Drug Class Review

Second-generation Antidepressants

Final Update 5 Report

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

STRUCTURED ABSTRACT

Purpose

We compared the effectiveness and harms of second-generation antidepressants in the treatment of major depressive disorder (MDD), dysthymia, subsyndromal depression, seasonal affective disorder, generalized anxiety disorder, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder, and premenstrual dysphoric disorder.

Data Sources

We searched PubMed, Embase, PsycINFO, the Cochrane Library, and the International Pharmaceutical Abstracts until September 2010. For additional data we also hand searched reference lists, US Food and Drug Administration medical and statistical reviews and dossiers submitted by pharmaceutical companies.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project review methods.

Results and Conclusions

Overall, we found no substantial differences in comparative efficacy and effectiveness of second-generation antidepressants for the treatment of depressive or anxiety disorders. Differences exist in the incidence of specific adverse events and the onset of action. Except for MDD, the evidence is limited to few direct comparisons for most indications. No head-to-head evidence is available for MDD in pediatric populations, dysthymia, subsyndromal depression, seasonal affective disorder, and premenstrual dysphoric disorder.

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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.[2] Major depressive disorder (MDD) is the most prevalent, affecting more than 16 percent (lifetime) of US adults.[3] In 2000, the economic burden of depressive disorders was estimated to be $83.1 billion.[4] More than 30 percent of these costs were attributable to direct medical expenses.

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

Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs. The first of the second-generation drugs was introduced to the US market in 1985, when bupropion was approved for the treatment of major depressive disorders. In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine. Since then, five other SSRIs have been introduced: sertraline (1991), paroxetine (1992), citalopram (1999), fluvoxamine (2000), and escitalopram (2002). The SNRIs were first introduced to the market in 1993 with the approval of venlafaxine. In 1994, nefazodone, which is essentially an SSRI with additional 5-hydroxytryptamine-2 (5-HT2) and 5-hydroxytryptamine-3 (5-HT3) antagonist properties, was FDA-approved. Mirtazapine, a drug that acts centrally on adrenergic autoreceptors, was added to the therapeutic arsenal in 1996.[5] Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), was approved for the treatment of MDD and diabetic peripheral neuropathic pain in 2004. The latest second-generation antidepressant approved for the treatment of MDD in adults was desvenlafaxine, an SNRI, which was FDA-approved in 2008. Desvenlafaxine is the major active metabolite of venlafaxine XR, which will lose patent protection in 2010.

The mechanism of action of most second-generation antidepressants is only poorly understood. In general, these drugs work through their effect on prominent neurotransmitters in the central nervous system. The SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) act by selectively inhibiting the reuptake of serotonin (5-hydroxy-tryptamine, 5-HT) at the presynaptic neuronal membrane. The SNRIs (desvenlafaine, venlafaxine) are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Mirtazapine, sometimes characterized as an SNRI, is believed to enhance central noradrenergic and serotonergic activity as a 5-HT2 and 5-HT3 receptor antagonist. Nefazodone is believed to inhibit neuronal uptake of serotonin and norepineprhine. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine.

Preclinical studies of duloxetine suggest that it is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake.

With the exception of fluvoxamine, which is approved only for the treatment of obsessive-compulsive disorder (OCD), all of the other second-generation antidepressants are approved for the treatment of MDD. Table 1summarizes 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 SSRIs and SNRIs, ranked third among this group, accounting for $10.9 billion in US prescription sales.[6] The serotonergic class dominates this market, accounting for 57.6 percent of market share in 2002.[6] 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 SSRIs and other second-generation antidepressant have comparable efficacy and comparable or better side effect profiles.[7, 8] However, comparative differences in efficacy, tolerability, and safety are not well defined for the second-generation drugs. The tremendous volume and large variability in the quality of evidence to support use of these products makes it difficult for clinicians and decision makers to make evidence-based decisions.

The purpose of this review is to help policymakers and clinicians make informed choices about the use of SSRIs and newer antidepressants. Given the prominent role of drug therapy in psychiatric disease and the prevalent use of these drugs, our goal is to summarize comparative data on the efficacy, tolerability, and safety of newer antidepressants. This review will focus on newer antidepressant agents: citalopram, escitalopram, desvenlafaxine, fluoxetine, fluvoxamine, paroxetine, sertraline, mirtazapine, duloxetine, venlafaxine, bupropion, and nefazodone. We will examine the role of these agents in treating patients with conditions in diagnostic categories classified by the Diagnostic and Statistical Manual of Mental Disorders (DSM); these include depressive disorders (MDD, dysthymic disorder, subsyndromal depression, and seasonal affective disorder), generalized anxiety disorder (GAD), OCD, panic disorder, post-traumatic stress disorder (PTSD), and social anxiety disorder. We focus this review on these disorders in adult outpatient populations.

Also, we examine the role of these agents in treating premenstrual dysphoric disorder (PMDD, known as late luteal phase dysphoric disorder [LLPDD] in the DSM, version III revised [III-R]) among adult outpatient populations. Technically, PMDD is not considered a discrete diagnostic entity by DSM version IV; instead, it is listed as an example of a Depressive Disorder Not Otherwise Specified. It does, however, have specific research criteria defined in DSM-IV; these are identical to LLPDD in DSM III-R except for the addition of one item. Of note, as of 1999, the FDA Neuropharmacology Advisory Committee supported the concept of PMDD as a distinct clinical entity.

Finally, we examine the role of these agents in treating MDD in pediatric outpatient populations. Tables 1 and 2 show included drugs, dosage forms and recommended doses, and FDA-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)	Citalopram[b]	Celexa®	10, 20, 40mg tabs; 1, 2 mg/ml solution	MDD (adult)
	Escitalopram	Lexapro®	10, 20 mg tabs 1 mg/ml solution	MDD (adult/adolescents); GAD[e]
	Fluoxetine[b]	Prozac®; Prozac Weekly®; Sarafem®	10, 20, 40mg caps; 10 mg tabs; 4 mg/ml solution; 90 mg pellets (weekly)	MDD (adult/ped); OCD; PMDD; Panic disorder
	Fluvoxamine[b]	Luvox® Luvox CR®	25, 50, 100 mg tabs	OCD 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[c]; Panic disorder; Social anxiety disorder; GAD[c]; PTSD[c]; PMDD[d]
	Sertraline	Zoloft®	25, 50, 100 mg tabs; 20 mg/ml solution	MDD (adult); OCD; Panic disorder; PTSD; PMDD; Social anxiety disorder
Selective Serotonin and Norepinephrine Reuptake Inhibitor (SSNRI)	Duloxetine	Cymbalta®	20, 30, 60 mg caps	MDD (adult) DPNP GAD
Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)	Desvenlafaxine	Pristiq®	50, 100 mg tabs	MDD (adult)
	Venlafaxine	Effexor®; Effexor XR®	25, 37.5, 50, 75, 100 mg tabs; 37.5, 75, 150 mg XR caps	MDD (adult); GAD[a]; Panic disorder; Social anxiety disorder[a]
Other second-generation antidepressants	Bupropion[b]	Wellbutrin®; Wellbutrin SR®; Wellbutrin XL®;	75, 100 mg tabs; 50, 100, 150, 200 mg SR tabs 150, 300 mg XL tabs	MDD (adult) Seasonal affective disorder
	Mirtazapine[b]	Remeron®	15, 30, 45 mg tabs; 15, 30, 45 mg orally disintegrating tabs	MDD (adult)
	Nefazodone[b]	Serzone®	50, 100, 150, 200, 250 mg tabs	MDD (adult)

[a] CR, SR, XL, and XR are registered trademarks referring to controlled, sustained, or extended-release dosage forms
GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; PMDD, premenstrual dysphoric disorder; DPNP, diabetic peripheral neuropathic pain
[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
Bupropion	Wellbutrin®	200-450 mg	Three times daily
	Wellbutrin SR®	150-400 mg	Twice daily
	Wellbutrin XL®	150-450 mg	Once daily
Citalopram	Celexa®	20-40 mg	Once daily
Desvenlafaxine	Pristiq®	50 mg	Once daily
Duloxetine	Cymbalta®	40-60 mg	Once or twice daily
Escitalopram	Lexapro®	10-20 mg	Once daily
Fluoxetine	Prozac®	10-80 mg	Once or twice daily
	Prozac Weekly®	90 mg (weekly)	Once weekly
Fluvoxamine	Luvox®	50-300 mg	Once or twice daily
Mirtazapine	Remeron®	15-45 mg	Once daily
Nefazodone[b]	Serzone®[c]	200-600 mg	Twice daily
Paroxetine	Paxil®	20-60 mg	Once daily
	Paxil CR®	12.5-75 mg	Once daily
Sertraline	Zoloft®	50-200 mg	Once daily
Venlafaxine	Effexor®	75-375 mg	Two to three times daily
	Effexor XR®	75-225 mg	Once daily

[a] CR, SR, XL, and XR are registered trademarks referring to controlled-, sustained-, or extended-release dosage forms.
[b] Brand-name product withdrawn from the US market effective June 14, 2004.
[c] Brand-name product no longer available in the US.

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 (DERP) 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 DERP in conjunction with experts in the fields of health policy, psychiatry, pharmacotherapy, and research methods. The participating organizations approved the following key questions:

1. For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders, do second-generation antidepressants differ in efficacy or effectiveness?
2. For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders, do second-generation antidepressants differ in safety or adverse events?

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

This report addresses the initial use of antidepressants. The use 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.[9] 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 FDA 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: - *gastrointestinal symptoms* - *hepatoxicity* - *hyponatremia* - *loss of libido* - *seizures* - *suicide* - *weight gain* - *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, n $\geq$ 1000

METHODS

A. Literature Search

To identify articles relevant to each key question we searched PubMed, Embase, The Cochrane Library, CINAHL, PsycINFO, 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 (MDD, dysthymia, subsyndromal depression, seasonal affective disorder, general anxiety disorder, PTSD, OCD, panic disorder, social anxiety disorder, PMDD), drug interactions, and adverse events with a list of 12 specific second-generation antidepressants (citalopram, desvenlafaxine, 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 2010 (September) to capture literature relevant to the scope of our topic. See Appendix A for complete search strategy.

We 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.04). Additionally, we handsearched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the FDA. The search strategy is summarized in Appendix A.

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.

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. RCTs 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 FDA approval as evidence for general efficacy; therefore, we did not review placebo-controlled trials for FDA-approved indications except when outcome measures assessed quality of life or other health outcomes that are not generally required for FDA 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 FDA. We reviewed all placebo-controlled trials for indications without FDA 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.[10] 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.

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)[11] and the National Health Service Centre for Reviews and Dissemination.[12] 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,[13] 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.

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

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

RESULTS

Overview

We identified 4,850 (1637) 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 were reported in abstract form only and were subsequently excluded (Appendix D).

In all, we included 275 (59) studies: 170 (13) RCTs, 40 (13) meta-analyses, 39 (15) observational studies, and 14 (4) studies of other design. Furthermore, we retrieved 175 (83) articles for background information. Five (Three) studies of interest could not be retrieved after multiple attempts.[14-18] Figure 1 (PRISMA flow chart) documents the disposition of the 1067 (278) articles for these studies.

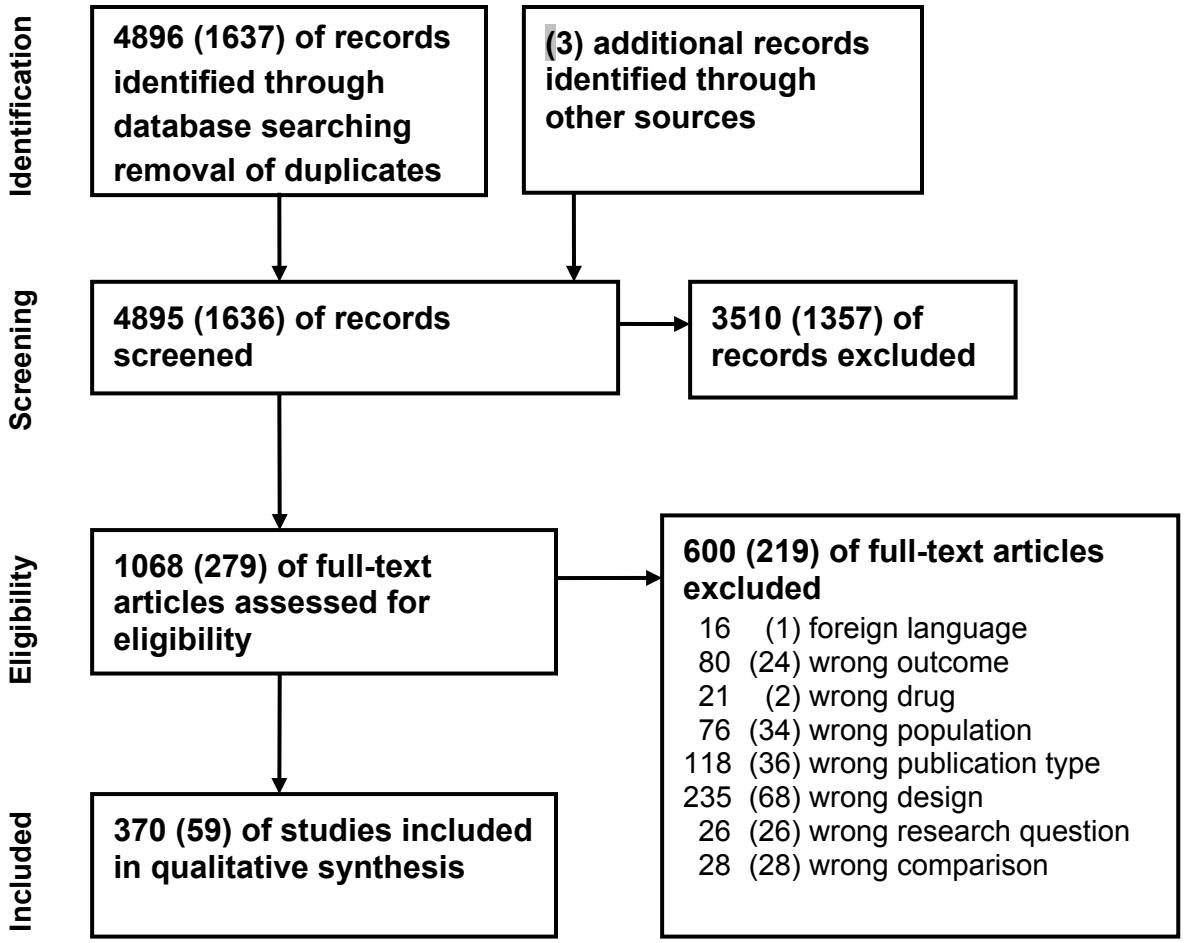
Reasons for exclusions were based on eligibility criteria or methodological criteria (Figure 1, PRISMA flow chart). Seventy-two studies (75 articles) that met the eligibility criteria were later rated as poor quality for internal validity and excluded from the analysis (Appendix C). The two main reasons for a poor quality rating among RCTs 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.[13]

Of 218 (45) included studies, 58 percent were financially supported by pharmaceutical companies; 23 percent were funded by governmental agencies or independent funds. For 19 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.

Figure 1. Results of literature search



[a] Numbers in parentheses are results of the literature search new to Update 5.
DERP uses a modified PRISMA flow diagram.[1]

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 130 RCTs, 28 meta-analyses, and 1 study of other design. Of the RCTs, 95 were head-to-head trials; 35 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 FDA for the treatment of depressive disorders in adults: citalopram, desvenlafaxine, escitalopram, fluoxetine, paroxetine, sertraline mirtazapine, duloxetine, venlafaxine, bupropion, and nefazodone.

Two comparative effectiveness reviews employing different methods of indirect comparisons of the pharmacological treatment of adult depression have been published.[19, 20] Neither review meets formal eligibility criteria because of the inclusion of both in- and outpatients. Nevertheless, we are summarizing the results of both studies because they present the most comprehensive summary of the comparative efficacy and safety of second-generation antidepressants in adult patients with MDD to date.

The first study conducted for AHRQ (Agency for Healthcare Research and Quality) employed head-to-head meta-analyses and indirect statistical methods to evaluate the comparative efficacy for each possible comparison among second-generation antidepressants.[19] Authors used meta-regression and network meta-analyses to conduct indirect comparisons of the HAM-D response rates of drugs with insufficient direct head-to-head evidence. They concluded that results from direct and indirect comparisons indicate that no substantial differences exist among second-generation antidepressants. Authors found statistically significant differences for some comparisons, however, the magnitudes of the differential effects were small (less than a relative risk reductions of 15%) and likely not clinically significant.

The second comparative effectiveness review was conducted by the MANGA (Meta-analysis of New Generation Antidepressants) study group.[20] Researchers used Baysian- based mixed treatment comparisons to determine the relative effectiveness of drugs that have not been compared in head-to-head trials. Results are different from the AHRQ review. Authors of the MANGA group state that escitalopram and sertraline have the best efficacy–acceptability ratio compared with other second-generation antidepressants. This study however, has been criticized for methodological shortcomings.[21-25] Specifically, authors included studies with high risk of bias in their statistical model. In addition, they assumed that a response on the HAM-D scale equals a response on MADRS or CGI despite a lack of evidence to support this assumption.[26]

Several other meta-analyses confirm that no substantial differences exist between duloxetine and SSRIs,[28] escitalopram and SSRIs,[29] fluoxetine and SSRIs[30] paroxetine and some second-generation antidepressants,[31] sertraline and SSRIs,[32] venlafaxine and SSRIs,[33] and SSRI and SNRI as classes.[34]

Since the publication of the above mentioned comparative effectiveness reviews, multiple new head-to-head trials have been published.[35-52] 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 and relevant information.

Fourteen systematic reviews and 75 RCTs compared the effectiveness or efficacy of one second-generation antidepressant to another for treating patients with MDD (Table 6).

Most subjects were younger than 60 years. Inclusion was generally determined on a criteria-based diagnosis (DSM-III-R, DSM-IV]) of MDD 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. Two European trials[53, 54] and one US trial[55] in primary care settings, with less stringent eligibility criteria, could be viewed as effectiveness trials. These studies also had long periods of follow-up.[54, 55] 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.

1. SSRIs compared to SSRIs in adult outpatients with major depressive disorder

Citalopram compared with escitalopram

Five published trials[56-60] and one unpublished[61] 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[56, 57, 59] (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.[56] 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.[61]

A pooled analysis of data from three RCTs concluded that escitalopram significantly improved sleep disturbance compared to citalopram.[62]

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[57]	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[58]	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[56]	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[59]	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)[61]	243	8 weeks	10-20 compared with 20-40	46 compared with 51 *P*=NR	NR	Fair
Yevtushenko et al., 2007[60]	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 1,759 patients and yielded a statistically significant additional treatment effect for escitalopram. The relative risk that a patient would respond was 1.15 (95% CI 1.06 to 1.24) for escitalopram relative to citalopram. Both random effects and fixed effects models presented similar, statistically significant results. The NNT to gain one additional responder based on the pooled risk difference is 13 (95% CI 8 to 39).

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 1.52 point reduction (95% CI 0.59 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.[63]

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 MDD attending general practices were randomly assigned to citalopram (20 mg/d) or fluoxetine (20 mg/d) over 8 weeks.[64] 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.[53] 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.[65] 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.[43, 44] 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.[44] 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).[43] 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).[43]

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 MDD.[36]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 MDD.[66, 67] 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).[67] 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 MDD.[66] 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.[68-74] Two RCTs were conducted in a population older then 60 years.[68, 71] 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).[68] 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[69-74] 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,[70, 71] four trials did not.[69, 72-74] 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.[68, 69, 72-74] A Canadian RCT assessed anxiolytic activity and akathisia as secondary outcome measures and could not detect any significant differences between treatment groups.[69] 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.[69]

We conducted a meta-analysis of five of these studies (excluding studies that did not report data on HAM-D or were conducted in elderly populations) comparing the effects of fluoxetine to paroxetine on HAM-D scores at the end of follow-up.[69, 70, 72-74] A "response" was

defined as an improvement of 50 percent or more on the HAM-D scale. The statistical analysis included 690 patients. Results (Exhibit 3) show that the response rate did not differ significantly between fluoxetine and paroxetine (RR: 1.03; 95% CI 0.92 to 1.16) 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.[54, 55, 73, 75-77] The top-level evidence consisted of two effectiveness trials[54, 55] and one efficacy trial[78] with long periods of follow-up.

Two fair-rated, multicenter trials from France were conducted in office settings (private psychiatrists and general physicians [GPs]).[54, 78] 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 RCT designed as an effectiveness study and carried out in a primary care setting (primary care physicians) over 9 months.[55] Treatments were randomly allocated. This study enrolled 601 patients at 76 primary care sites. Initial diagnosis for enrollment was not based on diagnostic criteria but rather on the judgment of the treating physician. Criteria-based evaluation classified 74 percent of patients as having MDD, 18 percent dysthymia, and 8 percent minor depression. Patients' treatments could be switched among study drugs or to other antidepressive medications as needed. Intention-to-treat analysis maintained the original randomization. Outcome measures assessing changes in depression and health-related quality of life measures (work, social and physical functioning, concentration and memory, sexual functioning) were administered over the telephone by a blinded third party. Range of dosage and loss to follow-up were incompletely reported. Results did not reveal any significant differences among drugs in any outcome measures at either 3 or 9 months. All treatment groups significantly improved during the study compared to baseline. Subgroup analyses did not show different effectiveness for patients with MDD 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).[73, 75, 77, 79] Treatment durations varied from 6 to 16 weeks. One study was conducted in 236 participants older than 60 years.[77, 79] In this RCT, outcome measures also included quality of life (Q-LES-Q) and cognitive assessments (Shopping List Task [SLT], MMSE, Digital Symbol Substitution Test). Results on these health outcome measures were similar for both drugs. A subgroup analysis of 75 patients 70 years of age or older showed a greater response rate for sertraline-treated patients (P=0.027).[79]

We conducted a meta-analysis of five of these studies comparing the effects of fluoxetine to sertraline on HAM-D scores at study endpoint.[54, 73, 75-77] All studies except one were financially supported by the manufacturer of sertraline. Results are presented in Exhibit 4. We

excluded two studies because different diagnostic scales measured the outcome.[55, 78] Our outcome measure was the relative risk of being a responder on HAM-D at study endpoint. A "response" was defined as an improvement of 50 percent or more on the HAM-D scale. Pooled results included 940 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 1.13 (95% CI 1.01 to 1.26) for sertraline relative to fluoxetine. Both random effects and fixed effects models presented similar, statistically significant results. The NNT to gain one additional responder based on the pooled risk difference is 13.

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 RCTs, one flexible-dose[80] and one fixed-dose,[81] compared the efficacy and safety of paroxetine and fluvoxamine. The flexible-dose trial was a fair 7-week RCT comparing the efficacy and safety of paroxetine (20-50 mg/d) and fluvoxamine (50-150 mg/d) in 60 outpatients with MDD.[80] 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.[81]

Paroxetine compared with sertraline

One fair-rated Swedish RCT compared paroxetine (20-40 mg/d) to sertraline (50-150 mg/d) in a 24-week study.[82] 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.[83] 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 RCT (N=64) randomly assigned asymptomatic patients with a history of unipolar depression and at least one episode within the past 28 months to prophylactic sertraline (100-200 mg/d) or fluvoxamine (200-300 mg/d) treatment for 24 months.[84, 85] 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.

2. Other second-generation antidepressants compared with SSRIs in adult outpatients with major depressive disorder

Duloxetine compared with fluoxetine

A fair 8-week RCT assigned 173 patients to duloxetine (40-120 mg/d), fluoxetine (20 mg/d), or placebo.[86] 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).[35, 40, 41] The longest study (N=295) lasted 24 weeks.[40] 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.[35] 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%; $P<0.05$).[40, 41]

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.[38, 39, 87] 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.[38] 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.[88] 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

Three trials assessed the efficacy of mirtazapine (15-45 mg/d) and paroxetine (20-40 mg/d).[49, 89, 90] In all three trials, paroxetine and mirtazapine were equally effective in reducing HAM-D and MADRS scores at the endpoint. Mirtazapine led to a faster response in two of the three trials.[89, 90] For example, in a German study, 23.2 percent of mirtazapine-treated patients and 8.9 percent of paroxetine-treated patients responded to the treatment at week 1 ($P < 0.002$).[90] A Kaplan-Meier analysis in the other trial also showed a significantly faster time to response for mirtazapine than for paroxetine (mean 26 days vs. mean 40 days; $P = 0.016$).[89] The NNT to yield one additional patient responding with mirtazapine at weeks 1 or 2 is 7. No significant difference in response rates on the CGI scale was noted. All three trials reported weight gain in significantly more patients treated with mirtazapine than with paroxetine ($P < 0.05$).

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.[91] 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).[92] 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 [93, 94]. A fair European, multinational study assigned 293 patients to escitalopram (10-20 mg/d) or venlafaxine XR (75-150 mg/d).[93] 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 [94]. 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.[95] 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[96, 97] or GAD.[98, 99] 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.[96] 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: $P=0.0004$).[96] Two studies reported significantly more dizziness ($P<0.001$) and sweating ($P<0.05$) in the venlafaxine group than in the fluoxetine group.[97-99]

Seven additional trials also provided predominantly consistent evidence on a similar efficacy of venlafaxine and fluoxetine.[45-48, 100-102] Only one study reported a significantly higher response rate of venlafaxine than fluoxetine (72% compared with 60%; $P=0.023$).[101]

We conducted a meta-analysis of eight studies comparing venlafaxine to fluoxetine.[45, 47, 96-98, 100-102] All studies were financially supported by the manufacturer of venlafaxine. Three studies were excluded because of missing data.[46, 48, 95] The main outcome measure was the response to treatment on HAM-D at study endpoint. Results (Exhibit 5), based on 2,593 patients, show no statistical difference between venlafaxine and fluoxetine (RR 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).[103] 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.[104, 105] A Spanish study compared venlafaxine (75-150 mg/d) to paroxetine (20-40 mg/d) in outpatients (N=84) with either MDD or dysthymia over 24 weeks.[104] 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).[105] 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[106, 107] and one fair[37] 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.[107] 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).[37, 106]

Bupropion compared with SSRIs

A recent, fair-rated meta-analysis compared the benefits and risks of bupropion to SSRIs as a class in 1,332 adult outpatients with MDD.[108] The age of the participants ranged from 36 to 70 years. The analysis included five double-blinded, head-to-head RCTs with study durations from 6 to 16 weeks. Three trials assessed the efficacy and safety of bupropion 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 SSRIs. However, the authors could not pool data on HAM-D and CGI-S because of lack of data.

Bupropion compared with escitalopram

A fair pooled data analysis of two identically designed RCTs assessed the comparative efficacy of bupropion XL (300-450 mg/d), escitalopram (10-20 mg/d), and placebo.[42]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.[109] 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 RCT compared efficacy and sexual side effects of bupropion SR (150-400 mg/d), fluoxetine (20-60 mg/d), and placebo in 456 outpatients with MDD.[110] 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 RCT 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.[111, 112] 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.[113] 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 RCTs compared the incidence of sexual dysfunction in 360 and 364 patients with MDD during 8 weeks of treatment with bupropion SR (150-400 mg/d), sertraline (50-200 mg/d), or placebo.[114, 115] 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.[114] 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 ($P<0.05$).[115]

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 MDD.[116-118] Data from these trials were pooled into one analysis.[118] A total of 125 patients with MDD and sleep disturbance were enrolled for 8 weeks. Loss to follow-up was 17 percent. Effects on sleep were measured by the Hamilton Depression Rating Scale (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).[119, 120] Patients who responded to acute treatment were enrolled in an open-label continuation phase (N=108) from w eek 8 to month 6.[120] 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.[121] 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.

3. SNRIs compared with SNRIs or other second-generation antidepressants in adult outpatients with major depressive disorder

Venlafaxine compared with duloxetine

The only available head-to-head evidence comparing venlafaxine with duloxetine was a pooled data analysis of two identical RCTs that have not been published individually[52]. The study pooled results of two RCTs with a 6-week fixed-dose period comparing venlafaxine XR (150mg/d) with duloxetine (60mg/d) followed by a 6-week flexible dose period in 667 patients with MDD. Both RCTs were funded by the makers of duloxetine. Overall, no significant differences in response (69.1 vs. 62.6) and remission (50.3 vs. 48.1) rates could be detected

between venlafaxine XR-and duloxetine-treated patients. Discontinuation rates, however, were significantly lower in the venlafaxine than in the duloxetine group (25 percent vs. 35 percent; P = 0.006)

Venlafaxine compared with bupropion

Two 8-week RCTs compared the efficacy and safety of venlafaxine XR and bupropion XR.[50, 51] One study was a fixed-dose trial in 591 patients treated with venlafaxine XR (75mg/d), bupropion XR (150 mg/d), or placebo.[51] The other study randomized 576 patients to venlafaxine XR (75-150 mg/d), bupropion XR (150-300 mg/d), and placebo.[50] After 8 weeks of treatment response, remission rates venlafaxine XR and bupropion XR were similar. For example in the flexible-dose study, MADRS response (65 percent vs. 57 percent; P = NR) and remission rates (51 percent vs. 47 percent; P = NR) did not differ significantly between patients on venlafaxine XR and bupropion XR. Likewise, no substantial differences in health outcomes (Q-LES-Q-SF, Shehan Disability Scale), were apparant at study endpoint.[50]

4. Summary of the evidence

Seventy-five head-to-head trials compared the effectiveness and efficacy of one SSRI or other second-generation antidepressant to another. All studies addressed initial use of antidepressants. 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 SSRIs and other second-generation antidepressants for the treatment of MDD with anxiety.[122] Generally, high rates of loss to follow-up limit the validity of many studies.

Effectiveness

One good[53] and two fair-rated[54, 55] 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.[54, 55] The effectiveness of citalopram and sertraline did not differ significantly in a subgroup analysis of patients with recurrent depression.[53] However, this finding is limited to a single trial.

Efficacy

Seventy-five efficacy studies and two comparative effectiveness reports 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.

Overall 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 fluoxetine, paroxetine, and sertraline (Table 7); bupropion maintains sexual satisfaction better than escitalopram, fluoxetine, paroxetine, and sertraline (Table 8); and nefazodone improves sleep quality (Table 9).

Three studies yielded fair evidence that mirtazapine has a significantly faster onset of action than fluoxetine, paroxetine and sertraline. The NNT to yield one additional responder at week 1 or 2 is 7. Two additional studies also reported a faster onset of response for mirtazapine than for fluoxetine and paroxetine but differences did not reach statistically significant levels.[49, 88] The overall efficacy did not differ significantly between mirtazapine and SSRIs. A well conducted meta-analysis comparing mirtazapine with SSRIs as a class confirms these findings.[123] This study did not meet formal eligibility citeria because it included in- and outpatient populations. Nevertheless, findings reported significantly higher response (RR 1.36, 95% CI 1.13 to 1.64) and remission (RR: 1.36; 95% CI 1.20 to 2.36) rates for mirtazapine compared with SSRIs as a class after 2 weeks of treatment.

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.[118] 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.[62]

Muliple studies comparing one SSRI to another provide good to fair evidence that no significant differences exist among SSRIs in improving health-related quality of life or measures of functional capacity (e.g., sleep quality, cognitive function).[36, 54, 57, 66, 71, 78, 80-82, 124]

Several other efficacy studies assessed quality of life and health-related functional capacity in SSRIs compared to other second-generation antidepressants.[37-41, 47, 91, 112, 121] 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.

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

Author, Year	Interventions	N	Results	Quality rating
SSRIs compared with SSRIs				
Burke et al., 2002[57]	Citalopram compared with Escitalopram	491	No differences	Fair
Colonna et al. 2005[58]	Citalopram compared with Escitalopram	357	Significantly more responders and remitters in the escitalopram group at 8 weeks but not at 24 weeks	Fair
Lader et al. 2005[62]	Citalopram compared with Escitalopram (pooled data)	1321	Greater efficacy of escitalopram in reducing sleep disturbance	Fair
Lepola et al., 2003, 2004[56, 125]	Citalopram compared with Escitalopram	471	Significantly more responders and remitters in the escitalopram group	Fair
Moore et al. 2005[59]	Citalopram compared with Escitalopram	280	Significantly more responders and remitters in the escitalopram group	Fair
SCT-MD-02, 2001 (unpublished)[61]	Citalopram compared with Escitalopram	243	No differences	Fair
Yevtushenko et al., 2007[60]	Citalopram compared with Escitalopram	330	Significantly more responders and remitters in the escitalopram group	Fair
Patris et al., 1996[64]	Citalopram compared with Fluoxetine	357	Faster onset of citalopram	Fair
Ekselius et al., 1997[53]	Citalopram compared with Sertraline	400	No differences	Good
Cipriani et al., 2009[29]	Escitalopram compared other with SSRIs (MA)	NR	No differences, except higher response and remission rates for escitalopram than citalopram.	Good
Kasper et al., 2005[65]	Escitalopram compared with Fluoxetine	518	No differences	Fair
Boulenger et al. ,2006[43]	Escitalopram compared with Paroxetine	454	Higher remission rates of escitalopram after 24 weeks	Fair
Baldwin et al., 2006[44]	Escitalopram compared with Paroxetine	323	No difference	Fair
Ventura et al., 2007[36]	Escitalopram compared with Sertraline	212	No difference	Fair
Cipriani et al., 2005[30]	Fluoxetine compared other with SSRIs (MA)	NR	No differences	Good
Dalery et al., 2003[66]	Fluoxetine compared with Fluvoxamine	184	Faster onset of fluvoxamine	Fair
Rapaport et al., 1996[67]	Fluoxetine compared with Fluvoxamine	100	No differences	Fair
Cassano et al., 2002[68]	Fluoxetine compared with Paroxetine	242	Faster onset of paroxetine	Fair
Chouinard et al., 1999[69]	Fluoxetine compared with Paroxetine	203	No differences	Fair

Author, Year	Interventions	N	Results	Quality rating
De Wilde et al., 1993[70]	Fluoxetine compared with Paroxetine	100	Faster onset of paroxetine	Fair
Gagiano et al., 1993[74]	Fluoxetine compared with Paroxetine	90	No differences	Fair
Schone et al., 1993[71]	Fluoxetine compared with Paroxetine	108	Faster onset of paroxetine	Fair
Fava et al., 1998[72]	Fluoxetine compared with Paroxetine	128	No differences	Fair
Bennie et al., 1995[75]	Fluoxetine compared with Sertraline	286	No differences	Fair
Boyer et al., 1998[78]	Fluoxetine compared with Sertraline	242	No differences	Fair
Fava et al., 2002[73]	Fluoxetine compared with Sertraline compared with Paroxetine	284	No differences	Fair
Finkel et al., 1999[79]	Fluoxetine compared with Sertraline	75	Faster onset of sertraline	Fair
Sechter et al., 1999[54]	Fluoxetine compared with Sertraline	238	No differences	Fair
Newhouse et al., 2000[77]	Fluoxetine compared with Sertraline	236	No differences	Fair
Kroenke et al., 2001[55]	Fluoxetine compared with Sertraline compared with Paroxetine	601	No differences	Fair
Katzman et al.,2007[31]	Paroxetine compared with other antidepressants	NR	No differences	Good
Aberg-Wistedt et al., 2000[82]	Paroxetine compared with Sertraline	353	No differences	Fair
Kiev et al., 1997[80]	Paroxetine compared with Fluvoxamine	60	No differences	Fair
Ushiroyama et al., 2004[81]	Paroxetine compared with Fluvoxamine	105	No differences	Fair
Cipriani et al., 2010[32]	Sertraline compared other with SSRIs (MA)	NR	No differences	Good
Nemeroff et al., 1995[83]	Sertraline compared with Fluvoxamine	97	No differences	Fair
Franchini et al., 1997, 2000[84, 85]	Sertraline compared with Fluvoxamine	64	No differences	Fair
SNRIs compared with SSRIs				
Girardi et al., 2009[28]	Duloxetine compared with SSRIs (MA)	6106	No differences	Good
Nierenberg et al., 2007[35]	Duloxetine compared with Escitalopram	684	No differences	Fair
Khan et al., 2007[41]	Duloxetine compared with Escitalopram	278	Higher response and remission rates for escitalopram	Fair
Wade et al, 2007[40]	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[87]	Duloxetine compared with Paroxetine	367	No difference	Fair
Lee et al., 2007[38]	Duloxetine compared with Paroxetine	478	No difference	Fair
Perahia et al., 2006[39]	Duloxetine compared with Paroxetine	392	No difference	Fair
Goldstein et al., 2002[86]	Duloxetine compared with Paroxetine	173	No difference	Fair

Author, Year	Interventions	N	Results	Quality rating
Hong et al., 2003[88]	Mirtazapine compared with Fluoxetine	133	No differences	Fair
Blier et al, 2009[49]	Mirtazapine compared with Paroxetine	40	No difference	Fair
Schatzberg et al., 2002[89]	Mirtazapine compared with Paroxetine	255	Faster onset of mirtazapine	Fair
Benkert et al., 2000[90]	Mirtazapine compared with Paroxetine	275	Faster onset of mirtazapine	Fair
Behnke et al., 2003[91]	Mirtazapine compared with Sertraline	346	Faster onset of mirtazapine	Fair
Machado et al., 2010[34]	SNRIs vs. SSRIs (MA)	3094	Higher remission rates for SNRIs	Good
Allard et al. 2004[92]	Venlafaxine compared with citalopram	151	No differences	Fair
Bielski et al., 2004[94]	Venlafaxine compared with escitalopram	198	No differences	Fair
Eckert et al., 2006[33]	Venlafaxine compared with escitalopram	3212	No differences	Fair
Montgomery et al., 2004[126]	Venlafaxine compared with escitalopram	293	No differences	Fair
Costa e Silva et al., 1998[95]	Venlafaxine compared with Fluoxetine	382	No differences	Fair
Alves et al., 1999[100]	Venlafaxine compared with Fluoxetine	87	Faster onset of venlafaxine	Fair
Corya et al., 2006[48]	Venlafaxine compared with Fluoxetine	119	No differences	Fair
Dierick et al., 1996[101]	Venlafaxine compared with Fluoxetine	314	Significantly higher response rate for venlafaxine	Fair
De Nayer et al., 2002[96]	Venlafaxine compared with Fluoxetine	146	Significantly greater improvement for venlafaxine	Fair
Nemeroff et al., 2007[47]	Venlafaxine compared with Fluoxetine	308	No differences	Fair
Schatzberg et al., 2006[46]	Venlafaxine compared with Fluoxetine	300	No differences	Fair
Tylee et al., 1997[102]	Venlafaxine compared with Fluoxetine	341	No differences	Fair
Ballus et al., 2000[104]	Venlafaxine compared with Paroxetine	84	No differences	Fair
Mehtonen et al., 2000[107]	Venlafaxine compared with Sertraline	147	Significantly higher response rate for venlafaxine	Good
Keller et al., 2007[45]	Venlafaxine ER compared with Fluoxetine	1096	No differences	Fair
Rudolph et al., 1999[97]	Venlafaxine XR compared with Fluoxetine	301	No differences	Fair
Silverstone et al., 1999[98, 99]	Venlafaxine XR compared with Fluoxetine	368	No differences	Fair
McPartlin et al., 1998[105]	Venlafaxine XR compared with Paroxetine	361	No differences	Fair
Shelton et al., 2006[37]	Venlafaxine XR compared with Sertraline	160	No differences	Fair
Sir et al. 2005[106]	Venlafaxine XR compared with Sertraline	163	No differences	Good
Weinmann et al., 2008[127]	Venlafaxine compared with SSRIs (SR)	3142	No difference	Good
Other second-generation antidepressants compared with SSRIs				

Author, Year	Interventions	N	Results	Quality rating
Clayton et al., 2006[42]	Bupropion compared with Escitalopram	830	No differences	Fair
Feighner et al., 1991[109]	Bupropion compared with Fluoxetine	123	No differences	Fair
Coleman et al., 2001[110]	Bupropion compared with Fluoxetine	456	No differences	Fair
Weihs et al., 2000[111, 112]	Bupropion SR compared with Paroxetine	100	No differences	Fair
Coleman et al., 1999[115]	Bupropion compared with Sertraline	364	No differences	Fair
Croft et al., 1999[114]	Bupropion compared with Sertraline	360	No differences	Fair
Kavoussi et al.,1997[113]	Bupropion compared with Sertraline	248	No differences	Fair
Nieuwstraten et al., 2001[108]	Bupropion compared with SSRIs (SR)	1,332	No differences	Good
Rush et al., 1998[118]	Nefazodone compared with Fluoxetine	125	No differences	Fair
Baldwin et al., 1996, 2001[119, 120]	Nefazodone compared with Paroxetine	206	No differences	Fair
Feiger et al., 1996[121]	Nefazodone compared with Sertraline	160	No differences	Fair
Panzer et al. 2005[122]	SSRIs compared with other 2nd generation antidepressants (SR)	NR	No differences in patients with comorbid anxiety	Fair
SNRIs compared with SNRIs or other second-generation antidepressants				
Perahia et al., 2008[52]	Venlafaxine compared with duloxetine (MA)	667	No difference	Fair
Hewett et al., 2009[50]	Venlafaxine XR compared with bupropion XR	576	No difference	Fair
Hewett et al., 2010[51]	Venlafaxine XR compared with bupropion XR	591	No difference	Fair

Abbreviations: MA, meta-analysis, SR, Systematic review

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[91]	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[90]	275	Paroxetine	Significantly more responders (23.2% compared with 8.9%) and remitters (8.8% compared with 2.4%) at day 7 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[88]	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[89]	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 greater sexual satisfaction with bupropion than escitalopram, fluoxetine, paroxetine, and sertraline

Study	Sample size	Comparison	Effect measure	*P* value	Comments
Higher rates of sexual satisfaction with bupropion					
Clayton et al., 2006[42]	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[110]	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[115]	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[114]	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)
Feighner et al. 1991[109]	61	Fluoxetine	NR	NR	Bupropion IR ; study does not report on differences in sexual adverse events
Kavoussi et al. 1997[113, 128]	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 ; No statistically significant differences in efficacy

Study	Sample size	Comparison	Effect measure	*P* value	Comments
			Women : 41% compared with 7% RRR : 0.85 RD : 0.38 NNT : 3 Men : 61% compared with 10% RRR : 0.84 RD : 0.51 NNT : 2		outcome measures at endpoint (week 16)
			Higher overall satisfaction with sexual functioning with bupropion SR at endpoint (79% compared with 58%) RRR : 0.50 RD : 0.21 NNT : 5	*P*<0.001	

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[118]	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 FDA for the treatment of dysthymia in adults: citalopram, escitalopram, fluoxetine, sertraline, mirtazapine, bupropion, and nefazodone.

We did not find any head-to-head trials among patients with dysthymia. Five placebo-controlled studies (Table 10) assessed efficacy and tolerability of fluoxetine, paroxetine, and sertraline in a population with dysthymia.[129-136]

1. SSRIs compared to placebo in adults with dysthymia

Fluoxetine compared with placebo

A good RCT determined the efficacy and safety of fluoxetine (10-60 mg/d) in elderly patients with dysthymia over 12 weeks.[135] 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.[136] 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.[133, 134] 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 RCT 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.[129-131] 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.[132] 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.[132, 134]

Efficacy

Evidence from one good study indicates that fluoxetine has only limited efficacy in elderly patients with dysthymia.[135] Fair evidence from two studies indicates that sertraline has a significantly greater efficacy in the treatment of dysthymia than placebo.[129-132] 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
SSRIs compared with placebo				
Devanand et al. 2005[135]	Fluoxetine compared with Placebo	90	No differences in response rates and quality of life	Good
Vanelle et al. 1997[136]	Fluoxetine compared with Placebo	111	Significantly more responders for fluoxetine	Fair
Barrett et al., 2001[133] Williams et al., 2000[134]	Paroxetine compared with Placebo compared with Behavioral therapy	656	Significantly more responders for paroxetine in patients older than 60 years	Fair
Thase et al., 1996[129-131]	Sertraline compared with Imipramine compared with Placebo	412	Significantly more responders for sertraline than placebo	Fair
Ravindran et al., 2000[132]	Sertraline compared with Placebo	310	Significantly more responders and remitters for sertraline	Fair

C. Subsyndromal Depressive Disorders in Adults

1. Head-to-head evidence

We did not find any head-to-head RCTs.

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.[137]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.[138] Improvements on depression scales (HAM-D, Beck Depression Inventory [BDI],

IDS-C) were statistically significantly greater for patients receiving fluoxetine than for those receiving placebo. Likewise, the overall severity of illness (CGI-S) improved statistically significantly more in the fluoxetine than in the placebo group (P=0.002). No significant differences could be detected in psychosocial outcomes.

Paroxetine 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.[133, 134] Participants were stratified into patients 60 years and older (N=415) and patients younger than 60 years (N=241) for ITT analysis.

In the 60 or older subgroup, patients receiving paroxetine showed a greater change in HSCL-D-20 scores than those receiving placebo (P=0.004), but those on paroxetine did not demonstrate more change than patients on behavioral therapy (P=0.17).[134] Effects were similar for patients with dysthymia and minor depression. Paroxetine was not more efficacious than placebo in patients with minor depression in the younger subgroup.[133]

3. Summary of the evidence

We identified no head-to head RCT. 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.[133, 134]

Efficacy

A nonrandomized open-label trial did not detect any differences in efficacy between citalopram and sertraline.[137] In placebo-controlled trials, significant differences in population characteristics make the evidence insufficient to identify differences between treatments.[133, 134, 138]

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

Author, Year	Interventions	N	Results	Quality rating
SSRIs compared with placebo				
Judd et al., 2004[138]	Fluoxetine compared with Placebo	162	Greater improvements on depression scales for fluoxetine than for placebo; no difference in psychosocial outcomes	Fair
Barrett et al., 2001[133] Williams et al., 2000[134]	Paroxetine compared with Placebo compared with Behavioral therapy	656	Significantly more responders for paroxetine in patients older than 60 years	Fair

D. Seasonal Affective Disorder in Adults

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

We found three publications that met our eligibility criteria. These describe two studies assessing SSRIs, one placebo controlled trial of sertraline, and one head-to-head RCT comparing fluoxetine to light therapy.[139-141] 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.[142, 143] 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,[140] or more broadly, major depression, depressive disorder NOS, bipolar disorder depressed, or bipolar disorder NOS with a seasonal pattern.[139] 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. SSRIs 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.[139] 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.[143] 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. SSRIs compared to light therapy in adult outpatients with Seasonal Affective Disorder

Fluoxetine compared with light therapy

One good RCT 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.[140] 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 RCT 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.[142] 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 RCT offers statistically significant evidence for the efficacy of sertraline in seasonal effective disorder.[139] One good RCT of fluoxetine compared with light therapy demonstrated no difference in efficacy between the two therapies.[140]

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
SSRIs compared with light therapy				
Lam et al., 2006[140]	Fluoxetine compared with light therapy	96	No difference in efficacy between fluoxetine and light therapy	Good
SSRIs compared with placebo				
Moscovitch et al., 2004[139]	Sertraline compared with placebo	187	Significantly greater efficacy of sertraline	Fair

E. Major Depressive Disorder in Children and Adolescents

Currently, fluoxetine is the only second-generation antidepressant approved by the FDA for treating MDD in both children (2 to 12 years) and adolescents (13 to 18 years). Based on two RCTs,[144 145] escitalopram was approved in 2009 for the acute and long-term treatment of adolescents (12 to 18 years) suffering from MDD. Published evidence is based on controlled clinical trials of children and adolescents 7 to 18 years of age. Fluvoxamine and sertraline are

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

In September 2004, the FDA completed a review of existing data for the risk of both suicidal ideation and suicide attempts in children taking antidepressant drugs for MDD. Based on this review, the FDA 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 FDA's analysis was based on pooled data from short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs 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.

In the published literature, we did not identify any head-to-head trials comparing one second-generation antidepressant to another for treating MDD in children and adolescents. We found seven fair controlled trials comparing a non-FDA-approved SSRI or SNRI 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 SSRIs and an SNRI.[146-148] Two reviews highlighted placebo-controlled evidence already included in this discussion,[147, 148] so we do not comment on them further here. One review, however analyzed published and unpublished data for citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine.[146] 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 MDD (DSM-III, DSM-IV) in addition to a predefined severity of disease (HAM-D $\geq$ 12; CDRS-R > 40; Children's Global Assessment Scale < 60, Montgomery-Åsberg Depression Rating Scale [MADRS] $\geq$ 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, OCD, 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 ($\geq$ 40%-50% reduction in depression score), or remission ($\leq$ 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. SSRIs 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 MDD to citalopram (20-40 mg/d) or placebo.[149] 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 FDA has already established its general efficacy and tolerability, we did review the Treatment for Adolescents with Depression Study (TADS) because it specifically compared fluoxetine, fluoxetine plus CBT, CBT alone, and placebo.[150] 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.[151] 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). Ten percent of the patients included in the TADS study reported at least one event related to suicidality. [152]

Paroxetine compared with placebo

Three multicenter, double-blinded, randomized-controlled trials compared flexible-dose paroxetine to placebo.[153-155] 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.[153] 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,[154] and one fair US based trial randomized 206 patients aged 7-17 to 8 weeks of paroxetine 10-50 mg/day or placebo.[155] All patients met DSM-IV criteria for MDD. 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.[154] 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 RCTs conducted in 53 centers.[156] 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).

2. SNRIs 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.[157] 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 SSRIs and SNRIs to placebo in pediatric outpatients with major depressive disorder

Three systematic reviews evaluated published and unpublished studies comparing a SSRI or SNRI to placebo in children and adolescents.[146-148] The largest report reviewed placebo-controlled studies on citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine, including data for 2,145 randomized participants (5 to 18 years).[146] The authors abstracted data on remission and response (where appropriate criteria were used), and mean depression score. Scales and responder definitions were different for each study. Risks were assessed by abstracting data on suicide-related behaviors and discontinuation of treatment due to adverse events. Risk-benefit profiles were evaluated for each drug. Fluoxetine was the only second-generation reported to have a favorable risk-benefit profile. Data from two unpublished citalopram trials supported a negative risk-benefit profile, although evidence of efficacy was stated to be limited. Published and unpublished data combined for paroxetine demonstrated no improvement in depressive symptoms and little effect on response; additionally, an increased risk of serious adverse events was reported. Unpublished data on sertraline indicated that it may be even less effective than reported in published trials. Combined, published and unpublished data on venlafaxine suggested a negative risk-benefit profile.

This review highlights distinctions between published and unpublished studies, revealing the potential for publication bias. In this study that reviewed more comprehensive evidence than published studies alone, the authors concluded that fluoxetine is the only second-generation antidepressant to demonstrate a favorable risk-benefit profile for the treatment of pediatric outpatients with MDD.

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 MDD.

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 RCTs, provides fair evidence that efficacy to improve health outcomes does not differ between placebo and citalopram, sertraline, paroxetine, and venlafaxine.[146-148] 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[146]	Citalopram ,Fluoxetine, Paroxetine, Sertraline, and Venlafaxine compared with Placebo (SR)	2,145	Only fluoxetine had favorable risk-benefit profile	Fair
Usala et al., 2008[147]	Citalopram ,Fluoxetine, Paroxetine, Sertraline, compared with Placebo (SR)	2,530	Only fluoxetine had favorable risk-benefit profile	Fair
Hetrick et al., 2007[148]	Citalopram ,Fluoxetine, Paroxetine, Sertraline, compared with Placebo (SR)	1,972	Only fluoxetine had favorable risk-benefit profile	Good
SSRIs compared with Placebo				
Wagner et al., 2004[149]	Citalopram compared with Placebo	174	Significantly greater efficacy for citalopram	Fair
March et al., 2004[150] March et al., 2007[151]	Fluoxetine plus CBT compared with Fluoxetine compared with CBT compared with placebo	439	Greater improvement for fluoxetine plus CBT compared to fluoxetine alone, CBT alone, or placebo. Results after 36 weeks equivocal.	Good
Keller et al., 2001[153]	Paroxetine compared with Imipramine compared with Placebo	275	No differences	Fair
Berard et al., 2006[154]	Paroxetine compared with Placebo	286	No differences	Fair
Emslie et al., 2006[155]	Paroxetine compared with Placebo	206	No differences	Fair
Wagner et al., 2003[156]	Sertraline compared with Placebo	376	Significantly greater efficacy for sertraline	Fair
SNRIs compared with placebo				
Mandoki et al., 1997[157]	Venlafaxine compared with Placebo	40	No differences	Fair

Abbreviations: CBT, cognitive behavioral therapy; 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 SSRIs – escitalopram and paroxetine – are approved by the FDA for the treatment of GAD (generalized anxiety disorder). In addition, one SNRI (venlafaxine) and one SSNRI (duloxetine), are approved for the treatment of GAD.

Four head-to-head trials compared one second-generation antidepressant to another for the treatment of GAD.[158-161] Two are rated fair[158, 160] and two rated poor.[159, 161] Additionally, we identified two trials (three publications) that assessed efficacy and tolerability of sertraline,[162-164] an SSRI currently not FDA-approved for GAD.

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 GAD 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 MDD, generally defined by a score of 16-17 or higher on the MADRS.

1. SSRIs compared to SSRIs in adult outpatients with GAD

Escitalopram compared with paroxetine

A fair rated RCT compared escitalopram to paroxetine (and placebo) in 681 patients over a 12 week duration.[158] All active arms were found to improve the symptoms of GAD 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 RCT compared paroxetine (10-40 mg/d) to sertraline (25-100 mg/d) in 55 patients with GAD.[160] 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. SSRIs compared to SNRIs in adult outpatients with GAD

Escitalopram compared with venlafaxine XR

One fair rated RCT (n = 404) compared escitalopram to venlafaxine XR (and placebo) over an 8 week duration.[165] The least square mean difference for venlafaxine XR and for escitalopram was similar (P = not reported).

In the case of CGI-I the response rates were also similar between escitalopram (60%) and venlafaxine XR (65.6%). Discontinuation rates due to adverse events were higher for venlafaxine XR (13%) than for escitalopram (7%), but the P-value was not reported.

Paroxetine compared with venlafaxine

A poor quality study compared venlafaxine and paroxetine.[159] 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 ($\geq$ 50% reduction in the HAM-A) were 90.5 percent for venlafaxine compared with 92 percent for paroxetine (P=0.855).

3. SNRIs compared to SSNRI in adult outpatients with GAD

Venlafaxine compared with duloxetine

A fair rated (n=581) RCT [166], which compared duloxetine 20 mg, duoloxetine 60-120mg and venlafaxine XR 75-225mg found no differences among the treatments. In this 10-week study,

with an overall attrition rate of 31.8%, the mean reduction in HAM-A total score was -14.7 for patients treated with duloxetine 20mg, -15.3 for patients on duloxetine 60-120mg,and -15.5 for patients in the venlafaxine XR group. The response and remission rates were also similar for the different treatment groups (60 percent vs. 65 percent vs. 61 percent, respectively). Treatment groups did not differ significantly in their rate of study discontinuation due to adverse events.

A poor quality study not included in this report showed results that were consistent with the findings described above. [161]

4. SSRIs compared to placebo in adult outpatients with GAD

Sertraline compared with placebo

Currently, sertraline is not FDA-approved for the treatment of GAD. We identified two placebo-controlled trials that assessed the efficacy and tolerability of sertraline in GAD.[162-164] Overall these studies found that sertraline could result in better efficacy than placebo in the treatment of GAD.

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.

5. Summary of the evidence

FDA-approved evidence confirms the general efficacy of duloxetine, escitalopram, paroxetine, and venlafaxine for treating GAD. Additional evidence supports the general efficacy of sertraline.[162, 163]

Overall, the evidence is too limited to draw firm conclusions about the comparative efficacy of one second-generation antidepressant to another for treating GAD.

Effectiveness

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

Efficacy

Based on two RCTs the efficacy of venlafaxine and duloxetine is similar.[166, Hartford, 2007 #2552] Likewise, one RCT reported similar efficacy between paroxetine and sertraline.[160]

One RCT reported a greater reduction of HAM-A for escitalopram than paroxetine. This finding, however, is limited to one study funded by the makers of escitalopram.[158]

The evidence for the comparison of paroxetine with venlafaxine is limited to one poor study and, therefore, insufficient to draw conclusions. [159]

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

Author, Year	Interventions	N	Results	Quality rating
SSRIs compared with SSRIs				
Baldwin et al. 2006[158]	Escitalopram compared with Paroxetine	681	Escitalopram 10 mg/day more efficacious in response then paroxetine 20 mg/day	Fair
Ball et al. 2005[160]	Paroxetine compared with Sertraline	55	No difference	Fair
SSRIs compared with SNRIs				
Bose et al. 2008[165]	Escitalopram compared with Venlafaxine XR	404	No difference	Fair
Kim et al. 2006[159]	Paroxetine compared with Venlafaxine	46	No difference	Poor
SNRIs compared with SSNRIs				
Hartford et al. 2007[161]	Venlafaxinecompared with Duloxetine	487	No difference	Poor
Nicolini et al. 2008[166]	Venlafaxine XR and Duloxetine compared with Placebo	581	No difference	Fair
SSRIs compared with Placebo				
Allgulander et al., 2004[162] Dahl et al., 2005[163]	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 [1641]	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 FDA has approved the following SSRIs for the treatment of OCD: fluoxetine, fluvoxamine, paroxetine, and sertraline.

Three head-to-head trials addressing the use of SSRIs or other second-generation antidepressants met our inclusion criteria for the review of OCD (Table 13) One of these head-to-head trials had a 12-week extension phase in which nonresponders were switched to the alternative treatment.[167] One additional trial compared citalopram plus mirtazapine to citalopram alone.[168] Additionally, one placebo-controlled trial was included because it evaluated an SSRI not covered in the reviews or approved by the FDA (Table 15). Four meta-analyses pooled data from studies comparing SSRIs to placebo. All systematic reviews included comparisons of

fluoxetine, fluvoxamine, and sertraline to placebo.[169-171] In addition, two reviews included a comparison of paroxetine to placebo[170] and one included placebo compared with citalopram.[172]

Generally, inclusion was based on a criteria-based diagnosis (DSM-III, DSM-IV) of OCD 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. SSRIs compared to SSRIs in adult outpatients with OCD

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.[173] 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 SSRIs in adult outpatients with OCD

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.[174] 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.[167] 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.[175] 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. SSRIs augmentation compared to SSRI alone in adult outpatients with OCD

A 12-week trial assessed the additional benefits of augmenting treatment with citalopram (40-80 mg/d) with mirtazapine (15-30 mg/d) in 49 outpatients with OCD.[168] 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. SSRIs compared to placebo in adult outpatients with OCD

Meta-analyses

Four meta-analyses reviewed available evidence from placebo-controlled studies;[169-172] we rated these analyses as fair quality and one as good quality.[172] One study pooled results from 10 trials that compared SSRIs *as a class* with placebo.[169] Data representing 1,076 patients were pooled to define the SSRI group, which consisted of fluvoxamine (five studies), fluoxetine (two studies), and sertraline (three studies). Several studies incorporated multiple dosing arms in the study design.[176, 177] For these trials, only the highest dosing arm was incorporated in the meta-analytic results.

As a class, SSRIs 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 SSRIs 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 SSRIs when compared to placebo.

A second meta-analysis evaluated placebo-controlled trials of fluvoxamine, fluoxetine, sertraline, and paroxetine.[170] Specifically, this study used meta-regression to identify sources of heterogeneity in these trials (and clomipramine trials). They identified 12 trials published before 2000 that compared SSRIs to placebo. Only studies that assessed efficacy with Y-BOCS were incorporated in the meta-regression. Effect sizes were estimated as the difference in improvement (decrease in Y-BOCS) between active drug and placebo.

Four fluvoxamine studies[178-181] showed a net improvement of -4.84 (95% CI -7.78 to -1.83). For the three fluoxetine studies,[182-184] net improvement was -1.61 (95% CI -2.18 to -1.04); for four sertraline studies,[185-188] 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;[171] two fluvoxamine studies;[178, 179] two sertraline studies;[185, 186] and two fluoxetine studies.[182, 183] Compared to placebo, effect sizes did not differ significantly between the three SSRIs evaluated.

A fourth meta-analysis included 17 studies and 3097 participants.[172] All consisted of placebo comparisons: 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. Three - citalopram, fluvoxamine and paroxetine - had a greater rate of nausea compared to placebo; two - 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 OCD characterized as stable for more than 6 months.[177] 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[173, 174, #2557] and four meta-analyses[169, 170: #3187, 171] 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;[174, 175, 189] in a follow-up study, 42 percent of nonresponders who switched to the alternative treatment achieved a response.[167] One fair placebo-controlled study showed a significantly greater improvement in disability for citalopram

compared to placebo.[177] 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.[168]

One study provides fair evidence that sertraline has a faster onset of action than fluoxetine[173] in the treatment of OCD. Another fair-rated study reported a faster response for venlafaxine XR compared to paroxetine.[174] A fair-rated study showed no difference between escitalopram and paroxetine throughout 24 weeks of treatment.[175]

FDA-approved evidence exists for the general efficacy of fluoxetine, sertraline, paroxetine, and fluvoxamine for treating OCD. Evidence is insufficient about the efficacy of mirtazapine, bupropion, and nefazodone for treating OCD. Additionally, one study provides fair evidence supporting a greater efficacy of citalopram than placebo.[177]

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

Author, Year	Interventions	N	Results	Quality rating
SSRIs compared with Placebo				
Ackerman et al., 2002[170]	SSRIs compared with Placebo (SR)	530	No differences among SSRIs	Fair
Montgomery et al., 2001[177]	Citalopram compared with Placebo	401	Significantly greater efficacy of citalopram	Fair
Piccinelli et al., 1995[169]	SSRIs compared with Placebo (SR)	1,076	Significantly greater efficacy of SSRIs	Fair
Soomro et al., 2008[172]	SSRIs compared with Placebo (SR)	3097	No differences among SSRIs	Good
Stein et al., 1995[171]	SSRIs compared with Placebo (SR)	516	No differences among SSRIs	Fair
SSRIs compared with SSRIs				
Bergeron et al., 2002[173]	Fluoxetine compared with Sertraline	150	No differences	Fair
Stein et al. 2007[175]	Escitalopram compared with Paroxetine	466	No differences at 12 or 24 weeks	Fair
SSRI compared with SSRI plus another second-generation antidepressant				
Pallanti et al., 2004[168]	Citalopram compared with Citalopram plus mirtazapine	49	No differences at 12 weeks	Fair
Other second-generation antidepressants compared with SSRIs				
Denys et al., 2003[167, 174, 189]	Venlafaxine compared with Paroxetine	150	No differences	Fair

Abbreviations: SR, Systematic Review

C. Panic Disorder

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

For panic disorder, we identified four head-to-head trials of fair quality comparing one SSRI, or other second-generation antidepressant to another.[190-194] We excluded one study – a single-blinded RCT with a poor quality rating for internal validity[191]– 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.[195-197]

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. SSRIs compared to SSRIs in adult outpatients with Panic Disorder

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

Citalopram 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.[190] 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 RCT randomized 225 patients with panic disorder to paroxetine (40-60 mg/d) or sertraline (50-150 mg/d).[192] 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.[191] 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 RCTs 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).[193, 194] 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%).[193] 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; $P<0.05$).[194] However, this study compared a high dose of venlafaxine ER to a medium dose of paroxetine.

2. SSRIs 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.[195-197] The first study enrolled 75 patients to fluvoxamine (50-300 mg/d), placebo, or cognitive therapy.[195] 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.[196] 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.[197] 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 RCT showed venlafaxine ER 225 mg/d to be superior to paroxetine 40 mg/d in reducing full-symptom panic attacks and in PDSS score,[194] the same effect was not seen when comparing venlafaxine ER 150 mg/d or 75 mg/d and paroxetine 40 mg/d.[193, 194]Two fair RCTs provide evidence that the efficacy of reducing panic attacks and improving quality of life does not differ significantly between citalopram and escitalopram[190] or between paroxetine and sertraline[192] 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.[196-199] FDA-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
SSRIs compared with Placebo				
Asnis et al., 2001[197]	Fluvoxamine compared with Placebo	188	Significantly greater efficacy of fluvoxamine	Fair
Black et al., 1993[198]	Fluvoxamine compared with Placebo	75	Significantly greater efficacy of fluvoxamine	Fair
Hoehn-Saric et al., 1993[196]	Fluvoxamine compared with Placebo	50	Significantly greater efficacy of fluvoxamine	Fair
SSRIs compared with SSRIs				
Bandelow et al., 2004[192]	Paroxetine compared with Sertraline	225	No difference	Fair
Pollack et al., 2007[193]	Venlafaxine ER compared with Paroxetine	664	No difference	Fair
Pollack et al., 2007[194]	Venlafaxine ER compared with Paroxetine	653	Significantly greater efficacy of venlafaxine ER 225 mg/d compared to paroxetine 40 mg/d	Fair
Stahl et al., 2003[190]	Citalopram compared with Escitalopram compared with Placebo	366	No difference	Fair

Abbreviations: ER, Extended Release

D. Post-Traumatic Stress Disorder

Currently, only paroxetine and sertraline have been FDA-approved for the treatment of post-traumatic stress disorder (PTSD). As in other chapters, we view FDA-approval as evidence for general efficacy and, therefore, do not review placebo-controlled trials on drugs that have been FDA-approved.

For PTSD, we found four head-to-head studies: one comparing citalopram to sertraline,[200] two comparing nefazodone to sertraline,[201, 202]and one comparing venlafaxine to sertraline.[203] 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 FDA-approved for the treatment of PTSD (Table 17).

Inclusion of patients was generally determined by a criteria-based (DSM-III-R, DSM-IV) diagnosis of PTSD in addition to a predefined threshold on a universally used PTSD 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 MDD or GAD or a history of alcohol and substance abuse.

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

Sertraline compared with Citalopram

A fair study randomized 59 outpatients with PTSD to 10 weeks of citalopram (20-50 mg/d), sertraline (50-200 mg/d), or placebo.[200] 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 RCT randomized 37 patients with PTSD to 12 weeks of sertraline (50-200 mg/d) or nefazodone (100-600 mg/d).[201] 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.[202] 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 RCT (N=538) evaluated the comparative efficacy and safety of sertraline (25-200 mg/d) and venlafaxine ER (37.5-300 mg/d).[203] 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. SSRIs compared to placebo in adult outpatients with PTSD

Fluoxetine compared with placebo

Three placebo-controlled RCTs provide conflicting results on the general efficacy of fluoxetine for the treatment of PTSD.[204, 205] A small fair-rated study enrolled 54 patients to 12 weeks of

fluoxetine (10-60 mg) or placebo.[204] Loss to follow-up was 31.5 percent. Using the Duke Global Rating for PTSD cut-off score of 1 (no symptoms) to define responders, the fluoxetine group had significantly more responders than the placebo group (59% compared with 19%; $P<0.005$). According to Duke Global Rating for PTSD cut-off scores of 1 (no symptoms) or 2 (minimal symptoms) to define responders, a nonstatistically significant trend toward fluoxetine was observed ($P=0.06$). Health-related secondary outcome measures (SIP, disability and stress subscales) showed significantly greater improvements for fluoxetine ($P<0.005$). A Kaplan-Meier analysis reported a significantly faster onset of efficacy for fluoxetine ($P<0.005$) than for placebo.

Two additional, fair studies did not detect any statistically significant differences between fluoxetine and placebo for the treatment of PTSD. One study was a 12-week, fixed-dose (fluoxetine 20 or 40 mg/d) trial (N=411) that enrolled primarily women (71%) with PTSD.[205] 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 RCT that compared fluoxetine (20-60 mg/d) to placebo, psychotherapy, or eye movement desensitization and reprocessing.[206] No significant differences in CAPS scores were detected at endpoint between fluoxetine- and placebo-treated patients.

Venlafaxine compared with placebo

A fair, 6-month, placebo-controlled RCT assessed the efficacy of venlafaxine ER (37.5-300 mg/d) in 329 patients with PTSD.[207] 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,[200] sertraline and nefazodone,[201] and sertraline and venlafaxine ER.[203] FDA-approved evidence exists for the general efficacy of paroxetine and sertraline for treating PTSD. Placebo-controlled trials report general efficacy of venlafaxine but not of fluoxetine in the treatment of PTSD. 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
SSRIs compared with SNRIs				
Davidson et al., 2006[203]	Sertraline compared with Venlafaxine ER	352	No difference in efficacy	Fair
SSRIs compared with SSRIs				
Tucker et al. 2005[200]	Citalopram compared with Sertraline	59	No difference in efficacy	Fair
SSRIs compared with placebo				
Connor et al., 1999[204]	Fluoxetine compared with Placebo	54	Significantly greater efficacy of fluoxetine	Fair
Martenyi et al., 2007[205]	Fluoxetine compared with Placebo	411	No difference in efficacy	Fair
Van der Kolk et al., 2007[206]	Fluoxetine compared with Placebo compared with Eye Movement Desensitization	88	No difference in efficacy between fluoxetine and placebo	Fair
Davidson et al., 2006[207]	Venlafaxine compared with Placebo	329	Significantly greater efficacy of venlafaxine	Fair
SSRIs compared with other second-generation antidepressants (DopRi, 5-HT$_2$)				
McRae et al., 2004[201]	Sertraline compared with Nefazodone	37	No difference in efficacy	Fair
Saygin et al., 2002[202]	Sertraline compared with Nefazodone	60	No differences in efficacy	Poor

E. Social Anxiety Disorder

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

Three head-to-head trials (with placebo arms) compared one second-generation antidepressant to another for the treatment of social anxiety disorder.[208-210] Two 12-week trials compared paroxetine to venlafaxine ER;[208, 210] a 24-week trial compared escitalopram to paroxetine.[209] 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 FDA-approved for social anxiety disorder. One meta-analysis compared fluvoxamine, paroxetine, and sertraline to placebo,[211] an additional meta-analysis summarized the comparative evidence and conducted indirect comparisons of second-generation antidepressants using network-analysis,[212] and one systematic review compared SSRIs to placebo.[213] In addition, 6 placebo-controlled studies evaluated second-generation antidepressants currently not approved by the FDA for social anxiety disorder: two escitalopram studies,[214, 215] two fluoxetine studies,[216, 217] one mirtazapine study,[218] and one nefazodone study.[219] (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.[208, 210, 216, 219] Additionally, several studies limited eligibility using a predefined cut-off point on a validated anxiety rating scale.[208-210, 215, 216]

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).[219]

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.[214] This study evaluated the rate of relapse between active treatment and placebo.

1. SSRIs compared to SSRIs in adult outpatients with social anxiety disorder

One fair-rated double-blinded RCT compared the efficacy and tolerability of one SSRI to another. In addition, a meta-analysis conducted indirect comparisons of second-generation antidepressants for the treatment of social anxiety disorder.

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.[209] 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 subscales, Clinical Global Impression of Improvement scale (CGI-I), Clinical Global Impression of Severity scale CGI-S, and the Sheehan Disability Scale (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.

Indirect comparisons of escitalopram, fluvoxamine, paroxetine, and sertraline

A good meta-analysis of second-generation antidepressants for social anxiety disorder utilized data of more than 6500 patients from three head-to-head trials and 15 placebo-controlled trials. To determine the comparative efficacy among drugs, authors employed network meta-analyses.[212] With the exception of one study, which included children and adolescents, trial populations consisted of adults with mean ages from 35 to 41 years and a relatively equal distribution of males and females. Baseline disease severity varied among participants (range of LSAS scores 74-97). Trials included in the analysis had to have a minimum duration of 12 weeks (range of study duration 12-28 weeks). Individual drugs were included in the network meta-

analysis when at least two similarly designed trials provided CGI-I data. Authors conducted a network-meta-analysis and found no significant differences in response among included SSRIs.

Because of the limited number of component studies, however, estimates of relative effects were imprecise with wide confidence intervals which encompassed potentially important differences.

2. SNRIs compared to SSRIs in adult outpatients with social anxiety disorder

A good meta-analysis conducted indirect comparisons of second-generation antidepressants for the treatment of social anxiety disorder. Two fair double-blinded RCTs compared the efficacy and tolerability of one second-generation antidepressant to an SSRI. An additional

Indirect comparisons of venlafaxine with SSRIs

The above mentioned good meta-analysis of second-generation antidepressants for social anxiety disorder conducted indirect comparisons of venlafaxine with various SSRIs (escitalopram, fluvoxamine, paroxetine, and sertraline) using network-meta-analysis of data on more than 6500 patients three head-to-head trials and 15 placebo-controlled trials.[212] The authors found no significant differences in any of the possible comparisons between venlafaxine and escitalopram, fluvoxamine, paroxetine, or sertraline. However, estimates had wide confidence intervals and encompassed potentially important differences.

Venlafaxine compared with paroxetine

Two 12-week multicenter trials compared venlafaxine ER to paroxetine and placebo.[208, 210] A European trial randomized 436 patients with social anxiety disorder[208] and an American trial randomized 440 patients with social anxiety disorder[210] 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. SSRIs compared to placebo in adult outpatients with social anxiety disorder

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

4. SSRIs compared with placebo

One systematic review evaluated the efficacy of SSRIs compared with placebo in the treatment of social anxiety disorder in adults.[213] This review included placebo-controlled trials of SSRIs ranging in duration from 10-24 weeks and converted treatment effects to standardized effect sizes. Authors concluded that, in general, SSRIs are more effective than placebo in treating social anxiety disorder.

Escitalopram compared with placebo

One fair 12-week study compared flexible doses of escitalopram to placebo.[215] 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.[209] 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.[214] 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.[216, 217] 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[217] 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 ($P<0.05$).

5. Other second-generation antidepressants compared with placebo

Mirtazapine compared with placebo

One fair 10-week trial compared mirtazapine to placebo in 114 women with social phobia.[218] 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 ($P=0.53$).

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.[219] 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%, $P<0.01$).

6. 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. These findings were confirmed in a network meta-analysis that did not find any significant differences in any of the possible comparisons between venlafaxine ER, escitalopram, fluvoxamine, paroxetine, or sertraline. 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.[209] Two comparative trials provide fair evidence of comparable efficacy between venlafaxine ER and paroxetine.[208, 210] 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.[211]

One network meta-analysis of head-to-head trials and placebo-controlled studies provides fair evidence of comparable efficacy between escitalopram, fluvoxamine, paroxetine, sertraline and venlafaxine ER.[212] Six trials and one systematic review.[213] provide fair evidence that SSRIs significantly improve health outcomes compared to placebo.[208-210, 215, 217, 218]

Two placebo-controlled trials did not support the efficacy of fluoxetine[216] and nefazodone.[219] Evidence from three placebo-controlled trials supports the efficacy of escitalopram,[209, 214, 215] and evidence from one placebo-controlled trial supports the efficacy of mirtazapine in women.[218] 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
SSRIs compared with SSRIs				
Hansen et al., 2008[212]	Escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, or venlafaxine ER (Meta-analysis and network analysis)	6,506	No differences among active treatments	Good
Lader et al., 2004[209]	Escitalopram compared with Paroxetine compared with Placebo	839	No difference between active treatments; escitalopram and paroxetine significantly better than placebo	Fair
SNRIs compared with SSRIs				
Allgulander et al., 2004[208]	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[210]	Venlafaxine ER compared with Paroxetine compared with Placebo	440	No difference between active treatments; venlafaxine and paroxetine significantly better than placebo	Fair
SSRIs compared with placebo				
Kasper et al., 2005[215]	Escitalopram compared with Placebo	358	Significantly greater efficacy of escitalopram	Fair
Montgomery et al., 2005[214]	Escitalopram compared with Placebo	372	Significantly lower risk of relapse for escitalopram	Fair
Davidson et al., 2004[217]	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[216]	Fluoxetine compared with Placebo	60	No differences in efficacy	Fair
Muehlbacher et al., 2005[218]	Mirtazapine compared with Placebo	66	Significantly greater efficacy of mirtazapine	Fair
Hedges et al., 2007[213]	SSRIs compared with Placebo (SR)	3,361	SSRIs superior to placebo	Fair
Other second-generation antidepressants compared with placebo				
Van Ameringen et al., 2007[219]	Nefazodone compared with Placebo	105	No significant difference in efficacy; nefazodone significantly higher incidence in some adverse events	Fair

Abbreviations: SR, Systematic Review; ER, Extended Release

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

The FDA has approved fluoxetine, sertraline, and paroxetine CR for the treatment of premenstrual dysphoric disorder (PMDD) and late luteal phase dysphoric disorder (LLPDD). We did not find any head-to-head studies comparing SSRIs or other second-generation antidepressants to each other. Two systematic reviews [220, 221] and two RCTs[222, 223] compared second-generation antidepressants to placebo. These studies are listed in Table 17.

Studies were conducted over two to six menstrual cycles. Some studies included in the meta-analyses [220, 221] compared intermittent luteal phase therapy with continuous treatment and with placebo. Included studies were conducted in women of reproductive age (18 to 49 years) with a clinical diagnosis of PMDD or LLPDD [220] or in women of any age who met the diagnostic criteria for PMS, PMDD and LLDD [221]. Women were required to meet DSM criteria in all two trials. The more recent meta-analysis included studies which used Self-Rating scales, confirmation by psychiatric evaluation or predefined diagnostic criteria for PMDD or LLPDD according to DSM-III or DSM-IV.[220] The detailed interviews required to determine a diagnosis of PMDD 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 PMDD 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.[222, 223] Patients monitored their symptoms through the use of diaries, calendars, or visual analog scales. In addition to patient reports of symptoms, one trial used the 21-item HAM-D.[222] Studies included in the meta-analyses used similar efficacy outcome measures.

1. SSRIs compared to placebo in adult outpatients with premenstrual dysphoric disorder or late luteal phase dysphoric disorder

SSRIs compared with placebo

The updated Cochrane Collaboration Report [220] reported on efficacy outcomes of FDA-approved and non-FDA-approved SSRIs. This good-quality meta-analysis pooled data from 22 trials comparing various SSRIs to placebo, including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

Citalopram was more effective than placebo with a SMD of -1.27 (95% CI -1.86 to -0.69) $P<0.0001$. (The three included studies were different arms of one study comparing placebo to citalopram in different dosages.) There was only one study with fluvoxamine and therefore no meta-analysis was conducted. This RCT did not fulfill our inclusion criteria due to the small sample size.

The second systematic review [221] provides consistent results. Citalopram was more effective than placebo (OR: 0.18; 95% CI 0.06 to 0.51).

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 RCT compared an SNRI, specifically a continuous daily dose of venlafaxine (50-200 mg/d), to placebo over four menstrual cycles.[222] 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 RCT compared a second-generation antidepressant, specifically both a continuous and intermittent daily dose of nefazodone (100-400 mg/d), to placebo over two menstrual cycles.[223] 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).

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.[220, 224]

3. Summary of the evidence

We identified no head-to-head trials. 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

Two meta-analyses provided good evidence that citalopram has a significantly greater efficacy than placebo in the treatment of PMDD and LLPDD. [220, 221] One fair RCT provides evidence that the efficacy is significantly greater for venlafaxine than for placebo.[222] Lastly, evidence from one fair RCT indicates that nefazodone does not have greater efficacy than placebo in the treatment of PMDD or LLPDD.[223] There is FDA-approved evidence of the efficacy of fluoxetine, paroxetine, and sertraline in the treatment of PMDD and LLPDD. We could not identify sufficient evidence on the efficacy of escitalopram, mirtazapine, and bupropion for treating either PMDD or LLPDD.

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
SSRIs compared with placebo				
Brown et al., 2009[220]	5 SSRIs compared with placebo (SR)	2,294	Significantly greater efficacy of SSRIs	Good
Freeman et al., 2001[222]	Venlafaxine compared with placebo	157	Significantly greater efficacy of venlafaxine	Fair
Landen et al, 2001[223]	Nefazadone compared with placebo	69	Significantly greater efficacy of nefazodone	Fair
Shah et al., 2008[221]	5 SSRIs compared with placebo (SR)	2,964	Significantly greater efficacy of SSRIs	Good

Abbreviations: SR, Systematic review

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 RCTs were designed to assess adverse events as primary outcomes. Most published studies were post hoc analyses or retrospective reviews of databases. We included observational studies if the sample size was larger than 100 and the study duration was at least 1 year (Table 21).

A. Tolerability and Discontinuation Rates

Nausea, headache, diarrhea, fatigue, dizziness, sweating, sexual side effects, tremor, dry mouth, and weight gain were commonly reported adverse events. Overall, second-generation antidepressants led to similar adverse events. The frequencies of specific adverse events, however, differed among some second-generation antidepressants.[29, 30, 32, 225]

Table 20 depicts the mean incidence and 95% CI for specific adverse events commonly reported in head-to-head 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 SSRIs. In six studies, the difference reached statistical significance.[93, 94, 97, 101, 102, 104] In six additional trials, the higher rates of nausea or vomiting for venlafaxine were not statistically significant.[95, 96, 98, 100, 105, 107] The rate of patients reporting nausea or vomiting ranged from 8 percent to 48 percent. A

meta-analysis compared the pooled relative risk of nausea and vomiting for venlafaxine with that for comparator SSRIs as a class.[225] The RR was 1.53 (95% CI, 1.26-1.86). The corresponding number needed to harm (NNH) was 9 (95% CI, 6-23). In a subgroup analysis authors limited studies to those with extended-release formulations. Pooled results still detected a higher risk of nausea and vomiting for venlafaxine extended-release than for SSRIs but the statistical significance was lost (RR 1.38; 95% CI 0.93-2.05)

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).[226] A meta-analysis of published and unpublished studies of duloxetine compared with escitalopram, fluoxetine, paroxetine, or venlafaxine as a class yielded similar risks for experiencing adverse events (RR 1.22; 95% CI 0.62-2.43).[28]Duloxetine, however, led to a significantly higher risk of overall discontinuation (RR 1.57; 95% CI 1.27-1.93) or discontinuation due to adverse events (RR 1.16; 95% CI 1.04-1.30) than the comparator drugs as a class.

In most studies, sertraline led to higher rates of diarrhea than did comparator drugs (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine).[53, 54, 73, 75, 77, 79, 82, 83, 91, 107, 113, 121] Incidence was 8 percent (95% CI, 3-11 percent) higher than with comparator drugs. The NNH was 13 (95% CI, 9-29).[225] These results have been confirmed by a Cochrane review. The pooled risk of diarrhea was significantly greater for patients on sertraline than patients treated with bupropion (OR 3.88; 95% CI 1.50-10.07) or mirtazapine (OR 2.74; 95% CI 1.52-4.97).[32]

Whether this finding can be extrapolated to comparisons of sertraline with other second-generation antidepressants remains unclear.

A British study pooled data from Prescription-Event-Monitoring (PEM) of general practitioners 6 months to 1 year after they had issued prescriptions.[227, 228] Included drugs were fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, and nefazodone. The final cohort exceeded 10,000 patients for each drug. Demographics and indications were comparable among study groups. Nausea and vomiting were the two most frequent clinical reasons for withdrawal in the first month of treatment for all drugs. Venlafaxine had the highest rate of nausea and vomiting per 1000 patient months. Like patients using paroxetine, venlafaxine patients also most frequently reported male sexual dysfunction. However, sweating, impotence, and ejaculation failure were significantly higher in the paroxetine group than in the other groups (P=0.004; P<0.001). In addition, patients using paroxetine and those using nefazodone most frequently reported drowsiness and sedation. Sertraline and fluoxetine had significantly lower rate ratios of agitation and anxiety. However, there were more reports of mania during 90 days with fluoxetine than with any other drug. The death and suicide rates did not differ significantly among study groups. Among SSRIs only, drowsiness and sedation were significantly higher in the fluvoxamine and paroxetine group than in the fluoxetine and sertraline group. Overall, the mean incidence density per 1000 patient months for SSRIs 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 RCTs were powered primarily to detect differences in adverse events between fluvoxamine and citalopram[229] and fluvoxamine and paroxetine,[80] and fluvoxamine and fluoxetine.[67] 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).[229] 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.[80] 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.[67] Fluoxetine-treated patients suffered under nausea significantly more often than fluvoxamine patients (42.5% compared with NR; *P*=0.03)

A fair-rated, Dutch prospective observational study followed 1,251 patients for up to 12 months to assess adverse events of sertraline (N=659) compared to other SSRIs (fluoxetine, fluvoxamine, paroxetine).[230] No exclusion criteria were applied. Psychiatrists recorded adverse events at each patient visit. The WHO adverse reaction terminology was used for outcome assessment. Significantly more sertraline patients had the diagnosis of depressive disorder at baseline (*P*<0.001). Overall, 74.1 percent of patients reported at least one adverse event. Diarrhea occurred more frequently in the sertraline group than in the other SSRI groups (*P*<0.05). However, abdominal pain was reported more frequently by other SSRI users than sertraline users (*P*<0.05). No other adverse event differed significantly across groups.

We pooled data from efficacy trials to assess differences in overall loss discontinuation rates, discontinuation rates because of adverse events, and discontinuation rates because of lack of efficacy of SSRIs as a class compared to other second-generation antidepressants in adult outpatients with MDD (Exhibit 6). Available data were insufficient to determine some results for desvenlafaxine 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 SSRIs (RR, 1.42; 95% CI 1.16 to 1.73). Overall, this finding was balanced by lower discontinuation rates because of lack of efficacy for venlafaxine (RR, 0.75; 95% CI 0.53 to 1.05). No significant differences could be detected between SSRIs and mirtazapine or between SSRIs and bupropion. Numerical differences in discontinuation rates attributed to adverse events generally favored SSRIs over mirtazapine and bupropion but did not reach statistical significance.

A meta-analysis of 15 RCTs did not find any statistically significant differences in discontinuation rates because of adverse events between fluoxetine and other SSRIs as a class.[231]

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	8.9% (2.6%-15.2%)	7.3% (0.1%-14.5%)	26.5% (20.5%-32.6%)	13.9% (8.4%-19.5%)	13.5% (8.8%-18.3%)	5.5% (-1.1%-12.0%)
Citalopram	9.1% (5.5%-12.6%)	7.6% (3.4%-11.9%)	15.6% (8.2%-23.0%)	10.3% (5.0%-15.5%)	12.7% (8.5%-16.9%)	12.3% (5.2%-19.4%)
Desvenlafaxine	NR	NR	NR	12.5% (-6.5%-31.6%)	22.5% (16.2%-28.9%)	NR
Duloxetine	17.4% (8.6%-26.2%)	16.4% (11.7%-21.2%)	18.5% (8.8%-28.1%)	12.6% (9.5%-15.7%)	29.0% (19.7%-38.2%)	11.4% (6.5%-16.3%)
Escitalopram	12.0% (6.1%-17.8%)	8.8% (4.6%-13.1%)	18.1% (10.7%-25.5%)	8.9% (5.9%-11.9%)	15.8 (11.9%-19.7%)	5.5% (1.4%-9.6%)
Fluoxetine	10.9% (8.3%-13.4%)	3.9% (2.8%-4.9%)	8.9% (6.1%-11.6%)	13.2% (10.7%-15.7%)	11.6% (9.8%-13.3%)	9.0% (6.8%-11.3%)
Fluvoxamine	18.9% (-13.4%-51.1%)	9.6% (7.9%-11.4%	10.4% (7.3%-13.6%)	31.0% (18.2%-43.8%)	42.5% (39.5%-45.5%)	13.3% (-11.5%-38.2%)
Mirtazapine	6.4% (0%-12.8%)	9.8% (6.2%-13.5%)	13.0% (10.9%-15.1%)	6.5% (1.3%-11.8%)	8.4% (5.6%-11.2%)	18.7% (10.3%-27.1%)
Nefazadone	12% (6.8%-17.1%)	20.4% (14.3%-26.6%)	38.3% (28.2%-48.4%)	14.0% (17.9%-20.2%)	22.6% (13.3%-32.0%)	24.1% (11.1%-37.1%)
Paroxetine	12.0% (9.5%-14.5%)	4.9% (3.3%-6.6%)	6.8% (4.1%-9.4%)	11.8% (9.2%-14.3%)	14.4% (12.7%-16.1%)	16.0% (11.4%-20.7%)
Sertraline	16.5% (13.4%-19.7%)	4.5% (2.8%-6.2%)	9.3% (6.5%-12.1%)	16.7% (6.3%-27.2%)	11.6% (9.4%-13.8%)	10.9% (8.0%-13.8%)
Venlafaxine	10.2% (6.2%-14.2%)	16.2% (11.2%-21.2%)	18.1% (14.4%-21.8%)	13.5% (9.3%-17.6%)	27.9% (24.1%-31.7%)	12.3% (8.6%-16.1%)

[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

A nested case control study examined the risk of sudden cardiac death or near death in patients treated with citalopram, fluoxetine, or venlafaxine.[232]. The study was based on the United Kingdom General Practice Research Database which included data on more than 207,000 patients who initiated treatment with citalopram, fluoxetine, or venlafaxine for MDD or anxiety. The follow-up time was an average of 3.3 years. Within the cohort, 568 cases of sudden cardiac arrest or near death occurred. These cases were matched with more than 14,000 controls. Results showed that no significant differences in risks for sudden cardiac death or near death were obvious between the examined medications. The adjusted odds ratio associated with venlafaxine relative to fluoxetine was 0.66 (95% CI 0.38-1.14), of venlafaxine relative to citalopram was 0.89 (95% CI 0.50-1.60).

We identified three case control studies examining anassociation between antidepressant use and the risk of stroke [233, 234, 235].

A well conducted Dutch study by Trifirò et al investigated the association between ischemic stroke and SSRIs in 996 Dutch patients, 65 years and older, included in a longitudinal

general practice research database (Integrated Primary Care Information Database). Results of this population-based, nested case-control study showed a significantly increased risk of stroke with respect to the current use of SSRIs compared with non-use (OR 1.55; 95% CI 1.07-2.25), particularly when antidepressants were used for less than six months. No excess risk could be found for the use of tricyclic and other antidepressant drugs.

Another good, nested case-control study conducted in patients on antidepressant medication included in an American multi-state managed care organization medical claims database found similar results. [233] The risk of ischemic stroke in current SSRI users compared with remote or nonusers was significantly increased. (adj. HR:1.55; 95% CI 1.00-2.39), whereas the risk of hemorrhagic stroke in current users of SSRIs was not significantly different compared to that of remote or nonusers. (adj. HR: 1.18; 95% CI 0.64-2.16)

Likewise, a fair case-control study including 916 cases of intracerebral or subarachnoid hemorrhage did also not detect any association between hemorrhagic stroke and SSRIs (OR: 1.1; 95% CI 0.7-1.8; P=0.63)[235].

A fair case-control study [236] evaluated the risk of idiopathic venous thromboembolism in 782 patients aged 70 years or younger with a first time diagnosis of venous thromboembolism and concurrent use of antidepressant medication. The study, which included SSRIs, tricyclic antidepressants and other antidepressants, found no increased risk of idiopathic venous thromboembolism among users of SSRIs. The unadjusted OR for current use of SSRIs compared with nonusers of any antidepressant (past use and nonusers combined) was 0.9 (95% CI 0.6-1.2).

Changes in weight

A 32-week acute and continuation trial assessed differences in weight changes among patients treated with fluoxetine, paroxetine, and sertraline.[124] 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.[73] 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 OCD patients also reported the lowest increase in weight gain for fluoxetine (+0.5 kg). Other SSRIs 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.[237] A pooled analysis of two RCTs comparing escitalopram and paroxetine reported a similar gain in body weight for both patient groups.[238] After 27 weeks of followup, patients on escitalopram gained 1.68 kg and patients on paroxetine gained 1.64 kg.

A double-blinded placebo-controlled 52-week acute and continuation trial assessed weight changes during bupropion treatment.[239] Bupropion-treated patients showed a modest but nevertheless significant decrease of body weight from baseline (-1.15 kg; P<0.001). The magnitude of weight change was closely related to the body mass index (BMI). Patients with a higher BMI experienced greater weight loss.

Consistently, studies comparing mirtazapine with other second-generation antidepressants reported higher weight gains for mirtazapine than for the comparator groups. In three RCTs, these differences reached statistical significance.[88-90] Mean weight gains ranged from 0.8 kg to 3.0 kg after 6 to 8 weeks of treatment.

Gastrointestinal bleeding

Evidence from one good[240] and two fair case-control studies[241, 242] indicate an increased risk of upper gastrointestinal tract bleeding during SSRI treatment. The good quality case control study matched 11,025 case patients suffering from bleeding abnormalities with 21,846 control patients. In addition, the study compared 1,008 patients with gastrointestinal bleeding with 1,990 control patients based on the ARNO database, a population-based database for drug use in Italy. This study excluded patients with a prescription for non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antihemorrhagics and antithrombotic agents.

Seven percent of case patients with any bleeding disorder and 6.9 percent of control patients, as well as 8.6 percentof case patients with upper gastrointestinal bleeding and 6.3 percent of control patients were on antidepressants (SSRIs, TCAs, and other antidepressants). None of the studied antidepressants of interest (citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, and venlafaxine) were individually associated with an increased risk for either bleeding abnormalities or gastrointestinal bleeding. Furthermore, SSRIs as a class also did not yield an increased risk of any bleeding abnormality (OR 0.99; 95% CI 0.89 - 1.10). With respect to gastrointestinal bleeding, SSRIs as a class exhibited a numerically increased risk that did not reach statistical significance (OR 1.31; 95% CI 0.91 - 1.88). [240]

The other two included studies confirm an increased risk for upper gastrointestinal bleeding for patients on second-generation antidepressants.[241, 242] In contrast to the Italian-based study reported above, the two studies also enrolled patients who were on NSAIDs and other drugs.

One study matched 1,552 case subjects with 68,590 control subjects using the Manitoba Population Health Research Data Repository. SSRIs were associated with a statistically significant increase in the risk of upper gastrointestinal bleeding (adjusted OR 1.43; 95% CI 1.09 - 1.89) [241]. Furthermore, this study investigated the effect of the combination of different drugs with SSRIs. The risk of suffering from upper gastrointestinal bleeding was higher in case subjects being medicated with SSRIs and non-steroidal anti-inflammatory drugs (NSAID) (OR 3.17; 95% CI 2.01 - 5.00). Proton pump inhibitors had a protective effect (albeit not statistically significant) on upper gastrointestinal bleeding in patients on SSRIs (OR 0.56; 95% CI 0.24 - 1.30).

The other case control study was based on data from the Health Improvement Network database in the United Kingdom and provided similar findings. The study revealed a statistically significant association between a higher risk of upper gastrointestinal tract bleeding and the use of SSRIs (OR1.6; 95% CI 1.2 - 2.1) as well as SNRIs (OR 2.9; 95% CI 1.5 - 5.6). [242]

Fractures

We identified two studies assessing the risk of fractures for subjects on antidepressant medication. [243, 244]. Both studies reported an increased fracture risk for patients with antidepressant intake. The larger study, a well conducted case-control study including 498,617 subjects (124,655 cases and 373,962 controls) from a Danish national prescription database, reported a significant dose-response relationship for citalopram, fluoxetine and sertraline with respect to an increase of the risk of fracture. [243] Amongst SSRIs, high-dose citalopram, fluoxetine, paroxetine, and sertraline were associated with the highest risk for hip fracture (OR 1.98, 95% 1.82-2.16) and other fractures except fractures of the forearm and spine (OR 1.38,

95% CI 1.33-1.44). Evidence regarding the impact of the duration of use on the risk of fractures was mixed for second-generation antidepressants.

Findings of the Danish cohort study described above were consistent with results of a fair, population - based, prospective cohort study on the risk of nonvertebral fractures during antidepressant treatment.[244] This study on 7983 Dutch men and women, aged 55 years or older, revealed a 2.35 times higher risk of nonvertebral fracture for current users of SSRIs compared with non-users of antidepressants. (95% CI, 1.32-4.18). Subjects, who had been using SSRIs for at least six months had a 3.36 fold higher risk of fractures (95% CI, 1.39-8.08).

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.[245] 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). An analysis of AERS data and a claims database on more than 60,000 patients who initiated duloxetine or venlafaxine found no difference in the risk of hepatic injury between the two drugs.[246]

Hyponatremia

Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of hyponatremia in patients treated with SSRIs. However, the methods of our report did not include case reports and case series. The published literature includes numerous case reports of hyponatremia and inappropriate secretion of antidiuretic hormone as rare side effects.[247] 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.

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 FDA data derived from approval reports indicated a higher risk of seizures for bupropion compared with other antidepressants.[248] 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 TCA or SSRI overdose.[249]

Sexual dysfunction

A subgroup analysis of a good Swedish RCT examined the incidence of sexual side effects from citalopram (20-60 mg/d) compared to those from sertraline (50-150 mg/d)[53, 250] in 308 study completers with MDD. Outcome assessment was conducted at baseline and at week 24. Citalopram and sertraline did not differ significantly in the magnitude and frequency of sexual side effects. 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.[251]

A good meta-analysis including data on 1,332 patients reported a significantly higher rate of sexual satisfaction in bupropion- than in SSRI-treated patients with MDD (RR 1.28; 95% CI 1.16 to 1.41).[108]

Multiple studies indicated that bupropion has a lower risk of sexual dysfunction than some SSRIs.[110, 114, 115, 128, 252] Three studies assessed the incidence of sexual dysfunction in depressed outpatients treated with bupropion or sertraline.[114, 115, 128]

Two fair-rated RCTs compared the incidence of sexual dysfunction in 360 and 364 patients with MDD during 8 weeks of treatment with bupropion (150-400 mg/d), sertraline (50-200 mg/d), or placebo.[114, 115] 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.[114] 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 ($P<0.05$).[115]

The third RCT assessed the sexual side effects of bupropion SR (150-400 mg/d) and sertraline (100-300 mg/d) in 248 depressed outpatients.[128] 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 NNT to yield one additional person who is satisfied with the overall sexual function is 7.

A fair, 8-week RCT compared efficacy and sexual side effects of bupropion (150-400 mg/d), fluoxetine (20-60 mg/d), and placebo in 456 outpatients with MDD.[110] 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 RCT comparing bupropion with paroxetine reported significantly lower rates of sexual dysfunction for bupropion than for paroxetine (Sex Effects Scale, $P<0.05$).[253] Subgroup analysis revealed that a significant difference in anti-depressant related sexual dysfunction was detected in men but not in women.

The largest observational study was a Spanish open-label, prospective study using the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) in 1,022 outpatients treated with various antidepressants.[254] All patients had normal sexual functioning at study onset. Overall, 59 percent of patients experienced some type of sexual dysfunction. Among second-

generation antidepressants, citalopram, paroxetine, and venlafaxine had the highest incidence of sexual dysfunction (73 percent, 71 percent, and 67 percent, respectively); mirtazapine and nefazodone had the lowest (24 percent and 8 percent, respectively). This study did not include data on bupropion and escitalopram. In another observational study, findings of a cross-sectional survey of patients on second-generation antidepressants presented similar results.[255] Paroxetine had the highest rate of sexual dysfunction; nefazodone and bupropion had the lowest**.**

Sexual side effects were also commonly reported adverse event for SSRIs and SNRIs in efficacy trials. Most of these studies did not report the use of targeted questions for sexual 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[72, 82, 83, 91, 113, 121] 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).[113] 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).[256]

Suicidality

In 2004 an Expert Working Group of the UK Committee on Safety in Medicines (CSM) investigated ongoing safety concerns about suicidal behavior with some second-generation antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, venlafaxine) in patients with MDD.[257] 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 SSRIs in adults. Results did not yield any evidence that SSRIs increase or protect against the risk of suicide (OR 0.85; 95% CI 0.20 to 3.40).[258] 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.[259] This study did not find any evidence that the risk of suicide (OR 0.57; 95% CI 0.26 to 1.25) or self-harm (OR 0.99; 95% CI 0.86 to 1.14) is greater in patients on second-generation antidepressants than in patients on TCAs.

Findings of other studies are mixed.[152, 260-277] A good meta-analysis of published data on more than 87,000 patients in SSRI trials for various conditions reported a significantly higher risk of suicide attempts for SSRI patients than for placebo-treated patients (2.25; 95% CI 1.14 to 4.55).[278] Furthermore, an increase in the odds ratio of suicide attempts was observed for SSRIs compared to interventions other than TCAs (OR 1.94; 95% CI 1.06 to 3.57). No significant difference existed in the pooled analysis of SSRIs compared to TCAs (OR 0.88; 95% CI 0.54 to 1.42).

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.[266] 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 (RR 2.1; 95% CI 1.1 to 4.1) and mianserin (RR 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.[279] A total of 555 cases of nonfatal suicidal behavior were matched with 2,062 controls. Compared to dothiepin, the risk of suicidal behavior was similar among users of amitryptilin (RR: 0.83; 95% CI 0.61 to 1.13), fluoxetine (RR 1.16; 95% CI 0.90 to1.50), and paroxetine (RR: 1.29; 95% CI 0.97 to 1.70).

A retrospective review of data in FDA summary reports compared the absolute suicide rate and the suicide rate by patient exposure-years of SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), other antidepressants (nefazodone, mirtazapine, bupropion, maprotiline, trazodone, mianserin, dothiepin, imipramine, amitriptyline, venlafaxine), and placebo.[268] Crude suicide rates and adjusted suicide rates did not differ significantly by patient exposure-years among patients assigned to SSRIs, other antidepressants, or placebo. A Spanish database review did not find significant differences in suicidal ideation between paroxetine, imipramine, amitriptylyne, clomipramine, mianserin, doxepin, maprotiline and placebo.[269] A retrospective cohort and a nested case control study using data from a New Zealand database reported a higher rate of self-harms in SSRI- than in TCA-treated patients (OR: 1.66; 95% CI 1.23 to 2.23) but no differences in suicides.[280] However, no differences in self-harm or suicides were apparent among citalopram-, fluoxetine-, or paroxetine-treated patients.

Findings of the CSM Expert Group on suicidality in children are consistent with results from an earlier NICE (National Institute for Clinical Excellence) report.[146] In patients younger than 18 years the risk of self-harm was significantly greater in patients on SSRIs than on TCAs (OR 1.59; 95% CI 1.01 to 2.50). Although no statistically significant differences among SSRIs were detected, the greatest risk of self-harm was among paroxetine users. A retrospective cohort study on almost 21,000 children who had initiated antidepressants [281] and an analysis of FDA data[282] reported similar results. The use of antidepressant drugs in pediatric patients was associated with statistically significant increase in suicidality (RR: 1.66; 95% CI 1.02 to 2.68) . The rate of suicidal event was 27.04 per 1000 patient years for children, compared with an event rate of 4.4 to 9.1 suicidal events per 1000 patient years in adult populations. [277, 281]

Results of other studies are mixed.[283-285] Two studies reported that second-generation antidepressants increase the risk of suicidality in adolescents but decrease the risk in adults [273, 274] The first study, a meta-analysis of observational studies in a combined population of more than 200,000 patients indicated that the use of SSRIs significantly increase the risk of attempted or completed suicides in adolescents (OR 1.92; 95% CI 1.51-2.44). The risk of attempted or

completed suicide among adults, however, was significantly decreased in adults (OR 0.57,95% CI 0.47–0.70) and among people aged 65 years or older (OR 0.46, 95% CI 0.27–0.79). [274] These findings are consistent with a case-control study of more than 1000 adolescents and adults treated with antidepressants for MDD[273] and an unpublished FDA data-analysis on more than 99,000 participants of 372 trials.[286] The FDA pointed out that the risk of suicidality is increased in children and patients 18 to 24 years but not in other adult patients.

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.[287]

A case-control study did not find an association between SSRIs and breast cancer.[215] 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 SSRIs are associated with hyponatremia, especially in older patients.[247] Similarly, reports of liver toxicity with nefazodone have not been confirmed by controlled trials and observational studies.[245] 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.

A case control study based on a cohort of 165,958 patients with depression included in the UK General Practice Research Database, selected a total of 2,243 cases of incident diabetes mellitus and 8,963 matched comparison subjects.[288]Results showed that recent long-term use (> 24 months) of antidepressants in moderate to high daily doses was associated with an increased risk of diabetes (incidence rate ratio, 1.84; 95% CI, 1.35-2.52). For users of SSRIs as a group, increased risk was observed only for recent long-term use of moderate to high daily doses (incidence risk ratio, 2.06; 95% CI, 1.20-3.52). When individual antidepressants were analyzed, increased risk estimates only in long-term users were observed for recent use of fluvoxamine, paroxetine and venlafaxine.

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 SSRIs, fluvoxamine has the highest mean incidence of adverse events.[227] Pooled estimates from efficacy trials suggest that venlafaxine has a statistically significantly higher rate of discontinuation because of adverse events than do SSRIs as a class. However, overall discontinuation rates do not differ significantly between venlafaxine and SSRIs.

Cardiovascular adverse events

Fair evidence from one case-control study with 568 cases of sudden cardiac death or near death revealed no significant differences in risk among citalopram, fluoxetine, or venlafaxine [232].

Evidence from two well conducted case-control studies, each including about 1000 cases, indicates that the use of SSRIs leads to a significantly increased risk of ischemic stroke compared to non-use.[233, 234] No association, however, between SSRIs and an increased risk for hemorrhagic stroke could be detected.[233, 235]

A fair rated case-control study reported no increased risk of idiopathic venous thromboembolism among users of SSRIs.[236]

Fractures

Evidence from a well conducted case control study including 124,655 cases indicates a dose-response relationship for citalopram, fluoxetine, paroxetine, and sertraline for risk of fracture.[243] Results of a fair rated prospective cohort study including individuals aged 55 and older, indicate an increased risk of nonvertebral fractures for current users of SSRIs compared with nonusers. (HR: 2.35, 95% CI 1.32-4.18).[244]

Gastrointestinal bleeding

Fair to good evidence from three case control studies indicate an increased risk of upper gastrointestinal tract bleeding during SSRI and SNRI treatment.[240-242] The combination of SSRIs and NSAIDs appears to further increase the risk of gastrointestinal bleeding.

Sexual dysfunction

Eight trials and a pooled analysis of two identical RCTs provide evidence that bupropion causes lower rates of sexual dysfunction than escitalopram,[42] fluoxetine [109, 110] paroxetine,[253] and sertraline.[110, 115, 128] The NNT to yield one additional person with a high overall satisfaction of sexual functioning is 7. This treatment effect was consistent across all studies.
A cross-sectional survey supports this evidence by reporting the lowest rates of sexual side effects for bupropion and nefazodone in patients treated with SSRIs or other second-generation antidepressants.[255] Multiple trials give fair evidence that paroxetine, sertraline, and mirtazapine tend to have higher rates of sexual side effects than other second-generation antidepressants.[72, 73, 82, 83, 91, 113, 121, 255]

Suicidality

Evidence from controlled trials and large observational studies is mixed about a higher risk of suicidality in patients treated with second-generation antidepressants. Large observational studies suggest that the risk is significantly increased in children, adolescents and young adults but not in older adult patients.[273, 274] Current data does not suggest any differences in risks among second-generation antidepressants.[146, 277, 282]

Weight changes

Multiple studies provide fair evidence that mirtazapine and paroxetine lead to a greater weight gain than do fluoxetine and sertraline.[89, 90, 124, 237] Additionally, one fair study presents evidence that bupropion treatment leads to a moderate loss of body weight.[239]

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[231]	Fluoxetine compared with SSRIs (SR)	NR	No difference in discontinuation rates because of adverse events	Good
Cipriani et al., 2005[30]	Fluoxetine compared with SSRIs (SR)	14,391	No differences in overall discontinuation rates	Good
Cipriani et al., 2010[32]	Sertraline compared with SSRIs (SR)	NR	Higher rates of diarrhea for sertraline	Good
Cipriani et al., 2009[29]	Escitalopram compared with SSRIs (SR)	NR	Similar rates of adverse events	Good
Gartlehner et al. 2008[225]	Venlafaxine compared with SSRIs	3,416	Higher rates of nausea and vomiting for venlafaxine	Good
Girardi et al. 2009[28]	Duloxetine compared with escitalopram, fluoxetine, paroxetine, venlafaxine	NR	Higher rates of overall discontinuation and discontinuation due to adverse events for duloxetine	Good
Greist et al., 2004[226]	Pooled analysis: Duloxetine compared with Paroxetine compared with Fluoxetine	2,345	No differences in nausea between duloxetine and paroxetine, and duloxetine and fluoxetine	N/A
Haffmans et al, 1996[229]	Fluvoxamine compared with Paroxetine	217	Significantly more diarrhea and nausea with fluvoxamine	Fair
Kiev et al., 1997[80]	Fluvoxamine compared with Paroxetine	60	Significantly more sweating with paroxetine	Fair
Mackay et al., 1997, 1999[227, 228]	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[230]	Sertraline compared with SSRIs (OS)	1251	Significantly more diarrhea with sertraline	Fair
Pigott et al., 2007[289]	Duloxetine compared with Escitalopram	296	Over 8 months higher discontinuation rates for duloxetine than for escitalopram	Fair
Rapaport et al., 1996[67]	Fluvoxamine compared with fluoxetine	100	Significantly more nausea with fluoxetine	Fair
Vanderkooy et al., 2002[252]	Bupropion compared with paroxetine compared with sertraline	193	Higher rates of sexual adverse events for paroxetine. Higher rates of gastrointestinal disorders for sertraline	Fair

Author, Year	Interventions	N	Results	Quality rating
	compared with venlafaxine			
Cardiovascular Events				
Chen et al.,2008[233]	Nested case-control study	1086 cases	Increased risk of ischemic stroke for SSRIs No excess risk for hemorrhagic stroke	Good
Jick et al., 2008[236]	Nested case-control study	782 cases	No increased risk of idiopathic venous thromboembolism for SSRIs	Fair
Kharofa et al., 2007[235]	Case-control study	916 cases	No increased risk for hemorrhagic stroke for SSRIs	Fair
Martinez et al., 2010[232]	Nested case-control study	568 cases	No difference in sudden cardiac death or near death of venlafaxine compared with fluoxetine or citalopram	Fair
Trifirò et al., 2010[234]	Nested case-control study	996 cases	Current use of SSRIs associated with increased risk of ischemic stroke compared with non-use	Good
Changes in Weight				
Benkert et al., 2000[90]	Mirtazapine compared with Paroxetine	275	Significant weight gain with mirtazapine	Fair
Fava et al., 2000[73]	Fluoxetine compared with Paroxetine compared with Sertraline	284	Highest weight gain with paroxetine	Fair
Kasper et al., 2009[238]	Escitalopram vs. paroxetine (pooled data)	777	No differences in weight gain between escitalopram and paroxetine	N/A
Maina et al. 2004[237]	Open-label SSRIs	149	Highest weight gain with paroxetine, fluvoxamine, and citalopram	Fair
Schatzberg et al., 2002[89]	Mirtazapine compared with Paroxetine	255	Significant weight gain with mirtazapine	Fair
Fractures				
Vestergaard et al., 2008 [243]	SSRIs Case-control study	124,655 cases	Increased risk of fracture for citalopram, fluoxetine, sertraline	Good
Ziere et al.,2008 [244]	SSRIs Prospective cohort study	7983	SSRIs increased the risk for nonvertebral fractures	Fair
Gastrointestinal Bleeding				
Barbui et al., 2009[240]	SSRIs Case-control study	35,869	No increased risk for gastrointestinal bleeding with SSRIs	Good
de Abajo et al., 2008[242]	SSRIs Case-control study	11,321	Increased risk of gastrointestinal tract bleeding with SSRIs	Fair

Author, Year	Interventions	N	Results	Quality rating
Targownik et al., 2009[241]	SSRIs Case-control study	70,142	Increased risk of gastrointestinal tract bleeding with SSRIs	Fair
Sexual Dysfunction				
Clayton et al., 2002[255]	Cross-sectional survey	6,297	Highest risk for paroxetine and mirtazapine; lowest risk for bupropion	N/A
Clayton et al., 2007[256]	Duloxetine compared with Escitalopram	114	Significantly more sexual adverse events with escitalopram	Fair
Coleman et al., 1999[115]	Bupropion compared with Sertraline	364	Significantly more sexual adverse events with sertraline	Fair
Coleman et al., 2001[110]	Bupropion compared with Fluoxetine	456	Significantly more sexual adverse events with fluoxetine	Fair
Croft et al., 1999[114]	Bupropion compared with Sertraline	360	No differences	Fair
Ekselius et al., 2001[250]	Citalopram compared with Sertraline	308	No differences	Fair
Kennedy et al., 2006[253]	Bupropion compared with Paroxetine	141	Significantly more sexual adverse events with paroxetine	Fair
Landen et al. 2005[251]	Citalopram compared with Paroxetine	119	No differences	Good
Montejo et al., 2001[254]	Prospective cohort study	1,022	Highest incidence of sexual dysfunction for citalopram, paroxetine and venlafaxine; lowest for mirtazapine and nefazodone	Fair
Nieuwstraten et al, 2001[108]	Bupropion compared with SSRIs (SR)	1,332	Significantly higher rate of sexual satisfaction in bupropion group	Good
Segraves et al., 2000[128]	Bupropion compared with Sertraline	248	Significantly more sexual adverse events with sertraline	Fair
Suicidality				
Acharya et al., 2006[271]	Duloxetine compared with placebo (pooled data)	2,996	No difference in suicide risk	Fair
Aursnes et al., 2005[263]	Paroxetine compared with placebo (pooled data)	1,466	Higher risk of suicides in patients on paroxetine	Fair
Barbui et al., 2009[274]	SSRIs (SR of observational studies)	➢ 200,000	SSRIs increase risk of suicides in adolescents but decrease risk in adults	Good
Bridge et al., 2007[283]	SSRIs (SR)	5,310	Higher risk of suicidality for SSRI-treated patients	Good
Didham et al. 2005[280]	SSRIs	57,000	No difference in suicides or self-harm among citalopram, fluoxetine, and paroxetine	Fair
Fergusson et al., 2005[278]	SSRIs compared	87,650	Higher risk of suicide	Good

Author, Year	Interventions	N	Results	Quality rating
	with placebo (SR)		attempts for SSRI-treated patients	
Gibbons et al., 2007[260]	SSRIs (retrospective cohort study)	226,866	SSRIs have a protective effect	Fair
Gunnell et al., 2005[258]	2nd gen. AD compared with placebo (SR)	40,000	No differences in adults	Good
Hammad et al., 2006[282]	SSRIs (SR)	4,582	Higher risk of suicidality for SSRI-treated patients	Good
Isacsson et al., 2005[264]	SSRIs (Case-control)l	41,279	No increased risk	Fair
Jick et al., 2004[267]	SSRIs (Case-control; database review)	159,810	No differences	N/A
Jick et al., 1995[266]	Antidepressants (database review)	172,598	Significantly higher risk of suicide with fluoxetine and mianserin compared to dothiepin	N/A
Khan et al., 2003[268]	Antidepressants (database review)	NR	No differences	N/A
Lopez-Ibor, 1993[269]	Antidepressants (database review)	4,686	No differences	N/A
Martinez et al.,2005[259]	Antidepressants (database review)	146,095	No differences	N/A
Nelson et al., 2007[262]	Sertraline compared with placebo (secondary analysis of RCT data)	752	No difference in suicidal thoughts between sertraline and placebo	Fair
Olfson and Marcus, 2008[273]	Anidepressants compared with no antidepressants	1,368	Antidepressants increase risk of suicides in adolescents but decrease risk in adults	Good
Pedersen et al., 2005[270]	Escitalopram compared with placebo (retrospective cohort study)	4,091	Higher rate of self-harm in escitalopram than in placebo	Fair
Rahme et al., 2008[275]	SSRIs (retrospective cohort study)	128,229	No increase of suicide death with SSRI use	Fair
Schneeweiss et al., 2010[281]	Antidepressants (retrospective cohort study)	20,906	No differences in risks of suicidality among antidepressants in children	Good
Schneeweiss et al., 2010[277]	Antidepressants (retrospective cohort study)	287,543	No differences in risks of suicidality among antidepressants in adults	Good
Tiihonen et al., 2006[265]	Antidepressants (retrospective cohort study)	15,390	Use of antidepressants was associated with an increased risk of attempted suicide	Fair
Tourian et al., 2010[276]	Desvenlafaxine compared with placebo (pooled	2,950	No difference in risk of suicidality	N/A

Author, Year	Interventions	N	Results	Quality rating
	data analysis)			
Valuck et al., 2004[285]	Antidepressants (retrospective cohort study)	24,119	No difference in risk of suicide attempts	Fair
Vanderburg et al., 2009[272]	Sertraline compared with placebo (pooled analysis)	19,923	No increase in suicidality risk	N/A
Vitiello et al., 2009[152]	Fluoxetine compared with placebo(RCT)	439	Risk of suicidality in adolescents does not decrease over time	Good
Other Adverse Events				
Alper et al., 2007[248]	Analysis of FDA trials data	33,885	Seizures more common in bupropion than in other antidepressants	Good
Andersohn et al. 2009[288]	Case control study	11,206	Long-term use of antidepressants in moderate or high daily doses was associated with an increased risk of diabetes	Fair
Buckley et al., 2002[287]	Database analysis	47,329	Highest rate of fatal toxicity for venlafaxine	N/A
Coogan et al., 2005[290]	Case-control	4,996	No association between breast cancer and SSRIs	Fair
Dunner et al., 1998[291]	Prospective observational	3,100	Rate of seizures for bupropion within range of other antidepressants	Fair
Johnston et al., 1991[292]	Prospective observational	3,341	Rate of seizures for bupropion within range of other antidepressants	Fair
Strombom et al., 2008[246]	Duloxetine compared with venlafaxine (Prescription Event Monitoring)	60,052	No difference in risk for hepatic injury between duloxetine and venlafaxine	N/A
Whyte et al., 2003[249]	Prospective observational	538	Seizures more common in venlafaxine overdose than TCA or SSRI overdose	Good

Abbreviations: SR, Systematic review

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, effectiveness, and tolerability of second-generation antidepressants between subgroups and the general population. However, several studies conducted subgroup analyses or used subgroups as the primary study population. Results can provide indirect evidence for Key Question 3. Included studies are presented in Table 22

A. Demographics

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.[137] 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 SSRIs. 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).[65] 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 RCTs were conducted in a population older than 60 years.[68, 71] 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, non-demented 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.[71] 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.[77, 79] 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 ($P = 0.027$).[79]

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.[55]

Mirtazapine compared with paroxetine

A fair trial randomized 255 elderly participants for eight weeks.[89] 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).[92] 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).[46] 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).[293] 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 SSRIs

A pooled data analysis combined original data from eight comparable, double-blind, active-controlled, randomized trials.[294, 295] 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.[295] Among patients treated with SSRIs, however, a significant interaction was observed between treatment and sex ($P=0.004$); older women had a poorer SSRI response (response rate: 28%) 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 SSRIs (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.[294] 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 RCT 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.[111, 112] 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.

2. Ethnicity

No studies directly compared the efficacy, effectiveness and harms of second-generation antidepressants among different races or ethnicities. Therefore, we summarize results of studies that compared second-generation antidepressants with placebo.

Duloxetine compared with placebo

Two pooled analyses of seven placebo-controlled duloxetine trials assessed the efficacy and tolerability of duloxetine in Hispanic[296] and African American patients[297] compared to Caucasian patients. The first analysis included 1,342 Caucasians and 120 Hispanics and found no difference in efficacy outcomes for Hispanics and Caucasians.[296] There were no significant differences between groups in discontinuation rates due to adverse events ir in the types or occurrence of specific adverse events. The second analysis of 1,300 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.[297]

Fluoxetine compared with placebo

An RCT examined ethnic differences in response to antidepressant treatment among depressed HIV-positive patients.[298] 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.[299]

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 MDD.[300]

We briefly describe it here because 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 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 SSRIs described above[294, 295]did not find any significant associations between sex and outcomes or sex and treatment of MDD. Among patients treated with SSRIs, however, a significant interaction was observed between treatment and sex (P=0.04); older women had a poorer SSRI response (28%) 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.[295]

A pooled analysis of data from four sertraline-RCTs conducted in populations with panic disorder, however, reported better responses of female patients on some outcome measures (panic attack frequency, time spent worrying).[301] No differences were apparent in quality of life measures.

Another pooled data analysis of four placebo-controlled duloxetine trials assessed safety and tolerability of duloxetine for the treatment of MDD in 560 men and 1,062 women.[302] 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%, $P < 0.008$).

In another pooled analysis of placebo-controlled trials of desvenlafaxine (n=2913) authors found a significantly higher risk of vomiting for women (OR, 3.36; 95% CI: 2.01-5.63) than for men (OR, 1.12; 95% CI, 0.47-2.63; P<0.03).[303] For efficacy and other safety outcomes the study did not reveal any significant sex-treatment interactions.

One fair study randomized patients to bupropion (150-300 mg/d) or paroxetine (20-40 mg/d).[253] 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).

A fair-rated meta-analysis[304] included experimental and observational studies to assess differences in sexual dysfunction between men and women taking citalopram, fluoxetine, paroxetine, sertraline, or venlafaxine. All drugs caused significantly higher rates of orgasm dysfunction (citalopram OR 4.60, 95% CI: 3.01 to 7.02, $P < 0.00001$; fluoxetine: OR 6.00, 95%

CI: 4.25 to 8.48; $P < 0.00001$; paroxetine: OR 5.60, 95% CI: 3.79 to 8.29; $P < 0.00001$; sertraline: OR 4.29, 95% CI: 3.01 to 6.12; $P < 0.00001$; venlafaxine: OR 7.60; 95% CI: 4.16 to 13.89; $P < 0.00001$) in men; for paroxetine and sertraline there was higher arousal dysfunction in women (paroxetine: OR 0.45, 95% CI 0.31 to 0.67; $P < 0.0001$; sertraline: OR 0.50, 95% CI 0.34 to 0.74; $P < 0.0005$).

In a study comparing fluvoxamine (50 mg/d) and paroxetine (20 mg/d), there was a significant difference in the decrease in hotflashes in menopausal women favoring paroxetine (-81.1 compared with -66.8, $P<0.01$).[81] 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 there was very little agreement in reporting clinical significance of drug-drug interactions.[305] 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, we did not identify any head-to-head trials specifically evaluating drug-drug interactions. We found one recent, fair quality population-based retrospective cohort study exploring the relationship between SSRI use and co-occuring tamoxifen use (a prodrug metabolized by the hepatic cytochrome P450 enzyme system) for breast cancer.[306] The authors used data from 2430 women (median age 74 years in the year before starting tamoxifen) and included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and venlafaxine in the analysis. They assessed death from breast cancer as a consequence of potential interaction between SSRIs and tamoxifen by cytochrome P450 inhibition. Risk of death from breast cancer in women receiving tamoxifen and paroxetine concurrently was significantly increased. The increased risk was directly related to the extent of co-prescribing. Absolute increases of 25 percent, 50 percent, and 75 percent in the proportion of time on tamoxifen that overlapped with use of paroxetine were associated with relative increases of 24 percent, 54 percent, and 91 percent in the risk of death from breast cancer, respectively (adjusted hazard ratios 1.24, 95% CI 1.08 to 1.42; 1.54, 95% CI 1.17 to 2.03, and 1.91, 95% CI 1.26 to 2.89, respectively). No such risk was found with citalopram, fluoxetine, fluvoxamine, sertraline, or venlafaxine.

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, FDA 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

We found no studies directly comparing the efficacy, effectiveness, and tolerability of second-generation antidepressants between depressed patients with comorbidities and the general population. Therefore, we only describe studies conducting subgroup analyses or studies using subgroups as the primary study population. In addition, we do not present findings under subheadings of drug classes for each comorbid condition.

1. Chronic conditions combined

SSRIs compared with placebo

A good meta-analysis using data from six placebo-controlled RCTs on 1299 patients with long-term SSRI-therapy (citalopram, paroxetine, sertraline) for the treatment of depression conducted a subgroup analysis of RCTs in patients with major chronic health conditions (myocardial infarction, stroke) and alcohol dependence.[307] Authors found that with respect to response, overall SSRIs were superior to placebo at 6 to 8 months (OR 1.66, 95 CI 1.12 to 2.48), but not among patients with comorbidities (OR 1.32, 95% CI 0.84 to 2.06). Also, participants without comorbidities had a significantly higher remission rate if treated with SSRIs as compared to those in the placebo group (OR 2.06, 95% CI 1.41 to 3.01); no such statistically significant treatment effect was found in participants with comorbidities (OR 0.87, 95% CI 0.44 to 1.72). Across the trials, the mean dropout rate was 48 percent (range 27%-77%) and authors rated the quality of the included trials as moderate.

2. Alcohol/substance abuse

Fluoxetine compared with placebo

Five randomized placebo-controlled trials assessed the efficacy and tolerability of fluoxetine for the treatment of depression with co-occurring alcoholism[308-311] or co-occurring substance use disorders.[312-314]

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).[308-310] 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 RCT 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.[312] 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 MDD.[313] 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 RCT 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 MDD and comorbid substance abuse disorder and conduct disorder.[314] 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%, RR = 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.

A small, fair-rated 12-week RCT of 50 patients compared the efficacy of fluoxetine (20mg/d) versus placebo for the treatment of depressive symptoms and drinking behavior in adolescents (15-20 years of age) with comorbid MDD and an alcohol use disorder.[311] All study participants also received sessions of cognitive behavioral therapy and motivation enhancement therapy. While participants in both arms experienced improvements in depressive symptoms and drinking-related outcomes, no significant differences in depressive symptoms or drinking behavior between the treatment groups were found.

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.[315] 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.[316] 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 RCTs compared sertraline and placebo in the treatment of patients with depression and co-occurring alcohol dependence.[317-319]

A 24-week study compared sertraline (50-150 mg/d) with placebo in recently detoxified alcohol-dependent patients with current depressive symptoms.[317] Response (≥ 50% decrease in MADRS score) was slightly higher in sertraline- than placebo-treated patients (44% compared with 39%). Both groups experienced significant improvements in HAM-D and MADRS scores during the study, but the two groups did not differ significantly. Relapse rates were higher in sertraline- than placebo-treated patients (31.8% compared with 23.1%) but the difference was not statistically significant (P=0.37). Adverse event rates were similar for both treatment groups. The overall attrition rate was greater than 40 percent; however, there was not a significant difference in withdrawal between groups (sertraline, 45% compared with placebo, 44%).

A 12-week trial showed similar results.[318] 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.[319] This study randomized 328 patients with co-occurring MDD and alcohol dependence to sertraline (50-200 mg/d) or placebo for 10 weeks. After the run-in period, two groups of patients were randomized separately based on HAM-D scores: Group A scores were ≥ 17 while Group B scores were ≤ 16. Mean reduction in HAM-D scores did not differ significantly between all sertraline-treated (-10.8) and placebo-treated (-9.6) patients (P=0.14). There were significant differences in HAM-D response rates by group stratification. In Group A, sertraline led to significantly higher response rate than placebo (64% compared with 47%, P=0.022). However, in Group B, sertraline patients had a significantly lower response rate than placebo patients (58% compared with 77%, P=0.018). There were no significant differences between medication groups in the reduction in BDI score from baseline to endpoint nor within Group A or Group B. No significant differences were detected between medication groups in drinking measures. Overall, the incidence of adverse events was similar between medication groups; however, significantly more sertraline-treated patients discontinued due to adverse events than placebo-treated patients (P<0.05).

3. Alzheimer's disease/dementia

Two randomized trials compared sertraline and placebo for patients with depression and comorbid Alzheimer's disease.[320, 321]

The first,[320] 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%) ($P<0.007$).

A second fair 12-week trial which randomized 133 patients with mild-to-moderate Alzheimer's disease and depression to either sertraline (100mg/d) or placebo did not replicate the above findings. Mood was assessed by the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change index and the CSDD. At the end of week 12, CSDD scores and remission rates did not differ between sertraline and placebo (OR 2.06, 95% CI 0.84 to 5.04, $P < 0.11$) with a high percentage of patients in both groups experiencing clinical improvements. Treatment with sertraline, however, was associated with more adverse events, specifically gastrointestinal adverse events than with placebo. Serious adverse events occurred in 20 percent of patients in the sertraline group compared with 11 percent in the placebo group.[321]

4. Arthritis

Our searches yielded only one trial that evaluated the efficacy of an antidepressants in depressed patients with comorbid arthritis.[322] This study is a subgroup analysis of a larger placebo-controlled trial in elderly patients randomized to duloxetine (60 mg/d) or placebo.[323] The subgroup analysis analyzed 233 subjects with MDD 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.

5. Cancer

Fluoxetine compared with placebo

We detected only one trial that studied the efficacy of fluoxetine in cancer patients;[324] 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.[325] 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.

6. Diabetes

Our searches yielded two trials that evaluated the efficacy of an antidepressants in depressed patients with comorbid diabetes.[322, 326] One fair-rated study randomized 89 depressed, low-income Hispanics and African Americans with diabetes to sertraline (50-100 mg/day) or placebo for 6 months.[326] HAM-D scores decreased significantly in both groups but there was no significant difference between sertraline-treated and placebo-treated patients. Quality of life measures improved significantly in both groups, but no difference was found between groups.

The details of the second study[322] are described above (in the 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.

7. HIV/AIDS

Two studies compared the efficacy and tolerability of fluoxetine and placebo in the treatment of patients with depression and comorbid HIV/AIDS.[298, 327]

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.[327] 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.[298] 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.

8. Multiple sclerosis

We detected only one study assessing the efficacy and tolerability of antidepressants for depression with comorbid multiple sclerosis (MS).[328] Forty-two MS patients diagnosed with MDD 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.

9. 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 nonsomatizing depressed participants.[329] 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.

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

We identified eight placebo-controlled trials,[322, 330-336] one pooled-data analysis,[337] and one systematic review[338] that addressed depression and co-occurring vascular disease of some type (chronic heart failure, coronary artery disease, post-myocardial infarction, stroke, and vascular disease). The majority of the trials evaluated a different drug (citalopram, duloxetine, fluoxetine, mirtazapine, sertraline, and SSRIs 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.[339] 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 MDD 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).[330] 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.(post-MI). A fair quality systematic review sponsored by AHRQ examined the role of depression in post-MI.[338] One section of this review addressed SSRI treatment for post-MI depression and included 11 studies. The authors concluded that SSRIs improve depression in post-MI 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 SSRIs in their review.

A 24-week trial randomized 369 patients with MDD and acute MI or unstable angina to sertraline (50-200 mg/d) or placebo.[335] 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 MI to fluoxetine (20-60 mg/d) or placebo for 25 weeks (9 weeks of acute treatment and an additional 16 week continuation phase).[332, 340] 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).[334] After 8 weeks of treatment, mirtazapine was superior to placebo based on BDI and CGI scales but not HAM-D. The difference between treatment groups in mean decrease in HAM-D score was not significant at 8 weeks (standardized effect size [SES] 1.30 compared with 0.96). Based on change in HAM-D score at 8 weeks, more mirtazapine-treated patients were responders (57% compared with 40%), but the difference was not significant (*P*=0.18). Mirtazapine-treated patients showed a significantly greater decrease in BDI score at 8 weeks (-4.6 compared with -1.72, *P*=0.02). Decrease in CGI score was greater in mirtazapine-treated patients but the difference was not statistically significant (*P*=0.06). The differences between groups in decrease in HAM-D scores and BDI scores over 24 weeks was not statistically significant (*P*=0.36 and *P*=0.07). The difference in CGI-scores over 24 weeks favored mirtazapine; the difference was significant (*P*=0.05). Mirtazapine patients experienced significantly more fatigue (*P*=0.02) and changes in appetite (*P*=0.02) over 24 weeks.

Stroke

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.[331] 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.

A fair 6-week trial of 150 patients assessed the efficacy and tolerability of fluoxetine (20-40 mg/d) compared with placebo and with a Chinese herbal formula in the treatment of post-stroke depression.[333] The fluoxetine and placebo groups consisted of 90 patients, all of which had a recent single ischemic or hemorrhagic stroke. Significantly higher clinical response rates were observed in the fluoxetine compared with the placebo group (60% versus 21.4%, χ^2= 15.9, P < 0.01). No serious side effects were reported.

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.[336] 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).

Peripheral vascular disease

We detected two trials addressing the efficacy of depressed patients with comorbid vascular disease.[322, 337] One trial that evaluated the efficacy of duloxetine (60 mg/d) and placebo in elderly patients.[322] 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 RCTs determined the safety and efficacy of sertraline (50-150 mg/d) in elderly patients with comorbid vascular disease.[337] 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

1. 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.[294] However, findings suggested that older women had a poorer response to SSRIs than younger women.[294, 295]

Eight studies provide fair to good indirect evidence that efficacy and tolerability for patients older than 60 years and those younger do not differ.[46, 55, 65, 68, 77, 79, 89, 92, 111, 112] Results of

these studies, all conducted in patients with MDD 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.[71] 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.[293]

For MDD, placebo-controlled evidence supports the efficacy of fluoxetine[341, 342] and sertraline.[156] 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 MDD in children and adolescents.[146] 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.[147, 148]

2. Ethnicity

Fair evidence from a pooled data study on paroxetine[299] and a single RCT on fluoxetine[298] 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[296] or between Caucasians and African Americans.[297] Altogether, the evidence is inconclusive to determine whether second-generation antidepressants differ between patients with diverse ethnic backgrounds.

3. Sex

Two pooled-data analyses did not find significant associations between sex and efficacy outcomes in patients treated for MDD.[294, 295, 303] A pooled analysis of data from four sertraline-RCTs conducted in populations with panic disorder reported better responses of female than male patients on some outcome measures.[301]

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 meta-analysis of RCTs found significant gender-related adverse events of antidepressants. Citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine caused higher rates of desire and orgasm dysfunction in men and higher arousal dysfunction in women.[304] A pooled data analysis indicated higher rates of vomiting in women than in men treated with desvenlafaxine.[303]

4. Concomitant medications

A fair retrospective cohort study found evidence of increased breast cancer mortality in women treated with tamoxifen for breast cancer and concurrent use of paroxetine. No evidence of increased risk was found with concurrent use of fluoxetine, sertraline, citalopram, fluvoxamine, or venlafaxine.[306] Evidence is insufficient to determine the influence of concomitant medications on the effectiveness or harms of SSRIs, SNRIs, or other second-generation antidepressants.

5. Comorbidities

We found no prospective study directly comparing the efficacy, effectiveness and tolerability of SSRIs, SNRIs, and other second-generation antidepressants in a population with a specific comorbid condition to a population without that same condition. A meta-analysis with a subgroup analysis yielded good evidence that overall, SSRIs were superior to placebo at 6 to 8 months for patients without comorbidities compared with patients with comorbidities (analyzed as a combined category).[307] However, we could not identify further studies analyzing outcomes after a follow-up of similar duration.

The majority of studies we identified are limited to depressive disorders in patients with a variety of disorders. Overall, evidence of treatment efficacy across various disease conditions and second-generation depressants is mixed.

For some comorbidities such as post-myocardial infarction[335, 338] or coronary artery disease [330] the evidence indicates a general efficacy of some second-generation-antidepressants for the treatment of depression.

For other conditions, however, such as methadone-maintained opioid addiction, cocaine abuse, HIV, multiple sclerosis, arthritis, diabetes, or cancer,[312, 313, 322, 324, 326-328] comorbid alcohol use disorder in depressed adolescents[311] or substance abuse in adolescents with comorbid conduct disorder,[314] second-generation antidepressants were unable to achieve response or remission rates that were statistically significantly better than placebo.

For some comorbid conditions the evidence was inconclusive. For depression with comorbid alcoholism, evidence of treatment efficacy of a SSRI compared with placebo,[308-310] lack of such an effect,[317, 319] or differential effect only for women in the treatment group[318] were identified. Also, treatment efficacy for post-stroke depression was not uniform across studies, with two trials showing second-generation antidepressant superior to placebo[331, 333] yet one trial[336] lacking a significant treatment effect. Inconclusive also the findings of trials with second-generation-antidepressants for Alzheimer's depression, with one study showing a treatment effect,[320] a second trial, however, lacking such an effect but with more adverse events in the treatment group.[321]

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[65]	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[68]	Fluoxetine compared with paroxetine	242	Faster onset of paroxetine	Fair
Schone and Ludwig, 1993[71]	Fluoxetine compared with paroxetine	108	Faster onset of paroxetine	Fair
Newhouse et al., 2000[77] Finkel et al., 1999[79]	Fluoxetine compared with sertraline	236	No differences	Fair
Kroenke et al., 2001[55]	Fluoxetine compared with sertraline compared with Paroxetine	601	No differences	Fair
Schatzberg et al., 2002[89]	Mirtazapine compared with paroxetine	255	Faster onset of mirtazapine; similar number of CGI responders at end of	Fair

Author, Year	Interventions	N	Results	Quality rating
			continuation phase	
Allard et al. 2004[92]	Venlafaxine compared with citalopram XR	151	No differences	Fair
Schatzberg and Roose, 2006[46]	Venlafaxine compared with fluoxetine	300	No differences	Fair
Oslin et al., 2003[293]	Venlafaxine compared with sertraline	52	No significant difference in efficacy; tolerability was lower for venlafaxine	Poor
Weihs et al., 2000[111] Doraiswamy et al., 2001[112]	Bupropion SR compared with paroxetine	100	No differences	Fair
Thase et al., 2005[295] Entsuah et al., 2001[294]	Pooled data analysis of venlafaxine (IR and XR) and SSRIs	2,045	Venlafaxine response not affected by age or sex; SSRI response poorer in older women; similar efficacy of venlafaxine and SSRIs, except in older women, but HRT appears to eliminate the difference	N/A
Whittington et al., 2004[146]	Meta-analysis	2,145	Only fluoxetine had favorable risk-benefit profile	Fair
Ethnicity				
Bailey et al., 2006[297]	Pooled analysis of duloxetine and placebo	1,423	No differences between Caucasians and African Americans	N/A
Lewis-Fernandez et al., 2006[296]	Pooled analysis of duloxetine and placebo	1,452	No differences in efficacy or tolerability outcomes between Hispanics and Caucasians	N/A
Roy-Byrne et al., 2005[299]	Pooled analysis of paroxetine compared with placebo	14,875	Slightly lower response rates for Hispanics and Asians than for Blacks and Whites	N/A
Wagner et al., 1998[298]	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				
Clayton et al., 2005[301]	Pooled data analysis of sertraline compared with placebo	673	Better response of female patients on some outcome measures	Fair
Kennedy et al., 2006[253]	Bupropion compared with paroxetine	141	No difference between drugs for sexual dysfunction in women	Fair
Kornstein et al., 2010[303]	Pooled data analysis of desvenlafaxine compared with placebo	2,913	No significant difference for efficacy outcomes; or for vomiting significantly greater in women	N/A
Serretti et al.,2009[304]	Meta-analysis of experimental and observational studies including bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine	NR	Citalopram, fluoxetine, paroxetine, sertraline, venlafaxine caused higher rates of desire and orgasm dysfunction in men and higher arousal dysfunction in women	Fair
Stewart et al., 2006[302]	Pooled data analysis of duloxetine compared with placebo	1,622	No differences in safety and tolerability	N/A
Thase et al., 2005[295] Entsuah et al., 2001[294]	Pooled data analysis of: venlafaxine (IR and XR) compared with SSRIs compared with placebo	2,045	Venlafaxine response not affected by age or sex; SSRI response poorer in older women; similar efficacy of venlafaxine and SSRIs, except in older women, but HRT appears to eliminate	N/A

Author, Year	Interventions	N	Results	Quality rating
			the difference	
Ushiroyama et al., 2004[81]	Fluvoxamine compared with paroxetine	105	Significant difference in % change for hot flashes favoring paroxetine	Fair
Other Medications-Drug Interaction				
Kelly, 2010[306]	5 SSRIs and venlafaxine (retrospective cohort study)	2,430	Significantly increased risk of death from breast cancer for paroxetine in women with breast cancer taking tamoxifen	Fair
Comorbidities				
Comorbidities combined				
Deshauer et al., 2008[307]	3 SSRIs compared with placebo (Meta-Analysis)	1,299	Statistically significant treatment effect of SSRIs in depressed patients without comorbidities, but no significant differences between SSRI and placebo in those with comorbidities (alcoholism, myocardial infarction, stroke)	Fair
Alcohol/substance abuse				
Riggs et al., 2007[314]	Fluoxetine compared with placebo	125	No significant differences in adolescents with MDD, SUD and CD	Fair
Schmitz et al., 2001[313]	Fluoxetine compared with placebo	68	No differences in depressed cocaine abusers	Poor
Cornelius et al., 1997, 1998, 2000[308-310]	Fluoxetine compared with placebo	54	Significantly greater efficacy for fluoxetine in depressed alcoholics	Fair
Cornelius et al., 2009[311]	Fluoxetine compared with placebo	50	No significant differences between fluoxetine and placebo in depressed adolescents with alcohol use disorder	Fair
Petrakis et al., 1998[312]	Fluoxetine compared with placebo	44	No difference in depressed opioid addicts	Fair
Book et al., 2007[316]	Paroxetine compared with placebo	42	Significantly greater reduction in LSAS total scores in paroxetine patients	Fair
Kranzler et al., 2006[319]	Sertraline compared with placebo		No differences	Fair
Gual et al., 2003[317]	Sertraline compared with placebo	83	No significant differences	Fair
Moak et al., 2003[318]	Sertraline compared with placebo	82	Greater depression improvement in females treated with sertraline; less drinking associated with greater depression improvement	Fair
Hernandez-Avila et al., 2004[315]	Nefazodone compared with placebo	41	No significant differences	Fair
Alzheimer's disease/dementia				
Lyketsos et al., 2003[320]	Sertraline compared with placebo	44	Sertraline associated with greater response	Fair
Rosenberg, 2010[321]	Sertraline compared with placebo	133	No significant differences in depressed patients with Alzheimer's disease; more adverse events in sertraline group, statistically more serious respiratory events in sertraline group	Fair
Arthritis				
Wise et al., 2007[322]	Duloxetine compared with placebo	233	No significant differences	Fair
Cancer				
Roscoe et al. 2005[325]	Paroxetine compared with placebo	94	Greater efficacy for paroxetine in depressed patients with breast cancer	Poor
Diabetes				
Echeverry et al., 2009[326]	Sertraline compared with Placebo	89	No significant differences between sertraline and placebo group	Fair
Wise et al., 2007[322]	Duloxetine compared with placebo	233	No significant differences	Fair

Author, Year	Interventions	N	Results	Quality rating
HIV/AIDS				
Rabkin et al, 1999[327]	Fluoxetine compared with placebo	120	No difference in depressed HIV/AIDS patients	Fair
Wagner et al., 1998[298]	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[328]	Paroxetine compared with placebo	42	No significant differences	Fair
Somatizing depression				
Linden et al., 1994[329]	Fluoxetine compared with paroxetine	89	No difference in GI-side effects in somatizing patients	Fair
Vascular disease (cardiovascular, cerebrovascular, or peripheral vascular)				
Andersen et al., 1994[331]	Citalopram compared with placebo	66	Significantly greater improvement in citalopram-treated post-stroke patients	Fair
Bush et al., 2005[338]	SSRIs (SR)	NR	SSRIs improve depression in post-MI patients	Fair
Glassman et al., 2002[335]	Sertraline compared with placebo	369	Significantly greater response with sertraline in post-MI patients	Fair
Honig et al., 2007[334]	Mirtazapine compared with placebo	91	Significantly greater CGI improvement with mirtazapine; no significant difference between groups in HAM-D and BDI scores in post-MI patients	Fair
Krishnan et al., 2001[337]	Sertraline compared with placebo	220	Vascular comorbidity not associated with more adverse events and premature discontinuation	Fair
Lesperance et al., 2007[330]	Citalopram compared with placebo	284	Significantly greater improvements in depressive symptoms in citalopram-treated patients	Fair
Li, 2008[333]	Fluoxetine compared with placebo compared with Chinese herbal formula	150	Fluoxetine superior to placebo in post-stroke patients	Fair
Murray et al., 2005[336]	Sertraline compared with placebo	123	No difference in response; greater improvements in QoL with sertraline in post-stroke patients	Fair
Strik et al., 2000[332, 340]	Fluoxetine compared with placebo	54	Significantly greater response with fluoxetine in post-MI patients	Good
Wise et al., 2007[322]	Duloxetine compared with placebo	233	No significant differences	Fair
Age				
Allard et al. 2004[92]	Venlafaxine compared with citalopram XR	151	No differences	Fair
Cassano et al., 2002[68]	Fluoxetine compared with paroxetine	242	Faster onset of paroxetine	Fair
Kasper et al., 2005[65]	Escitalopram compared with fluoxetine compared with placebo	518	No significant difference in response rates; remission rates lower for fluoxetine than escitalopram	Fair
Kroenke et al., 2001[55]	Fluoxetine compared with sertraline compared with Paroxetine	601	No differences	Fair
Newhouse et al., 2000[77] Finkel et al., 1999[79]	Fluoxetine compared with sertraline	236	No differences	Fair
Oslin et al., 2003[293]	Venlafaxine compared with sertraline	52	No significant difference in efficacy; tolerability was lower for venlafaxine	Poor
Schatzberg and Roose, 2006[46]	Venlafaxine compared with fluoxetine	300	No differences	Fair

Author, Year	Interventions	N	Results	Quality rating
Schatzberg et al., 2002[89]	Mirtazapine compared with paroxetine	255	Faster onset of mirtazapine; similar number of CGI responders at end of continuation phase	Fair
Schone and Ludwig, 1993[71]	Fluoxetine compared with paroxetine	108	Faster onset of paroxetine	Fair
Thase et al., 2005[295] Entsuah et al., 2001[294]	Pooled data analysis of venlafaxine (IR and XR) and SSRIs	2,045	Venlafaxine response not affected by age or sex; SSRI response poorer in older women; similar efficacy of venlafaxine and SSRIs, except in older women, but HRT appears to eliminate the difference	Fair
Weihs et al., 2000[111] Doraiswamy et al., 2001[112]	Bupropion SR compared with paroxetine	100	No differences	Fair
Whittington et al., 2004[146]	Meta-analysis	2,145	Only fluoxetine had favorable risk-benefit profile	Fair
Ethnicity				
Bailey et al., 2006[297]	Pooled analysis of duloxetine and placebo	1,423	No differences between Caucasians and African Americans	Fair
Lewis-Fernandez et al., 2006[296]	Pooled analysis of duloxetine and placebo	1,452	No differences in efficacy or tolerability outcomes between Hispanics and Caucasians	Fair
Roy-Byrne et al., 2005[299]	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[298]	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				
Clayton et al., 2005[301]	Pooled data analysis of sertraline compared with placebo	673	Better response of female patients on some outcome measures	Fair
Kennedy et al., 2006[253]	Bupropion compared with paroxetine	141	No difference between drugs for sexual dysfunction in women	Fair
Stewart et al., 2006[302]	Pooled data analysis of duloxetine compared with placebo	1,622	No differences in safety and tolerability	Fair
Thase et al., 2005[295] Entsuah et al., 2001[294]	Pooled data analysis of: venlafaxine (IR and XR) compared with SSRIs compared with placebo	2,045	Venlafaxine response not affected by age or sex; SSRI response poorer in older women; similar efficacy of venlafaxine and SSRIs, except in older women, but HRT appears to eliminate the difference	Fair
Ushiroyama et al., 2004[81]	Fluvoxamine compared with paroxetine	105	Significant difference in % change for hot flashes favoring paroxetine	Fair
Comorbidities				
Alcohol/substance abuse				
Book et al., 2007[316]	Paroxetine compared with placebo	42	Significantly greater reduction in LSAS total scores in paroxetine patients	Fair
Cornelius et al., 1997, 1998, 2000[308-310]	Fluoxetine compared with placebo	54	Significantly greater efficacy for fluoxetine in depressed alcoholics	Fair
Gual et al., 2003[317]	Sertraline compared with placebo	83	No significant differences	Fair
Hernandez-Avila et al., 2004[315]	Nefazodone compared with placebo	41	No significant differences	Fair
Kranzler et al., 2006[319]	Sertraline compared with placebo		No differences	Fair
Moak et al., 2003[318]	Sertraline compared with placebo	82	Greater depression improvement in females treated with sertraline; less	Fair

Author, Year	Interventions	N	Results	Quality rating
			drinking associated with greater depression improvement	
Petrakis et al., 1998[312]	Fluoxetine compared with placebo	44	No difference in depressed opioid addicts	Fair
Riggs et al., 2007[314]	Fluoxetine compared with placebo	125	No significant differences in adolescents with MDD, SUD and CD	Fair
Schmitz et al., 2001[313]	Fluoxetine compared with placebo	68	No differences in depressed cocaine abusers	Poor
Alzheimer's disease/dementia				
Lyketsos et al., 2003[320]	Sertraline compared with placebo	44	Sertraline associated with greater response	Fair
Arthritis				
Wise et al., 2007[322]	Duloxetine compared with placebo	233	No significant differences	Fair
Cancer				
Roscoe et al. 2005[325]	Paroxetine compared with placebo	94	Greater efficacy for paroxetine in depressed patients with breast cancer	Poor
Diabetes				
Wise et al., 2007[322]	Duloxetine compared with placebo	233	No significant differences	Fair
HIV/AIDS				
Rabkin et al, 1999[327]	Fluoxetine compared with placebo	120	No difference in depressed HIV/AIDS patients	Fair
Wagner et al., 1998[298]	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[328]	Paroxetine compared with placebo	42	No significant differences	Fair
Somatizing depression				
Linden et al., 1994[329]	Fluoxetine compared with paroxetine	89	No difference in GI-side effects in somatizing patients	Fair
Stroke				
Andersen et al., 1994[331]	Citalopram compared with placebo	66	Significantly greater improvement in citalopram-treated patients	Fair
Murray et al., 2005[336]	Sertraline compared with placebo	123	No difference in response; greater improvements in QoL with sertraline	Fair
Vascular disease (cardiovascular, cerebrovascular, or peripheral vascular)				
Bush et al., 2005[338]	SSRIs (SR)	NR	SSRIs improve depression in post-MI patients	Fair
Glassman et al., 2002[335]	Sertraline compared with placebo	369	Significantly greater response with sertraline in post-MI patients	Fair
Honig et al., 2007[334]	Mirtazapine compared with placebo	91	Significantly greater CGI improvement with mirtazapine; no significant difference between groups in HAM-D and BDI scores in post-MI patients	Fair
Krishnan et al., 2001[337]	Sertraline compared with placebo	220	Vascular comorbidity not associated with more adverse events and premature discontinuation	Fair
Lesperance et al., 2007[330]	Citalopram compared with placebo	284	Significantly greater improvements in depressive symptoms in citalopram-treated patients	Fair
Strik et al., 2000[340] Strik et al., 2006[332]	Fluoxetine compared with placebo	54	Significantly greater response with fluoxetine in post-MI patients	Good
Wise et al., 2007[322]	Duloxetine compared with placebo	233	No significant differences	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

SUMMARY

This report provides a comprehensive summary of the comparative efficacy, effectiveness, and harms of 12 second-generation antidepressants for the treatment of depressive, anxiety, and premenstrual dysphoric disorders. They include bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine.

From a total of 4,850 citations identified, we ultimately included 275 studies of good or fair quality. Of these, 170 were randomized controlled trials (RCTs) and the remaining 105 studies were meta-analyses or systematic reviews, observational studies and studies of other designs. Seventy-two studies that met the eligibility criteria were later rated as poor quality for internal validity and excluded from the analysis.

Overall, the new evidence (59 new studies) that we found during the update of the report from 2008 did not lead to changes in our main conclusion from that review—namely, that no substantial differences in efficacy exist among second-generation antidepressants for the treatment of MDD.

Strength of the Evidence

Table 23 summarizes principal findings and the strength of the underlying evidence. The strength of the evidence for the comparative efficacy for the treatment of MDD was generally good to fair. The strength of the evidence for other depressive disorders, such as dysthymia, subsyndromal depression, or seasonal affective disorders was poor with no comparative data available. Similarly, the strength of the comparative evidence for the treatment of MDD in children and adolescents was poor.

For anxiety disorders the strength of the comparative evidence was fair for some comparisons but poor for most others. For premenstrual dysphoric disorder, no comparative evidence could be found and the strength of the evidence was rated poor.

Good evidence indicates that second-generation antidepressants have similar adverse events profiles. Fair to good evidence also suggests that differences for some specific adverse events exist among some antidepressants. For example, mirtazapine causes higher rates of weight gain, venlafaxine leads to higher rates of nausea and vomiting, and sertraline has an increased risk of diarrhea than other antidepressants. Except for lower rates of sexual dysfunction for bupropion than for comparator drugs, the evidence on the comparative risks of serious adverse events such as suicidality, seizures, and others was rated poor.

Fair evidence indicates that no differences in efficacy for subgroups based on age. For all other subgroups the evidence on the comparative efficacy and harms was rated poor.

Limitations

As with other types of research, the limitations of this systematic review are important to recognize. These can be divided into 2 groups, those relating to applicability of the results and those relating to methodology within the scope of this review. The applicability of the results are limited by the scope of the key questions and inclusion criteria and by the applicability of the studies included. Most studies included narrowly defined populations of patients who met strict

criteria for case definition, had few comorbidities, and used few or no concomitant medications. Minorities, older patients, and the most seriously ill patients were underrepresented.

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies.

Unfortunately, for many drugs, there are few or no effectiveness studies and many efficacy studies. As a result, clinicians must make decisions about treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. An evidence report indicates whether or not there is evidence that drugs differ in their effects in various subgroups of patients, but it does not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these are decisions that must be informed by clinical judgment.

In the context of developing recommendations for practice, evidence reports are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. By themselves, they do not tell you what to do: Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is not true. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policies. Additional criteria include acceptability to physicians or patients, the potential for unrecognized harms, the applicability of the evidence to practice, and consideration of equity and justice.

Applicability

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

Effectiveness studies that would be most applicable to the broad population of depressed patients are generally lacking for most drugs. Effectiveness trials with less stringent eligibility criteria, patient-centered health outcomes, long study durations, and populations representative of patients encountered in primary care would be valuable to determine whether existing differences of second-generation antidepressants are clinically meaningful in "real world" settings. These trials should be powered to be able to assess minimal clinically significant differences. Furthermore, they could provide valuable information on differences in adherence among second-generation antidepressants.

Trials in Progress

We identified no trials in progress that would meet inclusion criteria for this review and would potentially change conclusions.

Table 23. Summary of principal findings and strength of the evidence

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Key Question 1. Comparative efficacy and effectiveness of second-generation antidepressants		
Major depressive disorder		
Comparative efficacy	Fair	Results from direct and indirect comparisons indicate that no substantial differences in efficacy exist among second-generation antidepressants.
Comparative effectiveness	Fair	Direct evidence from one good and two fair effectiveness studies and indirect evidence from efficacy trials indicate that no substantial differences in effectiveness exist among second-generation antidepressants.
Quality of life	Fair	Consistent results from 18 mostly fair studies indicate that the efficacy of second-generation antidepressants with respect to quality of life does not differ among drugs.
Onset of action	Fair	Consistent results from seven fair trials suggest that mirtazapine has a significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline. Whether this difference can be extrapolated to other second-generation antidepressants is unclear. Most other trials do not indicate a faster onset of action of one second-generation antidepressant compared with another.
Dysthymia		
Comparative efficacy	Poor	No head-to head evidence exists. Findings from five placebo-controlled trials were insufficient to draw conclusions about comparative efficacy.
Comparative effectiveness	Poor	One fair effectiveness study provides mixed evidence about paroxetine vs. placebo; patients older than 60 showed greater improvement on paroxetine; those younger than 50 did not show any difference.
Subsyndromal depression		
Comparative efficacy	Poor	One nonrandomized, open-label trial did not detect any difference between citalopram and sertraline. Findings from two placebo-controlled trials were insufficient to draw conclusions.
Comparative effectiveness	No evidence	
Seasonal affective disorder		
Comparative efficacy	Poor	No head-to head evidence exists. Findings from placebo-controlled trials were insufficient to draw conclusions about comparative efficacy.
Comparative effectiveness	No evidence	
Major depressive disorder in children		
Comparative efficacy	Poor	No head-to head evidence exists. Findings from placebo-controlled trials were insufficient to draw conclusions about comparative efficacy.
Comparative effectiveness	No evidence	
Generalized anxiety disorder		
Comparative efficacy	Fair to poor	Available head-to head evidence is limited to comparisons of fluoxetine with sertraline and paroxetine with escitalopram or venlafaxine. Except for one study favoring escitalopram over paroxetine, no major differences in efficacy could be detected.
Comparative effectiveness	No evidence	

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Obsesssive compulsive disorder		
Comparative efficacy	Fair to poor	Available head-to head evidence is limited to comparisons of paroxetine with escitalopram, sertraline, and venlafaxine and venlafaxine with duloxetine and escitalopram. Overall, no major differences in efficacy could be detected.
Comparative effectiveness	No evidence	
Panic disorder		
Comparative efficacy	Fair to poor	Available head-to head evidence is limited to comparisons of sertraline with citalopram, nefazodone, and venlafaxine. Overall, no major differences in efficacy between citalopram and escitalopram could be detected. The evidence on the comparative efficacy of paroxetine and venlafaxine ER is inconclusive.
Comparative effectiveness	No evidence	
Post-traumatic stress disorder		
Comparative efficacy	Fair to poor	Available head-to head evidence is limited to comparisons of sertraline with citalopram, nefazodone, and venlafaxine. Overall, no major differences in efficacy could be detected.
Comparative effectiveness	No evidence	
Social anxiety disorder		
Comparative efficacy	Fair to poor	Available head-to head evidence is limited to comparisons of paroxetine with with escitalopram and venlafaxine ER. Overall, no major differences in efficacy could be detected.
Comparative effectiveness	No evidence	
Premenstrual dysphoric and late luteal phase dysphoric disorder		
Comparative efficacy	Poor	No head-to head evidence exists. Findings from placebo-controlled trials were insufficient to draw conclusions about comparative efficacy.
Comparative effectiveness	No evidence	
Key Question 2. Comparative harms of second-generation antidepressants		
General tolerability		
Adverse events profiles	Fair	Adverse events profiles are similar among second-generation antidepressants. Differences in the incidence of specific adverse events exist.
Diarrhea	Fair	Evidence from multiple fair-quality studies indicates that sertraline has a higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine.
Discontinuation rates	Good	Meta-analyses of efficacy trials indicate that overall discontinuation rates are similar. Venlafaxine has a higher rate of discontinuations because of adverse events and a lower rate of discontinuations because of lack of efficacy than SSRIs as a class.
Nausea and vomiting	Good	Meta-analysis of 15 fair-quality studies indicates that venlafaxine has a higher rate of nausea and vomiting than SSRIs as a class.
Weight change	Fair	Seven fair trials indicate that mirtazapine leads to higher weight gains than citalopram, fluoxetine, paroxetine, and sertraline.
Severe adverse events		
Cardiovascular adverse events	Fair	No differences in risk of sudden cardiac death could be detected among citalopram, fluoxetine, and venlafaxine
Fractures	Poor	Overall, increased risk of fractures with use of SSRIs. Evidence is insufficient to determine the comparative risk.
Gastrointestinal bleeding	Poor	Overall, increased risk of gastrointestinal bleeding with use of SSRIs. Evidence is insufficient to determine the comparative risk.

Key Question, Disorder, and Outcome of Interest	Strength of Evidence	Findings
Hepatotoxicity	Poor	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of hepatotoxicity. Weak evidence indicates that nefazodone might have an increased risk of hepatotoxicity.
Sexual adverse events	Good	Five fair trials provide evidence that bupropion causes significantly less sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline. Among SSRIs, paroxetine has the highest rates of sexual dysfunction.
Seizures	Poor	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of seizures. Weak evidence indicates that bupropion might have an increased risk of seizures.
Serotonin syndrome	Poor	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of serotonin syndrome. Observational studies indicate no differences in risk among second-generation antidepressants.
Suicidality	Poor	Evidence from existing studies is insufficient to draw conclusions about the comparative risk of suicidality. Weak data suggests no differences among second-generation antidepressants.
Key Question 3. Comparative efficacy, effectiveness, and harms of second-generation antidepressants in subgroups		
Age	Fair	No study directly compared the efficacy, effectiveness, and harms in younger an older populations. Indirect evidence from multiple trials indicates that efficacy does not differ substantially among second-generation antidepressants for treating MDD in patients age 60 years or older.
Ethnicity	Poor	The evidence is insufficient to determine differences in efficacy, effectiveness, and harms among different ethnicities.
Sex	Fair	With some notable exceptions, the efficacy and safety of second-generation antidepressants are similar between men and women.
Comorbidities	Poor	The evidence is insufficient to determine differences in efficacy, effectiveness, and harms among patients with different comorbidities.

CONCLUSIONS

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

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

No or only limited conclusions can be drawn about the comparative efficacy and safety of second-generation antidepressants for the treatment of dysthymia, subsyndromal depression, seasonal affective disorders, depression in children, anxiety disorders, and premenstrual dysphoric disorder.

ADDENDUM

On January 21, 2011 the FDA approved vilazodone (*Viibyrd*; Clinical Data, 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 vilazodone in this report.

Vilazodone is a combined selective serotonin reuptake inhibitor and 5-hydroxytryptamine receptor agonist. The FDA approved 10 mg, 20 mg, and 40 mg for the treatment of MDD. Like other antidepressants, vilazodone carries a boxed warning and a patient medication guide describing the increased risk of suicidal thinking and behavior in children, adolescents, and young adults ages 18 to 24 during initial treatment. The warning also states that data did not show the increased risk in adults older than 24 and that patients aged 65 and older who take antidepressants have a decreased risk of suicidal thinking and behavior.

The FDA approval was based on two 8-week, placebo controlled RCTs (combined n of 869). In these studies, after 8 weeks of treatment, patients on vilazodone achieved a 3.2 points (5.2 to 1.3) and a 2.3 points (4.4 to 0.6) greater reduction on the MADRS than patients in the placebo groups.

No head-to-head trials comparing the efficacy and safety of vilazodone to any other second-generation antidepressants appear to be available to date.

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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[57]	491	40.1	65%	8 weeks	MADRS
Colonna et al., 2005[58]	357	46	75%	8 weeks	MADRS
Lepola et al., 2003[56]	471	43	72.1%	8 weeks	MADRS
Moore et al., 2005[59]	280	45.2	76.9%	8 weeks	MADRS
SCT-MD-02 (unpublished)[61]	243	41.9	52.6%	8 weeks	MADRS
Yevtushenko et al., 2007[60]	330	34.9	58.4%	6 weeks	MADRS

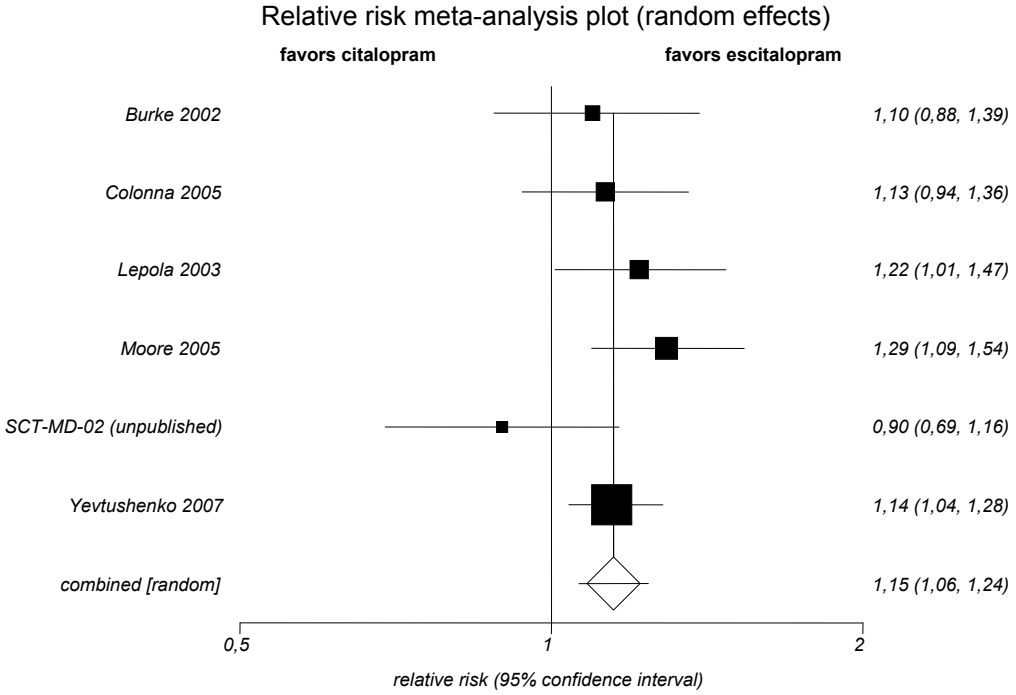


Exhibit 2. Effect size meta-analysis comparing citalopram to escitalopram on the MADRS

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Burke et al., 2002[57]	491	40.1	65%	8 weeks	MADRS
Colonna et al., 2005[58]	357	46	75%	8 weeks	MADRS
Lepola et al., 2003[56]	471	43	72.1%	8 weeks	MADRS
Moore et al., 2005[59]	280	45.2	76.9%	8 weeks	MADRS
SCT-MD-02 (unpublished)[61]	243	41.9	52.6%	8 weeks	MADRS
Yevtushenko et al., 2007[60]	330	34.9	58.4%	6 weeks	MADRS

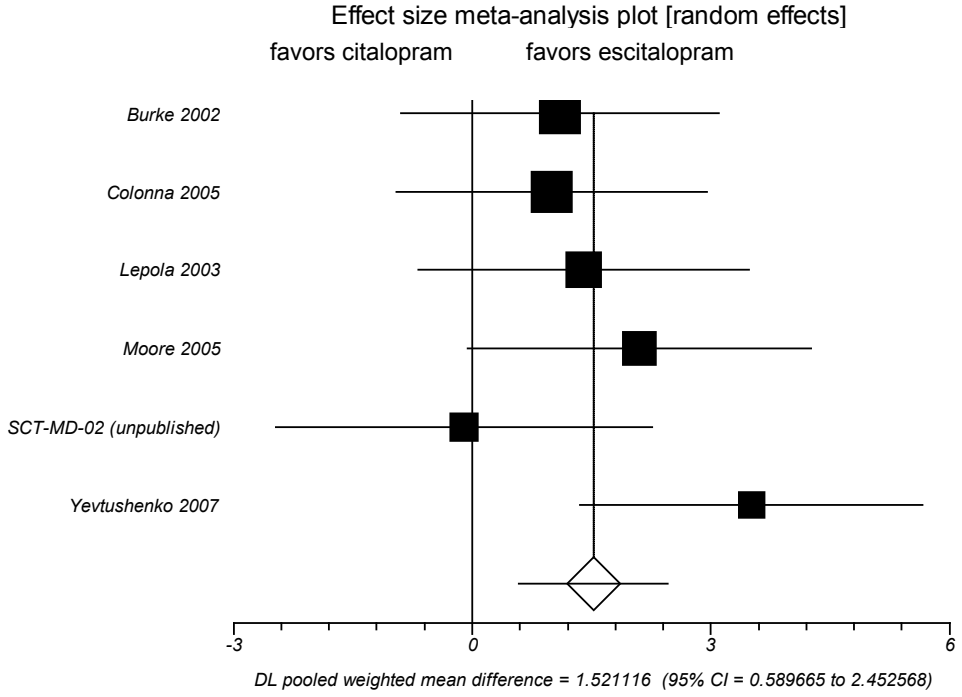


Exhibit 3. Meta-analysis of studies comparing fluoxetine to paroxetine

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Chouinard et al., 1999[69]	203	40.9	61%	12 weeks	HAM-D
De Wilde et al.,1993[70]	78	44.0	61%	6 weeks	HAM-D
Fava et al., 1998[72]	128	41.3	51%	10-16 weeks	HAM-D
Fava et al., 2002[73]	188	42.0	65%	10-16 weeks	HAM-D
Gagiano 1993[74]	90	38.7	80%	6 weeks	HAM-D

Characteristics of excluded studies

	Sample size	Mean Age	Women	Duration	Scale	Reason for exclusion
Cassano et al. 2002[68]	242	75.3	55%	52 weeks	HAM-D	Missing data
Schöne et al., 1993[71]	108	74.0	87%	6 weeks	HAM-D	Elderly population

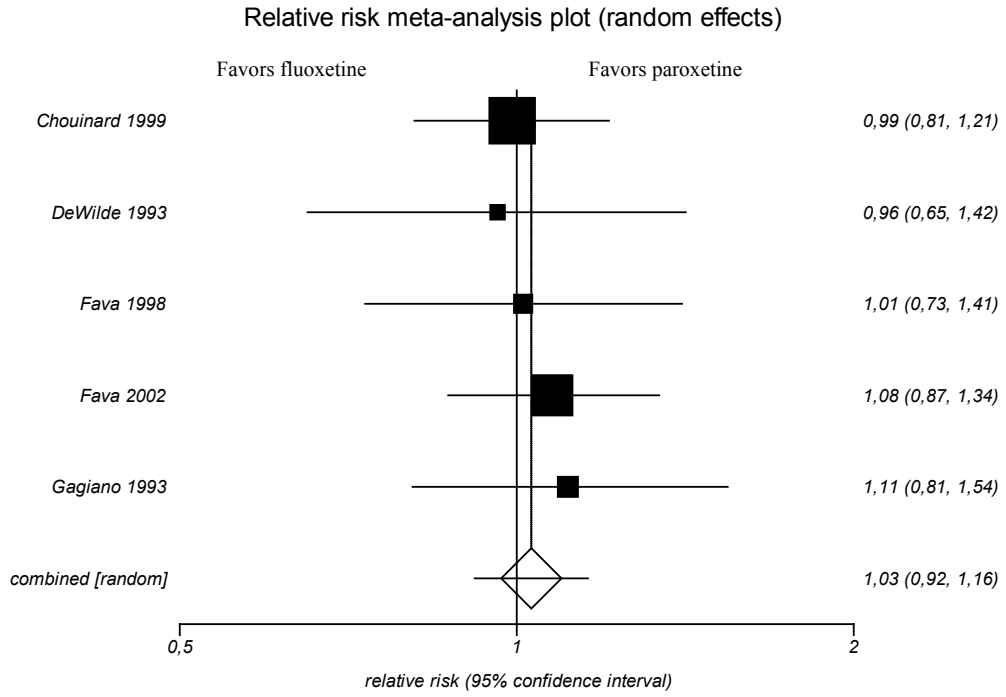


Exhibit 4. Meta-analysis of studies comparing fluoxetine to sertraline

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Bennie et al., 1999[75]	286	49.9	61%	6 weeks	HAM-D
Fava et al., 2002[73]	188	42.0	65%	10-16 weeks	HAM-D
Newhouse et al., 2000[77]	236	67.5	57%	12 weeks	HAM-D
Sechter et al., 1999[54]	238	42.8	67%	24 weeks	HAM-D

Characteristics of excluded studies

	Sample size	Mean Age	Women	Duration	Scale	Reason for exclusion
Boyer et al., 1998[78]	242	43.4	78%	26 weeks	MADRS	Different outcome measure
Kroenke et al., 2001[55]	601	46.1	74%	9 months	SF-36	Different outcome measure

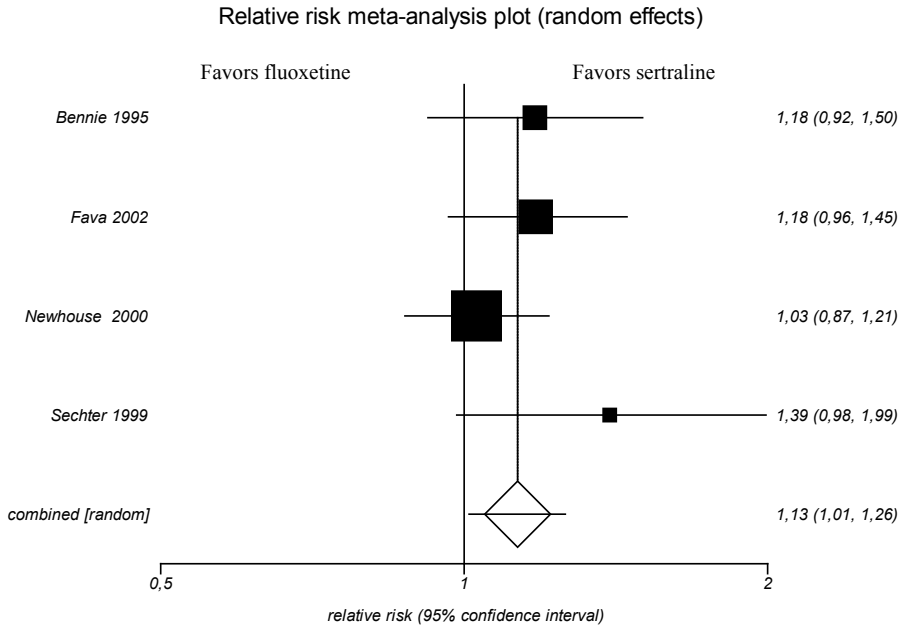


Exhibit 5. Meta-analysis of studies comparing venlafaxine to fluoxetine

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Alves et al., 1999[100]	87	43.8	92%	12 weeks	HAM-D
De Nayer et al., 2002[96]	146	42.7	68%	12 weeks	MADRS
Dierick et al., 1996[101]	314	43.4	64%	8 weeks	HAM-D
Keller et al., 2007[45]	1096	40.2	61%	10 weeks	HAM-D
Nemeroff et al., 2007[47]	308	39.0	67%	6 weeks	HAM-D
Rudolph et al., 1999[97]	301	40	69%	8 weeks	HAM-D
Silverstone et al., 1999[98]	378	41.9	60%	12 weeks	HAM-D
Tylee et al., 1997[102]	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[48]	119	45.7	72.5	12 weeks	HAM-D	Missing data
Costa e Silva et al., 1998[95]	382	40.1	53%	8 weeks	HAM-D	Missing data
Schatzberg et al., 2006[46]	300	71	50%	8 weeks	HAM-D	Missing data

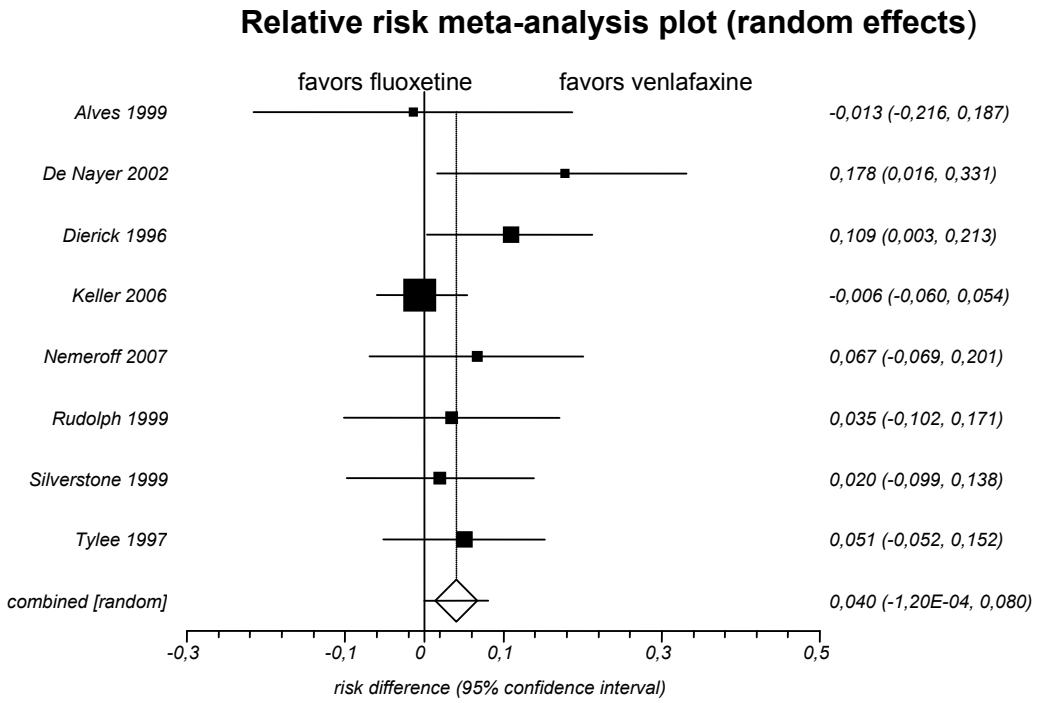
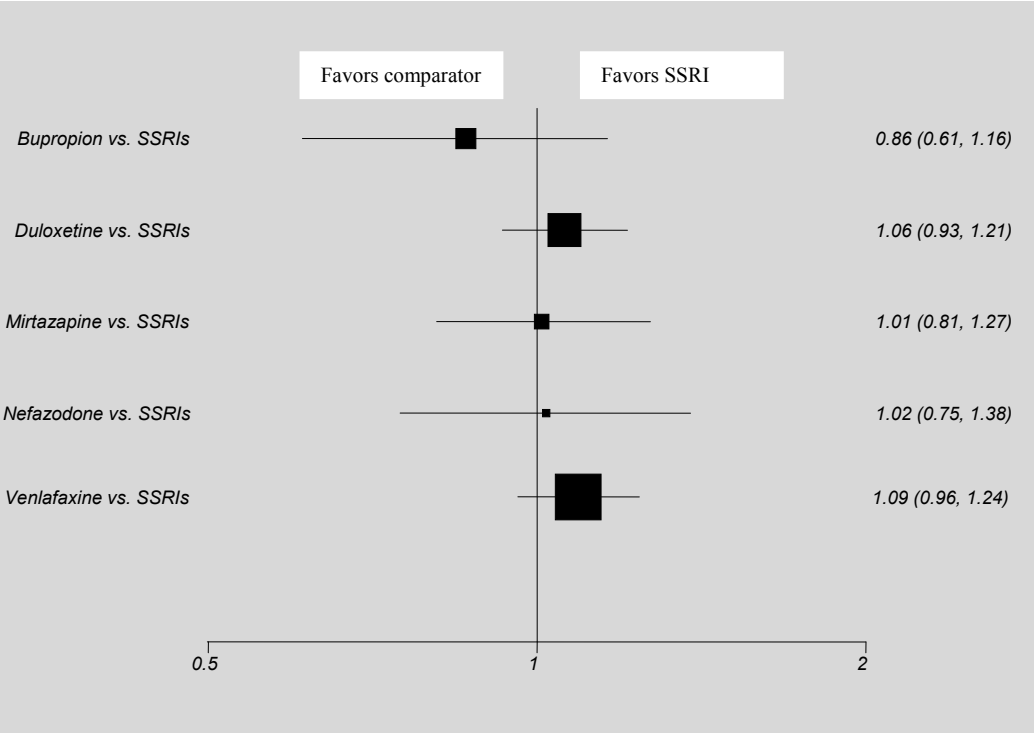

Relative risk meta-analysis plot (random effects)
favors fluoxetine
favors venlafaxine
Alves 1999
De Nayer 2002
Dierick 1996
Keller 2006
Nemeroff 2007
Rudolph 1999
Silverstone 1999
Tylee 1997
combined [random]
-0,013 (-0,216, 0,187)
0,178 (0,016, 0,331)
0,109 (0,003, 0,213)
-0,006 (-0,060, 0,054)
0,067 (-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

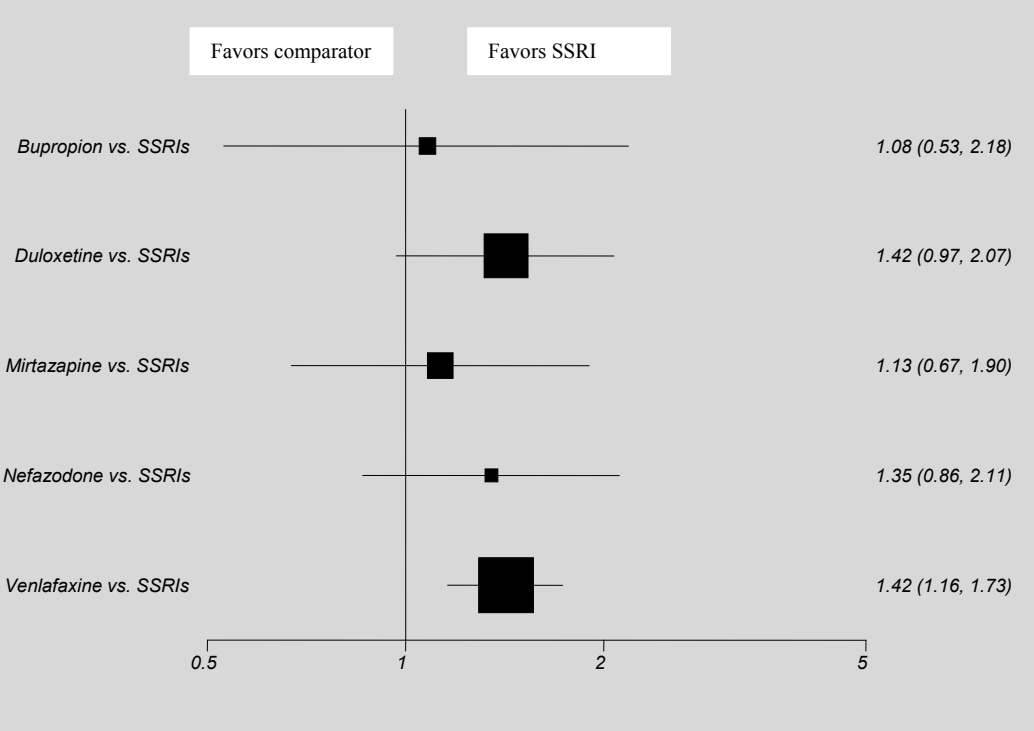
Average rates of overall discontinuation, discontinuation because of adverse events, and discontinuation because of lack of efficacy

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

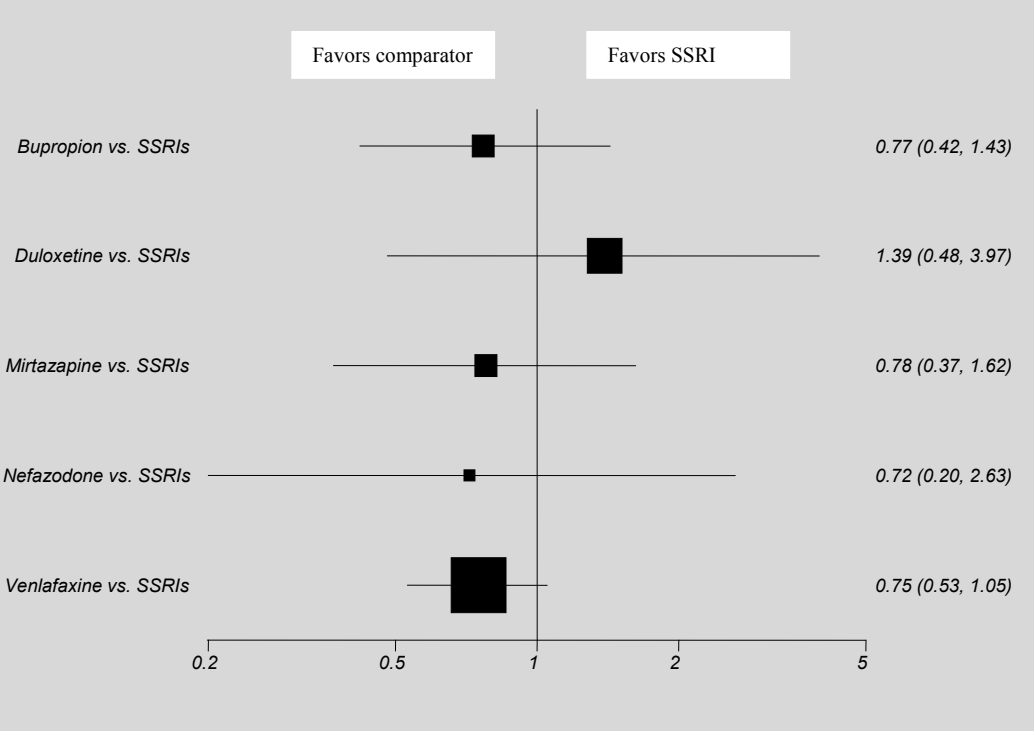
Relative risks of overall discontinuation



Relative risks of discontinuation because of adverse events



Relative risks of discontinuation because of lack of efficacy



Appendix A. Search strategy

DERP SGAU5 search March 23, 2010

PubMed

#1	Search "Antidepressive Agents, Second-Generation"[Mesh:NoExp] OR "Bupropion"[Mesh] OR "Citalopram"[Mesh] OR "duloxetine "[Substance Name] OR "O-desmethylvenlafaxine "[Substance Name] "Fluoxetine"[Mesh] OR "Fluvoxamine"[Mesh] OR "mirtazapine"[Substance Name] OR "nefazodone "[Substance Name] OR "Paroxetine"[Mesh] OR "Sertraline"[Mesh] OR "venlafaxine"[Substance Name] OR bupropion [Title/Abstract] OR citalopram [Title/Abstract] OR duloxetine [Title/Abstract] OR desvenlafaxine [Title/Abstract] OR escitalopram [Title/Abstract] OR fluoxetine [Title/Abstract] OR fluvoxamine [Title/Abstract] OR mirtazapine [Title/Abstract] OR nefazodone [Title/Abstract] OR paroxetine [Title/Abstract] OR sertraline [Title/Abstract] OR venlafaxine [Title/Abstract]	21497
#2	Search "Depressive Disorder"[Mesh:NoExp] OR "Depressive Disorder, Major"[Mesh]	606575
#3	Search "Dysthymic Disorder"[Mesh] OR "Seasonal Affective Disorder"[Mesh] OR "Anxiety Disorders"[Mesh] OR "Premenstrual Syndrome"[Mesh] OR “minor depression” OR "subsyndromal depression" Limits: All Adult: 19+ years	32792
#4	Search "Randomized Controlled Trial "[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh]	413330
#5	Search "Longitudinal Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Case-Control Studies"[MeSH] OR "Comparative Study "[Publication Type] OR "observation study" OR "observational study" OR "observation studies" OR "observational studies"	2356701
#6	Search #1 AND (#2 OR #3) AND #4 Limits: Humans, English, Publication Date from 2008/04/01	280
#7	Search #1 AND (#2 OR #3) AND #5 Limits: Humans, English, Publication Date from 2008/04/01	235
#10	Search #1 AND (#2 OR #3) Limits: Humans, Meta-Analysis, English, Publication Date from 2008/04/01	35
#11	Search #1 AND (#2 OR #3) Limits: Humans, Systematic Reviews, English, Publication Date from 2008/04/01	54
#12	Search #7 OR #8 OR #9 OR #10 OR #11	390

Cochrane

#1	MeSH descriptor Antidepressive Agents, Second-Generation, this term only	984
#2	MeSH descriptor Bupropion explode all trees	354
#3	MeSH descriptor Citalopram explode all trees	505
#4	MeSH descriptor Fluoxetine explode all trees	1031

#5	MeSH descriptor Fluvoxamine explode all trees	339
#6	MeSH descriptor Paroxetine explode all trees	673
#7	MeSH descriptor Sertraline explode all trees	515
#8	(bupropion OR citalopram OR duloxetine OR desvenlafaxine OR escitalopram OR fluoxetine OR fluvoxamine OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR venlafaxine):ti,ab,kw	7147
#9	MeSH descriptor Depressive Disorder, this term only	4059
#10	MeSH descriptor Depressive Disorder, Major explode all trees	1484
#11	MeSH descriptor Dysthymic Disorder explode all trees	110
#12	MeSH descriptor Seasonal Affective Disorder explode all trees	126
#13	MeSH descriptor Anxiety Disorders explode all trees	3712
#14	MeSH descriptor Premenstrual Syndrome explode all trees	347
#15	"minor depression" OR "subsyndromal depression"	161
#16	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	7245
#17	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)	9233
#18	(#16 AND #17), from 2008 to 2010	251

EMBASE

#1 'amfebutamone'/exp OR 'citalopram'/exp 'OR 'desvenlafaxine'/exp OR duloxetine'/exp OR 'escitalopram'/exp OR 'fluoxetine'/exp OR 'fluvoxamine'/exp OR 'mirtazapine'/exp OR 'nefazodone'/exp OR 'paroxetine'/exp OR 'sertraline'/exp OR 'venlafaxine'/exp	60,018
#2 'depression'/de OR 'major depression'/exp	198,078
#3 'dysthymia'/exp OR 'seasonal affective disorder'/exp OR 'anxiety disorder'/exp OR 'premenstrual syndrome'/exp AND ([adult]/lim OR [aged]/lim)	48,559
#4 'minor depression' AND ([adult]/lim OR [aged]/lim)	563
#5 'subsyndromal depression' AND ([adult]/lim OR [aged]/lim)	109
#6 #3 OR #4 OR #5 OR #6	230,506
#7 'longitudinal study'/exp OR 'cohort analysis'/exp OR 'case control study'/exp OR 'comparative study'/exp OR 'observational study'/exp	1,016,849
#8 #1 AND #6 AND #7 AND [humans]/lim AND [english]/lim AND [2008-2010]/py	379
#9 #1 AND #6 AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [humans]/lim AND [english]/lim AND [2008-2010]/py	652
#10 #9 OR #10 OR #11	942

IPA

S1	bupropion OR citalopram OR duloxetine OR desvenlafaxine OR escitalopram OR fluoxetine OR fluvoxamine OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR venlafaxine		3909
S2	major depressive disorder OR dysthymic disorder OR seasonal affective disorder OR anxiety disorders OR premenstrual syndrome OR minor depression OR subsyndromal depression		1568
S3	S1 AND (S2 OR S3)	Limiters - Published Date from: 20080401-; Language: English; Articles about Human Studies	131

PsycInfo

S1	bupropion OR citalopram OR duloxetine OR desvenlafaxine OR escitalopram OR fluoxetine OR fluvoxamine OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR venlafaxine		12080
S2	major depressive disorder		7898
S3	dysthymic disorder OR seasonal affective disorder OR anxiety disorders OR premenstrual syndrome OR minor depression OR subsyndromal depression	Limiters - Age Groups: Adulthood (18 yrs & older)	22046
S4	S1 AND (S2 OR S3)	Limiters - Published Date from: 20080401-; Language: English; Population Group: Human	276

SGAU5 Search 9.15.2010

Search	Most Recent Queries	Result
#1	Search "Antidepressive Agents, Second-Generation"[Mesh] OR "Bupropion"[Mesh] OR "Citalopram"[Mesh] OR "duloxetine "[Substance Name] OR "O-desmethylvenlafaxine "[Substance Name] "Fluoxetine"[Mesh] OR "Fluvoxamine"[Mesh] OR "mirtazapine"[Substance Name] OR "nefazodone "[Substance Name] OR "Paroxetine"[Mesh] OR "Sertraline"[Mesh] OR "venlafaxine"[Substance Name] OR bupropion [Title/Abstract] OR citalopram [Title/Abstract] OR duloxetine [Title/Abstract] OR desvenlafaxine [Title/Abstract] OR escitalopram [Title/Abstract] OR fluoxetine [Title/Abstract] OR fluvoxamine [Title/Abstract] OR mirtazapine [Title/Abstract] OR nefazodone [Title/Abstract] OR paroxetine [Title/Abstract] OR sertraline [Title/Abstract] OR venlafaxine [Title/Abstract]	22252
#2	Search "Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR “anxiety disorders”[mh] OR “premenstrual syndrome”[mh] OR "Seasonal Affective Disorder"[Mesh] OR “minor depression” OR "Dysthymic Disorder"[Mesh] OR "subsyndromal depression"	163352
#3	Search #1 AND #2	8821
#4	Search "adverse events" [tw] OR "drug hypersensitivity" [mh] OR "drug toxicity" [mh] OR hyponatremia [mh] OR seizures [mh] OR suicide [mh] OR "weight gain" [mh] OR "gastroesophageal reflux" [mh] OR libido [mh] OR hepatoxicity [tw] OR "Drug Interactions"[MeSH]	326709
#5	Search #3 AND #4	1753
#6	Search "Longitudinal Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Case-Control Studies"[MeSH] OR "Comparative Study "[Publication Type] OR (observation* [tw] AND study [tw]) OR (observation* [tw] AND studies [tw]) OR “observational study”	2546699
#7	Search #3 AND #6	2847
#8	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH]) OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	426867
#9	Search #3 AND #8	2775
#10	Search "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]	43092
#11	Search #3 AND #10	285
#12	Search "review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "systematic review"[All Fields]	1549302
#13	Search #3 AND #12	1391
#14	Search #5 OR #7 OR #9 OR #11 OR #13	5893

#15	Search #14 Limits: Humans, English, All Adult: 19+ years	3677
#16	Search ((#15) AND "2008/04/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date] Sort by: PublicationDate	471
#17	Search ((#15) AND "2008/01/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date] Sort by: Author	535

Analgolous terms were used to search The Cochrane Library, EMBASE, PsycINFO, and IPA databases.

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
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

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

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

Were the eligibility criteria specified?

Were outcome assessors blinded to the treatment allocation?

Was the care provider blinded?

Was the patient kept unaware of the treatment received?

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)

Did the study maintain comparable groups?

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

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)

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

How many patients were recruited?

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

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

Did the control group receive the standard of care?

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[343]	RCT	108	Sertraline vs. fluoxetine	High loss to follow-up; High differential loss to follow-up
Amini et al., 2005[344]	RCT	36	Mirtazapine vs. fluoxetine	No ITT analysis
Bauer et al., 2009[345]	Systematic review	7,155	Venlafaxine, SSRIs	No critical appraisal, no dual literature reviews
Benkert et al., 2006[346]	RCT	242	Mirtazapine vs. venlafaxine	High attrition; no baseline characteristics
Cookson et al., 2006[347]	Pooled analysis	2,656	Duloxetine vs. fluoxetine, paroxetine & placebo	No systematic literature search
Davidson et al., 2002[348]	Pooled analysis	1,097	Venlafaxine vs. fluoxetine	No systematic literature search
Eckert et al., 2006[349]	Systematic review	2,198	Duloxetine, Fluoxetine, Venlafaxine	No critical appraisal
Feiger et al., 2003[350]	Pooled analysis	1,088	Sertraline vs. fluoxetine	No systematic literature search
Flament et al., 2001[351]	RCT	286	Sertraline vs.fluoxetine	No ITT analysis
Goldstein et al., 2004[352]	RCT	353	Duloxetine vs. Paroxetine	High loss to follow-up
Gorman et al., 2002[353]	Meta-analysis	1,321	Escitalopram vs. citalopram	No systematic literature search
Grigoriadis et al., 2003[354]	Observational	201	Citalopram vs. fluoxetine	No ITT analysis
Herrera-Guzmán, et al., 2009[355]	RCT	73	Escitalopram, Duloxetine	Poor randomization
Herrera-Guzmán 2010[356]	RCT	73	Escitalopram, Duloxetine	Poor randomization
Kennedy et al., 2006[357]	Systematic review	2,687	Escitalopram, SSRI	No critical appraisal, no systematic literature search
Kennedy et al., 2009[358]	Systematic review	4,549	Escitalopram , SSRIs	No critical appraisal
Lapierre et al., 1987[359]	RCT	63	Fluvoxamine vs. placebo	No ITT analysis
Llorca et al., 2005[360]	Pooled analysis	506	Escitalopram vs. citalopram	No systematic literature search
March et al., 1990[361]	RCT	54	Fluvoxamine vs. placebo	No ITT analysis
Papakostas et al., 2007[362]	Systematic review	988	Trazodone & nefazodone vs. SSRIs	No quality appraisal
Papakostas et al., 2007[363]	Pooled analysis	1,672	Bupropion vs. SSRIs	No systematic literature search
Papakostas et al., 2008[364]	Pooled analysis	2,890	Bupropion vs. SSRIs	No systematic literature search
Papakostas et al., 2008[365]	Systematic review	1,904	Mirtazapine, SSRIs	no systematic literature search
Perahia et al., 2008[199]	Pooled analysis	667	Duloxetine vs. venlafaxine	No systematic literature search
Shelton et al. 2005[366]	Pooled analysis	1,391	Venlafaxine vs. Fluoxetine and paroxetien	No systematic literature search

Study	Design	Sample size	Intervention	Reason for exclusion
Stahl et al., 2000[367]	RCT	323	Citalopram vs. sertraline vs. Placebo	High loss to follow-up
Stahl et al., 2002[368]	Pooled analysis	1,622	Venlafaxine fluoxetine paroxetine placebo	No systematic literature search
Thase et al., 2001[369]	Pooled analysis	2,117	Venlafaxine vs. SSRI vs. placebo	No systematic literature search
Thase et al, 2005[370]	Meta-analysis	1,975	Bupropion vs. SSRI	No systematic literature search
Thase et al., 2006[371]	RCT	348	Bupropion vs. venlafaxine	High loss to follow-up
Thase et al., 2010[87]	Systematic review	1,484	Mirtazapine, SSRIs	No systematic literature search
Trkulja, 2010[27]	Systematic review	NR	Escitalopram vs. citalopram	No dual literature review
Wade et al., 2003[372]	RCT	197	Mirtazapine vs. paroxetine	High loss to follow-up
MDD-Ped				
DeVane et al., 1996[373]	Meta-analysis	61	Fluoxetine vs. placebo	No systematic literature search
Emslie et al., 1997, 1998[341, 374]	RCT	96	Fluoxetine vs. placebo	Loss to follow-up differential > 15 percentage points
Emslie et al., 2002[342]	RCT	219	Fluoxetine vs. placebo	Loss to follow-up differential > 15 percentage points
Mayes et al., 2007[375]	Pooled post hoc analysis	315	Fluoxetine vs. placebo	No systematic literature search
Generalized Anxiety Disorder				
Bielski et al., 2005[376]	RCT	123	Escitalopram vs. paroxetine	High loss to follow-up
Kelsey et al., 2000[377]	Pooled analysis	2,000	Venlafaxine vs. placebo	No systematic literature search
Stahl et al., 2007[378]	Post hoc pooled analysis	1,965	Venlafaxine vs. placebo	No systematic literature search
Wan et al., 2006[379]	Pooled analysis	1,839	Venlafaxine vs. placebo	No systematic literature search
OCD				
Cox et al., 1993[380]	Meta-analysis	Not reported	Clomipramine vs. fluoxetine vs. behavior therapy	Lack of information on included studies
Greist et al., 1995[381]	Meta-analysis	1530	Clomipramine vs. fluoxetine vs. fluvoxamine vs. sertraline	No systematic literature search
Kobak et al., 1998[382]	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[383]	RCT	148	Fluvoxamine vs. placebo	High loss to follow-up
PTSD				
Chung et al., 2004[384]	Open-label trial	113	Mirtazapine vs. Sertraline	Significant differences in patient characteristics at baseline
Davidson et al. 1998[385]	Open-label trial	15	Fluovoxamine	Open-label, high loss to follow-up
Davidson et al., 1998[386]	Open-label trial	17	Nefazodone	Open-label, high loss to follow-up
De Boer et al., 1992[387]	Open-label trial	24	Fluovoxamine	Open-label, high loss to follow-up

Study	Design	Sample size	Intervention	Reason for exclusion
Martenyi et al., 2002[388, 389]	RCT	301	Fluoxetine vs. placebo	High loss to follow-up
Smajkic et al., 2001[390]	RCT	40	Sertraline vs. paroxetine vs. venlafaxine	Small sample size, no ITT analysis
Tucker et al., 2001[391]	RCT	323	Paroxetine vs. placebo	High loss to follow-up
Social Anxiety Disorder				
Allgulander et al., 2001[392]	RCT	96	Paroxetine vs. placebo	No ITT analysis, lack of statistical comparisons
PMDD				
Diegoli et al., 1998[393]	RCT	120	Pyridoxine, alprazolam, fluoxetine, propanolol	Important information about study methodology not reported
Carr et al.,2002[394]	Systematic review	NR	fluoxetine	No critical appraisal of study quality; no description of review process
Subgroups				
Ashman et al., 2009[395]	RCT	52	Sertraline	No ITT
Beasley et al., 1991[396, 397] and Tollefson et al., 1994[398]	Meta-analysis	3,065	Fluoxetine vs. placebo	No systematic literature search
Desmarais et al, 2009 [399]	Systematic review	2,203	SSRI, SNRI, Tamoxifen	No critical appraisal, no systematic literature search
Gülseren et al. 2005[400]	RCT	25	Fluoxetine vs. paroxetine	High rate of post-randomization exclusions
Pettinati et al., 2010[401]	RCT	170	Sertraline	High attrition
Rajji et al., 2008[402]	Systematic review	Not reported	SSRI, SNRI, Placebo	no dual literature reviews
Roy-Byrne et al. 2000[403]	RCT	64	Nefazodone vs. placebo	High loss to follow-up
Soares et al., 2010[404]	RCT	607	Desvenlafaxine, Escitalopram	No ITT
Weintraub et al., 2010[405]	RCT	130	Sertraline, Placebo	High attrition
Adverse Events				
Baldwin et al., 2007[406]	Pooled analysis		Escitalopram vs. placebo	No systematic literature search
Croft et al., 2002[239]	RCT	432	Buprprion vs. placebo	High loss to follow-up
Demyttenaere et al. 2005 [407]	RCT	85	SSRIs vs. placebo	No ITT analysis
Ferguson et al., 2001[408]	RCT	72	Nefazodone vs. sertraline	Selection bias
Kennedy et al., 2000[409]	Prospective cohort	174	Paroxetine vs. sertraline vs. venlafaxine	No ITT analysis; high loss to follow-up
Letizia et al., 1996[410]	Systematic review	3,828	Fluvoxamine vs. TCA vs. placebo	Search strategy not reported; no critical appraisal of study quality
Thase et al., 2006[371]	RCT	348	Bupropion vs. venlafaxine	High loss to follow-up
Wernicke et al., 1997[411]	Meta-analysis	4,016	Fluoxetine, placebo ,TCA	No systematic literature search
Wernicke, 2007[412]	Pooled analysis	14,627	Duloxetine vs. placebo	No systematic literature search

Appendix D. 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 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 couble-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.
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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.

Appendix E. 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
Duloxetine	> 90%	*Major:*	CYP1A2; CYP2D6	*Moderate:*	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
Desvenlafaxine	30%	*Minor:*	CYP3A4	*Weak:*	CYP3A4

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

Clinically Significant Drug Interactions: SSRIs

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]
Warfarin	Monitor (1)	Monitor (2)	Monitor (3)[d]

[a] Decrease in second-generation antidepressant plasma levels
[b] I ncrease 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: SSRIs

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]

[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)	

[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)

[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 package insert
(10) Nefazodone package insert

Clinically Significant Drug Interactions: Mirtazapine, Venlafaxine

Interacting Drug	Duloxetine	Desvenlafaxine
Aspirin	Monitor (11)[d]	Monitor (12)[d]
Cimetidine	Monitor (11)[b]	
Ciprofloxacin	Monitor (11)[b]	
Desipramine	Monitor (11)[d]	Monitor (12)[d]
Enoxacin	Monitor (11)[b]	
Ketoconazole		Monitor (12)[b]
Lithium	Not recommended (11)	
Lorazepam	No significant interaction (11)	
MAOIs	Contraindicated (11)	Contraindicated (12)
Midazolam		Monitor (12)[c]
NSAIDS	Monitor (11)[d]	Monitor (12)[d]
Quinidine	Monitor (11)[b]	
Temazepam	No significant interaction (11)	
Triptans	Monitor (11)[b]	
Warfarin	Monitor (11)[d]	Monitor (12)[d]

[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
(11) Duloxetine package insert
(12) Desvenlafaxine package insert

Appendix F. Black box warnings of drugs approved by the US Food and Drug Administration

Trade names (active ingredients)	Boxed warnings, warnings and precautions
Wellbutrin®; Wellbutrin SR®; Wellbutrin XL® (bupropion hydrochloride)	**Boxed Warning** **Suicidality and Antidepressant Drugs** ***Use in Treating Psychiatric Disorders:*** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of WELLBUTRIN or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. WELLBUTRIN is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.) ***Use in Smoking Cessation Treatment:*** WELLBUTRIN®, WELLBUTRIN SR®, and WELLBUTRIN XL® are not approved for smoking cessation treatment, but bupropion under the name ZYBAN® is approved for this use. Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion for smoking cessation. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking bupropion who continued to smoke. All patients being treated with bupropion for smoking cessation treatment should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking ZYBAN in the

Trade names (active ingredients)	Boxed warnings, warnings and precautions
	postmarketing experience. When symptoms were reported, most were during treatment with ZYBAN, but some were following discontinuation of treatment with ZYBAN. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of ZYBAN. Advise patients and caregivers that the patient using bupropion for smoking cessation should stop taking bupropion and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of ZYBAN was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve. The risks of using bupropion for smoking cessation should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (See WARNINGS: Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment and PRECAUTIONS: Information for Patients.)
Celexa® (citalopram hydrobromide)	**Boxed Warning** **Suicidality and Antidepressant Drugs** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Celexa or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Celexa is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

Trade names (active ingredients)	Boxed warnings, warnings and precautions
Pristiq® (desvenlafaxine)	**Boxed Warning** **WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PRISTIQ® or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PRISTIQ is not approved for use in pediatric patients [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1)*].
Cymbalta® (duloxetine hydrochloride)	**Boxed Warning** **WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. [see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Information for Patients (17.2).]

Trade names (active ingredients)	Boxed warnings, warnings and precautions
Lexapro® (escitalopram oxalate)	**Boxed Warning** **Suicidality and Antidepressant Drugs** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)
Prozac®; Prozac Weekly®; Sarafem® (fluoxetine hydrochloride)	**Boxed Warnings** **WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PROZAC or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PROZAC is approved for use in pediatric patients with MDD and Obsessive Compulsive Disorder (OCD) *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]. When using PROZAC and olanzapine in combination, also refer to Boxed Warning section of the package insert for Symbyax.*

Trade names (active ingredients)	Boxed warnings, warnings and precautions
	WARNING Suicidality and Antidepressant Drugs — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SARAFEM or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SARAFEM is not approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). (See WARNINGS, PRECAUTIONS, Information for Patients, and PRECAUTIONS, Pediatric Use.)
Luvox®; Luvox CR® (fluvoxamine maleate)	**Boxed Warnings** **Suicidality and Antidepressant Drugs** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. LUVOX CR Capsules are not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

Trade names (active ingredients)	Boxed warnings, warnings and precautions
Remeron® (mirtazapine)	**Boxed Warnings** **Suicidality and Antidepressant Drugs** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of REMERON® (mirtazapine) Tablets or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. REMERON is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)
Serzone® (nefazodone)	**Boxed Warnings** **Suicidality in Children and Adolescents** Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-termstudies in children and adolescents with Major Depressive Disorder (MDD) and otherpsychiatric disorders. Anyone considering the use of [Insert established name] or any otherantidepressant in a child or adolescent must balance this risk with the clinical need. Patientswho are started on therapy should be observed closely for clinical worsening, suicidality, orunusual changes in behavior. Families and caregivers should be advised of the need for closeobservation and communication with the prescriber. [Insert established name] is not approvedfor use in pediatric patients. (See Warnings and Precautions: Pediatric Use)Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs(SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessivecompulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over4400 patients) have revealed a greater risk of adverse events representing suicidal thinking orbehavior (suicidality) during the first few months of treatment in those receivingantidepressants. The average risk of such events in patients receiving antidepressants was 4%,twice the placebo risk of 2%. No suicides occurred in these trials.

Trade names (active ingredients)	Boxed warnings, warnings and precautions
Paxil®; Paxil CR® (paroxetine hydrochloride)	**Boxed Warnings** **Suicidality and Antidepressant Drugs** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAXIL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PAXIL is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)
Zoloft® (sertraline hydrochloride)	**Boxed Warnings** **Suicidality and Antidepressant Drugs** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Zoloft or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

Trade names (active ingredients)	Boxed warnings, warnings and precautions
Effexor®; Effexor XR® (venlafaxine hydrochloride)	**Boxed Warnings** **Suicidality and Antidepressant Drugs** Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Effexor or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Effexor is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)

Appendix G. Abbreviation Guide

Abbreviation used	Term
ACT	Active-control trial
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BDI II	Beck Depression Inventory II
Beck's SSI	Scale for Suicide Ideation
bid	Twice daily
BMI	Body mass index
BQOL	Battelle Quality of Life Measure
CAPS	Clinician Administered PTSD Scale
CAS	Clinical Anxiety Scale
CCEI	Crown Crisp Experiential Index
CCT	Controlled clinical trial
CDRS	Cornell Dysthymia Rating Scale
CGI	Clinical Global Impressions
CGI – S	Clinical Global Impressions Severity Scale
CGI –I	Clinical Global Impressions Improvement Scale
CI	Confidence interval (reported in the following format: 95% CI, xx to xx)
CIS	Clinical Interview Schedule
CNS	Central nervous system
CR	Controlled release
CV	Cardiovascular
CVS	Cardiovascular system
d	Day
DB	Double-blind
dL	Deciliter
DSM – IV	Diagnostic and Statistical Manual of Mental Disorders, version IV
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection fraction
ER	Extended release
ESRS	Extrapyramidal Symptom Rating Scale
FDA	US Food and Drug Administration
FSQ	Functional Status Questionnaire
FU	Follow-up
g	Gram
GHQ	General Health Questionnaire
GI	Gastrointestinal

Abbreviation used	Term
GP	General practitioner
h	Hour
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
HDL-C	High density lipoprotein cholesterol
HMO HR	Health maintenance organization Hazard ratio
HRQOL	Health related quality-of-life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
IDAS	Irritability, depression, and anxiety scale
IDS C	Inventory for Depressive Symptomatology - Clinician Rated
IDS SR	Inventory for Depressive Symptomatology – Self Rated
IR	Immediate release
ITT	Intention-to-treat
L	Liter
LA	Long acting
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last Observation Carried Forward
LS means	Least squares means
MADRS	Montgomery Asberg Depression Rating Scale
MANCOVA	Multivariate analysis of covariance
mcg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
MMSE	Mini Mental State Examination
mo	Month
MOCI	Maudsley Obsessive Compulsive Inventory
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NR	Not reported
NS	Not significant
NSD	No significant difference
OR	Odds ratio
P	P value (uppercase and italicized, ie *P*=0189)
P	Placebo
PAS	Panic and Agoraphobia Scale

Abbreviation used	Term
PCT	Placebo-controlled trial
PGIS	Patient Global Improvement Scale
PPY	Per person year
PRIME MD	Primary Care Evaluation of Mental Disorder
PSE	Present State Examination
qd	Once daily
QLDS	Quality of Life in Depression Scale
QLSQ	Quality of Life Enjoyment and Satisfaction Questionnaire
QOL	Quality-of-life
RCIS	Revised Clinical Interview Schedule—Shona Version
RCT	Randomized controlled trial
RR	Relative risk
SADS	Schedule for Affective Disorders and Schizophrenia
SB	Single-blind
SCAG	Sandoz Clinical Assessment Geriatric Scale
SCID	Structured Clinical Interview for DSM III Revised
SCL 25	Hopkins Symptom Checklist 25 item version
SD	Standard deviation
SDS	Sheehan Disability Scale
SDS	Self rating Depression Scale
SE	Standard error
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
SLT	Shopping List Task
SR	Sustained release
SSQ	Shona Symptom Questionnaire
tid	Three times daily
VAS	Visual analog scale
vs	Compared with (versus)
WD	Withdrawal
XR	Extended release
y	Year
Y-BOCS	Yale Brown Obsessive Compulsive Scale

Appendix H. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see External Validity

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See Adverse Event

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See Blinding

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.