelnick DJ, Serlin RC. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. A meta-analysis. Arch Gen Psychiatry 1995;52(1):53-60.
36. Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ, Henk HJ. Behavioral versus pharmacological treatments of obsessive compulsive disorder: a meta-analysis. Psychopharmacology (Berl) 1998;136(3):205-16.
37. Nair NP, Bakish D, Saxena B, et al. Comparison of fluvoxamine, imipramine, and placebo in the treatment of outpatients with panic disorder. Anxiety 1996;2(4):192-8.
38. Chung MY, Min KH, Jun YJ, et al. Efficacy and tolerability of mirtazapine and sertraline in Korean veterans with posttraumatic stress disorder: a randomized open label trial. Hum Psychopharmacol 2004;19(7):489-94.
39. Davidson JRT, Weisler RH, Malik M, Tupler LA. Fluvoxamine in civilians with posttraumatic stress disorder. J Clin Psychopharmacol 1998;18(1):93-95.
40. Davidson JRT, Weisler RH, Malik ML, Connor KM. Treatment of posttraumatic stress disorder with nefazodone. Int Clin Psychopharmacol 1998;13(3):111-13.
41. De Boer M, Op den Velde W, Falger PJR, et al. Fluvoxamine treatment for chronic PTSD: a pilot study. Psychother Psychosom 1992;57:158-63.
42. Martenyi F, Brown EB, Zhang H, Prakash A, Koke SC. Fluoxetine versus placebo in posttraumatic stress disorder. J Clin Psychiatry 2002;63(3):199-206.
43. Martenyi F, Brown EB, Zhang H, Koke SC, Prakash A. Fluoxetine v. placebo in prevention of relapse in post-traumatic stress disorder. Br J Psychiatry 2002;181:315-20.
44. Smajkic A, Weine S, Djuric-Bijedic Z, et al. Sertraline, paroxetine, and venlafaxine in refugee posttraumatic stress disorder with depression symptoms. J Trauma Stress 2001;14(3):445-52.
45. Tucker P, Zaninelli R, Yehuda R, et al. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001;62(11):860-8.
46. Allgulander C, Nilsson B. A prospective study of 86 new patients with social anxiety disorder. Acta Psychiatr Scand 2001;103(6):447-52.
47. Diegoli MSC, da Fonseca AM, Diegoli CA, Pinotti JA. A double-blind trial of four medications to treat severe premenstrual syndrome. Int J Gynecol Obstet 1998;62:63-67.
48. Carr RR, Ensom MH. Fluoxetine in the treatment of premenstrual dysphoric disorder. Ann Pharmacother 2002;36(4):713-7.
49. Beasley CMJ, Dornseif BE, Bosomworth JC, et al. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. BMJ 1991;303(6804):685-92.
50. Beasley CM, Dornseif BE, Bosomworth JC, et al. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. Int Clinic Psychopharmacol 1992;6 Suppl 6:35-37.
51. Tollefson GD, Rampey AHJ, Beasley CMJ, Enas GG, Potvin JH. Absence of a relationship between adverse events and suicidality during pharmacotherapy for depression. J Clin Psychopharmacol 1994;14(3):163-9.
52. Gulseren L, Gulseren S, Hekimsoy Z, Mete L. Comparison of fluoxetine and paroxetine in type II diabetes mellitus patients. Arch Med Res 2005;36(2):159-65.

53. Roy-Byrne PP, Pages KP, Russo JE, et al. Nefazodone treatment of major depression in alcohol-dependent patients: a double-blind, placebo-controlled trial. J Clin Psychopharmacol 2000;20(2):129-36.
54. Baldwin DS, Reines EH, Guiton C, Weiller E. Escitalopram therapy for major depression and anxiety disorders. Ann Pharmacother 2007;41(10):1583-92.
55. Croft H, Houser TL, Jamerson BD, et al. Effect on body weight of bupropion sustained-release in patients with major depression treated for 52 weeks. Clin Ther 2002;24(4):662-72.
56. Demyttenaere K, Albert A, Mesters P, et al. What happens with adverse events during 6 months of treatment with selective serotonin reuptake inhibitors? J Clin Psychiatry 2005;66(7):859-63.
57. Ferguson JM. The effects of antidepressants on sexual functioning in depressed patients: a review. J Clin Psychiatry 2001;62 Suppl 3:22-34.
58. Kennedy SH, Eisfeld BS, Dickens SE, Bacchiochi JR, Bagby RM. Antidepressant-induced sexual dysfunction during treatment with moclobemide, paroxetine, sertraline, and venlafaxine. J Clin Psychiatry 2000;61(4):276-81.
59. Letizia C, Kapik B, Flanders WD. Suicidal risk during controlled clinical investigations of fluvoxamine. J Clin Psychiatry 1996;57(9):415-21.
60. Wernicke JF, Sayler ME, Koke SC, Pearson DK, Tollefson GD. Fluoxetine and concomitant centrally acting medication use during clinical trials of depression: the absence of an effect related to agitation and suicidal behavior. Depress Anxiety 1997;6(1):31-9.
61. Wernicke J, Lledo A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo-controlled studies. Drug Saf 2007;30(5):437-55.