Drug Class Review
on
Second Generation Antidepressants

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

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

Pharmacotherapy dominates the medical management of Axis I psychiatric disease. Before the late 1980s, pharmacologic treatment was limited to tricyclic antidepressants (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.[4] Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), was approved for the treatment of MDD and diabetic peripheral neuropathic pain in 2004.

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

serotonin and 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 1 summarizes the newer products that are available in the US by mechanism of action.

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

Compared to the first-generation antidepressants, the SSRIs and other second-generation antidepressant have comparable efficacy and comparable or better side effect profiles.[6, 7] However, comparative differences in efficacy, tolerability, and safety are not well defined for the second-generation drugs. The tremendous volume and large variability in the quality of evidence to support use of these products makes it difficult for clinicians and decision makers to make evidence-based decisions.

The purpose of this review is to help policymakers and clinicians make informed choices about the use of 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, 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 and dysthymic disorder), generalized anxiety disorder (GAD), OCD, panic disorder, post-traumatic stress disorder (PTSD), and social anxiety disorder. We focus this review on these disorders in adult outpatient populations.

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

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

Table 1: Approved Second-Generation Antidepressants

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

*CR, SR, XL, and XR are registered trademarks referring to controlled, sustained, or extended-release dosage forms
**GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; PMDD, premenstrual dysphoric disorder; DPNP, diabetic peripheral neuropathic pain
† Generic available for some dosage forms.
†† Only Paxil CR® (not Paxil®) is approved for the treatment of PMDD.
††† Only Effexor XR® is approved for the treatment of GAD and Social Anxiety Disorder
‡ Lexapro was denied approval for social anxiety disorder 3/30/2005

Table 2: Dosing Range and Frequency

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

*CR, SR, XL, and XR are registered trademarks referring to controlled, sustained, or extended-release dosage forms
**withdrawn from the US market effective June 14, 2004

B. Scope and Key Questions

The purpose of this review is to compare the efficacy, effectiveness, and tolerability (adverse events) of second-generation antidepressant medications. The participating organizations of the Drug Effectiveness Review Project (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.[8] The results of effectiveness studies are more applicable to the average patient than results from highly selected populations in efficacy studies.

For each of the three key questions, we evaluated specific outcome measures (where appropriate), as reported in Table 3. For efficacy and effectiveness, we focused on head-to-head trials comparing one second-generation antidepressant to another. When sufficient head-to-head evidence was not available, we evaluated placebo-controlled evidence of efficacy for medications not already approved by the 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: Outcomes and 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 vs. another
		• When sufficient evidence was not available for head-to-head trials within a specific diagnostic group, we evaluated:
		  • Placebo-controlled trials

Safety/ Tolerability	• Overall adverse effect reports
	• Withdrawals because of adverse effects
	• Serious adverse event reports
	• Specific adverse events or withdrawals because of specific adverse events, including:
	  • *hyponatremia*
	  • *seizures*
	  • *suicide*
	  • *hepatoxicity*
	  • *weight gain*
	  • *gastrointestinal symptoms*
	  • *loss of libido*
	  • *others*
		• Head-to-head randomized controlled clinical trials or meta-analyses evaluating:
		  • One second-generation antidepressant vs. another
		• When sufficient evidence was not available for head-to-head trials within a specific diagnostic group, we evaluated
		  • Placebo-controlled trials
		  • Observational studies

METHODS

A. Literature Search

To identify articles relevant to each key question we searched MEDLINE, Embase, The Cochrane Library, PsychLit, and the International Pharmaceutical Abstracts. We used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (MDD, dysthymia, general anxiety disorder, PTSD, OCD, panic disorder, social anxiety disorder, PMDD), drug interactions, and adverse events with a list of 11 specific second-generation antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, mirtazapine, duloxetine, venlafaxine, bupropion, and nefazodone). We limited the electronic searches to "human" and "English language." Sources were searched from 1980 to 2006 (April) to capture literature relevant to the scope of our topic. See Appendix A for complete search strategy.

We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses. We also manually searched reference lists of pertinent and relevant review articles and letters to the editor. All citations were imported into an electronic database (EndNote 8.0). Additionally, we handsearched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the FDA.

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

Our searches found 2,313 citations, unduplicated across databases. Additionally we detected 135 articles from manually reviewing the reference lists of pertinent review articles. One included study stemmed from pharmaceutical dossiers. The total number of citations included in the database was 2,449.

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 (based on the QUORUM[9] statement). 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.

If we could not find sufficient evidence about efficacy or effectiveness from at least one randomized, double-blinded head-to-head trial for an indication of interest, we reviewed placebo-controlled trials and controlled open-label trials for this specific indication. However, the strength of evidence of these results for comparing different drugs must be rated lower than results from the most preferred type of trial. Findings of placebo-controlled trials are hard to compare across studies because different populations may respond differently.

Overall, we included 789 articles on an abstract level and retrieved 537 of those as full text articles for background information or to be reviewed for inclusion into the evidence report. Studies included as abstracts but not retrieved as full text articles were mainly placebo-controlled trials with respect to key questions or indications for which sufficient evidence from head-to-head trials was available (see Appendix E).

C. Data Abstraction

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

D. Quality Assessment

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

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

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

Trials that had a fatal flaw in one or more categories were rated poor quality and not included in the analysis of the evidence report (Appendix C). Trials that met all criteria were rated good quality. The majority of trials received a quality rating of fair. This includes studies that presumably fulfilled all quality criteria but did not report their methodologies to an extent that answered all our questions. Thus, the “fair quality” category includes trials with quite different strengths and weaknesses. The results of some fair quality studies are *likely* to be valid; others are *probably* valid. From 202 eligible studies we excluded 44 on the grounds of poor methodological quality (Appendix C).

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 2,449 citations from searches and reviews of reference lists. We identified an additional five unpublished trials from dossiers submitted by pharmaceutical companies. Only abstracts of these five studies were available, and we subsequently excluded them.

In all, we included 158 studies: 118 RCTs, 14 meta-analyses, 15 observational studies, and 11 studies of other design. Furthermore, we retrieved 72 articles for background information. Two studies of interest could not be retrieved after multiple attempts.[13-16] Figure 1 (QUORUM Tree) documents the disposition of the 301 articles for these studies.

Reasons for exclusions were based on eligibility criteria or methodological criteria (Figure 1, QUORUM Tree). Forty-seven studies that met the eligibility criteria but were later rated as poor quality for internal validity were 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 or failure to maintain the units of the trials during statistical analysis were the main reasons for exclusions. A lack of systematic literature search leads to a selected spectrum of trials and subsequently to biased results. Similarly, pooling data of trials without maintaining the units of the individual trials during statistical analysis fails to preserve randomization and introduces bias and confounding.[12]

Some trials were clearly not powered to establish a greater efficacy of a particular drug but rather to present equivalency in efficacy between the pharmacotherapies (non-inferiority trials). This problem arose because drugs within the same class can achieve FDA approval based on non-inferiority. Furthermore, the sponsoring industry often has a specific interest in reporting efficacy equivalency between two drugs.

Of 158 included studies, 69 percent were financially supported by pharmaceutical companies; 15 percent were funded by governmental agencies or independent funds. For 16 percent of included studies, we could not determine funding source.

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

Table 4: Abbreviations and Diagnostic Scales

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. Efficacy

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

We included 105 RCTs, 9 meta-analyses, and 3 studies of other design. Of the RCTs, 64 were head-to-head trials; 40 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, escitalopram, fluoxetine, paroxetine, sertraline mirtazapine, duloxetine, venlafaxine, bupropion, and nefazodone.

Two systematic reviews and 54 RCTs compared the effectiveness or efficacy of one second-generation antidepressant to another for treating patients with MDD (Table 5). All included studies compared equivalent doses of the compared drugs. We did not find any head-to-head studies conducted in a population with dysthymia, but we included three studies with active or placebo controls conducted in a dysthymic population (Table 9).

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

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

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

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

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

Most studies received a *fair* rating for internal validity. The generalizability of the results was hard to determine and might often be limited. Most trials (60 %) were of short (6 to 8 weeks) or medium (9 to 11 weeks) duration; 40 percent reported a follow-up of 12 weeks or more. Two European trials[17, 18] and one US trial[19] in primary care settings, with less stringent eligibility criteria, could be viewed as effectiveness trials. These studies also had long periods of follow-up.[18, 19] Drug equivalency was present in all included studies.

Trial reporting was often incomplete. Most articles did not report the method of randomization or allocation concealment. Although last-observation-carried-forward methods (or LOCF analysis, which means that the last observed measurement serves as the substitute for missing values because of the drop out of patients at different time points) were a frequent method of intention-to-treat analysis, few authors reported the overall number of patients lost to follow-up from randomization to the end of the trial. The percentage of imputed measurements, a potential source of bias, was sometimes hard to assess. Many studies did not report the ethnic backgrounds of participants.

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

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

Citalopram vs. escitalopram

Four trials compared the efficacy of escitalopram and citalopram.[20-23] Three studies were conducted over 8 weeks, two of them as fixed dose trials[20, 21, 23] (escitalopram 10mg/d and 20mg/d to citalopram 20mg/d and 40mg/d). Overall, results favored escitalopram over citalopram. Two studies reported statistically significantly higher response rates for escitalopram than for citalopram treated patients (76.1% vs. 61.3%, $p < 0.05$ and 63.7% vs. 52.6%; $p = 0.021$). In both studies escitaloprom also led to higher remission rates than escitalopram. One trial was a fair-rated European/Canadian flexible dose study that compared the efficacy and tolerability of citalopram (20-40mg/d) to escitalopram (10-20mg/d) and placebo in 471 depressed outpatients attending primary care centers.[20] 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% vs. 52.6%; $p = 0.021$) and remitters (MADRS < 12; 52.1% vs. 42.8%; $p <$

0.036) than the citalopram group. Escitalopram was numerically better at all time points on all three efficacy scales (MADRS, CGI-I, CGI-S). The study did not assess health outcomes.

The fourth study was a fair fixed dose trial (escitalopram 10mg/d, citalopram 20mg/d) in 357 European primary care patients over 24 weeks.[22] Escitalopram patients had significantly higher response rates at week 8 (63% vs. 55%; $p < 0.05$) but not at week 24 (80% vs. 78%; p = NR). Escitalopram had a significantly lower CGI-S scores (1.75 vs. 2.00) and significantly fewer withdrawals (12.7% vs. 22.4%) than citalopram at week 24.

A pooled analysis of data from three RCTs concluded that escitalopram significantly improved sleep disturbance compared to citalopram.[24]

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 of studies comparing Citalopram to Escitalopram

Study	N	Duration	Dosage Esc. - Cit. mg/d	Response(%)	Remission(%)	Quality Rating
Burke et al., 2002[21]	491	8 weeks	20 vs. 40	51.2 vs. 45.6 p = NR (ns)	NR	Fair
			10 vs. 40	50 vs. 45.6 p = NR (ns)	NR	
Colonna et al., 2005[22]	357	8 weeks	10 vs. 20	63 vs. 55 $p < 0.05$	NR	Fair
		24 weeks	10 vs. 20	80 vs. 78 p = NR (ns)	NR	
Lepola et al., 2003[20]	471	8 weeks	10-20 vs. 20-40	63.7 vs. 52.6 p = 0.021	52.1 vs. 42.8 p = 0.036	Fair
Moore et al., 2005[23]	280	8 weeks	20 vs. 40	76.1 vs. 61.5 p = 0.009	56.1 vs. 43.6 p = 0.04	Fair

We conducted two meta-analyses of these studies comparing the effects of citalopram to escitalopram on MADRS scores at week 8. The outcome of the first meta-analysis was the relative risk of being a responder on the MADRS scale at week 8 (Exhibit 1). A "response" was defined as an improvement of 50 percent or more on the MADRS scale. Pooled results included 1,300 patients and yielded a statistically significant additional treatment effect for escitalopram. The relative risk that a patient would respond was 1.19 (95% CI, 1.08-1.30) 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 10 (95% CI: 7-22).

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 1.25 point reduction (95% CI: 0.10-2.39; 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.[25]

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 vs. fluoxetine

In a fair-rated trial from France, 397 outpatients with MDD attending general practices were randomly assigned to citalopram (20mg/d) or fluoxetine (20mg/d) over 8 weeks.[26] Loss to follow-up was 12.6 percent. No intention-to-treat analysis was conducted for efficacy measures. Citalopram had a faster onset of efficacy with significantly more patients rated as responding on the MADRS scale ($p = 0.048$) or completely recovered on MADRS and HAM-D scales ($p = 0.034$, $p = 0.025$) after 2 weeks. By 8 weeks, however, MADRS or HAM-D scores showed no statistically significant differences.

Citalopram vs. sertraline

A good-quality Swedish study assessed the effectiveness of citalopram (20-60mg/d) and sertraline (50-150mg/d) in 400 patients in general practice during 24 weeks of treatment.[17] 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.

Fluoxetine vs. fluvoxamine

Two fair studies evaluated the comparative effectiveness and safety of fluoxetine and fluvoxamine in outpatients with MDD.[27, 28] A 7-week flexible dose study (fluoxetine: 20-80 mg/d; fluvoxamine 100-150mg/d) did not identify any statistically significant differences in efficacy between the two treatment groups (HAM-D, HAM-A, CGI-S, Raskin-Covi Scale, Hopkins Symptoms Checklist).[28] Both treatment regimens significantly improved scores on assessment scales. The second study was a 6-week fixed dose European trial (fluoxetine 20mg/d; fluvoxamine 100mg/d) in 184 outpatients with MDD.[27] Results are consistent with those of the flexible-dose study; the primary outcome measure (HAM-D) was not significantly different at any time. The drugs were equally effective for secondary outcome measures (CGI, Clinical Anxiety Scale [CAS], the Irritability, Depression, and Anxiety Scale [IDAS], Beck's Scale for Suicide Ideation [Beck's SSI]) such as suicidal ideation, sleep, anxiety, and severity of illness at

endpoint. Fluvoxamine had significantly more responders on CGI-S (29% vs. 16%; $p < 0.05$) and a greater reduction of CGI-S scores ($p < 0.05$) at week 2 but not at weeks 4 or 6.

Fluoxetine vs. paroxetine

Seven fair-rated studies compared fluoxetine to paroxetine.[14, 29-34] Two RCTs were conducted in a population older then 60 years.[29, 32] The best trial was an Italian study lasting 1 year that enrolled 242 patients to compare the effects of fluoxetine (20-60mg/d) and paroxetine (20-40mg/d) on mood and cognitive function in depressed, nondemented persons (65 years or older).[29] Paroxetine had a faster onset of action and a significantly greater improvement of HAM-D scores during the first 6 weeks (week 3: $p < 0.05$; week 6: $p < 0.002$). For up to a year paroxetine was effective in a higher percentage of patients than fluoxetine ($p < 0.002$ by Kaplan-Meier analysis). Treatment groups did not differ significantly in CGI scores. Fluoxetine had more severe adverse events than paroxetine (22 versus 9; $p < 0.002$).

The other six studies[14, 30-34] 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,[31, 32] four trials did not.[14, 30, 33, 34] In one study paroxetine-treated patients older than 60 years had a significantly greater response rate on HAM-D and MADRS scales (37.5% vs. 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.[14, 29, 30, 33, 34] A Canadian RCT assessed anxiolytic activity and akathisia as secondary outcome measures and could not detect any significant differences between treatment groups.[30] However, study groups in this trial were not similar at baseline with respect to recurrent depression (paroxetine 76.5% vs. fluoxetine 59.5%), the validity of results might be limited.[30]

We conducted a meta-analysis of six of these studies comparing the effects of fluoxetine to paroxetine on HAM-D scores at the end of followup.[14, 30-34] A "response" was defined as an improvement of 50 percent or more on the HAM-D scale. The seventh study could not be included because the article did not provide the necessary data.[29] The statistical analysis included 795 patients. Results (Exhibit 3) show that the response rate did not differ significantly between fluoxetine and paroxetine (RR: 1.09; 95% CI 0.97 – 1.21) for the random effects model, and the fixed effects model was similarly nonsignificant. Tests for heterogeneity were not significant. Funnel plot, Kendell's test, and L'Abbe plot did not indicate major biases. However, given the small number of component studies, results of these tests must be viewed cautiously.

Fluoxetine vs. sertraline

Six studies compared fluoxetine to sertraline.[18, 19, 34-37] The top-level evidence consisted of two effectiveness trials[18, 19] and one efficacy trial[38] with long periods of follow-up.

Two fair-rated, multicenter trials from France were conducted in office settings (private psychiatrists and general physicians [GPs]).[18, 38] The psychiatrists' study randomized 238 patients for 24 weeks and the GP study 242 patients for nearly 26 weeks (180 days) to fluoxetine (20-60mg/d) or sertraline (50-150mg/d). The majority of patients had concomitant medical conditions. Both studies assessed quality of life as a secondary outcome measure (Sickness Impact Profile [SIP], Functional Status Questionnaire [FSQ]). Exclusion criteria were less stringent in the GP trial than the psychiatrist trial. Loss to follow-up was 4.5 percent in the GP trial and 29.8 percent in the psychiatrist trial. In the GP trial, researchers conducted outcome assessments only at day 120 and day 180, but patients could choose to consult the physician at any time. Intention-to-treat analyses in both studies did not reveal any statistically significant differences in any primary (MADRS, HAM-D, CGI) or secondary (Covi Anxiety Scale, HAD, SIP, Leeds Sleep Evaluation) efficacy measures 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.[19] 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).[34, 35, 37, 39] Treatment durations varied from 6 to 16 weeks. One study was conducted in 236 participants older than 60 years.[37, 39] 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 ($p = 0.027$).[39]

We conducted a meta-analysis of five of these studies comparing the effects of fluoxetine to sertraline on HAM-D scores at study endpoint.[18, 34-37] All studies except one were financially supported by the manufacturer of sertraline. Results are presented in Exhibit 4. We excluded one study because a different diagnostic scale measured the outcome.[19] Our outcome measure was the relative risk of being a responder on HAM-D or MADRS scales at study endpoint. A "response" was defined as an improvement of 50% or more on the HAM-D scale. Pooled results included 1,190 patients and yielded a modest additional treatment effect for sertraline just reaching statistical significance. The relative risk of being a responder at study endpoint was 1.10 (95% CI 1.01-1.22) for sertraline relative to fluoxetine. Both random effects and fixed

effects models presented similar, statistically significant results. The NNT to gain one additional responder based on the pooled risk difference is 17.

A meta-analysis of responders based only on the HAM-D scale did not yield different results. However, all included studies were of fair quality, with some having a loss to follow-up of more than 30 percent. Tests for heterogeneity were not significant. Funnel plot, 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 vs. fluvoxamine

One fair 7-week RCT compared the efficacy and safety of paroxetine (20-50mg/d) and fluvoxamine (50-150mg/d) in 60 outpatients with MDD.40 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% vs. 10%; $p = 0.028$)

Paroxetine vs. sertraline

One fair-rated Swedish RCT compared paroxetine (20-40mg/d) to sertraline (50-150mg/d) in a 24-week study.[41] 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% vs. 15.2%; $p < 0.01$). Patients in the paroxetine group had higher rates of fatigue (45.8% vs. 21.0%; $p < 0.01$), decreased libido in females (8.8% vs. 1.8%; $p < 0.05$), micturition problems (6.2% vs. 0.6%; $p < 0.05$), and constipation (16.4% vs. 5.7%; $p < 0.01$).

Sertraline vs. 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.[42] 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% vs. 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 (100-200mg/d) or fluvoxamine (200-300mg/d) treatment for 24 months.[43, 44] Patients who remained without recurrence ($n = 47$) prolonged their treatment for another 24 months in an open-label manner. Primary outcome measures were monthly HAM-D assessments. There was no loss to follow-up. Recurrence during the first 2 years of prophylactic treatment did not differ

significantly between treatment groups (single recurrence: 21.9% of sertraline-treated patients vs. 18.7% of fluvoxamine patients; z = 0.14, p = 0.88). At the 4-year follow-up, no significant differences in recurrences were apparent (sertraline, 13.6%; fluvoxamine, 20%). Adverse events did not differ significantly during the first 24 months of prophylactic treatment.

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

Duloxetine vs. fluoxetine

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

Duloxetine vs. paroxetine

A fair, 8-week, fixed-dose trial assessed the comparative efficacy of duloxetine (80mg/d), duloxetine (120mg/d), paroxetine (20mg/d), and placebo.[46] No statistically significant differences could be detected among duloxetine 80mg, duloxetine 120mg, and paroxetine 20mg in response (65%; 71%; 74%) and remission (46%; 52%; 44%). The PGI-I (Patient Global Impression of Improvement) score was significantly greater in patients on paroxetine than on duloxetine 80 mg/d. Important to note is that this trial compared a low to medium dose of paroxetine (20 mg) to a medium (80 mg) and high dose (120mg) of duloxetine.

Mirtazapine vs. fluoxetine

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

Mirtazapine vs. paroxetine

Two trials assessed the efficacy of mirtazapine (15-45mg/d) and paroxetine (20-40mg/d).[48, 49] The German study enrolled 275 patients in a 6-week trial.[48] The US trial randomized 255 participants for 8 weeks.[49] Loss to follow-up was 23 percent and 27 percent, respectively. In both trials, mirtazapine and paroxetine were equally effective in reducing HAM-D scores at the endpoint. Mirtazapine led to a faster response in both trials. In the German study, 23.2 percent of mirtazapine-treated patients and 8.9 percent of paroxetine-treated patients responded to the treatment at week 1 ($p < 0.002$). A Kaplan-Meier analysis in the US trial showed a significantly

faster time to response for mirtazapine than for paroxetine (mean 26 days versus mean 40 days; p = 0.016). No significant difference in response rates on the CGI scale was noted. Both trials reported weight gain in significantly more mirtazapine-treated patients than in paroxetine-treated patients ($p < 0.05$). Paroxetine-treated patients in the US study reported significantly higher rates of nausea, tremor, and flatulence ($p < 0.05$). The NNT to yield one additional responder at weeks 1 or 2 is 7.

Mirtazapine vs. sertraline

One fair-rated, recent multinational European study examined the onset of efficacy of mirtazapine (30-45mg/d) compared to that of sertraline (50-150mg/d) in 346 outpatients.[50] 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% vs. 3%; p = NR).

Venlafaxine vs. citalopram

A fair European 6-month study compared venlafaxine ER (37.5-150mg/d) to citalopram (10-30mg/d) for the treatment of depression in elderly outpatients (mean age 73 years).[51] No statistical differences in any outcome measures (MADRS< CGI-S, CGI-I) could be detected at study endpoint. The remission rates were 19 percent for venlafaxine and 23 percent for citalopram. Both treatment groups reached a 93 percent response rate.

Venlafaxine vs. escitalopram

Two fair 8-week studies assessed the comparative effectiveness of venlafaxine XR and escitalopram.[52, 53] A fair European, multinational study assigned 293 patients to escitalopram (10-20mg/d) or venlafaxine XR (75-150mg/d).[52] 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% vs. 17%; $p < 0.05$), sweating (12.5% vs. 6%; $p < 0.05$), and constipation (6% vs. 2%; $p < 0.05$).

The second trial reported similar results.[53] No statistically significant differences were apparent between venlafaxine XR and escitalopram in response (48% vs. 58.8%) and remission rates. Significantly more patients in the venlafaxine group withdrew because of adverse events (16% vs. 4%; $p < 0.01$) or reported nausea (24% vs. 6%; $p < 0.05$).

Venlafaxine vs. fluoxetine

A South American multicenter study with a good quality rating randomized 382 patients to venlafaxine (75-150mg/d) or fluoxetine (20-40mg/d) for 8 weeks.[54] 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[55, 56] or GAD.[57, 58] Only one study reported significantly greater response rates on HAM-D (71.9% vs. 49.3%; $p = 0.008$) and MADRS (75.0% vs. 49.3%; $p = 0.001$) for venlafaxine than for fluoxetine.[55] 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: $p = 0.0004$).[55] Two studies reported significantly more dizziness ($p < 0.001$) and sweating ($p < 0.05$) in the venlafaxine group than in the fluoxetine group.[56-58]

Three additional trials also provided inconsistent evidence on the efficacy of venlafaxine compared to fluoxetine.[59-61] One study reported a significantly higher response rate of venlafaxine than fluoxetine (72% vs. 60%; $p = 0.023$).[60] Two other trials did not support this finding,[59, 61] but venlafaxine showed a faster onset with significantly greater improvements of HAM-D and MADRS scores during weeks 1 to 4 ($p < 0.05$) in one trial.[59]

We conducted a meta-analysis of six studies comparing venlafaxine to fluoxetine.[55-57, 59-61] All studies were financially supported by the manufacturer of venlafaxine. One study was excluded because of missing data.[54] The main outcome measure was the response to treatment on HAM-D or MADRS scales at study endpoint. Results (Exhibit 5), based on 1,567 patients, show a modest additional treatment effect for venlafaxine just reaching statistical significance (RR 1.13; 95% CI 1.03-1.24) for the random effects model; the fixed effects model yielded similar significant results. 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.

The NNT based on the pooled risk difference is 34. However, most included studies were of fair quality, with some having a loss to follow-up of more than 30 percent.

These findings are similar to results of a meta-analysis recently reported by Smith et al. (2002).[62] Venlafaxine showed a modest but statistically significantly greater standardized effect size (-0.14; 95% CI -0.22 to -0.06) and a significantly greater odds ratio (OR) for remission (OR 1.42;

95% CI 1.17 to 1.73) compared to fluoxetine. The OR for response was numerically greater for venlafaxine but did not reach statistical significance (OR: 1.17; 95% CI 0.99 to 1.38). This study included inpatients and therefore did not meet the eligibility criteria for this report.

Venlafaxine vs. paroxetine

Two fair studies compared venlafaxine to paroxetine.[63, 64] A Spanish study compared venlafaxine (75-150mg/d) to paroxetine (20-40mg/d) in outpatients (n = 84) with either MDD or dysthymia over 24 weeks.[63] The majority (88%) of patients were female. The percentage of dysthymic patients was not reported, and the authors did not differentiate between dysthymia and mild or moderate depression. Loss to follow-up was 32 percent, with a substantially higher loss to follow-up in the venlafaxine group (39% vs. 26%). Intention-to-treat analysis yielded no significant differences between treatment groups on any primary outcome measures (HAM-D, MADRS, CGI) at 24 weeks. However, sample size for this study was small, and it was underpowered because it had been designed as a pilot study.

A 12-week, British fixed-dose trial randomized 361 mainly moderately ill patients (based on CGI severity score) treated in 43 general practices to either venlafaxine XR (75mg/d) or paroxetine (20mg/d).[64] 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 vs. sertraline

Two good trials compared the efficacy of sertraline to venalfaxine.[65, 66] A good quality Scandinavian trial compared venlafaxine (75-150mg/d) to sertraline (50-100mg/d) in 147 patients who were mainly moderately to markedly ill.[66] Study duration was 8 weeks; loss to follow-up was 19 percent. Both treatment groups showed statistically significant reductions in MADRS, HAM-D, and CGI scores. Response rates on the HAM-D scale were higher for venlafaxine at the endpoint (83% vs. 68%; p = 0.05), as were remission rates (68% vs. 45%; p = 0.008). No significant differences were noted for response or remission rates on MADRS and CGI scales. No significant differences were observed for adverse events. By contrast, another 8-week study did not find any differences in efficacy between sertraline(50-150mg/d) and venlafaxine XR (75-225mg/d).[65]

Bupropion vs. SSRIs

A recent, fair-rated meta-analysis compared the benefits and risks of bupropion to SSRIs as a class in 1,332 adult outpatients with MDD.[67] The age of the participants ranged from 36 to 70 years. The analysis included five double-blinded, head-to-head RCTs with study durations from 6 to 16 weeks. Three trials assessed the efficacy and safety of bupropion versus sertraline, one assessed bupropion versus paroxetine, and one assessed bupropion versus fluoxetine. The weighted mean differences of CGI-S and HAM-A scores did not differ significantly between bupropion and SSRIs. However, the authors could not pool data on HAM-D and CGI-S because of lack of data.

Bupropion vs. fluoxetine

A fair, 6-week study compared the efficacy of bupropion (225-450mg/d) and fluoxetine (20-80 mg/d) in 123 patients with moderate to severe depression.[68] 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 (150-400mg/d), fluoxetine (20-60mg/d), and placebo in 456 outpatients with MDD.[69] 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% vs. 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 vs. paroxetine

One fair RCT examined the efficacy of bupropion SR (100-300 mg/d) and paroxetine (10-40mg/d) in 100 outpatients ages 60 years or older (range 60-88 years) over 6 weeks.[70, 71] The majority of patients were white (bupropion SR: 98%, paroxetine: 90%) and female (bupropion SR: 54%, paroxetine: 60%) and had not used antidepressants for the current episode before enrollment (bupropion SR 83%; paroxetine 88%). The overall loss to follow-up was 16 percent with no significant difference between treatment groups. Statistical LOCF analysis showed that efficacy in any outcome measure did not differ significantly between treatment groups. Response rates ($\geq$ 50% reduction in HAM-D scores) were similar in both groups (bupropion SR 71%; paroxetine 77%). Both treatment groups improved significantly in quality-of-life scales (Quality-of-Life in Depression Scale [QLDS], Short Form-36 Health Survey [SF-36]) between baseline and endpoint ($p < 0.0001$), but the treatment groups did not differ significantly.

Bupropion vs. sertraline

A fair, 16-week trial assessed efficacy and tolerability of bupropion SR (100-300mg/d) and sertraline (50-200mg/d) in outpatients ($n = 248$) with moderate to severe depression.[72] 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% vs. 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 (150-400mg/d), sertraline (50-200mg/d), or placebo.[73, 74] 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.[73] 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 ($p < 0.05$).[74]

Nefazodone vs. fluoxetine

Three studies with identical protocols examined the effects of antidepressive treatment with either nefazodone or fluoxetine on sleep in outpatients with MDD.[75-77] Data from these trials were pooled into one analysis.[77] 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 vs. paroxetine

Another fair, multi-national study enrolled 206 moderately depressed patients to an 8-week, acute-phase trial comparing nefazodone (200-600mg/d) to paroxetine (20-40mg/d).[78, 79] Patients who responded to acute treatment were enrolled in an open-label continuation phase (n = 108) from w eek 8 to month 6.[79] Overall loss to follow-up was 27.2 percent during the acute trial and 32.4 percent during the continuation phase. Both groups showed significant improvements from baseline HAM-A, HAM-D, and MADRS scores in the acute phase without significant differences between study groups. Clinical improvement was either maintained or improved during the open-label continuation phase without significant differences between groups.

Nefazodone vs. sertraline

A fair, multicenter European study assessed the efficacy and tolerability of nefazodone (100-600mg/d) and sertraline.[80] 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. Summary of the evidence

Fifty-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.

Overall, effectiveness and efficacy were similar and the majority of trials did not identify substantial differences among drugs. The only exception is the comparison of citalopram to escitalopram. Four fair to good trials indicate consistently that escitalopram has a greater efficacy for the treatment of MDD than citalopram.[20-23] However, it may be significant that both citalopram and escitalopram are produced by the same manufacturer who has funded all the studies available. Citalopram is available as a generic drug whereas escitalopram is still patented.

For all the other comparisons, 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 adverse events, speed of response, and some aspects of health-related quality of life. For example, mirtazapine presents a faster onset of action than paroxetine and sertraline (table 7); bupropion has fewer sexual side effects than fluoxetine and sertraline (table 8); nefazodone improves sleep quality (Table 9); venlafaxine has a slightly higher response rate than sertraline and fluoxetine but a higher incidence of nausea and vomiting and a risk of seizures in overdose.

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.[81] Generally, high rates of loss to follow-up limit the validity of many studies.

Effectiveness

One good and two fair-rated[17-19]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.[18, 19] The effectiveness of citalopram and sertraline did not differ significantly in a subgroup analysis of patients with recurrent depression.[17] However, this finding is limited to a single trial.

Efficacy

Ten 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).[18, 21, 27, 32, 38, 40, 41, 82]

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.[77] 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.[24]

Several other efficacy studies assessed quality of life and health-related functional capacity in SSRIs compared to other second-generation antidepressants.[50, 71, 80] 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.

Forty-five efficacy studies 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 metaanalyses are likely not clinically significant.

We conducted a meta-analysis of five trials[18, 34-37]comparing fluoxetine to sertraline. Results suggest that sertraline has a modest but statistically significant additional treatment effect compared to fluoxetine as measured by the number of responders on the HAM-D and MADRS scales at endpoint. The NNT to yield one additional responder is 17. However, this meta-analysis is limited to response on only two diagnostic scales and the included studies are of fair quality.

Additonally, we conducted another meta-analysis of five studies[30-34] assessing the efficacy of fluoxetine and paroxetine. Results provide fair evidence that response rates on HAM-D and MADRS do not differ significantly at endpoint. However, this meta-analysis is also limited to response on only two diagnostic scales and the included studies are of fair quality.

Mixed evidence exists about a faster onset of action of paroxetine than fluoxetine. Three studies report a significantly faster onset of action of paroxetine,[29, 31, 32]four other trials do not support this finding.[14, 30, 33, 34] Four studies provide fair evidence that paroxetine and fluoxetine do not differ significantly in the improvement of anxiety in patients with anxious depression.[29, 30, 33, 34]

Seven good to fair studies provide mixed evidence about a higher efficacy and a greater anxiolytic effect of venlafaxine compared to fluoxetine.[54-57, 59-61] We conducted a meta-analysis of data from six of these studies. Results provide fair evidence that venlafaxine has a modest but statistically significant additional treatment effect compared to fluoxetine as measured by the number of responders on the HAM-D and MADRS scales at endpoint (RR 1.12; 95% CI 1.02-

1.23). The NNT to yield one additional responder is 34. However, this meta-analysis is limited to response on only two diagnostic scales and the included studies are of fair quality.

Two fair studies reported no statistically significant differences in response and remission rates between venlafaxine XR and escitalopram.[52, 53] Significantly more patients in the venlafaxine than in the escitalopram groups reported nausea.

Three studies yielded fair evidence that mirtazapine has a significantly faster onset of action than paroxetine and sertraline.[48-50] The NNT to yield one additional responder at weeks 1 or 2 is 7. A fourth study also reported a faster onset of response for mirtazapine than for fluoxetine but this did not reach statistically significant levels.[47] The overall efficacy did not differ significantly between mirtazapine and SSRIs.

Six trials[68-70, 72-74] and one meta-analysis[67] present fair evidence that efficacy is not significantly different between bupropion and fluoxetine, bupropion and paroxetine, and bupropion and sertraline. Three trials provide fair evidence that bupropion has fewer sexual side effects than sertraline and sertraline.[72-74] The NNT to yields one additional person with a high overall satisfaction of sexual functioning is 7. One fair trial reported significantly fewer sexual side effects of bupropion than fluoxetine.[69]

Several other studies compared SSRIs to other second-generation antidepressants.[26, 28, 40, 43, 44, 51, 63, 64, 66, 77, 79, 80] 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: Included studies for Major Depressive Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Burke et al., 2002[21]	Citalopram vs. Escitalopram	491	No differences	Fair
Colonna et al. 2005[22]	Citalopram vs. Escitalopram	357	Significantly more responders and remitters in the escitalopram group at 8 weeks but not at 24 weeks	Fair
Lader et al. 2005[24]	Citalopram vs. Escitalopram (pooled data)	1321	Greater efficacy of escitalopram in reducing sleep disturbance	Fair
Lepola et al., 2003, 2004[20, 83]	Citalopram vs. Escitalopram	471	Significantly more responders and remitters in the escitalopram group	Fair
Moore et al. 2005[23]	Citalopram vs. Escitalopram	280	Significantly more responders and remitters in the escitalopram group	Fair
Patris et al., 1996[26]	Citalopram vs. Fluoxetine	357	Faster onset of citalopram	Fair
Ekselius et al., 1997[17]	Citalopram vs. Sertraline	400	No differences	Good
Dalery et al., 2003[27]	Fluoxetine vs. Fluvoxamine	184	Faster onset of fluvoxamine	Fair
Rapaport et al., 1996[28]	Fluoxetine vs. Fluvoxamine	100	No differences	Fair
Cassano et al., 2002[29]	Fluoxetine vs. Paroxetine	242	Faster onset of paroxetine	Fair
Chouinard et al., 1999[30]	Fluoxetine vs. Paroxetine	203	No differences	Fair
De Wilde et al., 1993[31]	Fluoxetine vs. Paroxetine	100	Faster onset of paroxetine	Fair
Gagiano et al., 1993[14]	Fluoxetine vs. Paroxetine	90	No differences	Fair
Schone et al., 1993[32]	Fluoxetine vs. Paroxetine	108	Faster onset of paroxetine	Fair
Fava et al., 1998[33]	Fluoxetine vs. Paroxetine	128	No differences	Fair
Bennie et al., 1995[35]	Fluoxetine vs. Sertraline	286	No differences	Fair
Boyer et al., 1998[38]	Fluoxetine vs. Sertraline	242	No differences	Fair
Fava et al., 2002[34]	Fluoxetine vs. Sertraline vs. Paroxetine	284	No differences	Fair
Finkel et al., 1999[39]	Fluoxetine vs. Sertraline	75	Faster onset of sertraline	Fair
Sechter et al., 1999[18]	Fluoxetine vs. Sertraline	238	No differences	Fair
Newhouse et al., 2000[37]	Fluoxetine vs. Sertraline	236	No differences	Fair
Kroenke et al., 2001[19]	Fluoxetine vs. Sertraline vs. Paroxetine	601	No differences	Fair
Aberg-Wistedt et al., 2000[41]	Paroxetine vs. Sertraline	353	No differences	Fair
Kiev et al., 1997[40]	Paroxetine vs. Fluvoxamine	60	No differences	Fair
Nemeroff et al., 1995[42]	Sertraline vs. Fluvoxamine	97	No differences	Fair
Franchini et al., 1997, 2000[43, 44]	Sertraline vs. Fluvoxamine	64	No differences	Fair

Table 6: Interventions, Numbers of Patients, and Quality Ratings of Studies in Adults with Major Depressive Disorder, (continued)

Author, Year	Interventions	N	Results	Quality Rating
SNRIs versus SSRIs				
Detke et al., 2004[46]	Duloxetine vs. paroxetine	367	No difference	Fair
Goldstein et al., 2002[45]	Duloxetine vs. paroxetine	173	No difference	Fair
Hong et al., 2003[47]	Mirtazapine vs. Fluoxetine	133	No differences	Fair
Schatzberg et al., 2002[48]	Mirtazapine vs. Paroxetine	255	Faster onset of mirtazapine	Fair
Benkert et al., 2000[49]	Mirtazapine vs. Paroxetine	275	Faster onset of mirtazapine	Fair
Behnke et al., 2003[50]	Mirtazapine vs. Sertraline	346	Faster onset of mirtazapine	Fair
Bielski et al., 2004[53]	Venlafaxine vs. escitalopram	198	No differences	Fair
Montgomery et al., 2004[84]	Venlafaxine vs. escitalopram	293	No differences	Fair
Allard et al. 2004[51]	Venlafaxine vs. citalopram	151	No differences	Fair
Costa e Silva et al., 1998[54]	Venlafaxine vs. Fluoxetine	382	No differences	Fair
Alves et al., 1999[59]	Venlafaxine vs. Fluoxetine	87	Faster onset of venlafaxine	Fair
Tylee et al., 1997[61]	Venlafaxine vs. Fluoxetine	341	No differences	Fair
Dierick et al., 1996[60]	Venlafaxine vs. Fluoxetine	314	Significantly higher response rate for venlafaxine	Fair
De Nayer et al., 2002[55]	Venlafaxine vs. Fluoxetine	146	Significantly greater improvement for venlafaxine	Fair
Rudolph et al., 1999[56]	Venlafaxine XR vs. Fluoxetine	301	No differences	Fair
Silverstone et al., 1999[57, 58]	Venlafaxine XR vs. Fluoxetine	368	No differences	Fair
Ballus et al., 2000[63]	Venlafaxine vs. Paroxetine	84	No differences	Fair
McPartlin et al., 1998[64]	Venlafaxine XR vs. Paroxetine	361	No differences	Fair
Mehtonen et al., 2000[66]	Venlafaxine vs. Sertraline	147	Significantly higher response rate for venlafaxine	Good
Sir et al. 2005[65]	Venlafaxine XR vs. Sertraline	163	No differences	Good
Other second-generation antidepressants (DopRi, 5-HT$_2$) versus SSRIs				
Nieuwstraten et al., 2001[67]	Bupropion vs. SSRIs (SR)	1,332	No differences	Good
Panzer et al. 2005[81]	SSRIs vs. other 2nd generation antidepressants (SR)	NR	No differences in patients with comorbid anxiety	Fair
Feighner et al., 1991[68]	Bupropion vs. Fluoxetine	123	No differences	Fair
Coleman et al., 2001[69]	Bupropion vs. Fluoxetine	456	No differences	Fair
Weihs et al., 2000[70, 71]	Bupropion SR vs. Paroxetine	100	No differences	Fair
Coleman et al., 1999[74]	Bupropion vs. Sertraline	364	No differences	Fair
Croft et al., 1999[73]	Bupropion vs. Sertraline	360	No differences	Fair
Kavoussi et al.,1997[72]	Bupropion vs. Sertraline	248	No differences	Fair
Rush et al., 1998[77]	Nefazodone vs. Fluoxetine	125	No differences	Fair
Baldwin et al., 1996, 2001[78, 79]	Nefazodone vs. Paroxetine	206	No differences	Fair
Feiger et al., 1996[80]	Nefazodone vs. Sertraline	160	No differences	Fair

(SR)= Systematic review

Table 7: Studies Indicating a Faster Onset of Mirtazapine

Study	Sample size	Comparison	Effect size	p-value	Comments
Faster onset of mirtazapine					
Behnke et al., 2003[50]	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[49]	275	paroxetine	Significantly more responders (23.2% vs. 8.9%) and remitters (8.8% vs. 2.4%) at day 7 with mirtazapine. response: remission: RRR: 0.15 0.07 RD: 0.14 0.07 NNT: 8 15	response: $p = 0.002$ remission: $p = 0.03$	More responders and remitters in the mirtazapine group throughout the study. No statistically significant difference at endpoint (response: 58.3% vs. 53.7%; remission: 40.9% vs. 34.8%)
Hong et al., 2003[47]	133	fluoxetine	At day 28 significantly more responders with mirtazapine (53,3% vs. 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% vs. 51%)
Schatzberg et al., 2002[48]	255	paroxetine	Significantly more responders at day 14 with mirtazapine (27.8% vs. 13.3%); RRR: 0.17 RD: 0.14 NNT: 7 significantly greater decrease of HAM-D scores from day 7 to day 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% vs. 51%) at endpoint.

RRR : Relative Risk Reduction ; RD : Risk Difference ; NNT : Number Needed to Treat

Table 8: Studies Indicating Fewer Sexual Adverse Events for Bupropion

Study	Sample size	Comparison	Effect measure	p-value	Comments
Lower rate of sexual side effects with bupropion SR					
Coleman et al., 2001[69]	456	fluoxetine, placebo	Significanty 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[74]	364	sertraline	Beginning at day 21 significantly more patients on bupropion SR were satisfied with their sexual functioning (endpoint: 85% vs. 62%) Endpoint: RRR: 0.59 RD: 0.22 NNT: 5	$p < 0.05$	DSM-IV criteria for sexual dysfunction disorders No statistically significant differences in efficacy outcome measures at endpoint (week 8)
Croft et al., 1999[73]	360	sertraline placebo	Beginning at day 7 through day 42 significantly more bupropion SR patients were satisfied with overall sexual functioning; difference was not statistically significant at endpoint (75% vs. 65%) endpoint: RRR: 0.29 RD: 0.10 NNT: 10	$p < 0.05$	Assessment of sexual function in an investigator-conducted structured interview No statistically significant differences in efficacy outcome measures at endpoint (week 8)

Table 8: Studies Indicating Fewer Sexual Adverse Events for Bupropion (continued)

Study	Sample size	Comparison	Effect measure	p-value	Comments
Kavoussi et al. 1997[72, 85]	248	sertraline,	Significantly more patients on sertraline experienced orgasm delays and/or failure Women : 41% vs. 7% RRR : 0.85 RD : 0.38 NNT : 3 Men : 61% vs. 10% RRR : 0.84 RD : 0.51 NNT : 2 Higher overall satisfaction with sexual functioning with bupropion SR at endpoint (79% vs. 58%) RRR : 0.50 RD : 0.21 NNT : 5	p < 0.01 p < 0.001	Assessment of sexual function in an investigator-conducted structured interview ; No statistically significant differences in efficacy outcome measures at endpoint (week 16)
Feighner et al. 1991[68]	61	fluoxetine	NR	NR	bupropion IR ; study does not report on differences in sexual adverse events

RRR : Relative Risk Reduction ; RD : Risk Difference ; NNT : Number Needed to Treat

Table 9: Study Indicating a Better Sleep Profile with Nefazodone

Study	Sample size	Comparison	Effect measure	p-value	Comments
Better sleep profile with nefazodone					
Rush et al. 1998[77]	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 ;

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.[86-93]

1. SSRIs compared to placebo in adults with dysthymia

Fluoxetine vs. placebo

A good RCT determined the efficacy and safety of fluoxetine (10-60mg/d) in elderly patients with dysthymia over 12 weeks.[92] ITT results of this NIMH-funded study indicated that fluoxetine had limited efficacy. Response rates on HAM-D did not differ significantly between fluoxetine and placebo (27.3% vs. 19.6%; p = 0.4). Likewise, no difference in quality of life could be detected. Statistically significant differences were limited to treatment group – time interactions which presented greater improvements over time on HAM-D and the Cornell Dyshtymia Rating Scale (CDRS) for fluoxetine than for placebo.

A second study conducted in patients 18 years or older (mean 43 years) found that fluoxetine had significantly more responders (53.8% vs. 35.9%; p = 0.03) than placebo.[93] Remission rates favored fluoxetine but did not reach statistical significance (44.4% vs. 25.6%; p = 0.07)

Paroxetine vs. placebo vs. 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.[90, 91] 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% vs. 40%; p = 0.008).

Sertraline vs. imipramine vs. placebo

One RCT compared sertraline (50-200mg/d) to imipramine (50-300mg/d) and placebo in 416 patients who had had the diagnosis of dysthymia for more than 5 years.[86-88] 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% vs. 6.0%; $p = 0.001$).

Sertraline vs. placebo

A multinational study enrolled 310 dysthymic patients for 12 weeks to compare sertraline (50-200mg/d) to placebo.[89] 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.[89, 91]

Efficacy

Evidence from one good study indicates that fluoxetine has only limited efficacy in elderly patients with dysthymia.[92] Fair evidence from two studies indicates that sertraline has a significantly greater efficacy in the treatment of dysthymia than placebo.[86-89] In both trials, sertraline treatment led to a significantly greater improvement of quality of life and psychosocial functioning than placebo.

Table 10: Included Studies for Dysthymia

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus Placebo				
Barrett et al., 2001[90] Williams et al., 2000[91]	Paroxetine vs. Placebo vs. Behavioral therapy	656	Significantly more responders for paroxetine in patients older than 60 years	Fair
Devanand et al. 2005[92]	Fluoxetine vs. Placebo	90	No differences in response rates and quality of life	Good
Thase et al., 1996[86-88]	Sertraline vs. Imipramine vs. Placebo	412	Significantly more responders for sertraline than placebo	Fair
Ravindran et al., 2000[89]	Sertraline vs. Placebo	310	Significantly more responders and remitters for sertraline	Fair
Vanelle et al. 1997[93]	Fluoxetine vs. Placebo	111	Significantly more responders for fluoxetine	Fair

C. Major Depressive Disorder in Children and Adolescents

Currently, fluoxetine is the only second-generation antidepressant approved by the FDA for treating MDD in children (2 to 12 years) and adolescents (13 to 18 years). Published evidence is based on controlled clinical trials of children and adolescents 7 to 18 years of age. Fluvoxamine and sertraline are approved for the treatment of OCD in pediatric patients, although they are not approved for treating MDD.

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% in patients taking antidepressants; twice the placebo risk of 2%.

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

A thorough review of published and unpublished studies for citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline, venlafaxine, and mirtazapine was conducted by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA).[94] Based on analyses conducted by the Expert Working Group of the Committee on Safety of Medicines (CSM) of the MHRA, the agency concluded that only fluoxetine has been shown to have a favorable risk benefit profile. Conclusions were based on the fact that, with the exception of fluoxetine, clinical trial data failed to demonstrate efficacy in a pediatric population. In addition, an increased risk of suicidal thoughts and self-harm was observed consistently across drugs.

In the published literature, we did not identify any head-to-head trials comparing one second-generation antidepressant to another for treating MDD in children and adolescents. We found four fair controlled trials comparing a non-FDA-approved SSRI or SNRI to placebo (Table 11). Additionally, one good-rated trial compared fluoxetine, cognitive-behavioral therapy (CBT), and fluoxetine plus CBT to placebo.

In addition, two systematic reviews evaluated placebo-controlled evidence for the use of SSRIs and an SNRI.[95, 96] One review highlighted placebo-controlled evidence already included in this discussion,[95] so we do not comment on it further here. A second review analyzed published and

unpublished data for citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine.[96] 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 ≥ 12; CDRS-R > 40; Children's Global Assessment Scale < 60). Several studies used different inclusion cut-off points when defining severity of disease. All studies lasted between 6 and 10 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, or the Children's Depression Inventory [CDI]), response (≥ 40%-50% reduction in depression score), or remission (≤ 8 on the HAM-D). Secondary efficacy measures included additional measures of improvement, depression, or anxiety (CGI-I, 9-item subscale of the Kiddie Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version [K-SADS-L], MADRS, HAM-A), 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 vs. 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.97 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 vs. placebo

Although we did not review placebo-controlled evidence for fluoxetine because the FDA has already established its general efficacy and tolerability, we did review the Treatment for Adolescents with Depression Study (TADS) because it specifically compared fluoxetine, fluoxetine plus CBT, CBT alone, and placebo.[98] 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 ($p = 0.15$).

Paroxetine vs. placebo

An 8-week study randomized 275 adolescents (12 to 18 years) to double-blind flexible-dose treatment with paroxetine (20-40 mg/d), imipramine (200-300 mg/d), or placebo.[99] Eligible participants meeting DSM-IV criteria for MDD of at least 8 weeks' duration were evaluated at 12 centers in the US and Canada. Loss to follow-up was 31 percent. Significantly more imipramine-treated patients withdrew than paroxetine- or placebo-treated patients, primarily because of adverse events. Primary efficacy measures were mean change from baseline in HAM-D score and HAM-D response ($\geq$ 50% reduction or total score ≤ 8). In the LOCF intention-to-treat analysis, mean HAM-D change from baseline or response did not differ significantly between paroxetine-treated and placebo-treated patients ($p = 0.13$ and $p = 0.11$, respectively). Paroxetine was not statistically different from placebo on secondary measures of functioning, health status, and behavior (Autonomous Function Checklist, Self-Perception Profile, and Sickness Impact Profile). Compared to those on placebo, significantly more paroxetine-treated patients experienced somnolence or insomnia.

Sertraline vs. placebo

One published multinational (US, India, Canada, Costa Rica, and Mexico) study pooled data from two double-blind RCTs conducted in 53 centers.[100] These identically designed, concurrently conducted 10-week trials randomized 376 children and adolescents (6 to 17 years) to flexible-dose sertraline (50-200 mg/d) or placebo. Significantly more sertraline-treated patients were female ($p = 0.02$). Twenty percent of randomized participants did not complete the study. The primary efficacy measure was mean change from baseline score on the CDRS-R. In the intention-to-treat analysis, sertraline-treated patients had a significantly greater mean change in CDRS-R score ($p < 0.01$). Significant differences were observed as early as week 3. Secondary efficacy measures included treatment response ($\geq$ 40% decrease in CDRS-R or CGI-I score of 2 or lower), symptoms of anxiety (Multidimensional Anxiety Scale for Children [MASC]), patient's social functioning [CGAS], and quality of life [PQ-LES-Q]). Significantly more sertraline-treated patients were defined as treatment responders ($p < 0.05$). Statistically significant differences were not observed for measures of anxiety, social functioning, or quality of life. 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 vs. placebo

One 6-week trial randomized 40 children and adolescents (8 to 18 years) to treatment with venlafaxine and psychotherapy or placebo and psychotherapy.[101] 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 review of published and unpublished data comparing SSRIs and SNRIs to placebo in pediatric outpatients with major depressive disorder

One systematic review evaluated published and unpublished studies comparing a SSRI or SNRI to placebo in children and adolescents.[96] Studies comparing citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine to placebo were reviewed, including data for 2,145 randomized participants (5 to 18 years). The authors abstracted data on remission and response (where appropriate criteria were used), and mean depression score. Scales and responder definitions were different for each study. Risks were assessed by abstracting data on suicide-related behaviors and discontinuation of treatment due to adverse events. Risk-benefit profiles were evaluated for each drug. Fluoxetine was the only second-generation reported to have a favorable risk-benefit profile. Data from two unpublished citalopram trials supported a negative risk-benefit profile, although evidence of efficacy was stated to be limited. Published and unpublished data combined for paroxetine demonstrated no improvement in depressive symptoms and little effect on response; additionally, an increased risk of serious adverse events was reported. Unpublished data on sertraline indicated that it may be even less effective than reported in published trials. Combined, published and unpublished data on venlafaxine suggested a negative risk-benefit profile.

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

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. Recent evidence

from a systematic review of published and unpublished data suggests that only fluoxetine has a favorable risk-benefit profile in pediatric populations.

Effectiveness

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

Efficacy

Two placebo-controlled trials provide fair evidence that efficacy to improve health outcomes does not differ between placebo and sertraline, paroxetine, and venlafaxine.[99, 101] Two placebo-controlled trials support greater efficacy for citalopram and sertraline compared to placebo.[97, 100] Some FDA-approved evidence supports the efficacy of fluoxetine in treating MDD in children and adolescents; one trial supports greater efficacy of fluoxetine when combined with CBT.[98] Of note, however, published trials supporting the efficacy of fluoxetine[102, 103] were excluded from our review because of a differential loss to follow-up of more than 15 percentage points between active treatment and placebo control. Evidence is inconclusive about the efficacy of citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, mirtazapine, venlafaxine, bupropion, and nefazodone.

Table 11: Included Studies for Major Depressive Disorder

Author, Year	Interventions	N	Results	Quality Rating
Systematic Review				
Whittington et al., 2004[96]	Citalopram vs. Placebo (SR) Fluoxetine vs. Placebo Paroxetine vs. Placebo Sertraline vs. Placebo Venlafaxine vs. Placebo	2,145	Only fluoxetine had favorable risk-benefit profile	Fair
SSRIs versus Placebo				
Wagner et al., 2004[97]	Citalopram vs. Placebo	174	Significantly greater efficacy for citalopram	Fair
March et al., 2004[98]	Fluoxetine plus CBT vs. Fluxoetine vs. CBT vs. placebo	439	Greater improvement on the CDRS-R for fluoxetine plus CBT compared to fluoxetine alone, CBT alone, or placebo	Good
Keller et al., 2001[99]	Paroxetine vs. Imipramine vs. Placebo	275	No differences	Fair
Wagner et al., 2003[100]	Sertraline vs. Placebo	376	Significantly greater efficacy for sertraline	Fair
SNRIs versus placebo				
Mandoki et al., 1997[101]	Venlafaxine vs. Placebo	40	No differences	Fair

(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?

D. Generalized Anxiety Disorder

Currently, two SSRIs – escitalopram and paroxetine – are approved by the FDA for the treatment of GAD. In addition, one SNRI – venlafaxine – is approved for the treatment of GAD.

Two head-to-head trials compared one second-generation antidepressant to another for the treatment of GAD,[104, 105] although one was excluded from this review because of high loss to follow-up.[105] FDA-approved evidence supports the general efficacy of escitalopram, paroxetine, and venlafaxine for treating GAD. Additional placebo-controlled evidence supporting the general efficacy these drugs was not reviewed. . We included four placebo-controlled trials (eight publications) of escitalopram, paroxetine, and venlafaxine that included measures of quality of life,[106] functional capacity,[107-111] or somatic symptoms.[112, 113] Additionally, we identified one trial (two publications) that assessed efficacy and tolerability of sertraline[114, 115]– an SSRI currently not FDA-approved for GAD. Included placebo-controlled escitalopram, paroxetine, and venlafaxine trials addressed a range of health outcomes not commonly addressed in FDA approval. Two RCTs comparing paroxetine to placebo[109, 110] and one RCT comparing venlafaxine to placebo[108, 116] evaluated measures of functional capacity;[111] the paroxetine studies utilized the Sheehan Disability Scale (SDS) to assess health-related disability, and the venlafaxine trial used the Social Adjustment rating Scale-Self Report (SAS-SR). One escitalopram trial assessed quality of life with the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[106] A secondary analysis of pooled data from placebo-controlled venlafaxine XR trials reported on somatic and psychic symptoms.[112, 113]

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

One fair rated RCT compared paroxetine (10-40mg/d) to sertraline (25-100mg/d) in 55 patients with GAD.[104] 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.

A second RCT compared escitalopram (10-20mg/d) to paroxetine (20-50mg/d) in 121 patients with GAD.[105] Although we excluded this study because of high loss to follow-up, results were consistent with the only other comparative trial; no statistically significant differences in efficacy

were reported. The mean change in HAM-A scores were -15.3 and -13.3 for escitalopram and paroxetine, respectively (p = 0.13). The frequency of treatment-emergent adverse events was greater among paroxetine-treated patients than among escitalopram-treated patients (88.7% vs. 77.0%, respectively; p = NR).

2. SSRIs compared to placebo in adult outpatients with GAD

Escitalopram vs. Placebo

One fair-rated trial comparing escitalopram to placebo assessed quality of life.106 This US multicenter study randomized 315 outpatients with GAD to flexible doses of escitalopram (10-20 mg/d) or placebo. The primary efficacy measurement was the HAM-A total score, although the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire also was included. At baseline, the mean HAM-A total score was 23.4. Overall loss to follow-up was 23 percent. At 8 weeks, the mean change in HAM-A total score was –11.3 for escitalopram and –7.4 for placebo ($p < 0.001$). Escitalopram-treated patients also demonstrated significantly greater improvement than placebo-treated patients on all secondary outcome measures, including the Q-LES-Q ($p < 0.001$). The rate of discontinuation because of adverse events was not significantly different between escitalopram- and placebo-treated patients (p = 0.27), although more escitalopram-treated patients reported headache, nausea, somnolence, and upper respiratory infection (p = NR).

Paroxetine vs. placebo

Two fair studies comparing paroxetine to placebo included health outcome measures.[109, 110] One study conducted in the US and Canada randomized 566 patients to fixed doses of paroxetine 20 mg/d, paroxetine 40 mg/d, or placebo.[109] Participants 18 years and older with DSM-IV criteria for GAD were followed over 8 weeks. Loss to follow-up was 24.7 percent. The primary outcome measure was mean change from baseline on the HAM-A. The Sheehan Disability Scale (SDS) was included as a secondary outcome measure. Paroxetine-treated patients for both doses had a significant mean change from baseline on the HAM-A ($p < 0.001$). Compared to placebo, mean change from baseline on the SDS also was significantly greater for both paroxetine doses ($p < 0.001$). There were no statistical differences in withdrawals because of adverse events, although paroxetine-treated patients reported significantly more nausea, insomnia, dyspepsia, flu syndrome, delayed ejaculation, and sweating.

A second fair study compared flexible doses of paroxetine to placebo over 8 weeks.[110] This study randomized 331 patients, ages 18 or older, with DSM-IV criteria for GAD. Of randomized participants, 21 percent did not complete 8 weeks of follow-up. The primary efficacy measure was the mean change from baseline in the total score of the HAM-A. The change from baseline in illness-related impairment was assessed using the SDS. Beginning at week 6 and continuing through endpoint, the paroxetine group had a significantly greater reduction in the total HAM-A score, the anxious mood item, and the tension item ($p < 0.05$). At week 8, the paroxetine group had a significantly greater reduction than the placebo group in the total score of the SDS ($p < 0.001$). All adverse events were experienced by more paroxetine patients than placebo patients. Asthenia, constipation, abnormal ejaculation (men only), decreased libido, nausea, and

somnolence were reported in at least twice as many patients in the paroxetine group compared to placebo. More paroxetine-treated patients withdrew from the study because of adverse events (10.5% vs. 3.7% for placebo).

Sertraline vs. placebo

Currently, sertraline is not FDA-approved for the treatment of GAD. We identified one placebo-controlled trial that assessed the efficacy and tolerability of sertraline in GAD.[114, 115] This 12-week, multicenter, multicountry trial randomized 378 outpatients with a primary diagnosis of DSM-IV- defined anxiety disorder to sertraline 50-150 mg/d or placebo. Patients with a history of other psychiatric disorders, including MAD, were excluded. The primary efficacy measure was the HAM-A; secondary assessments included the CGI-I, CGI-S, MADRS, HADS, Q-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.

Venlafaxine vs. placebo

Placebo-controlled trials support the general efficacy and tolerability of venlafaxine. Pooled data from these trials have been previously analyzed for evidence of efficacy and tolerability.[112] One pooled analysis of Wyeth-sponsored venlafaxine XR trials provides additional evidence on somatic and psychic symptoms of anxiety.[113] Although trials pooled in these analyses do not appear to be selected based on a systematic literature search, we did not find evidence that negative trials were excluded from the pooled analysis; thus, we review the somatic and psychic symptoms analysis here.

The pooled analysis included venlafaxine XR study numbers 210, 214, 218, 377, and 378.[112, 113] The results of at least three constituent trials have been previously published.[117-119] All trials were conducted in nondepressed patients who met DSM-IV diagnostic criteria for GAD. Treatment duration was 8 weeks in 3 studies and 6 months in 2 studies. The 8-week intention-to-treat population consisted of 1,839 patients taking doses of 75-225 mg/d; the 24-week intention-to-treat population consisted of 767 patients taking similar doses. Patients from the active-comparator group were excluded from two trials. Somatic and psychic symptoms were assessed by the somatic and psychic factors of the HAM-A. At 8 and 24 weeks, venlafaxine XR-treated patients had significantly greater reductions in somatic and psychic factor scores compared to placebo-treated patients.

Additionally, a 24 week placebo-controlled trial (2 publications) of extended-release venlafaxine provided evidence on functional capacity.[107, 108] This trial randomized 544 outpatients who met DSM-IV criteria for GAD to 3 fixed doses of venlafaxine (37.5, 75, or 150 mg/d) or matched placebo. Primary outcome measures included the clinician-rated HAM-A and CGI. Social adjustment was measured using the SAS-SR, which assesses social adaptation. Venlafaxine showed a dose-related improvement in social adaptation compared to placebo; doses of venlafaxine greater than or equal to 75 mg/d showed significant improvement on most subscales of the SAS-SR at 8 and 24 weeks.

3. Summary of the evidence

Evidence is insufficient to compare one second-generation antidepressant to another for treating GAD.

Effectiveness

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

Efficacy

One head-to-head trial did not detect any significant differences in efficacy between paroxetine and sertraline.[104]

FDA-approved evidence shows the general efficacy of escitalopram, paroxetine, and venlafaxine for treating GAD. Additional evidence supports the general efficacy of sertraline.[114, 115] Evidence is insufficient about efficacy of citalopram, fluoxetine, fluvoxamine, mirtazapine, duloxetine, bupropion, and nefazodone for treating GAD. One trial provides evidence of greater improvement in quality of life for escitalopram compared to placebo,[106] and one trial provides evidence of greater improvement in quality of life and work productivity for sertraline than for placebo.[114] Two trials comparing paroxetine to placebo included measures of functional impairment.[109, 110] Significant improvement in Sheehan Disability Scale (SDS) total score was observed at endpoint in both studies. One analysis of pooled data from five trials provides evidence that treatment with venlafaxine XR leads to greater reduction in both psychic and somatic symptoms of GAD than does placebo.[113] One additional placebo-controlled trial provides evidence of better social adjustment for patients treated with venlefaxine XR.[107, 108]

Table 12: Included Studies for Generalized Anxiety Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus Placebo				
Ball et al. 2005[104]	Paroxetine vs. Sertraline	55	No difference	Fair
SSRIs versus Placebo				
Davidson et al., 2004[106]	Escitalopram vs. Placebo	315	Significantly greater improvement in QoL for escitalopram	Fair
Pollack et al. , 2001[110]	Paroxetine vs. Placebo	331	Significantly greater reduction in SDS for paroxetine	Fair
Rickels et al. , 2003[109]	Paroxetine vs. Placebo	566	Significantly greater reduction in SDS for paroxetine	Fair
Allgulander et al., 2004[114] Dahl et al., 2005[115]	Sertraline vs. Placebo	378	Significantly greater improvement in HAM-A total score; HAM-A psychic and somatic factors, QoL, and work productivity	Fair
Meoni et al., 2004[112, 113]	Venlafaxine XR vs. Placebo	1,839	Significantly greater reduction in psychic and somatic factor scores for venlafaxine	Fair

QoL = quality of life

E. Obsessive-Compulsive Disorder

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

Two 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.[120] One additional trial compared citalapram plus mirtazapine to citalopram alone.[121] Three meta-analyses pooled data from studies comparing SSRIs to placebo. Additionally, one placebo-controlled trial was included because it evaluated an SSRI not covered in the reviews or approved by the FDA (Table 13). All systematic reviews included comparisons of fluoxetine, fluvoxamine, and sertraline to placebo.[122-124] In addition, one review included a comparison of paroxetine to placebo.[123]

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 vs. fluoxetine

A multicenter Canadian study evaluated the use of sertraline (50-200 mg/d) and fluoxetine (20-80 mg/d) in 150 patients over a 24-week period.[125] 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 vs. paroxetine

A 12-week Dutch study evaluated the use of venlafaxine XR (75-300 mg/d) and paroxetine (15-60 mg/d) in 150 patients.[126] Loss to follow-up was 33%. At 12 weeks, efficacy as reported by the mean reduction in Y-BOCS total score did not differ significantly between the two groups. Analysis of Y-BOCS obsessions and compulsions subscales revealed an equally high treatment effect over time. Also, response rates (full response ≥ 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.[120] 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.

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 (40-80mg/d) with mirtazapine (15-30 mg/d) in 49 outpatients with OCD.[121] 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

Three meta-analyses reviewed available evidence from placebo-controlled studies;[122-124] we rated these analyses as fair quality. One study pooled results from 10 trials that compared SSRIs *as a class* with placebo.[122] 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.[127, 128] 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% Confidence Interval [CI], 0.33, 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, 0.74) and 0.52 (95% CI, 0.34, 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.[123] 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[129-132] showed a net improvement of -4.84 (95% CI, -7.78, -1.83). For the three fluoxetine studies,[133-135] net improvement was -1.61 (95% CI -2.18, -1.04); for four sertraline studies,[136-139] the pooled difference in Y-BOCS was calculated to be -2.47 (95% CI, -6.13, 1.20). Only one paroxetine study was included; the difference in improvement was estimated as -3.00 (95% CI, -4.91, -1.09).

A third meta-analysis assessed medication effect sizes in six published placebo-controlled trials;[124] two fluvoxamine studies;[129, 130] two sertraline studies;[136, 137] and two fluoxetine studies.[133, 134] Compared to placebo, effect sizes did not differ significantly between the three SSRIs evaluated.

Citalopram vs. placebo

A fair multicenter study conducted in Europe and South Africa compared various fixed-doses of citalopram to placebo in 401 outpatients with OCD characterized as stable for more than 6 months.[128] 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 (60mg) response reached statistical significance at week 3, whereas the lower doses (20mg and 40mg) reached statistical significance at week 7. On the patient-rated Sheehan Disability Scale, the citalopram-treated patients showed significant improvements for most items. 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 40mg citalopram group.

5. Summary of the evidence

Two fair head-to-head studies provide evidence that there is no difference in efficacy between fluoxetine and sertraline or venlafaxine 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

Two head-to-head trials[125, 126] and three meta-analyses[122-124] provide fair evidence that no difference in efficacy among evaluated second-generation antidepressants exists. One head-to-head trial provides fair evidence that the efficacy of venlafaxine XR and paroxetine does not differ in improving health outcomes;[126, 140] in a follow-up study, 42 percent of nonresponders who switched to the alternative treatment achieved a response.[120] One fair placebo-controlled study showed a significantly greater improvement in disability for citalopram compared to placebo.[128] In a second study, citalopram-treated patients augmented with mirtazpine had a faster response than patients treated with citalopram alone, although differences did not persist past 6 weeks.[121]

One study provides fair evidence that sertraline has a faster onset of action than fluoxetine[125] in the treatment of OCD. Another fair-rated study reported a faster response for venlafaxine XR compared to paroxetine.[126]

FDA-approved evidence exists for the general efficacy of fluoxetine, sertraline, paroxetine, and fluvoxamine for treating OCD. Evidence is insufficient about the efficacy of escitalopram, mirtazapine, bupropion, and nefazodone for treating OCD. Additionally, one study provides fair evidence supporting a greater efficacy of citalopram than placebo.[128]

Table 13: Included Studies for Obsessive-Compulsive Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Bergeron et al., 2002[125]	Fluoxetine vs. Sertraline	150	No differences	Fair
Other second-generation antidepressants versus SSRIs				
Denys et al., 2003[120, 126, 140]	Venlafaxine vs. Paroxetine	150	No differences	Fair
SSRI versus SSRI plus another second-generation antidepressant				
Pallanti et al., 2004[121]	Citalopram vs. Citalopram plus mirtazapine	49	No differences at 12 weeks	Fair
SSRIs versus Placebo				
Piccinelli et al., 1995[122]	SSRIs vs. Placebo (SR)	1,076	Significantly greater efficacy of SSRIs	Fair
Ackerman et al., 2002[123]	SSRIs vs. Placebo (SR)	530	No differences among SSRIs	Fair
Stein et al., 1995[124]	SSRIs vs. Placebo (SR)	516	No differences among SSRIs	Fair
Montgomery et al., 2001[128]	Citalopram vs. Placebo	401	Significantly greater efficacy of citalopram	Fair

(SR) = Systematic Review

F. Panic Disorder

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

For panic disorder, we identified only three head-to-head trials comparing one SSRI, or other second-generation antidepressant to another.[141-143] We excluded one study – a single-blinded

RCT with a poor quality rating for internal validity[142]– from our findings, but we discuss it here briefly because of the minimal amount of published research on this topic. Furthermore, we identified five placebo-controlled trials assessing the efficacy and tolerability of fluvoxamine,[144-146] sertraline,[147] and venlafaxine ER.[148] One additional RCT compared sertraline to placebo and assessed quality of life as a secondary outcome measure[147] (Table 14).

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 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, 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 quality of life and health-related functional capacity (Sheehan Disability Scale [SDS], Fear Questionnaire [FQ]), anxiety-related subscales of the MADRS and HAM-D, and global assessment methods (e.g., CGI).

1. SSRIs compared to SSRIs in adult outpatients with Panic Disorder

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

Citalopram vs. escitalopram

One multicenter study randomized 366 patients with panic disorder to citalopram (10-40mg/d), escitalopram (5-20mg/d), or placebo.[141] 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 vs. paroxetine

A German RCT randomized 225 patients with panic disorder to paroxetine (40 – 60 mg/d) or sertraline (50 – 150 mg/d).[143] 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 vs. paroxetine

A small Italian trial enrolled 58 patients to citalopram (20-50mg/d) and paroxetine (20-50mg/d) for 60 days.[142] 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.

2. SSRIs compared to placebo in adult outpatients with Panic Disorder

Fluvoxamine vs. placebo

Three fair-rated studies, all lasting 8 weeks, compared fluvoxamine (50-300mg/d) to placebo.[144-146] T he first study enrolled 75 patients to fluvoxamine (50-300mg/d), placebo, or cognitive therapy.[144] Loss to follow-up was 20 percent. Outcome measures included functional capacity (Sheehan Disability Scale). Statistical analysis did not fulfill accepted criteria for intention-to-treat analysis (only subjects who completed 3 weeks of medication were analyzed). Fluvoxamine showed significantly greater improvements in all primary (Panic Attack Severity Score, Clinical Anxiety Score [CAS], CGI, MADRS) and secondary (Sheehan Disability Scale) efficacy measures compared to placebo.

The second study randomized 50 patients to fluvoxamine (50-300mg/d) or placebo.[145] 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.[146] 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.

Sertraline vs. placebo

One fair 10-week trial compared the efficacy of sertraline (50-200mg/d) to placebo.[147] The study enrolled 168 patients with panic disorder. Loss to follow-up was 21.4 percent. Outcomes assessed included quality of life. Intention-to-treat analysis showed a significantly decreased number of panic attacks in the sertraline group (77% vs. 51%; $p = 0.03$). Sertraline-treated patients also showed significantly higher improvements in the HAM-A scale ($p = 0.03$), CGI ($p < 0.001$), and quality of life ($p = 0.006$).

Venlafaxine vs. placebo

A fair 10 week trial assessed the efficacy of venlafaxine ER (75 – 225mg/d) compared with placebo.[148] The study enrolled 361 patients with panic disorder, with and without agoraphobia. ITT-results presented statistically significantly greater response and remission rates ($p < 0.05$; data NR). No statistically significant difference, however, could be detected in the percentage of patients free of panic attacks, which was the primary outcome measure (data NR).

3. Summary of the evidence

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

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[141] or between paroxetine and sertraline[143] in outpatients with panic disorder. Fair evidence exists from five placebo-controlled trials that the improvement of health outcomes and functional capacity is significantly greater for fluvoxamine, sertraline, and venlafaxine ER than for placebo.[144-148] Three placebo-controlled trials provide fair evidence of significantly greater efficacy of fluvoxamine than placebo.[144-146] FDA-approved evidence supports the general efficacy of fluoxetine, paroxetine, and sertraline for the treatment of panic disorder. Evidence is insufficient about the efficacy mirtazapine, venlafaxine, bupropion, and nefazodone for treating panic disorder.

Table 14: Included Studies for Panic Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Bandelow et al., 2004[143]	Paroxetine vs. Sertraline	225	No difference	Fair
Stahl et al., 2003[141]	Citalopram vs. Escitalopram vs. Placebo	366	No difference	Fair
SSRIs versus Placebo				
Asnis et al., 2001[146]	Fluvoxamine vs. Placebo	188	Significantly greater efficacy of fluvoxamine	Fair
Black et al., 1993[149]	Fluvoxamine vs. Placebo	75	Significantly greater efficacy of fluvoxamine	Fair
Hoehn-Saric et al., 1993[145]	Fluvoxamine vs. Placebo	50	Significantly greater efficacy of fluvoxamine	Fair
Pohl et al., 1998[147]	Sertraline vs. Placebo	168	Significantly greater efficacy of sertraline	Fair
Bradwejn et al., 2005[148]	Venlafaxine ER vs. placebo	361	Significantly greater efficacy of sertraline except in percentage of patients free from panic attacks	Fair

G. Post-Traumatic Stress Disorder

For PTSD, we found two head-to-head studies; one comparing citalopram to sertraline,[150] and one comparing nefazodone to sertraline.[151] No other second-generation antidepressants were compared to one another. Currently only sertraline and paroxetine are FDA-approved for treating PTSD. We viewed FDA approval as evidence for general efficacy and did not review placebo-controlled trials of sertraline and paroxetine if no additional health outcomes were assessed.

We included four placebo-controlled trials assessing the efficacy of paroxetine, fluoxetine, and sertraline compared to placebo[152-156] (Table 15). One open-label continuation study[157] and a subsequent maintenance trial[158] assessed long-term effects of sertraline (Table 15).

Inclusion 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. All three trials assessed health outcomes as secondary outcome measures. Two trials were at least partially industry-supported,[152-155, 157, 158] the third was financed by grant from the National Institute of Mental Health (NIMH).[156]

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

Sertraline vs. Citalopram

A fair study randomized 59 outpatients with PTSD to 10 weeks of citalopram (20-50 mg/d), sertraline (50-200 mg/d), or placebo.[150] Primary outcomes measures (CAPS, BDI) did not indicate any statistically significant differences in efficacy between citalopram and sertraline and between the active treatments and placebo.

Sertraline vs. Nefazodone

A fair-rated RCT randomized 37 patients with PTSD to 12 weeks of sertraline (50-200mg/d) or nefazodone (100-600mg/d).[151] Setraline- and nefazodone-treated patients did not differ significantly on primary (CAPS2, CGI) and secondary outcome measures (DTS, MADRS, PSQI, SDS, HAM-A). Both treatment groups had statistically significant improvements within group from baseline to endpoint on all outcome measures. Loss to follow-up was 38 percent; the rate of post-randomization exclusion because of lack of data was 28 percent. However, treatment groups of analyzed participants did not differ in baseline characteristics.

2. SSRIs compared to placebo in adult outpatients with PTSD

Fluoxetine vs. placebo

A small fair-rated study enrolled 54 patients to 12 weeks of fluoxetine (10-60mg) or placebo.[156] Loss to follow-up was 31.5 percent. Using the Duke Global Rating for PTSD cut-off score of 1 (no symptoms) to define responders, the fluoxetine group had significantly more responders than the placebo group (59% vs. 19%; $p < 0.005$). According to Duke Global Rating for PTSD cut-

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

Paroxetine vs. placebo

One fair-rated, fixed-dose trial randomized 563 patients with PTSD to paroxetine 20mg/d, paroxetine 40mg/d, or placebo for 12 weeks.[155] The enrolled population represented a wide range of trauma. The large majority of participants were white (> 90%) and female (67%). Loss to follow-up was 37 percent. Intention-to-treat results showed a significantly greater change in CAPS Part 2 scores for paroxetine 20mg/d (p < 0.001) and paroxetine 40mg/d (p < 0.001) compared to placebo at endpoint. Improvements on the CGI-I were also significantly greater for both paroxetine groups (p < 0.001). Functional improvement was significantly greater for paroxetine-treated patients (SDS) in all three domains (work, social life, family life). Treatment response did not vary by trauma type, time since trauma, or severity of baseline PTSD scores.

Sertraline vs. placebo

Two fair studies with an identical design randomized patients (n = 187; n = 208) with moderate to severe PTSD to 12 weeks of sertraline (50-200mg) or placebo.[152, 153] Loss to follow-up was 28.9 percent and 32.2 percent, respectively. Outcomes assessed functional capacity (Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LESQ], Short Form-36 Health Survey [SF-36], Impact of Event Scale [IES], Davidson Trauma Scale) in addition to general efficacy measures (CGI, CAPS). Participants frequently suffered from concomitant MDD or GAD. Sertraline–treated patients had significantly greater improvements in CAPS scores (p = 0.02; p = 0.04, respectively) and other measures of efficacy. A pooled analysis of data presented significantly greater improvements in the sertraline group for quality of life (p = 0.01) and subscales of emotional and occupational role functioning compared to placebo at the end of the acute treatment phase.[154] Patients who completed the acute phase treatment could enter an open-label continuation phase for 24 weeks (n = 252);[157] 92 percent of sertraline-treated patients maintained response during this open-label treatment. Ninety-six patients who completed the continuation phase were randomized to sertraline (50-200 mg/d) or placebo in a 28-week, double-blind maintenance trial.[158] Treatment with sertraline yielded a significantly lower relapse rate than placebo (5% vs. 26%; p < 0.02). Kaplan-Meier analysis showed highly significant relapse prevention for sertraline (p = 0.0002).

3. Summary of the evidence

We identified one head-to-head trial comparing sertraline to nefazodone. Placebo-controlled trials report general efficacy of fluoxetine, paroxetine, and sertraline in the treatment of PTSD. Significant differences in population characteristics make this evidence insufficient to identify differences between treatments based on placebo-controlled evidence.

Effectiveness

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

Efficacy

Two head-to-head trials did not detect any differences in efficacy between citalopram and sertraline[150] and sertraline and nefazodone.[151] Four placebo-controlled studies provide fair evidence that, compared to placebo, fluoxetine, paroxetine, and sertraline have a significantly greater efficacy in the treatment of outpatients with PTSD and in the improvement of quality of life and functional capacity.[152-158] FDA-approved evidence exists for the general efficacy of paroxetine and sertraline for treating PTSD. Evidence is insufficient about the efficacy of citalopram, escitalopram, fluvoxamine, mirtazapine, venlafaxine, bupropion, and nefazodone for treating PTSD.

Table 15: Included Studies for Post-Traumatic Stress Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Tucker et al. 2005[150]	Citalopram vs. Sertraline	59	No difference in efficacy	Fair
Other second-generation antidepressants (DopRi, 5-HT$_2$) versus SSRIs				
McRae et al., 2004[151]	Sertraline vs. Nefazodone	37	No difference in efficacy	Fair
SSRIs versus Placebo				
Connor et al., 1999[156]	Fluoxetine vs. Placebo	54	Significantly greater efficacy of fluoxetine	Fair
Marshall et al., 2001[155]	Paroxetine vs. Placebo	563	Significantly greater efficacy of paroxetine	Fair
Brady et al., 2000[152, 154, 157, 158]	Sertraline vs. Placebo	187	Significantly greater efficacy of sertraline	Fair
Davidson et al., 2001[153]	Sertraline vs. Placebo	208	Significantly greater efficacy of sertraline	Fair

H. Social Anxiety Disorder

Currently, two SSRIs – 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 placebo-controlled head-to-head trials compared one second-generation antidepressant to another for the treatment of social anxiety disorder.[159-161] Two 12-week trials compared paroxetine to venlafaxine ER;[159, 161] a 24-week trial compared escitalopram to paroxetine.[160] 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 or if they included health outcome measures not commonly assessed in efficacy trials. One meta-analysis compared fluvoxamine, sertraline, and paroxetine to placebo.[162] In addition, four placebo-controlled studies evaluated second-generation antidepressants currently not approved by the FDA for social anxiety disorder: two escitalopram studies,[163, 164] one fluoxetine study,[165] two fluvoxamine studies,[166, 167] and one mirtazapine study[168] (Table 16). Evidence on specific health outcomes are included for seven additional placebo-controlled studies evaluating two SSRIs with FDA-supported efficacy (Table 16): paroxetine,[169-172] and sertraline.[173-175]

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.[159, 161, 165, 174, 175] Additionally, several studies limited eligibility using a predefined cut-off point on a validated anxiety rating scale.[159-161, 164-166, 169, 174, 175]

Main outcome measures examined were mean change in anxiety as measured by one of several measurement 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 frequently were 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 35 percent. One study had a loss-to-follow-up differential between treatment groups greater than 10 percentage points.[171] In two studies, withdrawals because of adverse effects were higher in the active treatment groups.[166, 173]

All included trials are characterized as efficacy studies. Two studies assessed relapse prevention; one randomized escitalopram responders (CGI-I score of 1 or 2) to 24 weeks of escitalopram or placebo,[163] and one study randomized open-label paroxetine responders to placebo or active treatment.[169] Both studies 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.

Escitalopram vs. paroxetine

One multinational study randomized 839 patients with social anxiety disorder to fixed doses of escitalopram (5, 10, or 20 mg/d), paroxetine 20 mg/d, or placebo.[160] Eligible patients had a baseline LSAS score of 70 or higher with a score of 5 or higher on one or more of the SDS subscales. Overall loss to follow-up in this 24-week trial was 29 percent. The primary outcome measure was mean change from baseline to week 12 in the LSAS total score; secondary outcome measures included the LSAS subscales, CGI-I, CGI-S, and SDS. No significant differences in LSAS total score were observed between any escitalopram treatment group and the paroxetine group in the intention-to-treat analysis. The authors did not report any intention-to-treat results for secondary outcome measures. In the observed-cases-analysis at 24 weeks, escitalopram 20 mg/d was superior to paroxetine 20 mg/d on the CGI-S. Significant differences (favoring escitalopram 20 mg/d) were noted on the SDS at weeks 16 and 20, but differences between escitalopram and paroxetine were not significantly different at week 24.

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

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

Venlafaxine vs. paroxetine

Two 12-week multicenter trials compared venlafaxine ER to paroxetine and placebo.[159, 161] A European trial randomized 436 patients with social anxiety disorder[159] and an American trial randomized 440 patients with social anxiety disorder[161] 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 randomixed 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 Eurpoean 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 and nine placebo-controlled trials provide additional evidence.

Fluvoxamine, paroxetine, and sertraline vs. placebo

One fair meta-analysis evaluated published and unpublished evidence comparing SSRIs with placebo in the treatment of social anxiety disorder.[162] Eight studies of unreported quality were included in the review: two fluvoxamine studies, two sertraline studies, and four paroxetine studies. Primary treatment outcomes included global improvement (CGI-I) and mean change in LSAS. Odds ratios for SSRI-treatment response compared to placebo varied between 2.1 and 26.2, favoring the SSRIs. Overall, evidence is inconclusive about differences in efficacy between fluvoxamine, sertraline, and paroxetine.

Escitalopram vs. placebo

One fair 12-week study compared flexible doses of escitalopram to placebo.164 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.160 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% vs 22%; p = NR).

One fair relapse prevention study openly treated 517 patients with generalized social anxiety disorder with escitalopram (10-20mg/d) for 12 weeks.[163] Responders (CGI-I score of 1 or 2) were randomized to 24 weeks of double-blind treatment with escitalopram or placebo. The primary efficacy parameter was time to relapse, defined as ≥ 10 point increase in LSAS total score from randomization. Of 372 randomized patients, 198 escitalopram-treated patients (65%) and 75 placebo-treated patients (41%) completed the 24-week study. In the escitalopram group, 42 patients relapsed (22%), while 91 patients (50%) relapsed in the placebo group. The median time to relapse was 407 days for escitalopram-treated patients and 144 days for placebo-treated patients ($p < 0.001$).

Fluoxetine vs. placebo

One fair study compared flexible doses of fluoxetine to placebo.[165] This trial randomized 60 participants meeting DSM-IV criteria for social anxiety disorder for at least 6 months to 14 weeks of fluoxetine (20-60 mg/d) or placebo. Loss to follow-up was 20 percent with a higher rate in the placebo control group than the active fluoxetine group (23% vs. 16%, respectively). The primary efficacy measure was the LSAS. Significant improvements in LSAS scores were

reported for fluoxetine and placebo, with no statistically significant differences between groups ($p = 0.901$). 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 ($p < 0.05$).

Fluvoxamine vs. placebo

Two 12-week trials compared fluvoxamine to placebo. One study randomized 92 participants with a primary diagnosis of social anxiety disorder and a score of 20 or greater on the BSPS to flexible doses of immediate release fluvoxamine (50-300 mg/d) or placebo.[166] Another trial randomized 300 participants with generalized social anxiety disorder to controlled release fluvoxamine (100-300 mg/d) or placebo.[167] Although loss to follow-up was not reported explicitly in the trial of immediate release fluvoxamine, 25 percent of fluvoxamine-treated patients and 9.1 percent of placebo-treated patients withdrew from the study because of adverse events. Likewise in the trial of controlled-release fluvoxamine, overall loss to follow-up was 32 percent; 26 percent of fluvoxamine-treated patients and 5% of placebo-treated patients withdrew from the study because of adverse events. Outcome measures included the LSAS, CGI-S, CGI-I, and SDS. LSAS scores were significantly more improved for fluvoxamine-treated patients compared to placebo-treated patients in both trials ($p < 0.05$). Significantly more immediate release fluvoxamine-treated patients were rated as CGI-I responders ($p < 0.05$); the number of responders was not statistically different in the comparison of controlled release fluvoxamine and placebo ($p = 0.078$). Both dosage forms of fluvoxamine were significantly better than placebo on all other anxiety scales and two of the three subscales of the Sheehan Disability Scale (work and family functioning). Compared to subjects on placebo, fluvoxamine-treated patients reported a difference of at least 10 percentage points in the incidence of nausea, insomnia, and somnolence.

Mirtazapine vs. placebo

One fair 10-week trial compared mirtazapine to placebo in 114 women with social phobia.[168] 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 ($p = 0.53$).

Paroxetine vs. placebo

FDA-approved evidence supports the general efficacy for paroxetine. In addition to efficacy, four placebo-controlled paroxetine studies evaluated health outcomes.[169-172] Two 12-week trials comparing paroxetine (20-50 mg/d) to placebo and one 12-week trial comparing controlled-release paroxetine (12.5-37.5 mg/d) to placebo measured disability.[170, 171] Compared to patients on placebo, those on immediate-release paroxetine showed significantly greater improvement in

both studies on the social life and work domains of the SDS; family life was statistically better in paroxetine-treated patients in one of the two immediate-release paroxetine trials.[170] Patients treated with controlled-release paroxetine showed significantly greater improvement than placebo-treated patients in SDS total score, family life, social life, and work domains.[172]

A 24-week, multinational, relapse prevention study randomized 323 paroxetine responders to 24 weeks of double-blind placebo-controlled continuation therapy after 12 weeks of open-label treatment with flexible dosing of paroxetine (20-50 mg/d).[169] Loss to follow-up was 20.5 percent, with a differential between the paroxetine and placebo groups of 9 percentage points (16% vs. 25%, respectively). Patient relapse was assessed based on an increase of at least two points on the CGI-S. Significantly fewer paroxetine-treated patients relapsed during 24 weeks of follow-up ($p < 0.001$). The estimated probability of relapse at any particular time was 3.29 times greater for placebo-treated patients ($p < 0.001$). Significantly greater improvement was observed in paroxetine-treated patients on the LSAS, SDS, SCL-90, and visual analogue scale of the EQ-5D. More subjects in the paroxetine group experienced significant weight gain (≥ 7% weight increase).

Sertraline vs. placebo

Three published controlled trials compared sertraline to placebo.[173-175] Each study assessed disability using the SDS, and significant improvement in SDS total score was observed at endpoint in all studies.[173-175] One study assessed health status with the SF-36 and reported a significant improvement in the mental health component.[175] Another study assessed quality of life using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[174] Compared to patients on placebo, sertraline-treated patients showed a significant improvement in quality of life.

2. 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 vs. paroxetine and venlafaxine ER vs. paroxetine. Additionally, indirect evidence from a meta-analysis of placebo-controlled trials provides evidence that there is no difference in efficacy between fluvoxamine, paroxetine, and sertraline.

Effectiveness

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

Efficacy

One comparative trial provides fair evidence of comparable efficacy between escitalopram and paroxetine for the treatment of social anxiety disorder.[160] Two comparative trials provide fair evidence of comparable efficacy between venlafaxine ER and paroxetine.[159, 161] One meta-analysis of placebo-controlled studies provided fair evidence of comparable efficacies of fluvoxamine, paroxetine, and sertraline for the treatment of social anxiety disorder.[162] Fourteen

trials provide fair evidence that SSRIs significantly improve health outcomes compared to placebo.[159-161, 164-167, 169-175]

FDA-approved evidence supports the general efficacy of paroxetine, sertraline, and extended release venlafaxine. One placebo-controlled trial did not support the efficacy of fluoxetine.[165] Evidence from three placebo-controlled trials supports the efficacy of escitalopram,[160, 163, 164] evidence from one placebo-controlled trial supports the efficacy of mirtazapine in women,[168] and two placebo-controlled trials supports the efficacy of fluvoxamine.[166, 167] Evidence is insufficient about the efficacy of citalopram, duloxetine, mirtazapine, bupropion, and nefazodone for treating social anxiety disorder.

Although no identified study addressed the use of second-generation antidepressants as a prophylactic treatment for social anxiety disorder, two studies evaluated continuation of therapy among responders.[163, 169] At 24 weeks, escitalopram-treated[163] and paroxetine-treated patients[169] were significantly less likely to relapse than placebo-treated patients; 22 percent of escitalopram-treated patients relapsed compared with 50 percent of placebo-treated patients ($p < 0.001$); 14 percent of paroxetine-treated patients relapsed compared with 39 percent of placebo-treated patients ($p < 0.001$).

Table 16: Included Studies for Social Anxiety Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Lader et al., 2004[160]	Escitalopram vs. Paroxetine vs. Placebo	839	No difference between active treatments; escitalopram and paroxetine significantly better than placebo	Fair
Other second-generation antidepressants versus SSRIs				
Allgulander et al., 2004[159]	Venlafaxine ER vs. Paroxetine vs. Placebo	436	No difference between active treatments; venlafaxine and paroxetine significantly better than placebo	Fair
Liebowitz et al., 2005[161]	Venlafaxine ER vs. Paroxetine vs. Placebo	440	No difference between active treatments; venlafaxine and paroxetine significantly better than placebo	Fair
SSRIs versus Placebo				
van der Linden et al., 2000[162]	Fluvoxamine vs. Placebo Paroxetine vs. Placebo Sertraline vs. Placebo (SR)	1,482	No differences between active treatments	Fair
Kasper et al., 2005[164]	Escitalopram vs. Placebo	358	Significantly greater efficacy of escitalopram	Fair
Montgomery et al., 2005[163]	Escitalopram vs. Placebo	372	Significantly lower risk of relapse for escitalopram	Fair
Kobak et al., 2002[165]	Fluoxetine vs. Placebo	60	No differences in efficacy	Fair
Stein et al., 1999[166]	Fluvoxamine vs. Placebo	92	Significantly greater efficacy of fluvoxamine	Fair
Westenberg et al., 2004[167]	Fluvoxamine (CR) vs. Placebo	300	Significantly greater improvement for fluvoxamine CR	Fair
Muehlbacher et al., 2005[168]	Mirtazapine vs. Placebo	66	Significantly greater efficacy of mirtazapine	Fair
Stein et al., 1998[171]	Paroxetine vs. Placebo	187	Significantly greater improvement in social life and work domains for paroxetine	Fair
Baldwin et al., 1999[170]	Paroxetine vs. Placebo	290	Significantly greater improvement in social life, family life, and work life for paroxetine	Fair
Stein et al., 2002[169]	Paroxetine vs. Placebo	323	Significant reduction in relapse for paroxetine	Fair
Lepola et al., 2004[172]	Paroxetine (CR) vs. Placebo	370	Significantly greater improvement in SDS for paroxetine CR	Fair
Van Ameringen et al., 2001[173]	Sertraline vs. Placebo	204	Significantly greater improvement in SDS for sertraline	Fair
Liebowitz et al., 2003[174]	Sertraline vs. Placebo	415	Significantly greater improvement in SDS and QoL for sertraline	Fair
Blomhoff et al., 2001[175]	Sertraline vs. Placebo	387	Significantly greater improvement in SDS and mental health for sertraline	Fair

(SR) = Systematic review

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

The FDA has approved fluoxetine, sertraline, and paroxetine for the treatment of PMDD and LLPDD.

We did not find any head-to-head studies comparing SSRIs or other second-generation antidepressants to each other. One meta-analysis (of 15 RCTs)[176, 177] and five RCTs[178-182] compared SSRIs or other second-generation antidepressants to placebo. These studies are listed in Table 17.

Studies were conducted over two to six menstrual cycles. Of the 15 studies in the meta-analysis, four examined intermittent luteal phase therapy; the others examined continuous therapy. Of the additional five placebo-controlled trials, one trial examined continuous therapy,[178] two examined intermittent therapy during the luteal phase only,[180, 182] and two examined both.[177, 181]

Included studies were conducted in women of reproductive age (18 to 45 years) with a clinical diagnosis of PMDD or LLPDD. Women were required to meet DSM criteria in all three trials and in 13 of the 15 studies in the meta-analysis. The detailed interviews required to determine a diagnosis of 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).

All five placebo-controlled trials used a patient-assessed daily symptom rating or report in addition to the CGI.[178-180, 182] Patients monitored their symptoms through the use of diaries, calendars, or visual analog scales. In addition to patient report of symptoms, one trial used the 21-item HAM-D.[178] Studies included in the meta-analysis used similar efficacy outcome measures. Two studies measured health outcomes including social adjustment and quality of life.[180, 181]

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

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

SSRIs vs. placebo

Only one study reported on efficacy outcomes of non-FDA-approved SSRIs.[176, 177] This good-quality meta-analysis pooled data from 15 trials comparing various SSRIs to placebo; seven used fluoxetine, five used sertraline, one used citalopram, one used paroxetine, and one used fluvoxamine. The investigators converted data from each trial to standardized mean differences (SMDs) for the proportion of patients who showed improvement in overall premenstrual symptoms; they used a random effects model to estimate pooled efficacy. The pooled SMD favoring SSRI over placebo was -1.066 (95% CI, -1.381, -0.750) equivalent to an odds ratio of 6.91 (95% CI, 3.90, 12.2). However, this meta-analysis also included cross-over studies.[177] In the more conservative analysis, which excluded

five studies with a cross-over design, the authors estimated a smaller SMD of -0.75 (95% CI, -0.98, -0.51).[176]

Paroxetine vs. placebo

One fair RCT not included in the meta-analysis assessed health outcomes.[182] This trial compared luteal phase dosing with paroxetine CR (12.5 and 25 mg/d) to placebo in 373 outpatients with PMDD. Mood was assessed on a visual analogue scale (Mood VAS) and disability was assessed with the Sheehan Disability Scale (SDS). Compared to placebo, paroxetine-treated patients (both doses) scored significantly better on the Mood VAS and SDS ($p < 0.05$ for all). Nausea and asthenia were more commonly reported among paroxetine-treated patients (12.3% and 12.3% for 12.5mg/d and 23.3% and 19% for 25mg/d, respectively) than among placebo-treated patients (1.7% and 4.2% respectively). The incidence of adverse events was higher in the "on treatment" windows and was highest during the first treatment cycle.

Sertraline vs. placebo

Two RCTs assessed health outcomes.[180, 181] One fair RCT compared an intermittent dose of sertraline (50-100mg/d) during the luteal phase only to placebo over three menstrual cycles and measured health outcomes using the Social Adjustment Scale and the Quality of Life Enjoyment and Satisfaction Questionnaire.[180] Sertraline-treated subjects had significantly more improvement on both scales than placebo-treated subjects. The second study compared intermittent and continuous sertraline therapy to placebo.[181] Both regimens significantly improved daily functioning (Subject Global Ratings of Functioning) and PMDD symptoms (Premenstrual Daily Symptom Rating Form) compared to placebo. No difference in efficacy was apparent between the two treatment regimens.

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

Venlafaxine vs. placebo

One fair RCT compared an SNRI, specifically a continuous daily dose of venlafaxine (50-200 mg/d), to placebo over four menstrual cycles.[178] It reported 36 percent of subjects as lost to follow-up. Venlafaxine-treated subjects had significantly lower premenstrual daily symptom report scores and 21-item HAM-D scores than placebo subjects. Sixty percent of venlafaxine-treated subjects were considered responders (e.g., had more than a 50% reduction in baseline symptom report score), whereas only 35 percent of placebo-treated subjects were characterized as responders.

Nefazodone vs. placebo

One fair RCT compared a second-generation antidepressant, specifically both a continuous and intermittent daily dose of nefazodone (100-400 mg/d), to placebo over two menstrual cycles.[179] This trial did not, however, compare intermittent and continuous therapy to each other. Twenty-two percent of subjects were reported as lost to follow-up in this trial. For both dosing methods, no significant differences were seen between nefazodone and placebo in either patient self-rated global

improvement or any of the individual symptoms assessed (irritability, depressed mood, affect lability, tension, breast tenderness, bloating, and food craving).

4. Summary of the evidence

We identified no head-to-head Good to fair evidence exists from 2 meta-analyses that the efficacy of SSRIs as a class is significantly greater than placebo. Five additional trials provide fair evidence that the efficacies of paroxetine, sertraline, and venlafaxine are significantly greater than the efficacy of placebo. Another study reported no significant treatment effect for nefazodone compared to placebo. Significant differences in study characteristics make this evidence insufficient to identify differences among treatments.

Effectiveness

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

Efficacy

One meta-analysis provides good evidence that SSRIs as a class have a significantly greater efficacy than placebo in the treatment of PMDD and LLPDD.[177] Among SSRIs that are not FDA approved, this meta-analysis includes data on citalopram and fluvoxamine. One fair RCT provides evidence that the efficacy is significantly greater for venlafaxine than for placebo.[178] One RCT provides evidence that intermittent dosing with paroxetine CR improves mood and daily functioning.[182] Two RCTs provides fair evidence that sertraline improves quality of life and daily functioning significantly more than placebo does.[180, 181] Lastly, evidence from one fair RCT indicates that nefazodone does not have greater efficacy than placebo in the treatment of PMDD or LLPDD.[179] 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.

Continuous Therapy as compared to Intermittent Therapy

We identified one trial examining the efficacy of intermittent (e.g., luteal phase only) sertraline therapy against continuous sertraline therapy.[181] Both sertraline groups improved significantly compared to placebo. Premenstrual dosing did not differ in efficacy from continuous dosing. A subgroup analysis in a good meta-analysis reported similar results.[177]

Table 17: Included Studies for Premenstrual Dysphoric Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Dimmock et al., 2000 [177]	5 SSRIs vs. Placebo (SR)	904	Significantly greater efficacy of SSRIs	Good
Wyatt et al., 2004*[176]	5 SSRIs vs. Placebo (SR)	844	Significantly greater efficacy of SSRIs	Fair
SSRIs versus Placebo				
Freeman et al., 2001[178]	Venlafaxine vs. Placebo	157	Significantly greater efficacy of venlafaxine	Fair
Steiner et al., 2005[182]	Paroxetine CR vs. Placebo	373	Significantly greater efficacy of paroxetine	Fair
Freeman et al., 2004[181]	Sertraline vs. Placebo	167	Significantly greater efficacy of sertraline; no difference between intermittent and continuous treatment	Fair
Halbreich et al., 2002[180]	Sertraline vs. Placebo	281	Significantly greater efficacy of sertraline	Fair

(SR) = Systematic review

* This meta-analysis, from the same authors as the Dimmock et al. meta-analysis, represents a more conservative analysis of the same studies; it excluded 5 of the 15 studies from the main effects calculation because of their use of a cross-over design.

KEY QUESTION 2. Adverse Events

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

Most of the studies that examined the efficacy of one drug relative to another also determined differences in tolerability. Methods of adverse events assessment differed greatly. Only six studies used objective scales such as the UKU-SES (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 18).

A. Tolerability and Discontinuation Rates

From 58 head-to-head studies reviewed for this report, 17 reported statistically significant differences in adverse events or discontinuation rates because of adverse events.

Nausea, headache, diarrhea, fatigue, dizziness, sweating, sexual side effects, tremor, dry mouth, and weight gain were the commonly reported adverse events. Table 18 depicts the mean incidence and 95% confidence interval for specific adverse events commonly reported in trials. Statistics are descriptive only and comparisons across different drugs should be made with caution given differences in assessment and reporting of adverse events across trials.

Discontinuation rates because of adverse events were generally not statistically significantly different, except in five trials. One study reported that significantly more patients on fluvoxamine than on sertraline discontinued treatment;[42] another showed a higher rate of discontinuations in citalopram than in escitalopram-treated patients;[22] another trial had significantly more patients on venlafaxine than on escitalopram drop out because of adverse events;[53] the other two trials provided conflicting evidence on the discontinuation rates of mirtazapine and paroxetine.[48, 49]

Venlafaxine had a consistently higher rate of nausea and vomiting than SSRIs. In six studies, the difference reached statistical significance.[52, 53, 56, 60, 61, 63] In six additional trials, the higher rates of nausea or vomiting for venlafaxine were not statistically significant.[54, 55, 57, 59, 64, 66] The rate of patients reporting nausea or vomiting ranged from 25 percent to 36 percent. A pooled analysis of published and unpublished trials of duloxetine did not find significant differences in nausea between duloxetine (40-120mg/d) and paroxetine (20mg/d) or between duloxetine (120mg/d) and fluoxetine (20mg/d).[183] Three trials reported a significantly higher rate of dizziness in the venlafaxine group than in the fluoxetine group.[56, 57, 61] Three other studies reported significantly higher rates of diarrhea in sertraline-treated patients than in comparison drugs.[34, 41, 50] In another trial conducted in patients 65

years and older, patients using fluoxetine had significantly more severe adverse events than patients treated with paroxetine.[29]

A British study pooled data from Prescription-Event-Monitoring (PEM) of general practitioners 6 months to 1 year after they had issued prescriptions.[184, 185] 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. Rate ratios are provided in Evidence Table 10. 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[186] and fluvoxamine and paroxetine,[40] and fluvoxamine and fluoxetine.[28] A Dutch multicenter trial was designed to assess between-group comparisons of gastrointestinal side effects between citalopram (20-40mg/d) and fluvoxamine (100-200mg/d).[186] A total of 217 patients were enrolled for 6 weeks. Overall, 57 percent of patients reported adverse events. Significantly more patients in the fluvoxamine group had an excess incidence of diarrhea (+13%; $p = 0.026$) or nausea (+16%; $p = 0.017$). However, the authors did not provide a baseline comparison of gastrointestinal illnesses between groups. Differences at baseline could bias results.

The second study enrolled 60 patients to fluvoxamine (50-150mg/d) or paroxetine (20-50mg/d) for 7 weeks.[40] Sweating was the only significantly higher adverse event: 30 percent in paroxetine patients vs.10 percent in fluvoxamine patents ($p = 0.028$).

The third trial assessed differences in adverse events between fluvoxamine (100-150mg/d) and fluoxetine (20-80mg/d) in 100 patients over 7 weeks.[28] Fluoxetine-treated patients suffered under nausea significantly more often than fluvoxamine patients (42.5% vs. NR; $p = 0.03$)

A meta-analysis of 15 RCTs did not find any statistically significant differences in discontinuation rates because of adverse events between fluoxetine and other SSRIs as a class.[187]
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).[188] 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 conducted meta-analyses to assess differences in the the overall loss to follow-up, the discontinuation rates because of adverse events, and the discontinuation rates because of lack of efficacy of SSRIs as a class compared to some other second-generation antidepressants (bupropion, mirtazapine, and venlafaxine) in adult outpatients with MDD (Exhibit 6). Available data were insufficient to determine results for duloxetine and nefazodone. The only statistically significant difference in pooled estimates was a higher discontinuation rate because of adverse events for venlafaxine-treated patients than for patients on SSRIs (RR: 1.36; 95% CI 1.04-1.77). Overall, this finding was balanced by lower discontinuation rates because of lack of efficacy for venlafaxine (RR: 0.69; 95% CI 0.47-0.99). Overall discontinuation rates did not differ significantly between venlafaxine and SSRIs (RR: 1.06; 95% CI 0.93-1.22). No significant differences could be detected between SSRIs and mirtazapine or between SSRIs and bupropion. Numerical differences in discontinuation rates attributed to adverse events generally favored SSRIs over mirtazapine and bupropion but did not reach statistical significance. Because of heterogeneity we did not pool data of discontinuation rates related to adverse events when comparing SSRIs to mirtazapine and SSRIs to bupropion

Table 18: Mean incidence of specific adverse events

Drug	Diarrhea	Dizziness	Headache	Insomnia	Nausea	Weight Gain
	Mean [*] *(95% confidence interval)*					
Bupropion	8.7% (1.2% - 16.1%)	12.5% (3.4% - 21.6%)	27.2% (18.4% - 36.0%)	16.0% (13.3% - 18.7%)	14.8% (8.9% - 20.6%)	NR
Citalopram	6.8% (1.8% - 11.8%)	NR	5% (0% - 24.1%)	6.4% (1.6% - 11.2%)	11.9% (0% - 24.8%)	NR
Duloxetine	NR	NR	NR	NR	10.9% (0% - 35.6%)	NR
Escitalopram	8.9% (1.6% - 16.1%)	NR	14.1% (0% - 29.9%)	8.7% (1.3% - 16.2%)	14.8% (6.1% - 23.5%)	NR
Fluoxetine	11.7% (6.8% - 16.6%)	7.2% (4.3% - 10.0%)	16.6% (10.2% - 23.0%)	13.7% (10.0% - 17.4%)	18.6% (15.1% - 22.1%)	4.1% (0% - 10.7%)
Fluvoxamine	NR	NR	14.5% (0% - 41.5%)	NR	22.2% (0% - 46.8%)	NR
Mirtazapine	8.8% (0% - 22.4%)	12.0% (2.9% - 21.2%)	12.1% (6.3% - 17.9%)	8% (0% - 49.2%)	4.3% (0% - 8.9%)	13.5% (10.5% - 16.4%)
Paroxetine	9.2% (5.6% - 12.9%)	10.6% (7.5% - 13.7%)	21.2% (11.1% - 31.3%)	14.3% (8.6% - 20.1%)	18.3% (11.1% - 25.6%)	9.6% (1.1% - 18.0%)
Sertraline	15.4% (10.2% - 20.6%)	7.5% (4.6% - 10.4%)	20.2% (12.8% - 27.6%)	15.0% (8.7% - 21.3%)	19.5% (14.4% - 24.6%)	7.6% (0% - 18.5%)
Venlafaxine	5.5% (1.0% - 10.1%)	15.7% (7.0% - 24.4%)	12.8% (8.0% - 17.6%)	11.2% (3.4% - 19.0%)	31.0% (27.4% - 34.0%)	NR

[*] Mean incidence calculated from randomized controlled trials; method and extent of adverse event assessment varied among studies and pooled incidence should be interpreted with caution.

B. Specific Adverse Events

1. Suicidality

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

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

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

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).[189] 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.[190] This study did not find any evidence that the risk of suicide (OR 0.57; 95% CI 0.26 to 1.25) or self-harm (OR 0.99; 95% CI 0.86 to 1.14) is greater in patients on second-generation antidepressants than in patients on TCAs. In patients younger than 18 years, however, the risk of self-harm was significantly greater in patients on SSRIs than on TCAs (OR 1.59; 95% CI 1.01 to2.50). Although no statistically significant differences among SSRIs were detected, the greatest risk of self-harm was among paroxetine users.

Findings of other studies are mixed. A recent, good meta-analysis of published data on more than 87,000 patients in SSRI trials for various conditions reported a significantly higher risk of suicide attempts for SSRI patients than for placebo-treated patients (2.25; 95% CI 1.14 to 4.55).[191] 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).

Findings of the CSM Expert Group on suicidality in children are consistent with results from an earlier NICE (National Institute for Clinical Excellence) report.[96] Results of other studies on suicidality in adults are mixed.[13, 192, 193] Included studies are presented in Table 19 and described below.

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.[192] 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.[193] 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 to 1.50), 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.[194] 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.[13] 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 1.23-2.23) but no differences in suicides.[195] However, no differences in self-harm or suicides were apparent among citalopram-, fluoxetine-, or paroxetine-treated patients. A retrospective analysis of escitalopram trails data found a higher rate of self-harm for escitalopram than for placebo but no differences in suicides.[196]

2. Sexual dysfunction

A subgroup analysis of a good Swedish RCT examined the incidence of sexual side effects from citalopram (20-60mg/d) compared to those from sertraline (50-150 mg/d)[17, 197] 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.[198]

A good meta-analysis including data on 1,332 patients reported a significantly higher rate of sexual satisfaction in bupropion- than in SSRI-treated patients with MDD (RR 1.28; 95% CI 1.16-1.41).[67]

Three studies assessed the incidence of sexual dysfunction in depressed outpatients treated with bupropion or sertraline.[73, 74, 85]

Two fair-rated RCTs compared the incidence of sexual dysfunction in 360 and 364 patients with MDD during 8 weeks of treatment with bupropion (150-400mg/d), sertraline (50-200mg/d), or placebo.[73, 74] 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.[73] 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 ($p < 0.05$).[74]

The third RCT assessed the sexual side effects of bupropion SR (150-400mg/d) and sertraline (100-300mg/d) in 248 depressed outpatients.[85] Study duration was 16 weeks; loss to follow-up was 31.5 percent. Sexual dysfunction was determined by investigator interviews and patient-completed questionnaires. Treatment groups were comparable at baseline. Intention-to-treat analysis showed that, beginning at day 7, significantly fewer bupropion-treated patients than sertraline-treated patients reported sexual dysfunction ($p < 0.001$) throughout the study. These findings were significant for males ($p < 0.05$) and for females ($p < 0.01$). Significantly more patients in the sertraline group developed sexual arousal disorder, orgasm dysfunction, or ejaculation disorder (men: 63% vs. 15%; $p < 0.001$; women: 41% vs. 7%; $p < 0.001$).

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

A fair, 8-week RCT compared efficacy and sexual side effects of bupropion (150-400mg/d), fluoxetine (20-60mg/d), and placebo in 456 outpatients with MDD.[69] Loss to follow-up was 36 percent. Efficacy did not differ significantly. Bupropion had more remitters than fluoxetine (47% vs. 40%) at endpoint. Bupropion also showed significantly fewer sexual side effects than fluoxetine throughout the study. Beginning at week 1 until endpoint, significantly more fluoxetine-treated patients were dissatisfied with their overall sexual function than bupropion-treated patients ($p < 0.05$).

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.[199] All patients had normal sexual functioning at study onset. Overall, 59 percent of patients experienced some type of sexual dysfunction. Among second-generation antidepressants, citalopram, paroxetine, and venlafaxine had the highest incidence of sexual dysfunction (73 percent, 71 percent, and 67 percent, respectively); mirtazapine and nefazodone had the lowest (24 percent and 8 percent, respectively). This study did not include data on bupropion, escitalopram, and trazodone. In another observational study, findings of a cross-sectional survey of patients on second-generation antidepressants presented similar results.[200] 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[33, 41, 42, 50, 72, 80] 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% vs. 13.5%; p = 0.004).[72]

3. Changes in weight

A 32-week acute and continuation trial assessed differences in weight changes among patients treated with fluoxetine, paroxetine, and sertraline.[82] 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.[34] 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.[201]

A double-blinded placebo-controlled 52-week acute and continuation trial assessed weight changes during bupropion treatment.[202] Bupropion-treated patients showed a modest but nevertheless significant decrease of body weight from baseline (-1.15 kg; p < 0.001). The magnitude of weight change was closely related to the body mass index (BMI). Patients with a higher BMI experienced greater weight loss.

Two RCTs assessing the efficacies of mirtazepine and paroxetine reported significantly greater weight gains in the mirtazapine group than in the paroxetine group.[48, 49]

4. Seizures

Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of seizures in patients taking any of the reviewed drugs, including bupropion. Two open-label trials examined the rate of seizures during bupropion treatment for 8 weeks.[203, 204] Both trials reported that the rate of seizures was within the range of other marketed antidepressants. However, the strength of this uncontrolled, open-label evidence must be rated as low. A recent chart review of 538 patients with deliberate self-poisening with antidepressants reported that seizures were more common in patients with venlafaxine overdose than in patients with TCA or SSRI overdose.[205]

5. Cardiovascular adverse events

A post hoc analysis examined pooled data from 3,744 patients participating in venlafaxine trials.[206] At 6 weeks, 11.5 percent of venlafaxine patients had a supine diastolic blood pressure (DBP) greater than 90 mm Hg (imipramine: 7.9%, placebo: 5.7%; p < 0.001). During continuation treatment (up to 12 months), significantly more venlafaxine subjects with normal supine DBPs developed elevated readings (p = 0.05). A randomized controlled trial comparing sertraline to venlafaxine detected an increase of supine diastolic blood pressure of 3.1 mm Hg for venlafaxine compared to a decrease of 1.4 mm Hg for sertraline after 8 weeks (p = 0.004).[65]

A post-hoc analysis of six RCTs (published and unpublished) comparing duloxetine to fluoxetine and paroxetine did not find any statistically significant differences in supine systolic or diastolic blood

pressure.[207] Duloxetine treated patients had a greater mean change in heart rates than fluoxetine-(+2.8beats/min. vs. -1.0 beat/min.) and paroxetine-treated patients (+1.0 beats/min. vs. -1.4 beats/min.)

6. Hyponatremia

Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of hyponatremia in patients treated with 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.[208] Even if this evidence is considered weak, it could be important in the absence of studies with the methodological strength to account for rare adverse events.

7. Hepatotoxicity

Evidence from controlled trials and observational studies is also insufficient to conclude for or against an increased risk of liver toxicity during nefazodone treatment. Nevertheless, numerous case reports not included in this report contain low-level quality but potentially important evidence citing an increased risk of liver toxicity during nefazodone treatment.[209] One maker of nefazodone has announced that it is withdrawing the drug from the US market by June 2004 because of safety concerns (websource: www.medscape.com/viewarticle/47852; accessed 5-20-2004).

C. Summary of the evidence

Fair to good evidence from multiple randomized controlled head-to-head trials and retrospective data analyses of prescription event monitoring documents that side-effects profiles differ significantly among reviewed 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.[184] 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 (RR 1.34; 95% CI 1.00 to 1.80). However, overall discontinuation rates do not differ significantly between venlafaxine and SSRIs.

Suicidality

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

Sexual dysfunction

Fair evidence from three RCTs indicates that the rate of sexual side effects is significantly lower for bupropion than for sertraline.[69, 74, 85] The combined NNT to yield one additional person who is satisfied with the overall sexual function is 7. An additional study reports fewer sexual side effects in bupropion-treated patients than in fluoxetine–treated patients.[72]

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.[200] Multiple trials give fair evidence that paroxetine, sertraline, and mirtazapine tend

to have higher rates of sexual side effects than other second-generation antidepressants.[33, 34, 41, 42, 50, 72, 80, 200]

Weight changes

Multiple studies provide fair evidence that mirtazapine and paroxetine lead to a greater weight gain than do fluoxetine and sertraline.[48, 49, 82, 201] Additionally, one fair study presents evidence that bupropion treatment leads to a moderate loss of body weight.[202]

Cardiovascular adverse events

A post hoc analysis of pooled data reports that venlafaxine significantly increases the supine DBP.[206] None of the controlled efficacy trials reported significant changes in heart rates or an increase in arrhythmias during treatment with SSRIs, SNRIs, or other second-generation antidepressants. Another post hoc analysis reports that duloxetine lead to higher heart rates than fluoxetine and paroxetine. [207]

Other adverse events

A database analysis in the UK on fatal toxicity of second generation antidepressants found vanmlafaxine to have the highest fatal toxicity rate (13.2/1,000,000 prescription)among second generation antidepressants.[210]

A case-control study did not find an association between SSRIs and breast cancer.[164] 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.[208] Similarly, reports of liver toxicity with nefazodone have not been confirmed by controlled trials and observational studies.[209] Owing to a lack of studies with the methodological strength to assess these rare events, conclusions should be made on other grounds such as comorbidities, taking case reports into consideration.

Table 19: Included Studies for Adverse Events

Author, Year	Interventions	N	Results	Quality Rating
Tolerability and Discontinuation				
Brambilla et al. 2005[187]	Fluoxetine vs. SSRIs (SR)	NR	No difference in discontinuation rates because of adverse events	Good
Greist et al. 2004[183]	Pooled analysis: Duloxetine vs. Paroxetine vs. Fluoxetine	2345	No differences in nausea between duloxetine and paroxetine, and duloxetine and fluoxetine	N/A
Haffmans et al, 1996[186]	Fluvoxamine vs. Paroxetine	217	Significantly more diarrhea and nausea with fluvoxamine	Fair
Kiev et al., 1997[40]	Fluvoxamine vs. Paroxetine	60	Significantly more sweating with paroxetine	Fair
Mackay et al., 1997, 1999[184, 185]	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[188]	Sertraline vs. SSRIs (OS)	1251	Significantly more diarrhea with sertraline	Fair
Rapaport et al., 1996[28]	Fluvoxamine vs. fluoxetine	100	Significantly more nausea with fluoxetine	Fair
Suicidality				
Didham et al. 2005[195]	SSRIs	57,000	No difference in suicides or self-harm among citalopram, fluoxetine, and paroxetine	Fair
Fergusson et al., 2005[191]	SSRIs vs. placebo (SR)	87,650	Higher risk of suicide attempts for SSRI-treated patients	Good
Gunnell et al., 2005[189]	2nd gen. AD vs. placebo (SR)	40,000	No differences in adults	Good
Jick et al., 2004[211]	Case-control; database review	159,810	No differences	N/A
Jick et al., 1995[192]	Open cohort; database review	172,598	Significantly higher risk of suicide with fluoxetine and mianserin compared to dothiepin	N/A
Khan et al., 2003[194]	Data review	NR	No differences	N/A
Lopez-Ibor 1993[13]	Database review	4686	No differences	N/A
Martinez et al.,2005[190]	Database review	146,095	No differences	N/A
Pederson et al., 2005[212]	Retrospective cohort study	4091	Higher rate of self-harm in escitalopram than in placebo	Fair
Sexual Dysfunction				
Nieuwstraten et al, 2001[67]	Bupropion vs. SSRIs (SR)	1332	Significantly higher rate of sexual satisfaction in bupropion group	Good
Clayton et al., 2002[200]	Cross-sectional survey	6297	Highest risk for paroxetine and mirtazapine; lowest risk for bupropion	N/A
Coleman et al., 2001[69]	Bupropion vs. Fluoxetine	456	Significantly more sexual adverse events with fluoxetine	Fair
Coleman et al., 1999[74]	Bupropion vs. Sertraline	364	Significantly more sexual adverse events with sertraline	Fair
Croft et al., 1999[73]	Bupropion vs. Sertraline	360	No differences	Fair
Ekselius et al., 2001[197]	Citalopram vs. Sertraline	308	No differences	Fair
Landen et al. 2005[198]	Citalopram vs. Paroxetine	119	No differences	Good
Segraves et al., 2000[85]	Bupropion vs. Sertraline	248	Significantly more sexual adverse events with sertraline	Fair

Montejo et al., 2001[199]	Prospective cohort study	1022	Highest incidence of sexual dysfunction for citalopram, paroxetine and venlafaxine; lowest for mirtazapine and nefazodone	Fair
Changes in Weight				
Maina et al. 2004[201]	Open-label SSRIs	149	Highest weight gain with paroxetine, fluvoxamine, and citalopram	Fair
Fava et al., 2000[34]	Fluoxetine vs. Paroxetine vs. Sertraline	284	Highest weight gain with paroxetine	Fair
Benkert et al., 2000[49]	Mirtazapine vs. Paroxetine	275	Significant weight gain with mirtazapine	Fair
Schatzberg et al., 2002[48]	Mirtazapine vs. Paroxetine	255	Significant weight gain with mirtazapine	Fair
Cardiovascular Events				
Thase et al., 1998[206]	Post hoc analysis	3744	Significantly higher diastolic blood pressure for venlafaxine	N/A
Thase et al. 2005[207]	Post hoc analysis	1873	Greater change in heart rate for duloxetine than for fluoxetine and paroxetine	N/A
Other Adverse Events				
Buckley et al., 2005[210]	Database analysis	47,329	Highest rate of fatal toxicity for venlafaxine	N/A
Coogan et al., 2005[213]	Case-control	4996	No association between breast cancer and SSRIs	Fair
Dunner et al., 1998[204]	Prospective observational	3100	Rate of seizures for bupropion within range of other antidepressants	Fair
Johnston et al., 1991[203]	Prospective observational	3341	Rate of seizures for bupropion within range of other antidepressants	N/A
Whyte et al., 2003[205]	Prospective observational	538	Seizures more common in venlafaxine overdose than TCA or SSRI overdose	Good

(SR)= Systematic review
(OS)= Observational study

KEY QUESTION 3. Subgroups

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

We did not find any studies directly comparing the efficacy and tolerability of second-generation antidepressants between subgroups and the general population. However, multiple studies conducted subgroup analysis or used subgroups as the study population. Results can provide indirect evidence for key question 3. Included studies are presented in Table 20.

A. Demographics

1. Age

SSRIs as a class

A pooled data data-analysis of trials comparing venlafaxine to SSRIs reported that older women responded poorer to SSRI-treatment than younger women. This difference could not be observed in men.[214]

Fluoxetine vs. paroxetine

Two RCTs were conducted in a population older then 60 years.[29, 32] The first trial was an Italian study lasting 1 year that enrolled 242 patients to determine the effects of fluoxetine (20-60mg/d) and paroxetine (20-40mg/d) on mood and cognitive function in depressed, nondemented persons (65 years or older). Both groups significantly improved on their HAM-D scores and cognitive performance. Paroxetine showed a faster onset of action and a significantly greater improvement of HAM-D scores during the first 6 weeks (Week 3: $p < 0.05$; Week 6: $p < 0.002$). A Kaplan-Meier analysis evaluating the percentage of responders over time revealed a significant difference in favor of paroxetine ($p < 0.002$). Treatment groups did not differ significantly in CGI scores. Fluoxetine had a significantly greater number of patients with severe adverse events than paroxetine (22 versus 9; $p < 0.002$). However, loss to follow-up in this study was 39.3 percent, so the validity of the results should be viewed cautiously.

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.[32] Loss to follow-up was not reported. An intention-to-treat analysis revealed no differences between the treatment groups in changes of scores on MADRS and HAM-D; the paroxetine group had significantly more responders at 6 weeks on MADRS and HAM-D scales (37.5%vs. 17.5%; $p = 0.04$). Patients on paroxetine also had significantly better MMSE and SCAG scores assessing cognitive function at Week 3 than did those on fluoxetine. No statistically significant differences in adverse events were reported.

A post hoc analysis of two placebo controlled trials of duloxetine reported that no differences in efficacy could be detected in women across different age groups.[215]

Fluoxetine vs. sertraline

One fair, 12-week study comparing fluoxetine to sertraline was conducted in 236 participants older than 60 years.[37, 39] Loss to follow-up was 32.2%. In this study, outcome measures also included quality of life (Q-LES-Q) and cognitive assessments (SLT, MMSE, Digital Symbol Substitution Test). Fluoxetine- and sertraline-treated patients did not differ significantly on primary outcome measures (MADRS, HAM-D). Response rates (fluoxetine, 71%; sertraline, 73%) and remission rates (46% vs. 45%) were similar. Quality of life and other patient-rated secondary efficacy measures were similar for both treatment groups at endpoint. Sertraline-treated patients showed a greater cognitive improvement on the Digit Symbol Substitution Test at endpoint ($p = 0.037$). A subgroup analysis of 75 patients 70 years of age or older showed a greater response rate for sertraline-treated patients ($p = 0.027$).[39]

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.[19]

An uncontrolled, open-label study of fluoxetine in patients with MDD did not present any differences in outcomes in men and women older than 45 years compared to those younger than 45 years.[216] Age did not have a significant effect on outcomes in patients with or without comorbid anxiety.

Paroxetine vs. placebo vs. behavioral therapy

A large, fair, primary-care-based study randomized 656 patients with dysthymia or minor depression to eleven weeks of paroxetine (10-40mg), placebo, or behavioral therapy.[90, 91] 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 HSCL-D 20 (Hopkins Symptom Checklist) scores than placebo-treated patients ($p = 0.004$) but not more than patients on behavioral therapy ($p = 0.17$). For older dysthymia patients with high or intermediate baseline functioning scores, paroxetine improved mental health functioning significantly compared to placebo. Overall, however, improvements for paroxetine-treated dysthymia patients were not statistically significant different from those on placebo. The younger subgroup did not show statistically significant differences between treatment groups on the HSCL-D scale. For dysthymia only, the remission rate was significantly higher in the paroxetine group than in the placebo group (80% vs. 40%; $p = 0.008$).

Another fair trial randomized 323 patients older than 60 years with MDD to paroxetine IR, paroxetine CR, or placebo.[217] Study duration was 12 weeks. Both active agents presented significantly higher rates of response and remission than placebo. However, no significant differences between paroxetine IR and paroxetine CR were apparent for any primary outcomes measures (HAM-D, CGI-I) or adverse events.

Mirtazapine vs. paroxetine

A fair trial randomized 255 elderly participants for eight weeks.[48] Loss to follow-up was 27 percent. Mirtazapine and paroxetine were equally effective in reducing HAM-D scores at the endpoint, but mirtazapine lead to a faster response. A Kaplan-Meier analysis showed a significantly faster time to response for mirtazapine (mean 26 days versus mean 40 days for paroxetine; $p = 0.016$). No significant difference in response rates on the CGI scale was noted. Significantly more mirtazapine-treated patients reported weight gain ($p < 0.05$). Paroxetine-treated patients reported a significantly higher rate of nausea, tremor, and flatulence ($p < 0.05$).

Venlafaxine versus citalopram

A fair European 6-month study compared venlafaxine ER (37.5-150mg/d) to citalopram (10-30mg/d) for the treatment of depression in elderly outpatients (mean age 73 years).[51] 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 versus sertraline

One study determined efficacy and safety of venlafaxine (25-100mg/d) compared to sertraline (18.5-150mg/d) in 52 frail nursing home residents.[218] Loss to follow-up was 44.2 percent; therefore, we deemed the efficacy analysis not to be valid. However, venlafaxine-treated patients had a significantly higher rate of severe adverse events ($p = 0.022$) and withdrawal because of severe adverse events or side effects ($p = 0.005$) than did the sertraline-treated patients.

Bupropion vs. paroxetine

One fair RCT examined the efficacy of bupropion SR (100-300 mg/d) and paroxetine (10-40mg/d) in 100 outpatients ages 60 years or older (range 60-88 years) over 6 weeks.[70, 71] 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 ($\geq$ 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.

A meta-analysis combined original data from eight comparable, double-blind, active-controlled, randomized trials.[219] A primary objective of this meta-analysis was to determine differences in response and remission based on sex and age. Analysis of the pooled data showed that neither age nor sex influenced the efficacy measures ($p > 0.05$); no significant interaction terms emerged for age by treatment, sex by treatment, or age by sex by treatment (all p values > 0.1).

We did not identify any head-to-head trials that compare one second-generation antidepressant to another in children and adolescents. There is FDA-approved evidence for the efficacy of fluoxetine and fair evidence from a pooled analysis of two placebo-controlled trials for the efficacy of sertraline.[100] Existing evidence does not support the efficacy of other second-generation antidepressants. Additional evidence suggests that sertraline may not be as efficacious as reported in previous reports. Based on a systematic review of published and unpublished studies comparing second-generation antidepressant to placebo, only fluoxetine was shown to be safe and effective in the treatment of MDD in children and adolescents.[96] This review reported an increased risk of suicidal thoughts and behavior for citalopram, paroxetine, sertraline, and venlafaxine, but not for fluoxetine.

2. Ethnicity

Paroxetine versus placebo

A pooled analysis of 104 paroxetine trials (14,875 patients) detected slightly lower response rates for Hispanics and Asians than for Blacks and Whites.[220]

Fluoxetine versus placebo

An RCT examined ethnic differences in response to antidepressant treatment among depressed HIV-positive patients.[221] A total of 118 patients were randomized to either fluoxetine (20-80mg/d) or placebo for 8 weeks. Of all participants, 67 percent were white, 19 percent black, and 14 percent Latino; only 1.1 percent (n = 2) were female. Loss to follow-up was significantly greater among Latinos (53%) than among blacks (14%) and whites (28%; $p < 0.05$). Ethnicity was not associated with the total number of treatment emergent side effects or dosage. Among completers within the active-treatment group, whites were more likely to respond to treatment than the other two groups (84% vs. 50% in blacks and. 67% in Latinos). Among completers in the placebo group, Latinos were more likely to show treatment response (80%) than were blacks (36%) or whites (43%). However, a statistical analysis of these findings was not possible because of the low number of Latinos who completed the study.

3. Sex

A meta-analysis described above[219] and a pooled data analysis of venlafaxine RCTs[214] did not find any significant associations between sex and outcomes or sex and treatment of MDD. A pooled analysis of data from four sertraline-RCTs conducted in populations with panic disorder, however, reported better responses of female patients on some outcome measures (panic attack frequency, time spent worrying).[222] No differences were apparent in quality of life measures.

B. Other Medications-Drug Interaction

The evidence for drug-drug interactions is limited. A recent study published in the *Journal of the American Pharmacists Association* reported that very little agreement in reporting clinical significance of drug-drug interactions.[223] In fact, the authors found that only 2.2 percent of major drug interactions were listed in all sources reviewed.

Based on our review criteria, head-to-head trials specifically evaluating drug-drug interactions were not identified. Most drug interaction studies use very small sample populations or a case series design, precluding them from our review. One larger study nonsystematically pooled data from fluoxetine trials to evaluate efficacy, agitation, and suicidal ideation. Based on this study, the clinical efficacy and safety of fluoxetine was not confounded by concomitant use of anxiolytics, sedatives, or antipsychotics.[224]

Several reviews summarize the evidence; however, they are not based on systematic searches of the literature and instead simply compile and discuss available evidence. One review explored cytochrome P450 metabolic enzymes (the CYP system) and their interaction with SSRIs.[225] The authors concluded that the relationship between SSRIs and P450s does not predict clinically significant interactions but that it can be used as a cue to monitoring, especially among drugs with narrow therapeutic index or in patients taking multiple drugs. Another review evaluated the evidence for drug-drug interactions between SSRIs and other CNS drugs. It concluded that the SSRIs are not equivalent in their potential for drug interactions and that each combination must be assessed individually. The authors also noted a general trend in which, compared to other antidepressants, citalopram and sertraline appeared to have less propensity for important interactions.[226]

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

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

Because only limited evidence supports drug interactions among the second-generation antidepressants, our review focuses on the potential for drug interactions. In addition to published literature cited previously, we reviewed dossiers submitted by pharmaceutical companies, 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

Fluoxetine versus paroxetine

A retrospective evaluation of 89 patients from two trials comparing fluoxetine (20-80mg/d) to paroxetine (20-50mg/d) determined whether depressed, somatizing patients with a gastrointestinal (GI) component have a higher degree of GI side effects than nonsomatizing depressed participants.[227] 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.

Fluoxetine versus placebo

A fair study of 51 depressed alcoholics assessed the efficacy of fluoxetine (20-40mg/d) in a 12-week, placebo-controlled, acute-phase trial and a subsequent 1-year follow-up period with a naturalistic treatment by physicians unrelated to this study (n = 31).[228-230] Outcome measures included changes on HAM-D and BDI and in alcohol consumption. Results of the acute phase trial showed significantly greater improvements of depressive symptoms for fluoxetine-treated patients ($p < 0.05$) on HAM-D but not on BDI. During the 1-year open-label follow-up, HAM-D scores remained significantly lower for the fluoxetine group than for the placebo group. However, no additional improvement during the follow-up treatment was reported. A subgroup analysis showed that depressed alcoholics who were cocaine abusers (n = 17) had a significantly worse outcome than depressed alcoholics who were not (n = 34). Cocaine abusers showed significantly worse outcomes on both the HAM-D ($p = 0.17$) and the BDI ($p = 0.001$).

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

A fair placebo-controlled trial lasting 8 weeks determined the efficacy of fluoxetine (dosage range not reported) in 120 depressed patients with HIV and AIDS.[232] The majority of patients were male (97.3%) and white (65%). Loss to follow-up was 27.5 percent. The main outcome measures were response to treatment defined as a 50 percent improvement on the HAM-D scale, a score lower than 8, and a CGI score of 1 or 2. According to these criteria, the rate of response

did not differ significantly between treatment groups (fluoxetine 57%, placebo 41%). Using the HAM-D scale alone as a criterion, the investigators reported a significantly greater response rate for fluoxetine-treated patients (79% vs. 57%; p = 0.03). The treatment groups did not differ significantly in adverse events.

A fair placebo-controlled European trial lasting 5 weeks studied the efficacy of fluoxetine in 91 cancer patients with depression or adjustment disorder.[233] The majority of the patients were female; 13% in the fluoxetine group and 5% in the placebo group had metastatic disease. Outcome measures included quality of life. Loss to follow-up was 24.2 percent. Efficacy according to the main, observer-rated outcome measures (HADS, MADRS, HAS) did not differ significantly between the active drug and placebo groups. Improvements were generally greater in the fluoxetine group but statistically significant only for the SCL90-R (33% vs. 15%; p = 0.04), which measures global psychological adjustment. No statistically significant difference in quality of life was reported. However, study duration was short and a substantially greater percentage of patients in the fluoxetine group had a more advanced stage of cancer at baseline. Fluoxetine-treated patients had a significantly greater drop-out rate than placebo-treated patients (33% vs. 15%; p = 0.04).

A fair, small RCT assessed the efficacy and tolerability of fluoxetine treatment (20-60mg/d) compared to placebo in 44 methadone-maintained opioid addicts.[234] 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 differe 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).

Paroxetine versus placebo

A 6-week placebo controlled RCT in depressed breast cancer patients on chemotherapy reported greater efficacy of paroxetine (20mg/d) than placebo in reducing depression.[235] Although this study was rated poor because of lack of ITT analysis, we included it because it was the only study conducted in cancer patients. No differences between treatment groups were apparent with respect to fatigue.

Sertraline vs. Placebo

A fair, retrospective analysis of pooled data of two RCTs determined the safety and efficacy of sertraline (50-150mg/d) in elderly patients with comorbid vascular disease.[236] Vascular comorbidity was not associated with an increase of severity of adverse events or premature discontinuation. However, these findings were not based on an unbiased literature search and the validity must be viewed cautiously.

D. Summary of the Evidence

Age

We found no study that directly compared efficacy and safety of treatments in an elderly population compared to a younger population. A fair-to-poor meta-analysis did not find significant associations between age and outcomes or age and treatment.[219] Findings from a pooled data analysis of, however, suggested that older women had a poorer response to SSRIs than younger women.[214]

Eight studies provide fair to good indirect evidence that efficacy and tolerability for patients older than 60 years and those younger do not differ.[29, 37, 39, 48, 51, 70, 71, 91, 215, 218] 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.[32] 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.[218]

An uncontrolled open-label trial did not present differences in efficacy of fluoxetine in patients older than 45 years compared to those younger than 45 years, regardless of concomitant anxiety.[216]

We did not identify any head-to-head trials that compare one second-generation antidepressant to another in children and adolescents. For MDD, placebo-controlled evidence supports the efficacy of fluoxetine[102, 103] and sertraline.[100] Existing evidence does not support the efficacy of other second-generation antidepressants. Additional evidence suggests that sertraline may not be as efficacious as reported in previous reports. Based on a systematic review of published and unpublished studies comparing second-generation antidepressants to placebo, only fluoxetine was shown to be safe and effective in the treatment of MDD in children and adolescents.[96] This review reported an increased risk of suicidal thoughts and behavior for citalopram, paroxetine, sertraline, and venlafaxine, but not for fluoxetine.

Ethnicity

Fair evidence from a pooled data study on paroxetine[220] and a single RCT on fluoxetine[221] 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.

Sex

A meta-analysis rated fair to poor did not find significant associations between sex and outcomes or sex and treatment.[219] A fair pooled analysis of data from four sertraline-RCTs conducted in populations with panic disorder reported better responses of female patients on some outcome measures.[222]

Concomitant medications

Evidence is insufficient to determine the influence of concomitant medications on the effectiveness of SSRIs, SNRIs, or other second-generation antidepressants.

Comorbidities

No prospective study directly compared the efficacy 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. Two retrospective data analyses provide fair evidence that efficacy does not differ between patients with vascular disease and somatizing depressions and patients without these co-morbidities.[227, 236] Various other trials conducted in populations with different comorbidities can provide indirect evidence.[228-230, 232-235] Two placebo-controlled trials provided fair evidence that treatment effects do not differ between placebo and fluoxetine in methadone-maintained opioid addicts or depressed cancer patients.[233, 234] Two different trials reported fair evidence that response rates for fluoxetine-treated alcoholics and depressed HIV patients are significantly higher than for placebo-treated subjects.[228-230, 232] A placebo controlled RCT in depressed breast cancer patients reported greater efficacy of paroxetine than placebo in reducing depression but no differences with respect to fatigue.[235]

Table 20: Included Studies for Subgroups

Author, Year	Interventions	N	Results	Quality Rating
Age				
Burt et al. 2005[215]	Duloxetine vs. placebo	117	No difference	N/A
Cassano et al., 2002[29]	Fluoxetine vs. Paroxetine	242	Faster onset of paroxetine	Fair
Cassano et al., 2004[216]	Fluoxetine	384	No differences in age groups	Fair
Schone et al., 1993[32]	Fluoxetine vs. Paroxetine	108	Faster onset of paroxetine	Fair
Newhouse et al., 2000[37]	Fluoxetine vs. Sertraline	236	No differences	Fair
Kroenke et al., 2001[19]	Fluoxetine vs. Sertraline vs. Paroxetine	601	No differences	Fair
Rapaport et al., 2003[217]	Paroxetine vs. Placebo	323	Significantly more responders and remitters for paroxetine IR and paroxetine CR than for placebo	Fair
Williams et al., 2000[91]	Paroxetine vs. Placebo	415	No differences	Fair
Wagner et al., 2003[100]	Sertraline vs. Placebo	376	Significantly greater efficacy for sertraline	Fair
Schatzberg et al.., 2002[48]	Mirtazapine vs. Paroxetine	255	Faster onset of mirtazapine	Fair
Allard et al. 2004[51]	Venlafaxine vs. citalopram	151	No differences	Fair
Thase et al. 2005[214]	Pooled data analysis of venlafaxine and SSRIs	2045	Among women, poorer response to SSRI in the older age group	Fair
Weihs et al., 2000[70] Doraiswamy et al., 2001[71]	Bupropion SR vs. Paroxetine	100	No differences	Fair
Entsuah et al., 2001[219]	Meta-analysis	2,045	No significant interaction between age and treatment	Fair
Whittington et al., 2004[96]	Meta-analysis	2,145	Only fluoxetine had favorable risk-benefit profile	Fair
Ethnicity				
Roy-Byrne et al., 2005[220]	Pooled analysis of paroxetine vs. placebo	14,875	Slightly lower response rates for Hispanics and Asians than for Blacks and Whites	Fair
Wagner et al., 1998[221]	Fluoxetine vs. 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[222]	Pooled data analysis of sertraline vs. placebo	673	Better response of female patients on some outcome measures	Fair
Entsuah et al., 2001[219]	Meta-analysis	2,045	No significant interaction between sex and treatment	Fair

Table 20 (continued)

Comorbidities				
Linden et al., 1994[227]	Fluoxetine vs. Paroxetine	89	No difference in GI-side effects in somatizing patients	Fair
Cornelius et al., 1997, 1998, 2000[228-230]	Fluoxetine vs. Placebo	51	Significantly greater efficacy for fluoxetine in depressed alcoholics	Fair
Rabkin et al, 1999[232]	Fluoxetine vs. Placebo	120	No difference in depressed HIV/AIDS patients	Fair
Razavi et al, 1996[233]	Fluoxetine vs. Placebo	91	No difference in depressed cancer patients	Fair
Roscoe et al. 2005[235]	Paroxetine vs. Placebo	94	Greater efficacy for paroxetine in depressed patients with breast cancer	Poor
Petrakis et al., 1998[234]	Fluoxetine vs. Placebo	44	No difference in depressed opioid addicts	Fair
Krishnan et al., 2001[236]	Sertraline vs. Placebo	220	Vascular comorbidity not associated with more adverse events and premature discontinuation	Fair

Exhibit 1. Meta-Analysis- Relative Risk of response rates Citalopram - Escitalopram

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Burke et al., 2002[21]	491	40.1	65%	8 weeks	MADRS
Colonna et al., 2005[22]	357	46	75%	8 weeks	MADRS
Lepola et al., 2003[20]	471	43	72.1%	8 weeks	MADRS
Moore et al., 2005[23]	280	45.2	76.9%	8 weeks	MADRS

Exhibit 2. Meta-analysis- Effect size on the MADRS Citalopram - Escitalopram

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Burke et al., 2002[21]	491	40.1	65%	8 weeks	MADRS
Colonna et al., 2005[22]	357	46	75%	8 weeks	MADRS
Lepola et al., 2003[20]	471	43	72.1%	8 weeks	MADRS
Moore et al., 2005[23]	280	45.2	76.9%	8 weeks	MADRS

Exhibit 3*:* Meta-analysis- Fluoxetine -Paroxetine

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Chouinard et al., 1999[30]	203	40.9	61%	12 weeks	HAM-D
De Wilde et al.,1993[31]	78	44.0	61%	6 weeks	HAM-D
Fava et al., 1998[33]	128	41.3	51%	10-16 weeks	HAM-D
Fava et al., 2002[34]	188	42.0	65%	10-16 weeks	HAM-D
Gagiano 1993[14]	90	38.7	80%	6 weeks	HAM-D
Schöne et al., 1993[32]	108	74.0	87%	6 weeks	HAM-D

Characteristics of excluded studies

	Sample size	Mean Age	Women	Duration	Scale	Reason for exclusion
Cassano et al. 2002[29]	242	75.3	55%	52 weeks	HAM-D	Missing data

Exhibit 4: Meta-analysis- Fluoxetine - Sertraline

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Bennie et al., 1999[35]	286	49.9	61%	6 weeks	HAM-D
Boyer et al., 1998[36, 38]	242	43.4	78%	26 weeks	MADRS
Fava et al., 2002[34]	188	42.0	65%	10-16 weeks	HAM-D
Newhouse et al., 2000[37]	236	67.5	57%	12 weeks	HAM-D
Sechter et al., 1999[18]	238	42.8	67%	24 weeks	HAM-D

Characteristics of excluded studies

	Sample size	Mean Age	Women	Duration	Scale	Reason for exclusion
Kroenke et al., 2001[19]	601	46.1	74%	9 months	SF-36	Different outcome measure

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

Estimates with 95% confidence intervals:

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

NNT [risk difference] (rounded up) = 17

Exhibit 5: Meta-analysis- of Venlafaxine - Fluoxetine

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Alves et al., 1999[59]	87	43.8	92%	12 weeks	HAM-D
De Nayer et al., 2002[55]	146	42.7	68%	12 weeks	MADRS
Dierick et al., 1996[60]	314	43.4	64%	8 weeks	HAM-D
Rudolph et al., 1999[56]	301	40	69%	8 weeks	HAM-D
Silverstone et al., 1999[57]	378	41.9	60%	12 weeks	HAM-D
Tylee et al., 1997[61]	341	44.5	71%	12 weeks	HAM-D

Characteristics of excluded studies

	Sample size	Mean Age	Women	Duration	Scale	Reason for exclusion
Costa e Silva et al., 1998[54]	382	40.1	53%	8 weeks	HAM-D	Missing data

Number needed to treat (empirical results using observed counts only)
Estimates with 95% confidence intervals:
Odds ratio of event in treated cf. controls = 1.129828 (0.901642 to 1.415737)
Relative risk reduction (controls-treated) = -0.055055 (-0.162471 to 0.041808)
Risk difference (controls-treated) = -0.030054 (-0.083946 to 0.023975)
NNT [risk difference] (rounded up) = 34

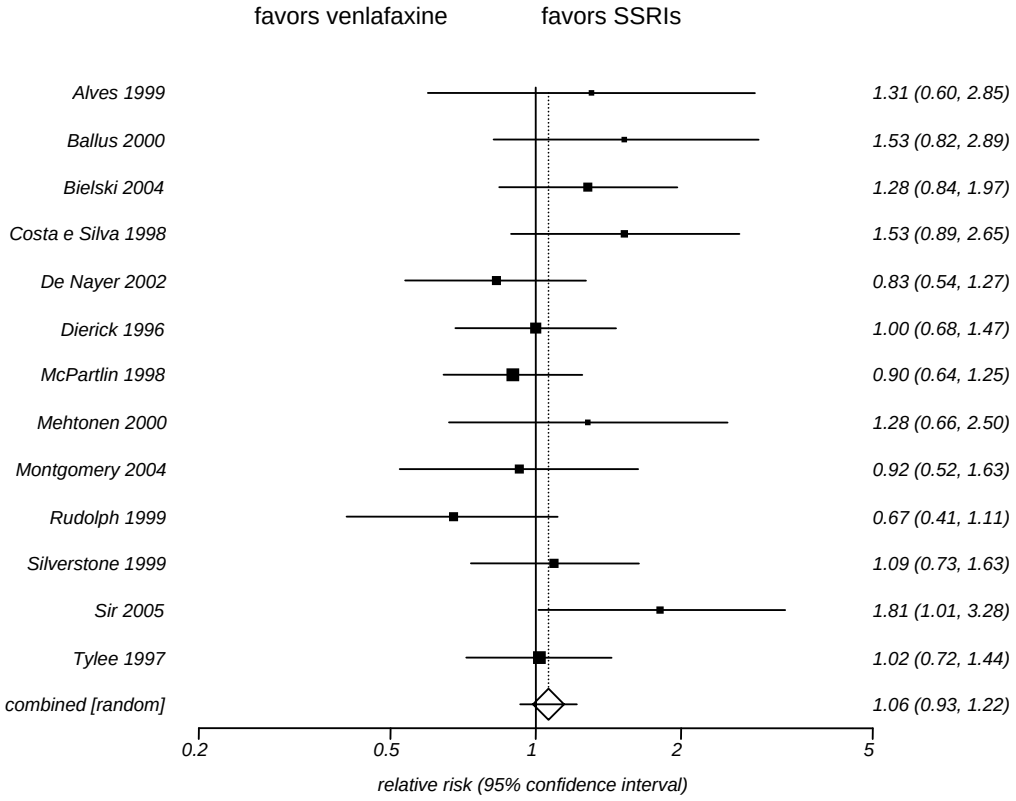
Exhibit 6: Meta-analysis- Discontinuation rates

Reasons for treatment discontinuation and overall loss to follow-up of venlafaxine compared to SSRIs

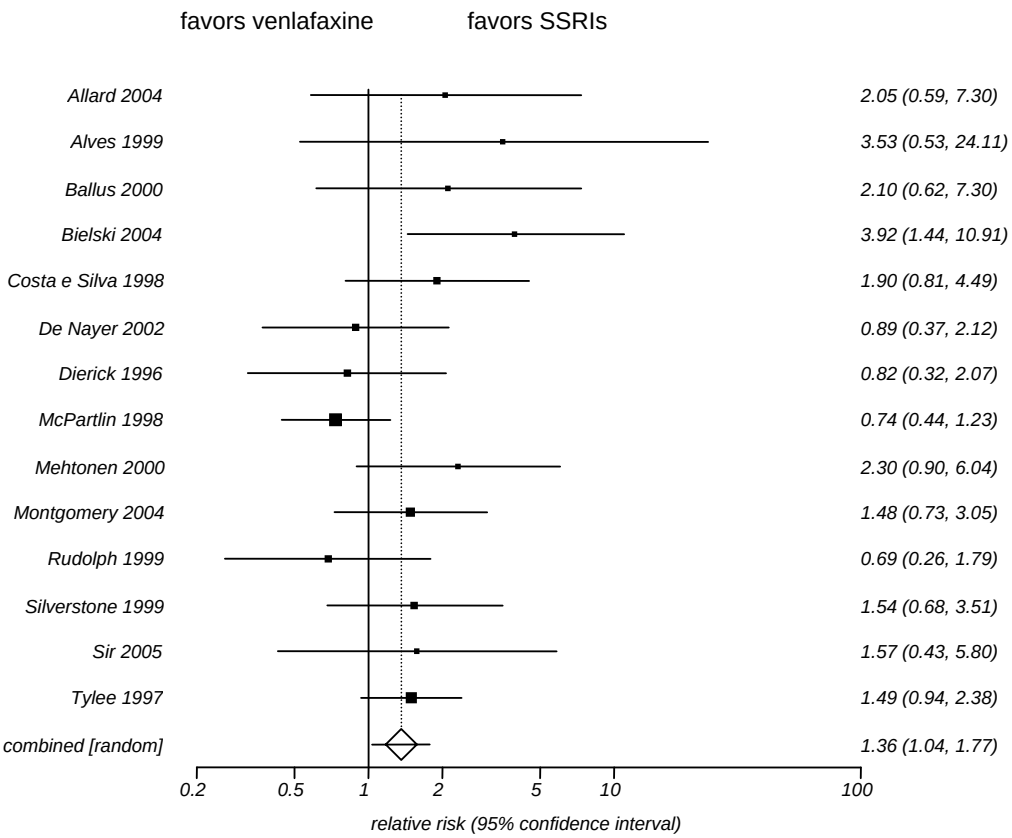
Reason (%)	Venlafaxine (n= 1489)	SSRIs (n=1479)	p*
Overall loss to follow-up	362(24.3)	337 (22.8)	0.599
Adverse events	171 (11.4)	125(8.5)	0.011
Lack of efficacy	45 (3.5)[1]	73 (5.6)[2]	0.011

* Fisher's exact test; two-sided mid p-value
[1] based on available data (45/1305)
[2] based on available data (73/1302)

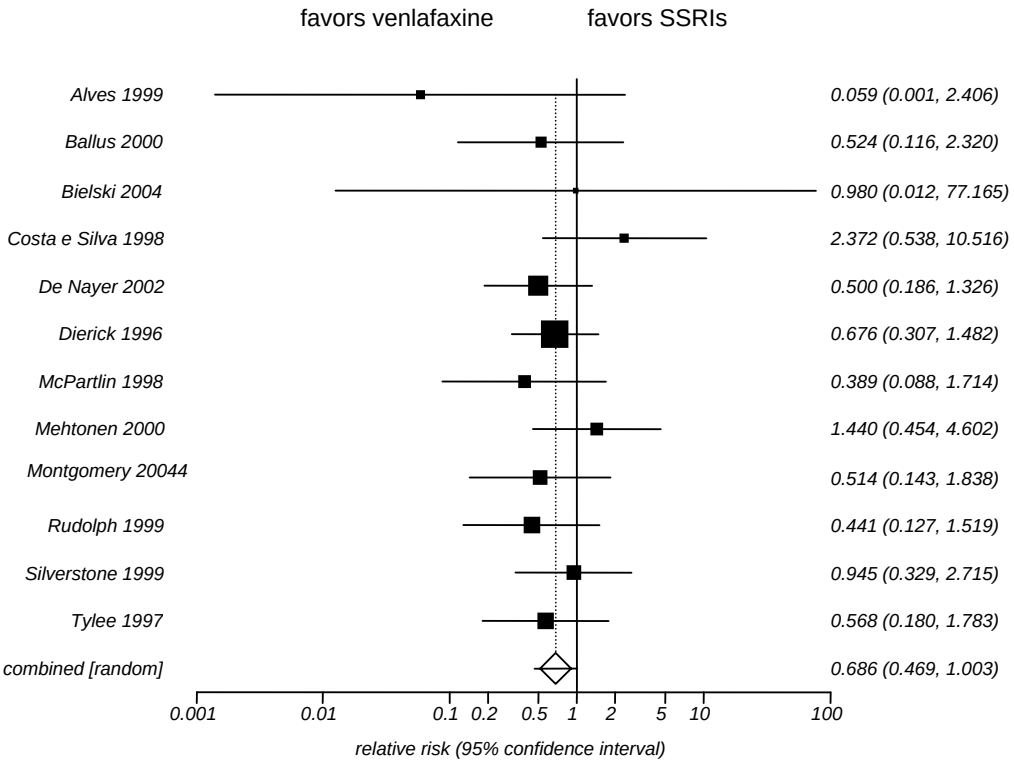
Relative risk meta-analysis of overall loss to follow-up comparing SSRIs to venlafaxine (random effects)



Relative risk meta-analysis of discontinuation rates due to adverse events comparing SSRIs to venlafaxine (random effects)



Relative risk meta-analysis of discontinuation rates due to lack of efficacy comparing SSRIs to venlafaxine (random effects)

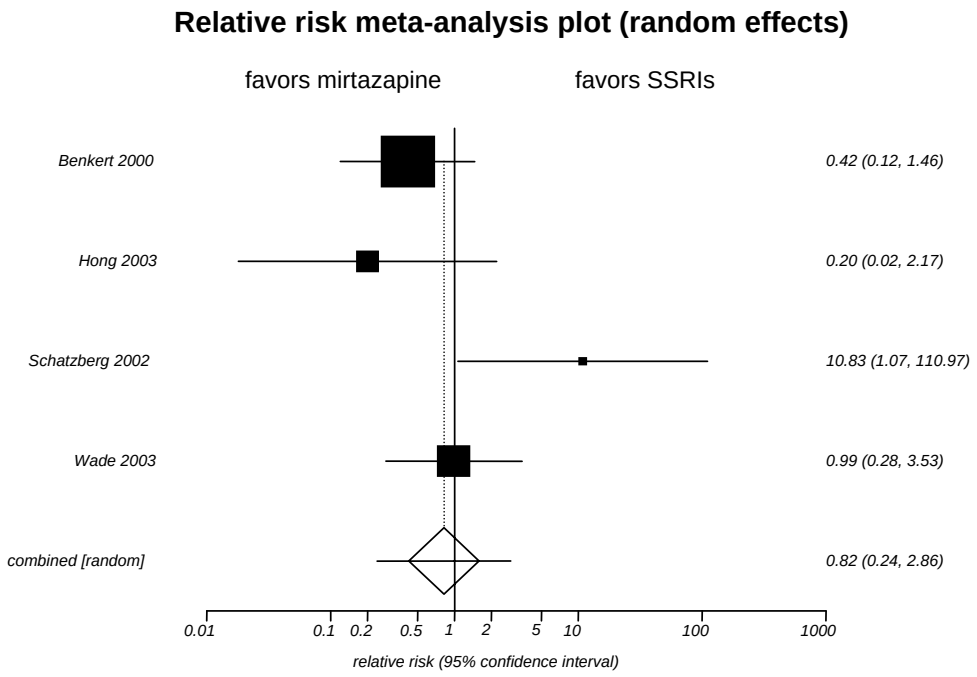


Reasons for treatment discontinuation and overall loss to follow-up of mirtazapine compared to SSRIs

Reason (%)	Mirtazapine (n= 608)	SSRIs (n=596)	p*
Overall loss to follow-up	182 (29.0)	185 (21.0)	0.677
Adverse events	86 (14.1)	80 (13.4)	0.718
Lack of efficacy	12 (2.0)	13 (2.2)	0.185

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

Relative risk meta-analysis of overall loss to follow-up comparing SSRIs to mirtazapine



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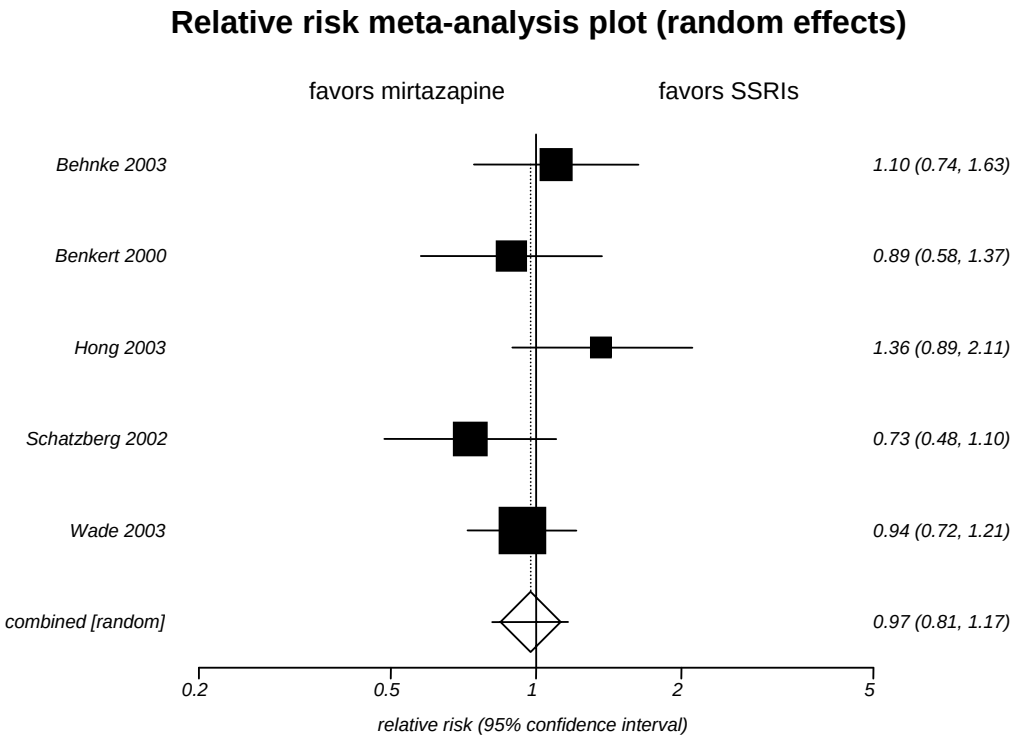
Relative risk meta-analysis of discontinuation rates due to lack of efficacy comparing SSRIs to mirtazapine

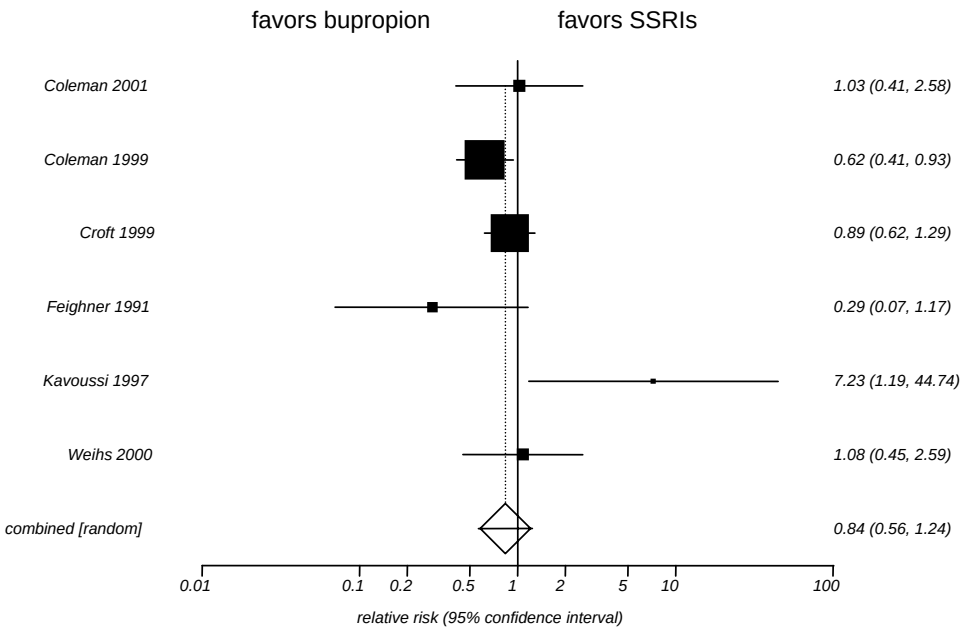


Reasons for treatment discontinuation and overall loss to follow-up of bupropion compared to SSRIs

Reason (%)	Bupropion (n= 623)	SSRIs (n=631)	p*
Overall loss to follow-up	88 (14.1)	106 (16.8)	0.192
Adverse events	42 (6.7)	42 (6.7)	0.952
Lack of efficacy	18 (3.1)	24 (4.1)	0.379

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

Relative risk meta-analysis of overall loss to follow-up comparing SSRIs to bupropion



Relative risk meta-analysis of discontinuation due to lack of efficacy comparing SSRIs to bupropion

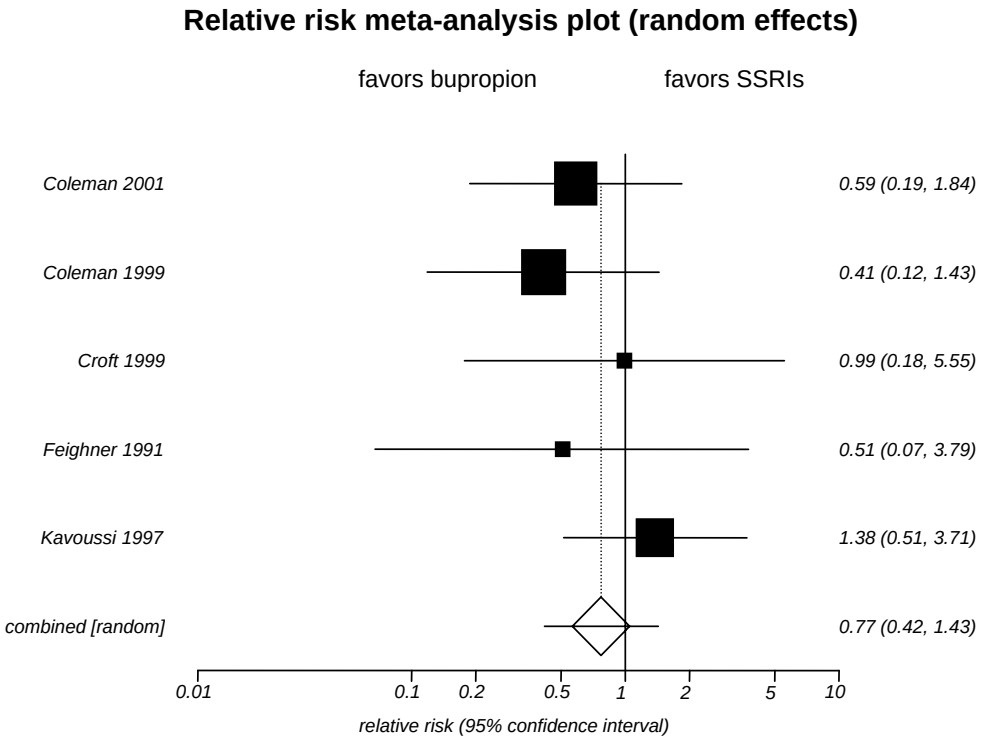
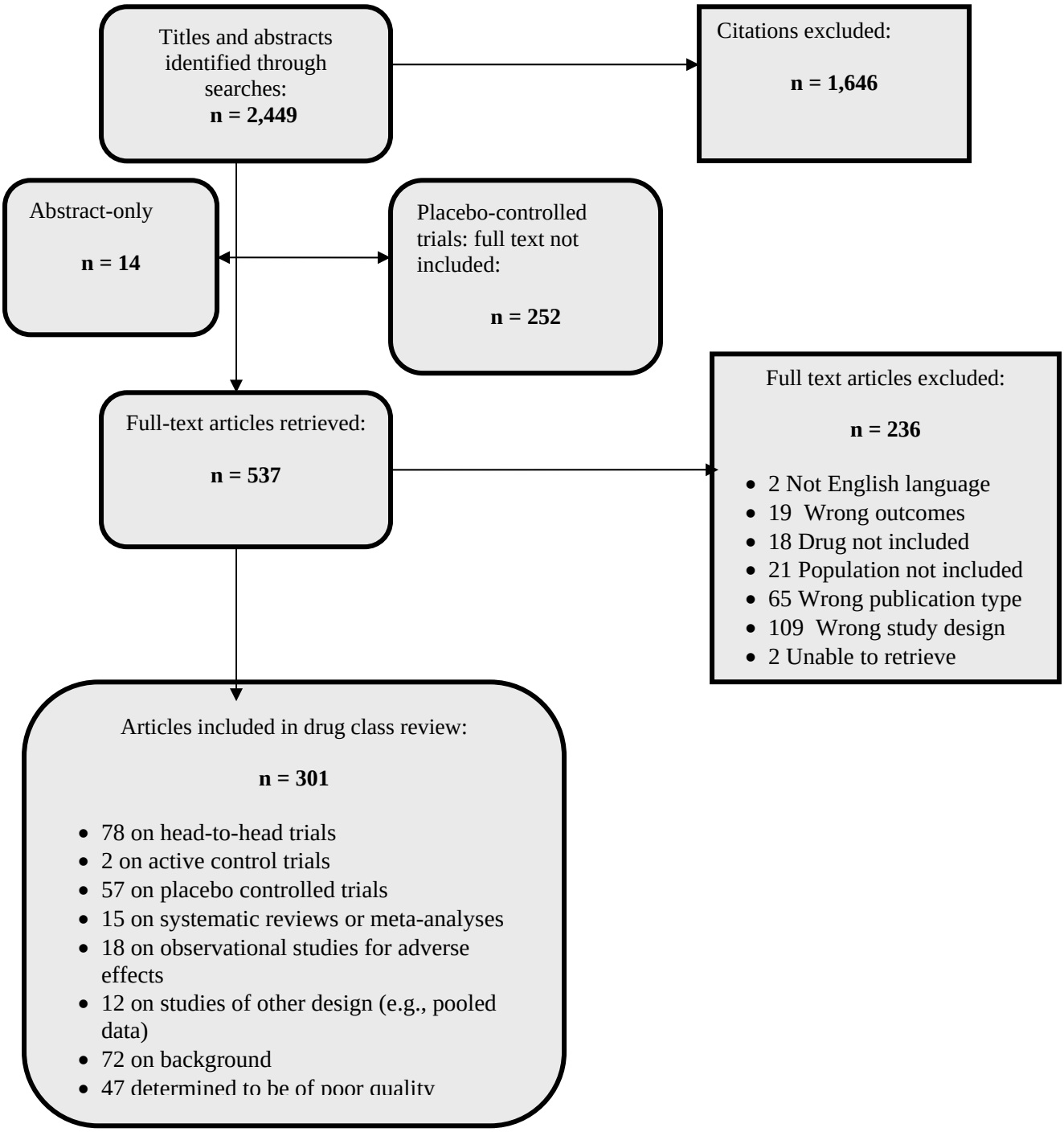


Figure 1: Results of Literature Search



EVIDENCE TABLES

Evidence Table 1: Major Depressive Disorder Adults

STUDY:	***Authors:*** **Aberg-Wistedt A, et al.**[41] ***Year:*** **2000** ***Country:*** Sweden			
FUNDING:	Pfizer, Inc.			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 353			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-150 mg/d 24 weeks	Paroxetine 20-40 mg/d 24 weeks		
INCLUSION:	Age 18 and over; met DSM-III-R criteria for MDD; MADRS score of $\geq$ 21 at baseline with less than 25% improvement during washout			
EXCLUSION:	Negative pregnancy test and stable use of oral contraceptive for 3 months; current or past history of mania; hypomania; alcoholism; substance abuse; dementia; epilepsy; presence of psychotic depression or organic affective illness; history of suicide attempts or high risk; current use of psychotropic meds; treatment with lithium or MAOI in the month prior to screening; history of intolerance or allergic reaction to either study drug; clinically evidence of hepatic or renal disease or other acute or unstable medical condition; use of any meds that would interfere with safe conduct of the study			
OTHER MEDICATIONS/ INTERVENTIONS:	Nitrazepam, oxazepam, flunitrazepam			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 43 ***Gender*** (% Female): 67.4% ***Ethnicity:*** Not reported ***Other population characteristics:*** 8% over 65 years, 53% less than 45 years, 33% married or live with significant other			

Authors: **Aberg-Wistedt A, et al.** ***Year:*** **2000** ***Country:*** Sweden	
OUTCOME ASSESSMENT:	***Measures:*** MADRS, CGI-S, Secondary Battelle Quality of Life Measure (BQOL), SCID-II before and after treatment ***Timing of assessments:*** Primary measures at baseline and weeks 1, 2, 3, 4, 6, 8, 12,16, 20 and 24
RESULTS:	• Response-LOCF at 24 weeks: sertraline: 72%, paroxetine 69% • Response-Observed Cases at 24 weeks: sertraline 89%, paroxetine 89% • No significant difference at endpoint or at any other study point measures • No significant difference in CGI severity change score or improvement score • Relapse during weeks 9-24: paroxetine 8.6%, sertraline 1.9% (no p value reported) • No significant differences on QOL measures
ANALYSIS:	***ITT:*** LOCF ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 35.4%; sertraline 36.4%, paroxetine 34.5% ***Withdrawals due to adverse events:*** Not reported ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Diarrhea: sertraline 35.2%, paroxetine 15.2% ($p < 0.01$) • Constipation: sertraline 5.7%, paroxetine 16.4% ($p < 0.01$) • Fatigue: sertraline 21.0%, paroxetine 45.8% ($p < 0.01$) • Decreased libido female: sertraline 1.8%, paroxetine 8.8% ($p < 0.05$) • Micturition problems: sertraline 0.6%, paroxetine 6.2% ($p < 0.05$)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder

STUDY:	**Authors: Allard P, et al.**[51] **Year: 2004** **Country:** Sweden and Denmark		
FUNDING:	Wyeth		
DESIGN:	**Study design:** RCT **Setting:** 12 centers **Sample size:** 151		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Venlafaxine ER 37.5-150 mg/day 6 months 73	Citalopram 10-30 mg/day 6 months 75	
INCLUSION:	Male or female outpatients 65 years or older; DSM-IV for major depression; MADRS greater than 20 with less than a 20% decrease from pre-study to baseline visits (one week)		
EXCLUSION:	Cognitive impairment; alcohol or drug abuse; psychotic disorder not associated with depression; psychiatric inpatient treatment within the last year; acute suicidal tendencies; anti-psychotic drug, ECT or sumatriptan within last 30 days; bipolar, clinically evident or diagnosed dementia; mental disorders due to medical conditions; history of seizure, significant CVD, cerebrovascular disorder or uncontrolled hypertension		
OTHER MEDICATIONS/ INTERVENTIONS:	Zopiclone 7.5 mg/day or less; zolpidem 5 mg/day or less for sleep; medications for the treatment of somatic disorders provided they were not expected to associated with significant toxicity		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Mean age:** venlafaxine: 73.6, citalopram: 72.5 **Gender (% female):** venlafaxine: 73.6%, citalopram 72.7% **Ethnicity:** NR **Other population characteristics:** Baseline MDRS: venlafaxine: 27.6, citalopram: 27.0		

<table>
<tr><td colspan="4">Authors: Allard P, et al.
Year: 2004
Country: Sweden and Denmark</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: MADRS at 8 weeks

Secondary Outcome Measures: MADRS responders and remitters, time to sustained response using MADRS and CGI-I; CGI-S and GDS-20 scores at weeks 8 and 22

Timing of assessments: Pre-study, baseline and weeks 2,4,6,8,16,22,24</td></tr>
<tr><td>RESULTS:</td><td colspan="3">• No statistical differences between groups in MADRS, CGI-S, CGI-I, and GDS-20 were observed
• At week 22 both groups had a 93% response rate
• MADRS remission rate was 19% for venlafaxine and 23% for citalopram</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions: Yes (3)</td></tr>
<tr><td>ATTRITION:
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:
Loss to follow-up differential high:</td><td>Overall
22.2%
6%</td><td>Venlafaxine

(6) 8%</td><td>Citalopram

(3) 4%</td></tr>
<tr><td>ADVERSE EVENTS:</td><td colspan="3">• Spontaneously reported adverse events venlafaxine: 62%, citalopram: 43%
• Tremor more common during citalopram; nausea/vomiting during venlafaxine treatment</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Alves C, et al.**[59] ***Year:*** **1999** ***Country:*** Portugal			
FUNDING:	Wyeth-Ayerst International			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (3 centers) ***Sample size:*** 87			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine 75-150 mg/day 12 weeks	Fluoxetine 20-40 mg/day 12 weeks		Doses could be increased from day 15 if needed
INCLUSION:	18-65 yrs; DSM-IV criteria for major depression; ≥ 20 on HAM-D-21			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; history of seizures, mental or neurological disorders; alcohol or substance abuse; existing suicidal risk; use of study drugs, sumatriptan, or antipsychotic drugs within 30 days; fluoxetine within 21 days; anxiolytic or sedative within 7 days; stable dose of 3 months for drugs with psychotropic effects like b-blockers; clinically relevant medical disease; known sensitivity to venlafaxine or fluoxetine			
OTHER MEDICATIONS/ INTERVENTIONS:	Diazepam			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** venlafaxine: 45.4, fluoxetine: 42.3 ***Gender*** (% female): venlafaxine: 92.5%, fluoxetine: 91.5% ***Ethnicity:*** Not reported ***Other population characteristics:*** CGI diagnosis: • Moderately ill: venlafaxine: 45%, fluoxetine: 50%. • Markedly ill: venlafaxine: 33%, fluoxetine: 38%. • Severely ill: venlafaxine: 15%, fluoxetine: 6%. • Previous antidepressant treatment: venlafaxine: 45%, fluoxetine: 55%			

Authors: **Alves C, et al.** ***Year:*** **1999** ***Country:*** Portugal	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D, MADRS, CGI ***Timing of assessments:*** Baseline, days 7, 14, 21, 28, 42, 56, 70, 84
RESULTS:	• There were no significant differences between study groups in any outcome measures at endpoint • Venlafaxine showed a faster onset with significant differences in various outcome measures during weeks 1 to 4: mean decreases of HAM-D and MADRS scores were significantly greater with venlafaxine ($p < 0.05$) during weeks 1-4 • Suicide ideation scores at week 6 were significantly lower for venlafaxine on MADRS and HAM-D scales • Remission (HAM-D < 8) at week 3 was found in 30% of venlafaxine treated patients and 11% of fluoxetine treated patients ($p = 0.03$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 21.8% ; venlafaxine: 25%, fluoxetine: 19% ***Withdrawals due to adverse events:*** venlafaxine: 7%, fluoxetine: 2% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• There were no significant differences between study groups in the frequency of adverse events • At least one adverse event was recorded in 56% of the venlafaxine group and 51% of the fluoxetine group • Nausea was the most common adverse event: venlafaxine: 33.3%, fluoxetine: 27.7% • No clinically significant changes in laboratory parameters, body weight, heart rate, or blood pressure were recorded in either treatment group
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Baldwin DS, et al.**[78, 79] ***Year:*** **1996, 2001** (continuation phase) ***Country:*** UK, Ireland			
FUNDING:	Bristol Myers Squibb			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center, 20 psychiatric outpatient clinics ***Sample size:*** 206			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Nefazodone 200-600 mg/d Mean dose: 472.0 mg 8 weeks, twice a day	Paroxetine 20-40 mg/d Mean dose: 32.7 mg 8 weeks, twice a day		Continuation Phase: from week 8 to month 6 dose was gradually reduced wherever possible
INCLUSION:	18 years or older; non-psychotic depression; HAM-D score of ≥ 18; moderately ill on CGI-S scale Continuation Phase: patients who responded to treatment during the 8 weeks acute treatment phase			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; history of psychotic disorders; alcohol or substance abuse; existing suicidal risk; electroconvulsive therapy within last 6 months; previously failed to respond to at least 2 antidepressant therapies; clinically relevant progressive disease; hypersensitivity to study medication			
OTHER MEDICATIONS/ INTERVENTIONS:	Benzodiazepines, antipyretics, analgesics, supportive psychological treatment			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 38; Continuation phase mean age: 38.8 ***Gender:*** (female %) nefazodone: 60%, paroxetine: 50%. Continuation phase: nefazadone: 51%, paroxetine: 55% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Baldwin DS, et al.** ***Year:*** **1996, 2001** ***Country:*** UK, Ireland	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** HAM-D, CGI-S, CGI-I, Patient's Global Assessment: Baseline, weeks 1, 2, 3, 4, 6, 8, HAM-A: weeks 2 and 8, MADRS: weeks 4 and 8 *Continuation Phase*: weeks 12, 16, 20, and 24
RESULTS:	• Both groups showed significant improvements from baseline HAM-D, HAM-A, and MADRS scores • There were no significant differences between the treatment groups • The proportion of CGI responders was also similar between treatment groups *Continuation Phase:* • No statistically significant differences between study groups regarding efficacy • Clinical improvement either maintained or improved in continuation phase
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 27.2 %; nefazodone: 26.7%, paroxetine: 27.7%. *Continuation Phase:* 32.4 %; nefazodone: 33%, paroxetine: 32.7% ***Withdrawals due to adverse events:*** 13.5%; nefazodone: 14%, paroxetine: 13%. *Continuation Phase:* nefazodone: 7%, paroxetine: 8% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• 84% of nefazodone treated patients and 78% of paroxetine treated patients reported side effects • Frequencies among adverse events were similar except a higher frequency of somnolence in the paroxetine group (24% vs. 16%) and higher frequencies of headache (35% vs. 25%) and dizziness (17% vs. 9%) in the nefazodone group *Continuation Phase:* 75% of nefazodone treated patients and 81% of paroxetine treated patients reported side effects • Most common adverse events in paroxetine group were nausea (34% vs. 16% in nefazodone group) and somnolence (27% vs. 20%) • Most common adverse event in nefazodone group was headache (31% vs. 28% in paroxetine group)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Ballus C, et al.**[63] ***Year:*** **2000** ***Country:*** Spain			
FUNDING:	Not reported (several authors have affiliations with Wyeth)			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 84			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine 75-150 mg/day 24 weeks	Paroxetine 20-40 mg/day 24 weeks		Initial dose of each drug could be increased after 4 weeks
INCLUSION:	Age 18-70 years; ICD-10 criteria for mild to moderate depression or dysthymia; minimum score of 17 on the 21 item HAM-D; less than a 20% decrease in HAM-D score between screening and baseline			
EXCLUSION:	Sensitivity to either study drug; history of significant illness; pregnant or breastfeeding; suicidal tendencies; psychotic disorder not associated with depression; drug or alcohol dependence; use of investigational drugs or treatments shortly before the study			
OTHER MEDICATIONS/ INTERVENTIONS:	Yes			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** venlafaxine: 44, paroxetine: 45.1 ***Gender*** (% female): venlafaxine: 88%, paroxetine: 88% ***Ethnicity:*** Not reported ***Other population characteristics:*** Both groups have similar clinical characteristics; mild to moderate depression; dysthymia diagnosis not differentiated			

Authors: **Ballus C, et al.** ***Year:*** **2000** ***Country:*** Spain	
OUTCOME ASSESSMENT:	***Measures:*** 21 item HAM-D, MADRS, CGI scale ***Timing of assessments:*** Baseline, weeks 1, 2, 4, 6, 8, 12, 16, 24
RESULTS:	• No significant differences between groups on the HAM-D, MADRS, or CGI scales at 24 weeks or endpoint • At week 12 the percent of patients with a HAM-D score $\leq$ 8 was significantly greater in the venlafaxine group than the paroxetine group (57% vs. 33%; p = .011) • More patients exhibited a drug response ($\geq$ 50% decrease in HAM-D) on venlafaxine than paroxetine at week 6 (p = 0.03)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 32%, venlafaxine: 39%, paroxetine: 26% ***Withdrawals due to adverse events:*** 11%, venlafaxine: 15%, paroxetine: 8% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Venlafaxine: nausea: 28%, headache: 18%, dry mouth: 15% • Paroxetine: headache: 40%, constipation: 16%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Behnke K, et al.**[50] ***Year:*** **2003** ***Country:*** Multinational			
FUNDING:	Organon NV			
DESIGN:	***Study design:*** RCT ***Setting:***, Multi-center ***Sample size:*** 346			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Sertraline 50-150 mg/day 8 weeks	 Mirtazapine 30-45 mg/day 8 weeks		
INCLUSION:	DSM IV criteria for major depression; HAM-D score ≥ 18; age 18-70 yrs			
EXCLUSION:	Other psychiatric disorders; epilepsy or history of seizures; pregnancy, lactation, childbearing potential; substance abuse; chronic and unstable physical disease; current episode ≥ 12 months or 2 ≤ weeks; lack of response to at least 2 prior antidepressant therapies; previous hypersensitivity; use of sildinafil			
OTHER MEDICATIONS/ INTERVENTIONS:	Oxazepam, temazepan, zolpidem, zopiclone			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 41.5 yrs; mirtazapine 42, sertraline: 41 ***Gender*** (% female): sertraline: 61.5%, mirtazapine: 55.7 % ***Ethnicity:*** Not reported ***Other population characteristics:*** Previous episodes of major depression: sertraline: 69.8%, mirtazapine: 73.3 %			

Authors: **Behnke K, et al.** ***Year:*** **2003** ***Country:*** Multinational	
OUTCOME ASSESSMENT:	***Measures and timing of assessment:*** HAM-D, MADRS, CGI at baseline, and days 4, 7, 10, 14, 28, 42, 56 or on premature withdrawal, changes in sexual function questionnaire at baseline and biweekly thereafter
RESULTS:	• Onset of action was faster in the mirtazapine group • At all assessments during the first two weeks the mean change of HAM-D from baseline was significantly greater in the mirtazapine group than in the sertraline group ($p < 0.05$) • After week 2 the difference remained greater with mirtazapine but lacked statistical significance • Reduction in sleep disturbance was significantly greater in the mirtazapine group at all assessments ($p \leq 0.01$) • CGI scores did not show significant differences throughout the study • Changes in sexual function scores did not show significant differences although the mirtazapine group showed greater improvements
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 20.8%; sertraline: 18%, mirtazapine: 23% ***Withdrawals due to adverse events:*** mirtazapine: 11.9%, sertraline: 3% ***Loss to follow-up differential high:*** Loss to follow up: 20.8%, sertraline: 23%, mirtazapine: 18%
ADVERSE EVENTS:	• Percentage of patients reporting at least one adverse event was similar in both groups (mirtazapine: 64%, sertraline: 68%) • A significantly higher number of patients withdrew from the mirtazapine group (21 vs. 5 in sertraline group; p = NR) • Significantly more patients reported nausea (38 vs. 13; $p < 0.01$), libido decrease (10 vs. 2; $p < 0.01$) and diarrhea (16 vs. 7; $p < 0.01$) in the sertraline-treated group • Somnolence was significantly higher in the mirtazapine group (35 vs. 13; $p < 0.01$) • Weight increase higher in the mirtazapine group (16 vs. 3; p = 0.01)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Benkert O, et al.**[49] ***Year:*** **2000** ***Country:*** Germany			
FUNDING:	Organon, GmBH, Munich, Germany			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (50 centers) ***Sample size:*** 275			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Mirtazapine 15-45 mg/d 6 weeks	Paroxetine 20-40 mg/d 6 weeks		
INCLUSION:	18-70 years of age; DSM-IV criteria for major depression; ≥ 18 on HAM-D-17			
EXCLUSION:	Depressive episode longer than 12 months; other psychiatric or psychotic disorder; alcohol or substance abuse; suicidal risk; significant physical illness; non-responders to antidepressants; recent medication with similar drugs; pregnancy			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** mirtazapine: 47.2, paroxetine: 47.3 ***Gender*** (% female): mirtazapine: 63%, paroxetine: 65% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Benkert O, et al.** ***Year:*** **2000** ***Country:*** Germany	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-17, HAM-A, CGI-S, CGI-I, BDI-II, Welzel-Kohnen Colored Scales, Short Form 36 ***Timing of assessments:*** Screening, baseline, weeks 1, 2, 3, 4, 6
RESULTS:	• Mirtazapine and paroxetine were equally effective in reducing mean HAM-D-17 score (58.3% vs. 53.7%) • Significantly more mirtazapine patients responded at weeks 1 & 4 on the HAM-D-17 than paroxetine patients; week 1 response: mirtazapine: 23.2%, paroxetine: 8.9% ($p < 0.002$).
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 23%; mirtazapine: 21.6%, paroxetine: 24.2% ***Withdrawals due to adverse events:*** 8%; mirtazapine: 8.6%, paroxetine: 7.4% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Significantly more mirtazapine patients experienced weight increase ($p < 0.05$) • At least one adverse event reported: mirtazapine: 68.1%, paroxetine: 63.4% • Dry mouth: mirtazapine: 14.1%, paroxetine: 8.2% • Headache: mirtazapine: 9.6%, paroxetine: 10.4% • Nausea: mirtazapine: 4.4%, paroxetine: 11.2% • Flu like symptoms: mirtazapine: 9.6%, paroxetine: 3.7% • Differences all $p < 0.1$
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Bennie EH, et al.**[35] ***Year:*** **1995** ***Country:*** UK			
FUNDING:	Pfizer			
DESIGN: Multi-center, UK (20 centers)	***Study design:*** RCT ***Setting:*** Multi-center (20 centers) ***Sample size:*** 286			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-100 mg/d 6 weeks	Fluoxetine 20-40 mg/d 6 weeks		
INCLUSION:	18 yrs or older; DSM-III-R criteria for major depression; ≥ 18 on HAM-D-17; higher score on the Raskin scale than on the Covi anxiety scale			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; previous treatment with sertraline or fluoxetine; history of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; previously failed to respond to antidepressant therapy; clinically relevant progressive disease; hypersensitivity to study drug class			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate (500-1000 mg), temazepam (10-20 mg)			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 49.9, fluoxetine: 49.9 ***Gender*** (% female): sertraline: 57.7%, fluoxetine: 64.6% ***Ethnicity:*** Not reported ***Other population characteristics:*** Recurrent episode: sertraline: 53.5%, fluoxetine53.5%; duration of current episode: sertraline: 5.4 mo., fluoxetine: 5.2 mo.			

Authors: **Bennie, et al.** ***Year:*** **1995** ***Country:*** UK	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D, HAM-A, CGI-I, CGI-S, Covi Anxiety Scale, Raskin Depression Scale, Leeds Sleep Questionnaire ***Timing of assessments:*** Baseline, weeks 1, 2, 4, 6
RESULTS:	• There were no significant differences between treatment groups in any of the outcome measures at any point in time (changes in HAM-D, HAM-A, CGI, Raskin, Covi scales) • Both groups showed significant improvements from baseline • Response rate (≥ 50% improvement on HAM-D): sertraline: 59%, fluoxetine: 51% • Both treatment groups showed significant improvement in the Leeds Sleep Questionnaire
ANALYSIS:	***ITT:*** No ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 13.3% ***Withdrawals due to adverse events:*** sertraline: 14%, fluoxetine: 13% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• No significant difference between treatment groups in the occurrence of adverse events • Incidence of adverse events: sertraline: 56%, fluoxetine: 60% • Most common adverse events: nausea: sertraline: 21%, fluoxetine: 25%; headache: sertraline: 14.1%, fluoxetine: 14.6%; agitation: sertraline: 4.9%, fluoxetine: 5.6% • 3 patients in each treatment group experienced severe drug related adverse events
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	**Authors: Bielski RJ, et al.**[53] **Year: 2004** **Country:** US		
FUNDING:	Forest Laboratories		
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (8 sites) ***Sample size:*** 198		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Escitalopram 20 mg/d 8 weeks 98	 Venlafaxine XR 225 mg/d 8 weeks 100	
INCLUSION:	Male and female patients 18 to 65 years of age; met DSM-IV criteria for MDD; minimum score of 20 on the HAM-D-24 at screening and baseline		
EXCLUSION:	Pregnant or lactating women; patients with a primary diagnosis for other Axis I disorder; history of schizophrenia or other psychotic disorder; severe personality disorder; history of substance abuse; suicidal risk; unstable significant medical illness		
OTHER MEDICATIONS/ INTERVENTIONS:	No psychoactive drugs allowed except zolpidem or zaleplon as needed for sleep		
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** No (more women in escitalopram group) ***Mean age:*** Escitalopram: 37.3; venlafaxine: 37.5 ***Gender*** (% female): Escitalopram: 69.4%; venlafaxine 47.0% ***Ethnicity*** (% white): Escitalopram: 77.6 %; venlafaxine: 73.0 % ***Other population characteristics:*** Not reported		

Authors: Bielski RJ, et al. **Year: 2004** **Country:** US	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** MADRS ***Secondary Outcome Measures:*** HAM-D-24; HAM-D somatic subscale; HAM-A; CGI-S; CES-D; Q-LES-Q; CGI-I ***Timing of assessments:*** Evaluations were conducted at baseline and weeks 1,2,4,6, and 8 for the MADRS, HAM-D-24, CGI-I, and CGI-S. Anxiety symptoms were measured at baseline and weeks 2 and 8
RESULTS:	• No significant differences between treatment groups observed in the LOCF analysis for any of the outcome measures • Response rates favored escitalopram (MADRS: 58.8% vs. 48.0%; Ham-D: 61% vs. 48%); no statistical significance was reached • No significant differences in remission rates between escitalopram and venlafaxine XR
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 30% (60); escitalopram: 27% (26); venlafaxine XR: 34% (34) ***Withdrawals due to adverse events:*** 10% (20); escitalopram: 4% (4); venlafaxine XR: 16% (16) ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Significantly more patients in the venlafaxine XR than in the escitalopram group (16% vs. 4%; $p < 0.01$) group withdrew due to adverse events • Significantly more patients in the venlafaxine XR group than in the escitalopram group (24% vs. 6.1%; $p < 0.05$) reported nausea • Significantly more patients had ejaculation disorders in the venlafaxine XR than in the escitalopram group (22.6% vs. 6.7%; $p < 0.05$)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Boyer P, et al.**[38] ***Year:*** **1998** ***Country:*** France			
FUNDING:	At least 1 author is affiliated with Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center, primary care settings (57 general practitioners) ***Sample size:*** 242			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluoxetine 50-150 mg/d 180 days	Sertraline 20-60 mg/d 180 days		Mean daily dose: Fluoxetine -26 mg/d, Sertraline -55 mg/d
INCLUSION:	18-65 yrs; DSM-IV criteria for major depression; ≥ 20 on MADRS			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; concurrent major psychiatric disorders; alcohol or substance abuse; existing suicidal risk; previous course of antidepressant treatment ≤ 3 weeks; clinically severe medical illness; history of allergy to related drugs			
OTHER MEDICATIONS/ INTERVENTIONS:	Allowed medications for medical diseases			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** fluoxetine: 43.7, sertraline: 43.0 ***Gender*** (% female): fluoxetine: 79.1%, sertraline: 77.6% ***Ethnicity:*** Not reported ***Other population characteristics:*** Previous depression: fluoxetine: 38.3 %, sertraline: 34.5%; concomitant medical conditions: fluoxetine: 72%, sertraline: 78%			

Authors: **Boyer P, et al.** ***Year:*** **1998** ***Country:*** UK	
OUTCOME ASSESSMENT:	***Measures:*** MADRS, CGI, FSQ (Functional Status Questionnaire) ***Timing of assessments:*** Baseline, 120, 180 days
RESULTS:	• No significant differences in changes in MADRS, FSQ, CGI-I, and CGI-S scores between treatment groups • No significant differences in response rates (improvement of MADRS ≥ 50%) between the treatment groups • Day 120: fluoxetine: 54.3%, sertraline: 49% • Day 180: fluoxetine: 42.6%, sertraline: 47.4%
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 4.5%; fluoxetine: 4.2%, sertraline: 4.9% ***Withdrawals due to adverse events:*** fluoxetine: 8.6%, sertraline: 7.7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	No significance between group differences in the numbers of patients who experienced adverse events, fluoxetine: 51.3%, sertraline: 57.8%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Burke WJ, et al.**[21] ***Year:*** **2002** ***Country:*** US			
FUNDING:	Forest Pharmaceuticals			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (35 US centers) ***Sample size:*** 491			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** Fixed dose trial (patients in escitalopram 20 mg/d & citalopram group were started at half dose & titrated up to randomized dose.)	Placebo N/A 8 weeks	Escitalopram 10 mg/day 8 weeks	Escitalopram 20 mg/day 8 weeks	Citalopram 40 mg/day 8 weeks
INCLUSION:	Outpatients 18-65 yrs; DSM-IV criteria for major depression; ≥ 22 score on MADRS; ≥ 2 score on item 1 of the HAM-D scale			
EXCLUSION:	DSM-IV Axis I disorder; history of substance abuse; suicide attempt past year; active suicidal ideation; pregnant or lactating women; women childbearing age without contraception; psychotropic medication			
OTHER MEDICATIONS/ INTERVENTIONS:	Zolpedim 3 times/week			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** placebo: 40.1, escitalopram 10 mg: 40.7, escitalopram 20 mg: 39.6, citalopram 40 mg: 40.0 ***Gender*** (% female): placebo: 60, escitalopram 10 mg: 70, escitalopram 20 mg: 68, citalopram 40 mg: 62 ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Burke WJ, et al.** ***Year:*** **2002** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** MADRS, HAM-D, CGI-I, CGI-S at weeks 1, 2, 4, 6, 8, HAM-A, CES-D, QOL ***Timing of assessments:*** Baseline and week 8
RESULTS:	• There were no significant differences in the mean change of MADRS and CGI-S from baseline to endpoint between escitalopram 20 mg and citalopram 40 mg • Escitalopram 10 mg was equally effective as citalopram 40 mg on the majority of outcome measures (MADRS, HAM-D, CGI-I, CGI-S) • No further treatment group comparisons reported • All treatment groups were significantly more efficacious than the placebo group • Observed case analysis was consistent with ITT analysis
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes (6)
ATTRITION:	***Loss to follow-up:*** 24% ***Withdrawals due to adverse events:*** placebo 2.5%, escitalopram 10 mg: 4.2%; escitalopram 20 mg: 10.4%; citalopram 40 mg: 8.8% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Nausea, diarrhea, insomnia, dry mouth ejaculatory disorder occurred in more than 10% of the treatment population • No statistical difference in adverse events between placebo and escitalopram 10 mg • Escitalopram 10 mg and citalopram had significantly higher incidence of nausea than placebo but not different from each other
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Cassano GB, et al.**[29] ***Year:*** **2002** ***Country:*** Italy			
FUNDING:	SmithKline Beecham, Ravizza Farmaceutici			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (38) ***Sample size:*** 242			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20-40 mg/day 1 year	Fluoxetine 20-60 mg/day 1 year		
INCLUSION:	65 yrs or older; ICD-10 criteria for depression; ≥ 18 on HAM-D-17; mini mental state ≥ 22; Raskin score higher than Covi Anxiety score			
EXCLUSION:	History of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; clinically relevant progressive disease; depot neuroleptics within 6 months			
OTHER MEDICATIONS/ INTERVENTIONS:	Treatments for concomitant systemic diseases; short or intermediate half-life benzodiazepines; temazepam for insomnia			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** paroxetine: 75.6, fluoxetine: 74.9 ***Gender*** (% female): paroxetine: 61%, fluoxetine: 50% ***Ethnicity:*** Not reported ***Other population characteristics:*** Duration of present episode was less than 6 months for 60% of patients and more than 1 year for 25%, 40% had already been treated for present episode			

Authors: **Cassano GB, et al.** ***Year:*** **2002** ***Country:*** Italy	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** HAM-D, CGI, Clinical Anxiety Scale at baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52 *Cognitive tests:* Buschke Selective Reminding Test; Blessed Information and Memory Test; Clifton Assessment Schedule; Cancellation Task Test; Wechsler Paired Word Test; MMSE at baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52
RESULTS:	*Cognitive function:* • Both treatment groups showed significant improvements in cognitive performance on all test scales • There were no significant differences between treatment groups and cognitive performance except for the Buschke test at week 3 and 6 where paroxetine showed a significantly greater improvement on a number of tests *Depressive symptoms:* • Both treatment groups significantly improved the HAM-D total scores • Paroxetine showed a greater improvement of HAM-D scores during the first 6 weeks (week 3: $p < 0.05$; week 6: $p < 0.002$), otherwise there were no differences between the treatment groups • A Kaplan Meier analysis evaluating the percentage of responders (HAM-D $\leq$ 10) over time showed a significant difference in favor of paroxetine ($p < 0.03$) • No significant differences on CGI scores
ANALYSIS:	***ITT:*** No ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 39.3%; paroxetine: 40.6%, fluoxetine:37.8% ***Withdrawals due to adverse events:*** 15% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• At least 1 adverse event: paroxetine: 27.6%, fluoxetine: 32.8% • Fluoxetine had significantly more severe adverse events than paroxetine (22 vs. 9; $p < 0.02$)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Chouinard G, et al.**[30] ***Year:*** **1999** ***Country:*** Canada			
FUNDING:	One author is employee of SmithKline Beecham			
DESIGN:	***Study design:*** RCT, double blind ***Setting:*** Multicenter ***Sample size:*** 203			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20-50 mg/d 12 weeks	Fluoxetine 20-80 mg/d 12 weeks		
INCLUSION:	Meeting DSM IIIR criteria for MDD with symptoms for at least 1 month prior to screening; min. score on HAM-D_{21} of 20 and score of "2" on the first item			
EXCLUSION:	Significant coexisting illness including renal, hepatic, GI, neurological, non-stabilized diabetes; other current Axis I disorders; organic brain syndrome; past or present abuse of alcohol or other illicit drugs; significant suicide risk; pregnant or lactating; ECT or continuous lithium therapy in the prior 2 months; MAOI or oral neuroleptics use in prior 21 days; any antidepressant or sedative hypnotic in prior 7 days; fluoxetine in prior 35 days or current therapy with an anticoagulant or type 1C anti-arrhythmic; subjects with clinically significant abnormalities on physical examination, ECG, or lab			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for hypnotic			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 40.9; paroxetine: 40.6, fluoxetine: 41.2 ***Gender*** (% female): paroxetine: 63.7%, fluoxetine: 59.4% ***Ethnicity:*** 96.5% white, 1.5 % Asian ***Other population characteristics:*** 2 or more depressive episodes: paroxetine 76.5%, fluoxetine 59.5%			

Authors: **Chouinard G, et al.** ***Year:*** **1999** ***Country:*** Canada	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D_{21} measured at baseline, weeks 1-6, 8, 10 and 12. Response $\geq$ 50% reduction from baseline, remission score < 10 (HAMD) ***Timing of assessments:*** Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12
RESULTS:	• No statistically significant differences in response rates: (Observed cases at 12 weeks) paroxetine 85.7%, fluoxetine 88.4%; (LOCF endpoint) paroxetine 67.0%, fluoxetine 68.4% • No statistically significant differences in remission rates: (Observed cases at 12 weeks) paroxetine 77.8%, fluoxetine 81.2%, (LOCF endpoint) paroxetine 58.0%, fluoxetine 59.2%
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes (5)
ATTRITION:	***Loss to follow-up:*** 36%; paroxetine: 39.2%, fluoxetine: 32.67% ***Withdrawals due to adverse events:*** Not reported ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	No significant differences between groups
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Coleman CC, et al.**[74] ***Year:*** **1999** ***Country:*** US			
FUNDING:	Glaxo Wellcome			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (9 centers) ***Sample size:*** 364			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/d 8 weeks	Buproprion SR 150-400 mg/d 8 weeks	Placebo N/A 8 weeks	
INCLUSION:	DSM-IV criteria for major depression; minimum score of 18 on the first 21 items of the 31 item HAM-D; ≥18 years of age; be in a stable relationship, have normal sexual functioning, and sexual activity at least once every 2 weeks; currently experiencing recurrent major episode of duration 2-24 months			
EXCLUSION:	Predisposition to seizure or taking med that lowers seizure threshold; history or current diagnosis of an eating disorder; pregnant, lactating or unwilling to take contraceptives; history of alcohol or substance abuse; suicidal tendencies; prior treatment with buproprion or sertraline; used any psychoactive drug within 1 week of study (2 weeks for MAOI or 4 weeks for fluoxetine)			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep (first 2 weeks only)			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 38.3, buproprion SR: 38.1, placebo: 38.5 ***Gender*** (% female): 59%; sertraline: 54%, buproprion SR: 56%, placebo: 59% ***Ethnicity:*** sertraline: white: 92%, black: 8%; buproprion SR: white: 87%, black: 11%, other: 2%; placebo: white: 88%, black: 9%, other: 3% ***Other population characteristics:*** No significant differences at baseline			

Authors: **Coleman CC, et al.** ***Year:*** **1999** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual functioning by investigator questions: sexual desire disorder, sexual arousal disorder, orgasm dysfunction, premature ejaculation, patient rated overall sexual function ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, and 8
RESULTS:	• Mean HAM-D scores in the buproprion SR but not the sertraline group were statistically better than placebo (by day 28 $p < 0.05$) • There was no significant difference between the buproprion SR and sertraline groups • CGI-I and CGI-S for buproprion SR significantly better than placebo but not better than sertraline • Sertraline not statistically better than placebo • No differences in HAM-A; significantly fewer buproprion SR patients had sexual desire disorder than sertraline patients ($p < 0.05$) • There was no significant difference between either active treatment group and placebo • Orgasm dysfunction occurred significantly more in sertraline patients compared with placebo or buproprion SR patients ($p < 0.05$) • Diagnosed with at least one sexual dysfunction: sertraline: 39%, buproprion SR: 13%, placebo: 17%
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 30%; sertraline: 36%, buproprion SR: 22%, placebo: 32% ***Withdrawals due to adverse events:*** 5%; sertraline: 8%, buproprion SR: 6%, placebo: 2% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Headache was the most commonly reported event in all treatment groups • Nausea, diarrhea, dyspepsia occurred more frequently in sertraline patients than buproprion SR or placebo • Insomnia and agitation were reported more frequently in buproprion SR patients than sertraline or placebo
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Coleman CC, et al.**[69] ***Year:*** **2001** ***Country:*** US			
FUNDING:	Glaxo Wellcome			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (15 centers) ***Sample size:*** 456			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Buproprion SR 150-400 mg/d 8 weeks	Fluoxetine 20-60 mg/d 8 weeks	Placebo N/A 8 weeks	
INCLUSION:	DSM-IV criteria for major depression; minimum score of 20 on the 21 item HAM-D; ≥18 years of age; have sexual activity at least once every 2 weeks; currently experiencing episode lasting 2-24 months; currently in a stable relationship			
EXCLUSION:	Predisposition to seizure or taking med that lowers seizure threshold; history or current diagnosis of anorexia or bulimia; pregnant, lactating or unwilling to take contraceptives; history of alcohol or substance abuse; suicidal tendencies; prior treatment with buproprion SR or fluoxetine; used any psychoactive drug within 1 week of study (2 weeks for MAOI or protriptyline or any investigational drug; non-responders to antidepressant treatment			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** fluoxetine: 37.1, buproprion SR: 36.6, placebo: 36.7 ***Gender*** (% female): fluoxetine: 66%, buproprion SR: 63%, placebo: 61% ***Ethnicity:*** fluoxetine: white 82%, black 11%, other 7%; buproprion SR: white 83%, black 11%, other 5%; placebo: white 82%, black 14%, other 4% ***Other population characteristics:*** More patients in the fluoxetine and buproprion SR groups had sexual desire disorder than at baseline the placebo group			

Authors: **Coleman CC, et al.** ***Year:*** **2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** 21 item HAM-D, sexual function assessment, substance-induced arousal disorder and orgasm dysfunction. Assessed: orgasm dysfunction, sexual desire disorder, sexual arousal disorder, overall patient sexual functioning (1-6 scale) ***Timing of assessments:*** Assessments made at baseline and weeks 1, 2, 3, 4, 5, 6, 7, and 8
RESULTS:	• Mean HAM-D scores were not statistically different between the three groups (in ITT analysis) • No difference in responders (≥ 50 decrease in HAM-D), remitters (HAMD < 8) • More buproprion SR remitters (47%) compared to placebo (32%). • Orgasm dysfunction occurred significantly more in fluoxetine patients compared with placebo or buproprion SR patients ($p < 0.001$) • At endpoint, more fluoxetine treated patients had sexual desire disorder than buproprion SR treated patients ($p < 0.05$). • More fluoxetine-treated patients dissatisfied with sexual function beginning at week 1 ($p < 0.05$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 34%; fluoxetine: 37%, buproprion SR: 37%, placebo: 33% ***Withdrawals due to adverse events:*** 6%; fluoxetine: 4%, buproprion SR: 9%, placebo: 3% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Headache was the most commonly reported event in all treatment groups • Headache, diarrhea, and somnolence occurred more frequently in fluoxetine patients than buproprion SR or placebo • Dry mouth, nausea, and insomnia were reported more frequently in buproprion SR patients than fluoxetine or placebo • Buproprion SR group had mean increases in DBP (1.7 mm Hg) and fluoxetine group (0.3 mm Hg) and heart rate (3.8 beats/min), authors state these were not clinically significant • Buproprion SR group had mean increases in heart rate (3.8 beats/min) and fluoxetine group had a mean decrease in heart rate (-2.8 beats/min), authors state these were not clinically significant
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder

STUDY:	**Authors: Colonna L, et al.**[22] **Year: 2005** **Country:** Europe		
FUNDING:	H Lundbeck A/S		
DESIGN:	**Study design:** RCT **Setting:** 66 primary care centers **Sample size:** 357		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Escitalopram 10 mg/day 24 weeks 181 (ITT=165)	 Citalopram 20 mg/day 24 weeks 177 (ITT=174)	
INCLUSION:	Outpatients; 18-65 years old; MDD according to the DSM-IV; baseline MADRS of 22 - 39		
EXCLUSION:	Pregnant; breast-feeding; adequate contraception; DSM-IV criteria for bipolar disorder, schizophrenia, psychotic disorder, OCD, or eating disorders; mental retardation; score of 5 or more on MADRS item 10 (suicidal thoughts); receiving treatment with antipsychotics, antidepressants, hypnotics, anxiolytics, antiepileptics, barbiturates, chloral hydrate, 5 HT receptor agonists; ECT CBT or psychotherapy; investigational drug within 30 days; history of drug abuse; lack of response to more than one antidepressant in current episode		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** 46 **Gender (% female):** escitalopram: 73%, citalopram: 76% **Ethnicity:** NR **Other population characteristics:** **Mean MADRS (SD):** escitalopram: 29.5 (4.3), citalopram 30.2 (4.7) **Mean CGI-S (SD):** escitalopram: 4.2 (0.8), citalopram: 4.3 (0.8) **Moderately depressed patients (MADRS < 30) n (%):** escitalopram: 85 (51.5), citalopram: 85 (48.9) **Severely depressed patients (MADRS of 30 or more) n(%):** escitalopram: 80 (48.5)m, citalopram: 89 (51.1)		

<table>
<tr><td colspan="4">Authors: Colonna L, et al.
Year: 2005</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: MADRS total score
Secondary Outcome Measures: CGI-S, Responders (50% reduction in MADRS) and remitters (MADRS total score 12 or less)
Timing of assessments: Screening, baseline weeks 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24. Final safety assessment 30 days after last assessment</td></tr>
<tr><td>RESULTS:</td><td colspan="3">All results are escitalopram vs. citalopram at 24 weeks
• No significant differences in changes of MADRS scores from baseline to endpoint 8.3 vs. 9.3 p = NR
• CGI-S mean 1.75 vs. 2.00 p < 0.05
Moderately depressed 1.57 vs. 1.95 p < 0.05
Severely depressed 2.02 vs. 2.13
▪ Responders: 80% vs. 78% p = NR
▪ Remitters: 76% vs. 71% p = NR
▪ Overall, statistically significantly fewer withdrawals in the escitalopram than in the citalopram group 13% vs. 22% p < 0.05
▪ Total withdrawals in the moderately depressed was 10 (11.8%) vs. 26 (30.6%) p < 0.01
▪ Total withdrawals in the severely depressed was 11 (13.8%) vs. 13 (14.6%) p = NR</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions: Yes (18)</td></tr>
<tr><td>ATTRITION (%):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:
Loss to follow-up differential high:</td><td><u>Overall</u>
17.7
8.3
1.5
No</td><td><u>Escitalopram</u>
12.7
6.1
1.2</td><td><u>Citalopram</u>
22.4
10.3
1.7</td></tr>
<tr><td>ADVERSE EVENTS:</td><td colspan="3">▪ All results are escitalopram versus citalopram n(%)
▪ Patients with AEs: 110 (62.9) vs. 131 (72.0)
Nausea: 28 (16.0) vs. 18 (9.9), Rhinitis: 17 (9.7) vs. 12 (6.6), Headache: 12 (6.9) vs. 16 (8.8), Back pain: 11 (6.3) vs. 15 (8.2), Accidental injury: 10 (5.7) vs. 8 (4.4), Bronchitis: 10 (5.7) vs. 7 (3.8), Weight increase: 2 (1.1) vs. 12 (6.6)</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Costa e Silva JC, et al.**[54] ***Year:*** **1998** ***Country:*** South America			
FUNDING:	Wyeth-Ayerst International			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 382			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine 75-225 mg/d 8 weeks	Fluoxetine 20-40 mg/d 8 weeks		
INCLUSION:	18-60 yrs; DSM-III-R criteria for major depression; ≥ 20 on HAM-D-21; symptoms for at least 1 month			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; history of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; investigational drugs within 30 days; clinically relevant cardiac, hepatic, or renal disease; abnormalities on screening examination; known sensitivity to venlafaxine or fluoxetine			
OTHER MEDICATIONS/ INTERVENTIONS:	Zopiclone 7.5 mg			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** venlafaxine: 40.5, fluoxetine: 39.8 ***Gender*** (% female): venlafaxine: 80.1%, fluoxetine: 77.4% ***Ethnicity:*** Not reported ***Other population characteristics:*** Previous history of depression: venlafaxine: 79.6%, fluoxetine: 76.3%, CGI: Moderately ill: venlafaxine: 33.7%, fluoxetine: 36.3%. Markedly ill: venlafaxine: 43.0%, fluoxetine: 43.4%. Severely ill: venlafaxine: 20.2%, fluoxetine: 17.0%			

Authors: **Costa e Silva JC, et al.** ***Year:*** **1998** ***Country:*** South America	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** HAM-D, MADRS, CGI at baseline, days 7, 14, 21, 28, 42, 56. SCL-61 or SCL-90 administered baseline, days 28 and 56
RESULTS:	• HAM-D and MADRS scores decreased significantly in both treatment groups ($p < 0.05$) • There were no significant differences between treatment groups in any primary efficacy measures (HAM-D, MADRS, CGI) • Global response (≥ 50% decrease in HAM-D or MADRS and CGI score of 1 or 2) was achieved by 86.8% in the venlafaxine group and 82% in the fluoxetine group ($p = 0.074$) • Remission was observed in 60.2% of patients in each group • In patients who increased their dose to venlafaxine 150 mg and fluoxetine 40 mg after 3 weeks significantly more achieved a CGI score of 1 in the venlafaxine group ($p < 0.05$) • There was no significant difference in remission rates between treatment groups
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** No
ATTRITION:	***Loss to follow-up:*** 12.3%; venlafaxine: 14.8%, fluoxetine:9.7% ***Withdrawals due to adverse events:*** venlafaxine: 7.2%, fluoxetine: 3.8% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• There were no significant differences between groups for specific adverse events • At least one adverse event: venlafaxine: 69.4%, fluoxetine: 65% • There were no clinically significant changes in laboratory parameters, ECG, or blood pressure in either group • Nausea: venlafaxine: 28.9%, fluoxetine: 18.9% • Headache: venlafaxine: 11.3%, fluoxetine: 7%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Croft H, et al.**[73] ***Year:*** **1999** ***Country:*** US			
FUNDING:	Glaxo Wellcome			
DESIGN:	***Study design:*** RCT (active and placebo control) ***Setting:*** Multi-center (8 centers) ***Sample size:*** 360			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/d 8 weeks	Buproprion 150-400 mg/d 8 weeks	Placebo N/A 8 weeks	
INCLUSION:	DSM-IV criteria for major depression; minimum score of 18 on the first 21 items of the 31 item HAM-D; ≥ 18 years of age; in a stable relationship; have normal sexual functioning and sexual activity at least once every 2 weeks; current depressive episode of 8 weeks to 24 months			
EXCLUSION:	Predisposition to seizure or taking med that lowers seizure threshold; history or current diagnosis of eating disorder; pregnant, lactating or unwilling to take contraceptives; history of alcohol or substance abuse; suicidal tendencies; prior treatment with buproprion or sertraline; used any psychoactive drug within 1 week of study (2 weeks for MAOI or protriptyline or 4 weeks for fluoxetine or any investigational drug)			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 36.0, buproprion: 35.9, placebo: 37.4 ***Gender*** (% female)***:*** sertraline: 50%, buproprion: 51%, placebo: 50% ***Ethnicity:*** sertraline: white: 87%, black: 8%, other: 4%; buproprion: white: 86%, black: 9%, other: 5%; placebo: white: 88%, black: 8%, other: 3% ***Other population characteristics:*** Not reported			

Authors: **Croft H, et al.** ***Year:*** **1999** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual function assessment by investigator interview-sexual desire disorder, sexual arousal disorder, orgasmic dysfunction, premature ejaculation, overall patient satisfaction with sexual functioning, vital signs ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, and 8
RESULTS:	• Mean HAM-D scores in both the buproprion and sertraline group were statistically better than placebo ($p < 0.05$) • No significant difference in HAM-D scores between the buproprion and sertraline groups • CGI-S and CGI-I improvement compared to placebo but no differences between drugs at any week • No difference in changes of HAM-A scores for any group • By day 42 significantly fewer buproprion sr treated patients had sexual desire disorder than sertraline or placebo-treated patients ($p < 0.05$) • At day 56, both buproprion and sertraline had higher sexual arousal disorder ($p < 0.05$) than placebo • Orgasmic dysfunction occurred significantly more in sertraline patients compared with placebo or buproprion patients ($p < 0.001$) • At day 56 no difference in overall satisfaction with sexual function between treatment groups
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 32% ***Withdrawals due to adverse events:*** (12); sertraline: 3%, buproprion sr: 3%, placebo: 7% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Headache was the most commonly reported event in all treatment groups • Somnolence and insomnia occurred more frequently in sertraline patients than buproprion patients • Nausea and diarrhea occurred more frequently with sertraline than buproprion or placebo
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Dalery J, et al.**[27] ***Year:*** **2003** ***Country:*** Europe			
FUNDING:	Solvay Pharmaceuticals			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 184			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluvoxamine 100 mg/day 6 weeks	Fluoxetine 20 mg/day 6 weeks		
INCLUSION:	18-70 years; DSM-III-R criteria for major depression; ≥ 17 on HAM-D			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; history of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; previously failed to respond to SSRI therapy; clinically relevant progressive disease; concomitant warfarin, lithium, insulin, theophylline, carbamazepine			
OTHER MEDICATIONS/ INTERVENTIONS:	Oxazepam, nitrazepam			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** fluvoxamine: 42.0, fluoxetine: 42.1 ***Gender*** (% female): fluvoxamine: 63.3%, fluoxetine: 62.7% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Dalery J, et al.** ***Year:*** **2003** ***Country:*** Europe	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** HAM-D-17 Weeks 1, 2, 4, 6, CGI, CAS (Clinical Anxiety Scale), IDAS (irritability, depression and anxiety scale), SSI (Beck's scale for suicidal ideation) at all visits
RESULTS:	• Both treatment groups resulted in significant improvements of symptoms • There were no significant differences between the study groups in changes of HAM-D scores from baseline at any point in time • After 2 weeks of treatment, the percentage of patients who responded was significantly higher in the fluvoxamine group (29% vs. 16%; $p \leq 0.05$), as was the improvement of CGI-I scores ($p \leq 0.05$). This significant difference was not evident after week 2 • Improvement in sleep disturbance sub scores (HAM-D) was significantly greater in the fluvoxamine group at week 4 and at the endpoint ($p \leq 0.05$) • Overall sleep evaluation was not significantly different
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 20.9%; fluvoxamine: 23.3%, fluoxetine: 18.7% ***Withdrawals due to adverse events:*** Not reported ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• No significant differences • No clinically significant changes in vital signs or body weights in either group • Most common adverse events: nausea: fluvoxamine, 24%; fluoxetine, 20%; headache: fluvoxamine-13%, fluoxetine-14%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	**Authors: Detke MJ, et al.**[46] **Year: 2004** **Country:** US			
FUNDING:	Eli Lilly			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (number of centers NR) ***Sample size:*** 367			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** *Acute phase:* *Continuation:* ***Sample size:***	 Duloxetine (low dose) 80 mg/d 8 weeks 6 months 95	 Duloxetine (high dose) 120 mg/d 8 weeks 6 months 93	 Paroxetine 20 mg/d 8 weeks 6 months 86	 Placebo N/A 8 weeks 6 months 93
INCLUSION:	Patients ≥ 18 yrs old; met DSM-IV and MINI criteria for MDD; CGI-S rating ≥ 4; HAM-D-17 score ≥ 15 at entry			
EXCLUSION:	Pregnant, Current primary DSM-IV diagnosis other than MDD; any anxiety disorder as a primary diagnosis; previous diagnosis of bipolar disorder, psychosis, or schizoaffective disorder; history of substance abuse; failed to respond to two courses of antidepressant therapy; serious suicidal risk; serious medical illness			
OTHER MEDICATIONS/ INTERVENTIONS:	Nonprescription analgesic medications allowed; no prescription analgesics			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Duloxetine 80: 43.1, Duloxetine 120: 44.7, Paroxetine 20: 42, placebo: 42 ***Gender*** (% female): Duloxetine 80: 70%, Duloxetine 120: 70%, Paroxetine 20: 58%, placebo: 58% ***Ethnicity*** (% white): Duloxetine 80: 95%, Duloxetine 120: 92%, Paroxetine 20: 86%, placebo: 86% ***Other population characteristics:*** Mean baseline HAM-D: Duloxetine 80: 19.9, Duloxetine 120: 20.2, Paroxetine: 20.3, placebo: 19.9; Mean baseline HAM-A: Duloxetine 80: 17.8, Duloxetine 120: 18, Paroxetine 20: 18.5, placebo: 17.9			

Authors: Detke MJ, et al. **Year: 2004** **Country:** US	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** HAM-D-17 ***Secondary Outcome Measures:*** HAM-D-17 subscales; MADRS; HAM-A; Visual Analog Scales for pain; CGI-S; PGI; Sheehan Disability Scale; Somatic Symptom Inventory ***Timing of assessments:*** HAM-D-17 administered at baseline and weeks 1,2,4,6 and 8.
RESULTS:	• Response and remission rates did not differ significantly among duloxetine 120 mg (71%; 52%), duloxetine 80 mg (65%; 46%) and paroxetine (74%; 44%) • No significant differences in HAM-D-17 score reduction found between the duloxetine groups and the paroxetine group • 120 mg/d duloxetine had significantly greater improvement on MADRS than 80 mg/d duloxetine ($p \leq 0.05$) • PGI score significantly superior in patients receiving paroxetine than patients receiving 80 mg/d duloxetine ($p \leq 0.05$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 13.3%; duloxetine, low-dose: 12.6%; duloxetine, high-dose: 9.7%; paroxetine: 11.6%; placebo 19% ***Withdrawals due to adverse events:*** Duloxetine, low-dose: 4.2%; duloxetine, high-dose: 3.2%; paroxetine: 3.5%; placebo: 3.2% ***Loss to follow-up differential high:*** Not reported
ADVERSE EVENTS:	**Acute Phase:** • At endpoint, diastolic blood pressure was significantly elevated in the duloxetine 120mg group compared to the paroxetine group (+0.7 mm Hg; $p < 0.05$) • No statistically significant differences in other adverse events **Continuation Phase:** • No significant between group differences were found
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **De Wilde J, et al.**[31] ***Year:*** **1993** ***Country:*** Belgium			
FUNDING:	SmithKline, Beecham Pharma.			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 100			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20-40 mg/day 6 weeks	Fluoxetine 20-60 mg/day 6 weeks		
INCLUSION:	Age 18-65; MDD by DSM III criteria; HAM-D 21 score ≥ 18			
EXCLUSION:	Pregnancy or lactation; severe concomitant disease; alcohol or substance abuse; severe suicide risk; ECT within 3 months; MAOI or oral neuroleptics within 14 days; depot neuroleptics with 4 wks; lithium			
OTHER MEDICATIONS/ INTERVENTIONS:	Temazapam, other short-acting benzodiazepines, stable doses of long-acting benzodiazepines			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** paroxetine: 44.6, fluoxetine: 44.1 ***Gender*** (female%): paroxetine: 57%, fluoxetine: 66% ***Ethnicity:*** Not reported ***Other population characteristics:*** 65% of paroxetine group and 70% group of fluoxetine had prior depression			

Authors: **De Wilde J, et al.** ***Year:*** **1993** ***Country:*** Belgium	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D_{21}, MADRS, HSCL58, CGI ***Timing of assessments:*** Baseline, weeks 1, 3, 4 & 6
RESULTS:	Responders at week 6 (i.e., reduction > 50% from baseline HAM-D_{21}): paroxetine: ~ 67%, fluoxetine: ~ 62%, not significantly different
ANALYSIS:	***ITT:*** Not reported ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 21.2% ***Withdrawals due to adverse events:*** paroxetine: 4%, fluoxetine:8% ***Loss to follow-up differential high:*** Not reported
ADVERSE EVENTS:	• No significant differences • No vital sign or laboratory changes reported • Paroxetine: n = 3 had weight gain > 7%, fluoxetine: n = 2 had weight gain > 7%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **De Nayer A, et al.**[55] ***Year:*** **2002** ***Country:*** Belgium			
FUNDING:	Not reported (author affiliation with Wyeth)			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center; 14 psychiatric practices ***Sample size:*** 146			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine 75-150 mg/day 12 weeks	Fluoxetine 20-40 mg/day 12 weeks		
INCLUSION:	Age 18-70 yrs; HAM-D-21 score 18-25; ≥ 8 Covi Anxiety scale			
EXCLUSION:	Concomitant psychiatric disease; history of substance abuse; suicide attempt past year; active suicidal ideation; pregnant or lactating women, childbearing age without contraception; psychotropic medication; fluoxetine within 21days of baseline; MAOI within 14 days; non-psychotropic within 7 days of baseline unless dose stable for 1 month			
OTHER MEDICATIONS/ INTERVENTIONS:	2 mg lormetazepam at bedtime			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** venlafaxine: 41.6, fluoxetine: 43.9 ***Gender*** (% female): venlafaxine: 71.2%, fluoxetine: 65.8% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **De Nayer A, et al.** ***Year:*** **2002** ***Country:*** Belgium	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D, MADRS, Covi Anxiety Scale, CGI ***Timing of assessments:*** Baseline, weeks 1, 2, 4, 8, 12 (inferred from table)
RESULTS:	• The venlafaxine group showed significantly higher response rates in MADRS scores (75.0 vs. 49.3%, p = 0.001) and HAM-D scores (71.9% vs. 49.3%; p = 0.008) compared to the fluoxetine group • Venlafaxine treated patients also showed significantly greater improvements in the Covi Anxiety scores (p = 0.0004) and the CGI scores (p = 0.016) • MADRS and HAM-D scores at week 2 improved significantly more in the venlafaxine group • (HAM-D, p = 0.0058) • At the final visit 59.4% of venlafaxine patients were in remission vs. 40.3 % of fluoxetine patients (p = 0.028) • Fewer venlafaxine patients required a dose increase (37.1% vs. 52.9%)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 36.3%; venlafaxine: 32.9%, fluoxetine: 39.7% ***Withdrawals due to adverse events:*** venlafaxine: 11%, fluoxetine: 12.3% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• No significant differences • Overall most common adverse event: nausea (28.6% in venlafaxine group vs. 21.4% in fluoxetine group) • 55.7% in the venlafaxine group and 67.1% in the fluoxetine group experienced at least one adverse event • Most common adverse events that lead to withdrawal: venlafaxine: headache, diarrhea, nausea; fluoxetine: insomnia, dyspepsia, nausea, anxiety, nervousness
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Dierick M, et al.**[60] ***Year:*** **1996** ***Country:*** France			
FUNDING:	Wyeth-Ayerst			
DESIGN:	***Study design:*** RCT ***Setting:*** ***Sample size:*** 314			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine 75-150 mg/d 8 weeks	Fluoxetine 20 mg/d 8 weeks		Mean daily dose for venlafaxine: 109-122 mg/d from day 15 forward
INCLUSION:	18 yrs or older; DSM-III-R criteria for major depression; ≥ 20 on HAM-D-21			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; history of seizures; organic mental disorder; personality disorders; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; use of investigational drug; MAO inhibitor; ECT within 14 days; clinically relevant progressive disease; concomitant warfarin, lithium, insulin, theophylline, carbamazepine; hypersensitivity to or use of antidepressant within 14 days; use of anxiolytic that could not be withdrawn			
OTHER MEDICATIONS/ INTERVENTIONS:	Oxazepam, chloral hydrate			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** venlafaxine: 43.7, fluoxetine: 43.2 ***Gender*** (% female): venlafaxine: 65%, fluoxetine: 64% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Dierick M, et al.** ***Year:*** **1996** ***Country:*** France	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D, MADRS, CGI ***Timing of assessments:*** Baseline, days 7, 14, 21, 28, 56
RESULTS:	• Both treatment groups improved significantly in efficacy outcomes from baseline • Response rate on HAM-D scale was significantly higher in the venlafaxine group at week 6: venlafaxine: 72%, fluoxetine: 60% (p = 0.023) • No differences between groups on MADRS • In a low dose comparison there were no significant differences between groups
ANALYSIS:	***ITT:*** Yes ***Post randomisation exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 24.8%; venlafaxine: 25%, fluoxetine: 25% ***Withdrawals due to adverse events:*** venlafaxine: 9%, fluoxetine: 4% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Significantly more patients reported nausea in the venlafaxine group: 28% vs. 14% (p = 0.003) • Anticholinergic side effects greater in venlafaxine group: 15% vs. 7 % • No clinically significant changes in vital signs, ECG or lab parameters • 1 patient on fluoxetine committed suicide after 1 week treatment
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Ekselius L, et al.**[17] ***Year:*** **1997** ***Country:*** Sweden			
FUNDING:	Swedish Medical Research Council, Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (general physicians) ***Sample size:*** 400			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** (patients > 65) sertraline:50-100 mg/d citalopram: 20-40 mg/d	Sertraline 50-100 mg/d 24 weeks	Citalopram 20-60 mg/d 24 weeks		
INCLUSION:	18-70 yrs; DSM-III-R criteria for major depression; ≥ 21 on MADRS			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; history of psychotic disorders; alcohol or substance abuse; existing suicidal risk; therapy refractory depression; previous failure on sertraline or citalopram; psychotropic medication; clinically significant hepatic or renal disease; concomitant warfarin, lithium, cimetidine, or tryptopan			
OTHER MEDICATIONS/ INTERVENTIONS:	All other medications except: psychotropic medication, warfarin, and cimetidine Patients instructed to minimize use of nitrazepam, flunitrazepam, and oxazepam.			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 47.0, citalopram: 47.2 ***Gender*** (% female): sertraline: 71%, citalopram 72.5% ***Ethnicity:*** Not reported ***Other population characteristics:*** Concomitant medications: sertraline: 55%, citalopram: 44.5% Recurrent depression: sertraline: 56%, citalopram: 65%			

Authors: **Ekselius L, et al.** ***Year:*** **1997** ***Country:*** Sweden	
OUTCOME ASSESSMENT:	***Measures:*** CGI-S, MADRS ***Timing of assessments:*** Weeks 2, 4, 8, 12, 16, 20, 24
RESULTS:	• Both treatment groups showed significant decreases in MADRS and CGI scores from baseline at all weeks starting at week 2 • There were no significant differences between treatment groups in any primary outcome variables at any time • Response rates week 12: sertraline: 69.5%; citalopram: 68.0%; week 24: sertraline: 75.5%; citalopram: 81.0% • *Subgroup analysis:* There were no significant differences between treatment groups in any primary outcome variables in patients with recurrent depression
ANALYSIS:	***ITT:*** Yes. LOCF ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 22% ***Withdrawals due to adverse events:*** sertraline: 12.5%, citalopram: 9.0% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• No significant differences between treatment groups • At least one adverse event: sertraline: 90%, citalopram: 85.5% • Nausea: sertraline: 6%, citalopram: 2.5% • Diarrhea: sertraline: 8.5%, citalopram: 5.5% • Increased sweating: sertraline: 13%, citalopram 17% • Dry mouth: sertraline: 18.5%, citalopram: 16% • Headache: sertraline: 9%, citalopram: 6.5% • Sexual dysfunction was experienced in 8% of the sertraline group and 13.5% of the citalopram group
QUALITY RATING:	**Good**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Fava M, et al.**[33] ***Year:*** **1998** ***Country:*** US			
FUNDING:	SmithKline Beecham Pharmaceuticals			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 128			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Paroxetine 20-50 mg/d (Initial dosage of 20 mg/d could be increased weekly by 10 mg/d up to 50 mg/d) 12 weeks	 Fluoxetine 20-80 mg/d (Initial dosage of 20 mg/d could be increased weekly by 20 mg/d up to 80 mg/d) 12 weeks	 Placebo N/A 12 weeks	
INCLUSION:	Raskin Depression score of $\geq$ 8 (and larger in value than the Covi anxiety scale) score of $\geq$ 18 on the 21 item HAM-D			
EXCLUSION:	Serious concomitant medical illness; suicidal risk; alcohol or drug abuse; patients previously treated with paroxetine; hypersensitive to fluoxetine; diagnosed with another primary psychiatric disorder; other psychotropic drugs within 14 days; ECT within 3 months; pregnancy or no acceptable contraception			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 41.3 ***Gender*** (% female): 50% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Author: **Fava M, et al.** ***Year:*** **1998** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** 21 item HAM-D, Covi Anxiety Scale, vital signs at weeks 1, 2, 3, 4, 6, 9, 12 ***Timing of assessments:*** Laboratory evaluations at weeks 3, 6, 9, 12
RESULTS:	No significant differences among the three treatment groups in the degree of depression and anxiety improvement
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 28%; paroxetine: 29%, fluoxetine: 31%, placebo: 21% ***Withdrawals due to adverse events:*** 12% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Gastrointestinal effects were reported in 47% of paroxetine patients, 48% fluoxetine patients • 25% of paroxetine patients reported sexual dysfunction; this was significantly more than the fluoxetine (7%) or placebo groups (0%)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Fava M, et al.**[34] ***Year:*** **2002** ***Country:*** US			
FUNDING:	Eli Lilly Research			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 284			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluoxetine 20-60 mg/day 10-16 weeks	Sertraline 50-200 mg/day 10-16 weeks	Paroxetine 20-60 mg/day 10-16 weeks	
INCLUSION:	≥ 18 years of age; DSM-IV for atypical MDD; HAM-D-17 ≥ 16; episode ≥ 1month			
EXCLUSION:	Pregnancy or lactation; lack of adequate contraception; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; previously failed to respond to antidepressant therapies; clinically relevant progressive disease; hypersensitivity to study medication; serious comorbid illness not stabilized; anxiolytic or psychotropic within 7 days; MAOI within 2 weeks			
OTHER MEDICATIONS/ INTERVENTIONS:	Thyroid medications, chloral hydrate			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** fluoxetine: 42.1, sertraline: 44.0, paroxetine: 42.5 ***Gender*** (female%): fluoxetine: 63.0, sertraline: 57.3, paroxetine: 58.3 ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Fava M, et al.** ***Year:*** **2002** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-17, CGI-S, HAM-D sleep disturbance ***Timing of assessments:*** Not reported
RESULTS:	• No statistical differences between fluoxetine, sertraline and paroxetine in all outcome measures • Response rate: 64.8%, 72.9%, and 68.8% respectively • Remission rates: 54.4%, 59.4%, and 57.0% respectively • No statistical differences in sleep disturbance factor scores. No significant differences of treatment groups in patients with high or low insomnia *Subgroup analysis (Fava 2000)]: Anxious depression* • No significant differences between treatment groups and changes over time • Response: fluoxetine: 73%, sertraline: 86%, paroxetine: 77%, overall p = 0.405 • Remission: fluoxetine: 53%, sertraline: 62%, paroxetine: 50%, overall p = 0.588 • Fluoxetine and sertraline had a significantly greater improvement than paroxetine in week 1 on the HAM-D anxiety score
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 27.1%; fluoxetine: 26.1%, sertraline: 27.1%, paroxetine: 28.1% ***Withdrawals due to adverse events:*** fluoxetine: 8.7%, sertraline: 6.3%, paroxetine: 11.5% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Pairwise comparisons indicated that the paroxetine-treated patients reported more constipation than the fluoxetine-treated patients, and the fluoxetine-treated patients reported more twitching and cough increase than the sertraline-treated patients • Most common adverse events: Fluoxetine: headache (25%); sertraline: headache (28.1%), diarrhea (26.0%), insomnia (26%), nausea (20.8%); paroxetine: nausea (25.0%), headache (21.9%), insomnia (20.8%), abnormal ejaculation (20.8%) • There was a significant increase in weight for the paroxetine group, fluoxetine treated patients showed a significant decrease in weight and the sertraline group a non-significant decrease in weight from baseline to endpoint *Subgroup analysis (Fava 1999)* • Adverse events were similar among treatments; only “flu syndrome” was significantly higher in the sertraline treated group overall (p = 0.021)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Feiger A, et al.**[80] ***Year:*** **1996** ***Country:*** Europe			
FUNDING:	Bristol-Myers Squibb			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 160			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Nefazodone 100-600 mg/d 6 weeks	Sertraline 50-200 mg/d 6 weeks		
INCLUSION:	18 yrs or older; DSM-III-R criteria for major depression; ≥ 20 on HAM-D-17 after washout period			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; Axis I diagnosis; history of seizures; alcohol or substance abuse; existing suicidal risk; previous nefazodone trial; sertraline treatment within 1 year; clinically relevant progressive disease; known hypersensitivity to study drugs; psychotropic medication within 6 months; participation in other trial within 3 months; use of any other antidepressant within 3 weeks			
OTHER MEDICATIONS/ INTERVENTIONS:	Concomitant medications			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** sertraline group had a significantly higher rate of recurring illness than the nefazodone group (73% vs. 57%; p = 0.01) ***Mean age:*** 43.7; sertraline: 43, nefazodone: 44.5 ***Gender*** (% female): 51%; sertraline: 48%, nefazodone: 55% ***Ethnicity:*** white: 84%, black: 11%, Hispanic: 7%, Asian: 1%, other: 1%; sertraline: white: 79%, nefazodone: 90% white ***Other population characteristics:*** Concomitant medication taken by 85% in the nefazodone group and 78% in the sertraline group; recurrent illness: sertraline: 57%, nefazodone: 73%			

Authors: **Feiger A, et al.** ***Year:*** **1996** ***Country:*** Europe	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-17, CGI, sexual function questions ***Timing of assessments:*** Weekly
RESULTS:	There were no statistically significant differences between treatment groups; response rates: nefazodone: 59%, sertraline: 57%
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 24.4%; nefazodone: 24.4%, sertraline: 24.4% ***Withdrawals due to adverse events:*** nefazodone: 19.2%, sertraline: 12.2% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Reported at least one adverse event: sertraline: 95%, nefazodone: 96% • Overall satisfaction with sexual function was significantly higher in the nefazodone group ($p < 0.1$) • 67% of men in the sertraline group reported difficulty with ejaculation vs. 19% in the nefazodone group ($p < 0.01$) • No significant differences in other adverse events • No clinically significant effects on the cardiovascular system in either group; no differences in withdrawals due to adverse events. • Headache: sertraline: 55%, nefazodone: 55% • Nausea: sertraline: 27%, nefazodone: 32% • Dizziness: sertraline: 7%, nefazodone: 32%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Feighner JP, et al.**[68] ***Year:*** **1991** ***Country:*** US			
FUNDING:	Burroughs Wellcome Co.			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (2 centers) ***Sample size:*** 123			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Bupropion 225-450 mg/d 6 weeks	Fluoxetine 20 mg for 3 weeks, then 20-80 mg 6 weeks		
INCLUSION:	At least 18 years; DSM-III criteria for nonpsychotic depression; current depressive episode for at least 4 weeks but less than 2 yrs; ≥ 20 on HAM-D scale; considered clinically appropriate for bupropion or fluoxetine treatment			
EXCLUSION:	Predisposition to seizures; hepatic or renal dysfunction; thyroid disorder; anorexia; bulimia; other unstable medical condition; pregnant, lactating, no acceptable contraception method; history of alcohol or substance abuse; psychoactive drugs; MAO inhibitors within 1 week before treatment; four weeks of investigational drugs; suicidal ideation; current treatment with tryptophan, warfarin, digoxin, or thyroid preparations; unable to conduct meaningful conversation			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** bupropione: 40.9, fluoxetine: 42.9 ***Gender*** (female%): bupropione: 62%, fluoxetine: 61% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Feighner JP, et al.** ***Year:*** **1991** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D (21), CGI-S, CGI-I, HAM-A ***Timing of assessments:*** Weekly
RESULTS:	• No significant differences in changes of the HAM-D score between treatment groups • No significant differences in percentage of clinical responders (more than 50% HAM-D scale reduction) between treatment groups, bupropion: 62.7%, fluoxetine: 58.3% • No significant differences in changes of CGI-S, CGI-I, and HAM-A scores
ANALYSIS:	***ITT:*** Yes ***Post randomisation exclusions:*** Yes. 3 patients
ATTRITION:	***Loss to follow-up:*** 7.3%; buproprion: 3.3%, fluoxetine: 11.3% ***Withdrawals due to adverse events:*** Bupropion: 10%, fluoxetine: 7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	No significant differences of adverse events between treatment groups
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Finkel SI, et al.**[39] ***Year:*** **1999** ***Country:*** US			
FUNDING:	Two authors are affiliated with Pfizer, Inc.			
DESIGN:	***Study design:*** RCT, subgroup analysis ***Setting:*** Multi-center ***Sample size:*** 75			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Sertraline 50-100 mg/day 12 weeks	 Fluoxetine 20-40 mg/day 12 weeks		
INCLUSION:	DSM III-R criteria for major depression; HAM-D: ≥ 18; age 70 or older			
EXCLUSION:	Significant medical problems; Axis I psychiatric disorders; cognitive impairment; suicidal risk; drug abuse or dependence; failure to respond to antidepressant treatment			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate, temazepam			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** No-Fluoxetine group had higher rate of prior episodes of depression. ***Mean age:*** sertraline: 74, fluoxetine 75 ***Gender:*** (female%): sertraline: 57%, fluoxetine 49% ***Ethnicity:*** 97% white, 3% black; sertraline 95%, fluoxetine: 100% ***Other population characteristics:*** Prior depressive episodes: sertraline: 45%, fluoxetine 61%			

Authors: **Finkel SI, et al.** ***Year:*** **1999** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** HAM-D, Baseline (pre & post washout), weeks 2, 4, 6, 8, 10, 12, 3 POMS (baseline, weeks 2,4, 8, 12), 2. Q-Les-Q (baseline, week 12), cognitive tests: 1. DSST from the WAIS-R, 2. shopping list task, both given, Mini-Mental SE (baseline and week 12)
RESULTS:	• Overall no significant differences between treatment groups on endpoint scores • Significantly more patients in the sertaline group achieved a clinical response on HAM-D (reduction from baseline of 50% or greater) between weeks 6 to 12 • Changes in the Vigor Subscale of POMS, and 2 subscales of the Q-LES-Q (physical health, psychological health) showed significant differences favoring sertraline (p = 0.04; p = 0.03; p = 0.03)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes. 1 person excluded from ITT because lack of measures
ATTRITION:	***Loss to follow-up:*** 37.3%; sertraline: 36%, fluoxetine: 39% ***Withdrawals due to adverse events:*** sertraline: 9%, fluoxetine: 30% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Sertraline-treated patients reported “shaking” to a greater degree (14.3%) than did fluoxetine treated patients (0%) (p = 0.03) • Fluoxetine-treated patients lost more weight than sertraline-treated patients (week 12: 2.8 vs. 0.6 pounds; p = 0.05)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Franchini L, et al.**[43, 44] ***Year:*** **1997, 2000** ***Country:*** Italy			
FUNDING:	Not reported			
DESIGN:	***Study design:*** RCT ***Setting:*** Single center ***Sample size:*** 64 (4-year follow-up: enrolled 47)			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 100-200 mg/d 24/48 months	Fluvoxamine 200-300 mg/d 24/48 months		
INCLUSION:	Asymptomatic patients; unipolar patients with prior episodes; depressive episode within past 18 months; at least 4 months of remission confirmed by absence of symptoms according to DSM-IV; absence of other Axis I diagnosis *4-year follow-up:* patients who remained without recurrence after 2 years of prophylactic treatment (HAMD >15)			
EXCLUSION:	Other Axis I diagnosis; low compliance with past treatments; mania or hypomania; prior long-term maintenance treatment; recurrence cycle not longer than 18 months			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 47.3, fluvoxamine: 49.0 ***Gender*** (% female): sertraline: 78%, fluvoxamine: 75% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Franchini L, et al.** ***Year:*** **1997, 2000** ***Country:*** Italy	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D ***Timing of assessments:*** Monthly
RESULTS:	• 21.9% of sertraline-treated patients and 18.7% of fluvoxamine-treated patients had a single recurrence (z = 0.14; p = 0.88) *4-year follow-up:* • No significant difference in recurrences between the treatment groups; sertraline: 13.6%, fluvoxamine: 20%
ANALYSIS:	***ITT:*** No but not necessary since 100% completed trial with outcome assessments ***Post randomization exclusions:*** No
ATTRITION:	***Loss to follow-up:*** 0 ***Withdrawals due to adverse events:*** 0 ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• No significant differences in adverse events. • Most common adverse events: Sertraline: nausea (6.2%), abnormal ejaculation (12.5%) Fluvoxamine: nausea: (9.4%), anorexia (9.4%) *4-year follow-up:* Not reported
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Gagiano CA**[14] ***Year:*** **1993** ***Country:*** South Africa			
FUNDING:	Not reported			
DESIGN:	***Study design:*** RCT ***Setting:*** Single center (University hospital) ***Sample size:*** 90			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Fluoxetine 20-60 mg/d 6 weeks	 Paroxetine 20-40 mg/d 6 weeks		
INCLUSION:	Age 18-65 years; met DSM-III-R criteria for MDD; HAM-D (21-item scale) score of $\geq$ 18			
EXCLUSION:	Pregnant or lactating women; underlying renal, hepatic, neurological, gastrointestinal or severe cardiovascular disease, schizophrenia, organic brain syndrome and unstable diabetes; recent treatment with MAOIs or neuroleptics, lithium therapy, ECT in the previous three months and alcohol or drug abuse; patients considered to be at severe risk of suicide; any patient with 20% improvement in their HAMD score over one-week placebo washout period was not randomized to active treatment			
OTHER MEDICATIONS/ INTERVENTIONS:	Short-acting benzodiazepines such as temazepam; any other concomitant therapy already being employed prior to treatment was to be continued where possible			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** fluoxetine: 39.6, paroxetine: 37.8 ***Gender*** (% female): fluoxetine: 80%, paroxetine: 80% ***Ethnicity:*** Not reported ***Other population characteristics:*** Previous depression fluoxetine: 60%, paroxetine: 53%			

Authors: Gagiano CA ***Year:* 1993** ***Country:*** South Africa	
OUTCOME ASSESSMENT:	***Measures:*** Physical exam, HAM-D, MADRS, CGI, HAM-A, routine hematology and biochemistry on blood samples at baseline and end of week 6 ***Timing of assessments:*** Baseline and weekly intervals except week 5
RESULTS:	• No significant differences between treatment groups in HAM-D subfactor scores at any time point • No significant differences in mean total scores for HAM-D, HAM-A, and MADRS at endpoint or at any other study point measures • No significant difference in CGI severity change score or improvement score • No significant difference in patients responding (at least 50% improvement of HAM-D) between treatment groups (paroxetine: 70%, fluoxetine: 63%; no p value reported) • No significant differences in groups on HAMD (item 3) measure for suicidal ideation, both groups showed reduction over six-week period
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** No
ATTRITION:	***Loss to follow-up:*** 21%; fluoxetine 22%, paroxetine 14% ***Withdrawals due to adverse events:*** 6.7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Fluoxetine-treated patients experienced a statistically significant weight loss from baseline to endpoint (-1.46 kg; p = 0.001) • Headache: fluoxetine 47.0%, paroxetine 53.0% • Nausea: fluoxetine 33.0%, paroxetine 36.0% • Diarrhea: fluoxetine 13.0%, paroxetine 13.0% • Insomnia: fluoxetine 20.0%, paroxetine 11.0% • Vomiting was noted for only four (8.9%) patients in each group
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	**Authors: Goldstein DJ, et al.**[45] **Year: 2002** **Country:** US		
FUNDING:	Eli Lilly		
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (8 sites) ***Sample size:*** 173		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Duloxetine 40-120 mg/d 8 weeks 70	 Fluoxetine 20 mg/d 8 weeks 33	 Placebo N/A 8 weeks 70
INCLUSION:	Male and female outpatients 18-65 years; met DSM-IV and MINI criteria for MDD; CGI-S score of at least 4 at visit 1; HAM-D-17 score of at least 15 at visits 1 and 2		
EXCLUSION:	Any primary DSM-IV Axis I disorder diagnosis other than MDD; anxiety disorder as primary diagnosis within the past year; history of substance abuse or dependence; failed two or more courses of antidepressant therapy		
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported		
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** duloxetine: 42.3, Fluoxetine: 39.7, placebo: 41.4 ***Gender*** (% female): duloxetine: 62.9%, fluoxetine: 57.6%, placebo: 68.6% ***Ethnicity:*** White: 83%; African-American: 8.1%; other: 9.2%; percent white by drug-duloxetine: 88.6%, fluoxetine: 72.7%, placebo: 81.4% ***Other population characteristics:*** Mean baseline HAM-D-17: duloxetine: 18.4, fluoxetine 17.9, placebo 19.2		

Authors: Goldstein DJ, et al. **Year: 2002** **Country:** US	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** HAM-D-17 ***Secondary Outcome Measures:*** MADRS; CGI; HAM-A; PGI ***Timing of assessments:*** HAM-D-17 measured at baseline and weekly
RESULTS:	• No statistically significant differences between duloxetine and fluoxetine in response (49% vs. 45%) and remission (43% vs. 30%) rates • Duloxetine showed a significantly greater mean change from baseline in HAM-D-17 than placebo at week 8 (p = 0.009) • Duloxetine showed a greater change from baseline in HAM-D-17 than placebo at week 8 but the difference was not statistically different • Duloxetine patients showed significantly greater improvement on the MADRS (p = 0.047), CGI-S (p = 0.007), CGI-I (p = 0.005), and PGI (p = 0.006) than placebo
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 35% (60); duloxetine: 34.3% (24); fluoxetine: 36.4% (12); placebo: 34.3% (24) ***Withdrawals due to adverse events:*** 6.4% (11); duloxetine: 10% (7); fluoxetine: 3% (1); placebo 4.3% (3) ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Significantly more duloxetine patients experienced asthenia (17.1% vs. 4.3%; p = 0.026), and insomnia (20.0 % vs. 7.1%; p = 0.046) than placebo • Most common adverse events (duloxetine vs. fluoxetine): dry mouth: 30.0% vs. 21.2%; headache: 20% vs. 33.3%; insomnia: 20% vs. 9.1%; nausea: 12.9% vs. 18.2%; diarrhea: 14.3% vs. 30.3%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Hong CJ, et al.**[47] ***Year:*** **2003** ***Country:*** Taiwan			
FUNDING:	NV Organon, Oss, the Netherlands			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 133			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Mirtazapine: 15 mg-45 mg/d 6 weeks	Fluoxetine 20 mg-40 mg/d 6 weeks		
INCLUSION:	18-75 years; DSM-IV diagnosis of major depression; ≥ 15 HAM-D score (17); current episode between 1 week and 1 year			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; actual suicide risk; bipolar disorder or history of psychotic disorders; alcohol or substance abuse; DSM-IV of anxiety; history of seizures; clinically relevant progressive disease; psychotropic medication			
OTHER MEDICATIONS/ INTERVENTIONS:	Lorazepam, estazolam, supportive psychotherapy, medication for mild physical illness			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 47.2 ***Gender*** (% female): 63%; mirtazapine 62%, fluoxetine 64% ***Ethnicity:*** Chinese ***Other population characteristics:*** Not reported			

Authors: **Hong CJ, et al.** ***Year:*** **2003** ***Country:*** Taiwan	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D, CGI ***Timing of assessments:*** Days 7, 14, 28, 42
RESULTS:	• No significant differences in HAM-D scores reduction between treatment groups • No significant differences in HAM-D responders (mirtazapine: 58% vs. fluoxetine: 51%) • Mirtazapine had more remitters and responders at all time points, however no statistical significance in differences was reached
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 39.4%; mirtazapine: 45.5%, fluoxetine: 33.3% ***Withdrawals due to adverse events:*** Mirtazapine: 19.7%, fluoxetine: 12.1% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• No statistically significant differences between treatment groups • 71.2% of mirtazapine and 57.6% of fluoxetine treated subjects reported adverse events • Mirtazapine: dizziness 19.7%, constipation 15.2%, weight increase 13.6%, somnolence 12.1% • Fluoxetine: dizziness 13.6%, influenza-like symptoms 13.6%, constipation 9.1%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Kavoussi et al.**[72] ***Year:*** **1997** ***Country:*** US			
FUNDING:	Glaxo			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 248			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Bupropion SR 100-300 mg/d 16 weeks	Sertraline 50-200 mg/d 16 weeks		
INCLUSION:	Ages 18-76 ; DSM-IV criteria for MDD with current episode ≥ 4 weeks but ≤ 24 months; in a stable relationship with normal sexual functioning			
EXCLUSION:	Pregnant, lactating; history of bulimia or anorexia; predisposition to seizures; actively suicidal; no prior treatment with buproprion sr or sertraline; no psychoactive drug within 1 week; (2 weeks for MAOI or protryptyline, 4 weeks for fluoxetine)			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate allowed, no other psychoactive agents, allowed non-psychoactive agents not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 39.5; buproprion SR: 39, sertraline: 40 ***Gender*** (female%): 48%, buproprion SR: 48%, sertraline: 48% ***Ethnicity:*** 93.5 % white, 4.5 % black, 2% other; bupropion 93% white, sertraline 94% white ***Other population characteristics:*** Prior antidepressant use for current episode: bupropion SR: 22%, sertraline: 21%			

Authors: **Kavoussi et al.** ***Year:*** **1997** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D_{21}, HAM-A, CGI ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8, 12, 16
RESULTS:	• HAM-D_{21} similar changes in scores over study, no differences at any point in study • CGI, CGI-S, HAMA: no differences between groups
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 31.5%; bupropion SR: 28.7%, sertraline: 34.1% ***Withdrawals due to adverse events:*** buproprion SR: 3%, sertraline: 13% (p = 0.004) ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Significant differences (p < 0.05): Nausea: bupropion SR: 10%, sertraline: 30% Diarrhea: bupropion SR: 3%, sertraline: 22% Somnolence: bupropion SR: 2%, sertraline: 13%, • Sexual dysfunction: bupropion SR: 10%, sertraline: 61% • Orgasm failure or delay: men – bupropion SR: 10%, sertaline: 61% (p < 0.001); women – bupropion SR: 7%, sertraline: 41% (p < 0.001)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder

STUDY:	***Authors:*** **Kiev A, et. al.**[40] ***Year:*** **1997** ***Country:*** US			
FUNDING:	Solvay Pharma, Upjohn			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (2 centers) ***Sample size:*** 60			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluvoxamine 50-150 mg/d 7 weeks	Paroxetine 20-50 mg/d 7 weeks		
INCLUSION:	Age 18-65; DMS-IIIR criteria for single or recurrent MDD; minimum score of 20 on HAM-D_{21} (incl min score of 2 on depressed mood item)			
EXCLUSION:	Not fluent in written or oral English; history of medication non-compliance; demonstration of placebo response during run-in; history of substance abuse; severe suicide risk or auto-aggressive behavior; used a drug within 30 days with anticipated major organ toxicity; pregnancy or lactation; hypersensitivity to SSRIs; participation in previous fluvoxamine studies; other significant organic disease; clinically significant lab abnormalities; other primary psychiatric diagnoses; transportation difficulties			
OTHER MEDICATIONS/ INTERVENTIONS:	Antacids, laxatives, acetaminophen, aspirin, ibuprofen, chloral hydrate			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** fluvoxamine: 42.7; paroxetine: 39.9 ***Gender*** (% female): fluvoxamine: 53%; paroxetine: 53% ***Ethnicity:*** fluvoxamine: white 87%, non-white 13%; paroxetine: white: 93%, non-white: 7% ***Other population characteristics:*** (mean weight) fluvoxamine: 180.1 lbs; paroxetine: 175.8 lbs (mean height) fluvoxamine: 67.2 in; paroxetine: 65.8 in			

Authors: **Kiev A, et. al.** ***Year:*** **1997** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-21 ***Timing of assessments:*** Baseline and weeks 1,2,3,5,7
RESULTS:	• There was a mean change in HAM-D score for fluvoxamine: -13.45 and for paroxetine: -12.86, p = 0.763
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 31%; fluvoxamine: 34.5%; paroxetine: 27.6% ***Withdrawals due to adverse events:*** fluvoxamine: 6.8%; paroxetine: 13.8% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Significant differences in sweating was reported: fluvoxamine 10% and paroxetine 33% (p = 0.028) • Treatment-emergent adverse events were reported by 97% of fluvoxamine patients and 100% of paroxetine patients • One trend that was reported although not statistically significant: fluvoxamine patients reported more sleep-related side effects and paroxetine patients reported more GI side efects
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Kroenke K, et al.**[19] ***Year:*** **2001** ***Country:*** ***Trial name:*** ARTIST (A randomized trial investigating SSRI treatment)			
FUNDING:	Eli Lilly			
DESIGN:	***Study design:*** RCT (open label) ***Setting:*** Multi-center (76 primary care physicians) ***Sample size:*** 601			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20 mg/day 9 months	Fluoxetine 20 mg/day 9 months	Sertraline 50 mg/day 9 months	Mean dose at 9 months: Paroxetine: 23.5mg Fluoxetine: 23.4mg Sertraline: 72.8mg
INCLUSION:	18 years or older; depressive disorder as determined by the primary care physician (PCP); had home telephone			
EXCLUSION:	Cognitive impairment; lack of reading/writing skills; terminal illness; nursing home resident; actively suicidal; SSRI within past 2 months; other antidepressant therapy; bipolar disorder; pregnancy; lactation			
OTHER MEDICATIONS/ INTERVENTIONS:	Yes			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** paroxetine: 47.2, fluoxetine: 47.1, sertraline: 44.1 ***Gender*** (% female): paroxetine: 76; fluoxetine: 86; sertraline: 75 ***Ethnicity:*** (white) paroxetine: 85%; fluoxetine: 88%; sertraline: 79%; (black) paroxetine: 13%; fluoxetine: 9%; sertraline: 17% (other) paroxetine: 2%; fluoxetine: 3%; sertraline: 4% ***Other population characteristics:*** (MDD) total: 74%, paroxetine: 71%, fluoxetine: 74%; sertraline: 73%; (dysthymia) total: 18%, paroxetine: 22%, fluoxetine: 17%, sertraline: 18%; (minor depression) total: 8%, paroxetine: 7%, fluoxetine: 9%, sertraline: 9%			

Authors: **Kroenke K, et al.** ***Year:*** **2001**	
OUTCOME ASSESSMENT:	***Measures:*** Computer assisted telephone interview: SF-36, MSC (mental component summary), SCL-20 (symptoms checklist), PRIME-MD (primary care Evaluation of mental disorders), subscales of: medical outcomes study questionnaire (MOS): patient health questionnaire, health and daily living form, quality of social interaction scale, quality of close relationship scale, work limitations questionnaire ***Timing of assessments:*** Months 1, 3, 6, 9
RESULTS:	• All 3 treatment groups showed significant improvements in depression and other health related quality of life domains (social function, work function, physical function) • There were no significant differences between treatment groups in any of the 3 and 9 months outcome measures • Subgroup analysis showed that there were no differences in treatment effects for patients with MDD and for patients older than 60 years • Switch rate to other medication: paroxetine: 22%, fluoxetine: 14%, sertraline: 17%
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** **24.3%** (numbers provided are conflicting)**;** paroxetine: 24.8%, fluoxetine: 22.5%, sertraline: 25.7% ***Withdrawals due to adverse events:*** paroxetine: 30%, fluoxetine: 23%, sertraline: 24%. ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	No significant differences in adverse events between treatment groups
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder

STUDY:	**Authors: Lader M, et al.**[24] **Year: 2005** **Country:** UK and Denmark (meta-analysis) US and Europe (included trials)
FUNDING:	H. Lundbeck A/S; Forest Laboratories Inc
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 1,321
AIMS OF REVIEW:	To investigate the effect of escitalopram on sleep seen in clinical trials in the treatment of patients with depression based on single item scores of the Montgomery Asberg depression rating scale (MADRS) and reported treatment-emergent adverse effects, such as sedation and insomnia
STUDIES INCLUDED IN META-ANALYSIS	US: Burke et al., 2002; Rapaport et al., 2004 Europe: Lepola et al., 2003
TIME PERIOD COVERED:	NR
CHARACTERISTICS OF INCLUDED STUDIES:	Double blind; RCT; placebo-controlled; 8 week studies; 1 week single-blind placebo run-in; primary efficacy measure MADRS
CHARACTERISTICS OF INCLUDED POPULATIONS:	DSM-IV criteria for MDD; minimum MADRS score of 22 for inclusion; patients aged 18-65 (2 studies) or 18-80 (Rapaport)

Authors: Lader M, et al. **Year: 2005** **Country:** UK and Denmark				
CHARACTERISTICS OF INTERVENTIONS:	Patients randomized to escitalopram, citalopram, or placebo; no concomitant psychotropic medication allowed except zolpidem or benzodiazepines for insomnia			
MAIN RESULTS:	• Mean change from baseline in total MADRS score was -11.2 for placebo, -13.1 citalopram, and -13.8 for escitalopram; not a significant difference between the active drug groups in the LOCF analysis • Escitalopram patients with sleep problems shows statistically greater improvement ($p \leq 0.05$) in item 4 of the MADRS (sleep disturbance) than citalopram patients at weeks 1,4,6, 8, and endpoint (LOCF analysis)			
ADVERSE EVENTS: • **Insomnia** • **Somnolence**	Citalopram 8.6% 4.7%	Escitalopram 9.2% 6.9%	Placebo 3.9% 2.2%	
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	NR			
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes			
QUALITY RATING:	**Fair**			

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Lepola, et al.**[20] ***Year:*** **2003** ***Country:*** Europe, Canada			
FUNDING:	H. Lundbeck A/S			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (primary care) ***Sample size:*** 471			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Citalopram 20-40 mg/d 8 weeks	Escitalopram 10-20 mg/d 8 weeks	Placebo N/A 8 weeks	
INCLUSION:	Age 18 to 65 years; met DSM-IV criteria for MDD; MADRS score of ≥ 22 at baseline			
EXCLUSION:	Negative pregnancy test and stable use of oral contraceptive for 3 months; current or past history of mania; hypomania; alcoholism; substance abuse; dementia; epilepsy; presence of psychotic depression or organic affective illness; history of suicide attempts or high risk; current use of psychotropic meds; behavior therapy; psychotherapy			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 43 ***Gender*** (% female): citalopram: 69.4%, escitalopram 74.8%, placebo 72.1% ***Ethnicity:*** not reported ***Other population characteristics:*** Not reported			

Authors: **Lepola et al.** ***Year:*** **2003** ***Country:*** Europe, Canada	
OUTCOME ASSESSMENT:	***Measures:*** MADRS, CGI-S, CGI-I ***Timing of assessments:*** (Primary measures) baseline, weeks 1, 2, 3, 4, 6, 8
RESULTS:	• Significantly more escitalopram patients responded to treatment at study endpoint on the MADRS scale than citalopram patients (63.7% vs. 52.6%; p =0.009) • Significantly more escitalopram than citalopram-treated patients were in remission at endpoint (52.1% vs. 42.8%; p < 0.036) • Escitalopram was numerically better than citalopram at all time points on all 3 efficacy scales • Analysis of time to response showed that escitalopram–treated patients were responders 8.1 days faster than citalopram-treated patients
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 7**%**; citalopram 5%, escitalopram 6%, placebo 10% ***Withdrawals due to adverse events:*** citalopram 3.8%, escitalopram 2.6%, placebo 2.6% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• No significant differences between study groups • Nausea the most common adverse event: citalopram 14.4%, escitalopram 17.4%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	**Authors: Lepola UA, et al.**[83] **Year: 2004** **Country:** Multi-national (Canada, Europe, US)
FUNDING:	Not reported
DESIGN:	***Study design:*** Pooled analysis ***Number of patients:*** 977
AIMS OF REVIEW:	Compare efficacy of escitalopram (10-20 mg/d) versus citalopram (20-40 mg/d) by pooling the data from two published clinical trials
STUDIES INCLUDED IN META-ANALYSIS	Burke et al. (2002) and Lepola et al. (2003)
TIME PERIOD COVERED:	8 weeks
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs of escitalopram versus citalopram
CHARACTERISTICS OF INCLUDED POPULATIONS:	Outpatients male or female 18-65 years old who met DSM-IV criteria for major depressive episode; MADRS score of 22 or higher; Burke study et al., 2002 HAMD-17 score of 2 on item 1 was an additional requirement in the fixed dose study

Authors: Lepola UA, et al. **Year: 2004**	
CHARACTERISTICS OF INTERVENTIONS:	Escitalopram 10-20 mg/d for 8 weeks; citalopram 20-40 mg/d for 8 weeks
MAIN RESULTS:	• Statistically significantly greater proportion of patients responded to escitalopram than to citalopram (56.8% vs. 48.9%; p = 0.033) • Remission rates favored escitalopram but did not reach statistical significance (46.4% vs. 40.8%; p = 0.123). • Escitalopram-treated patients had a significant reduction in HAMD-17 total score compared to citalopram-treated patients (estimated difference 1.62; p = 0.034, LOCF)
ADVERSE EVENTS:	Headache (placebo 20%, escitalopram 16%, citalopram 19%) ;nausea (placebo 8%, escitalopram 16% (p < 0.05 vs placebo) ; citalopram 18% (p < 0.05 vs placebo) were reported by ≥10% of the patients in any treatment group in the pooled analysis
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Analysis includes the only 2 published studies. Authors state that data of a third, unpublished trial were not included
STANDARD METHOD OF APPRAISAL OF STUDIES:	No
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **McPartlin GM, et. al.**[64] ***Year:*** **1998** ***Country:*** UK			
FUNDING:	Wyeth-Ayerst			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (43 general practice sites) ***Sample size:*** 361			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine XR 75 mg/day 12 weeks	Paroxetine 20 mg/day 12 weeks		Fixed dose trial
INCLUSION:	At least 18 yrs; DSM-IV criteria for major depression; ≥ 19 on MADRS; symptoms for at least 14 days			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; history of seizures; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; use of investigational drug or antipsychotic drug within 30 days; clinically relevant medical disease or abnormalities in ECG or laboratory parameters; sumatriptan; MAOI; anxiolytic or sedative hypnotic within 30 days			
OTHER MEDICATIONS/ INTERVENTIONS:	Temazepam, zopiclone			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** venlafaxine xr: 45, paroxetine: 44 ***Gender*** (% female): venlafaxine xr: 68.3%, paroxetine: 68.5% ***Ethnicity:*** Not reported ***Other population characteristics:*** CGI severity: • Moderately ill-venlafaxine xr: 68%, paroxetine: 66% • Markedly ill-venlafaxine xr: 25%, paroxetine: 24% • Severely ill-venlafaxine xr: 3%, paroxetine: 3%			

Authors: **McPartlin GM, et al.** ***Year:*** **1998** ***Country:*** UK	
OUTCOME ASSESSMENT:	***Measure and timing of assessments:*** MADRS, HAM-D-17, CGI at days 7, 14, 21, 28, 42, 56, 84, quality of life questionnaire at day 84
RESULTS:	• Mean MADRS and HAM-D scores decreased significantly in both treatment groups ($p < 0.05$) • There were no significant differences in outcome measures between treatment groups • Global response (HAM-D, CGI, MADRS rates were at 76% for both treatment groups • Remission rates (≤ 6 on MADRS) were 48% for venlafaxine XR and 46% for paroxetine • Both treatment groups produced significant improvements on the quality of life scale without showing differences between groups
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 27.4%; venlafaxine XR: 26%, paroxetine: 29% ***Withdrawals due to adverse events:*** Overall: 14.1%; venlafaxine XR: 12%, paroxetine: 16% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• There were no significant differences in the frequency of adverse events between the treatment groups • 70% of patients in each group experienced at least 1 adverse event • Most common adverse events: nausea: venlafaxine XR: 25.4%, paroxetine: 24.9%; headache: venlafaxine XR: 8.8%, paroxetine: 11.9%; dizziness: venlafaxine XR: 16.6%, paroxetine: 9.6% • 3 patients in the paroxetine group experienced clinically significant increases in blood pressure vs. 1 patient in the venlafaxine group • No significant changes in weight or ECG findings were observed
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Mehtonen OP, et al.**[66] ***Year:*** **2000** ***Country:*** Scandinavia			
FUNDING:	Wyeth-Ayerst International			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 147			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine 75-150 mg/d 8 weeks	Sertraline 50-100 mg/d 8 weeks		
INCLUSION:	18-65 years; ≥ 18 on HAM-D-21			
EXCLUSION:	Pregnancy, lactation, or lack of adequate contraception; known sensitivity to venlafaxine or sertraline; history of seizures; dementia; history of psychotic disorders; alcohol or substance abuse; existing suicidal risk; clinically relevant progressive disease (cardiac, hepatic, renal;, investigational drugs within 30 days)			
OTHER MEDICATIONS/ INTERVENTIONS:	Oxazepam, temazepam			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** venlafaxine: 44.1, sertraline: 41.0 ***Gender*** (% female): venlafaxine: 65%, sertraline: 67% ***Ethnicity:*** Not reported ***Other population characteristics:*** Majority moderately or markedly ill on CGI scale			

Authors: **Mehtonen OP, et al.** ***Year:*** **2000** ***Country:*** Scandinavia	
OUTCOME ASSESSMENT: Response: 50% reduction in HAMD or MADRS and a CGI response Remission: HAMD score < 10	***Measures:*** HAM-D, CGI, MADRS ***Timing of assessments:*** Baseline, days 7, 14, 28, 42, 56
RESULTS:	• Both treatment groups showed significant reductions of MADRS, CGI, and HAM-D scores from baseline to week 8 • No significant differences between groups were observed at any point in time • Response rates (decrease ≥ 50% on HAM-D) were higher for venlafaxine at week 6 (74% vs. 59%; p = 0.04) and at the endpoint (83% vs. 68%; p = 0.05) • Remission rates (HAM-D ≤ 10) at endpoint were higher for the venlafaxine treated group (68% vs. 45%; p = 0.008) • No significant differences were noted in response rates on MADRS and CGI scales • Remission rates for patients who increased their dose was higher for the venlafaxine group (67% vs. 36%; p < 0.05)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 19%; venlafaxine: 21%, sertraline: 17% ***Withdrawals due to adverse events:*** 11.5%; venlafaxine: 16%, sertraline: 7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• No significant differences were observed between treatment groups for adverse events • Most common adverse events: nausea: venlafaxine: 36.0%, sertraline: 29.2%; headache: venlafaxine:28.0%, sertraline: 29.2%; diarrhea: venlafaxine: 8.0%, sertraline: 13.9%; sexual dysfunction: venlafaxine: 8.0%, sertraline: 5.6% • No clinically relevant changes in pulse, blood pressure or weight in either group
QUALITY RATING:	**Good**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	**Authors: Montgomery SA, et al.**[84] **Year: 2004** **Country:** Multinational (8 European countries)		
FUNDING:	H. Lundbeck A/S		
DESIGN:	***Study design:*** RCT ***Setting:*** Multicenter (44 sites) ***Sample size:*** 293		
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** ***Sample size:***	 Escitalopram 10-20 mg/d 8 weeks 148	 Venlafaxine XR 75-150 mg/d 8 weeks 145	
INCLUSION:	18-85 years of age; DSM-IV diagnosis of MDD; score of at least 18 on the MADRS		
EXCLUSION:	History of mania or bipolar disorder; schizophrenia or any psychotic disorder; currently suffering from OCD, eating disorders, mental retardation, any pervasive development disorder, or cognitive disorder; alcohol or drug abuse; treatment with antipsychotics, antidepressants, psychotropics, serotonin receptor agonists, lithium, carbamazepine, valproate, valpromide, electroconvulsive treatment; pregnant or breastfeeding		
OTHER MEDICATIONS/ INTERVENTIONS:	Medications thought to interfere with the study were excluded.		
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 48 ***Gender*** (% female): 72% ***Ethnicity:*** Not reported ***Other population characteristics:*** MADRS score: 28.8; HAM-D-17 score: 20.1		

Authors: Montgomery SA, et al. **Year: 2004** **Country:** Multinational	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** MADRS total score ***Secondary Outcome Measures:*** HAM-D-17; response and remission rates ***Timing of assessments:*** Baseline, weeks 1,2,3,4,6, and 8.
RESULTS:	• No statistically significant differences between escitalopram and venlafaxine XR in response (77.4 % vs. 79.6%) and remission (69.9% vs. 69.7%) • In the LOCF analysis there was no difference between groups in total MADRS or HAM-D-17 scores • Survival analysis of the ITT group showed that escitalopram patients achieved sustained remission 6.6 days faster than the venlafaxine XR patients ($p < 0.01$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 13.7%; escitalopram: 14%; venlafaxine XR: 13% ***Withdrawals due to adverse events:*** Escitalopram: 7.5%; venlavaxine XR: 11.2% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Nausea: venlafaxine XR: 26%; escitalopram: 17% ($p < 0.05$). • Increased sweating: venlafaxine XR: 12.5%; escitalopram: 6% ($p < 0.05$). • Constipation: venlafaxine XR: 6%; escitalopram: 2% ($p < 0.05$)
QUALITY RATING:	**Fair**

Evidence Table 1 **Major Depressive Disorder**

STUDY:	**Authors: Moore N, et al.** **Year: 2005** **Country:** NR		
FUNDING:	H. Lundbeck A/S		
DESIGN:	**Study design:** RCT **Setting:** Clinic and general practice **Sample size:** 280		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Escitalopram 20 mg 8 weeks 138	Citalopram 40 mg 8 weeks 142	
INCLUSION:	Outpatients, age 18-65 years; DSM IV MDD; MADRS of at least 30		
EXCLUSION:	Other primary diagnosis of Axis 1 disorders or a history of; substance abuse within 12 months; use of a depot antipsychotic within 6 months or any antipsychotic, anxiolytic or anticonvulsant within 2 weeks before start		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** Escitalopram: 44.1; citalopram: 46.2 **Gender (% female):** escitalopram: 81.7%, citalopram: 72% **Ethnicity:** NR **Other population characteristics:** **Baseline MADRS:** escitalopram: 16.6, citalopram: 15.7 **Baseline CGI-S:** escitalopram: 5.1, citalopram: 5.1		

Authors: Moore N, et al. **Year: 2005** **Country:** NR			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** MADRS; CGI-S **Secondary Outcome Measures:** MADRS-S **Timing of assessments:** Baseline, weeks 1, 4 and 8		
RESULTS:	• MADRS adjusted for baseline MADRS and investigator specialty Esc -22.4 Cit -20.3 ($p < 0.05$), between groups mean difference 2.1 (95% CI 0.01-4.21; $p < 0.05$) • Responders: (50% decrease in MADRS) Esc 76.1% Cit 61.3 ($p = 0.008$) • Remitters: Esc 56.1% Cit 43.6% ($p = 0.04$); NNT for remission: 9 • MADRS-S Esc -9.9 Cit -8.6 ($p < 0.05$) • CGI-S Esc -2.3 Cit -2.12 ($p = 0.65$) • Overall discontinuation was significantly higher in the Cit (10.6%) than in the Esc (4.3%) group ($p = 0.005$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes, 14 (11 protocol violations and 3 GCP violations)		
ATTRITION: **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy**: **Loss to follow-up differential high:**	Escitalopram 6 (4.3%) 4 (2.9%) 1 (0.7%)	Citalopram 15 (10.6%) 9 (6.3%) 4 (2.8%)	
ADVERSE EVENTS:	• 46 patients had adverse events escitalopram: 21 (14.8%), citalopram: 25 (16.4%) ($p = 0.70$) • No significant difference was reported between treatment groups		
QUALITY RATING:	**Fair**		

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Nemeroff CB, et al.**[42] ***Year:*** **1995** ***Country:*** US			
FUNDING:	Solvay Pharmaceuticals			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 95			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluvoxamine 50-150 mg/day Mean dose: 123.75 mg 7 weeks	Sertraline 50-200 mg/day Mean dose: 137.10 mg 7 weeks		
INCLUSION:	18-65 years; DSM-III-R criteria for major depression; HAM-D ≥ 20; minimum score of 2 on depressed mood item of HAMD; ≥ 8 Raskin Depression Scale; Covi anxiety score less than Raskin score; depressive symptoms for more than 2 weeks			
EXCLUSION:	Use of study drugs within 1 month; history of psychosis; lack of English fluency; response during washout; suicidal; psychoactive drugs, electroconvulsive therapy within 2 weeks; drug/alcohol dependence; pregnancy/lactation; clinically significant medical diseases/abnormalities; history of noncompliance; drug use within 30 days that could have toxic effects on organs; patients intolerant to SSRI side effects			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep, meds to treat GI disturbances and headache			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** No. Fluvoxamine group had a significantly higher rate of severe depression at baseline; setraline group had significantly more non-caucasians. ***Mean age:*** fluvoxamine: 38.5, sertraline: 41.2 ***Gender*** (female%): fluvoxamine: 61.2%, sertraline: 60.9% ***Ethnicity:*** non-caucasian: fluvoxamine: 2.0%; sertraline: 15.2% ***Other population characteristics:*** Recurrent episode: fluvoxamine: 61.0%, sertraline: 56.5%, more melancholic patients in fluvoxamine group (77.6% vs. 58.7%)			

Authors: **Nemeroff CB, et al.** ***Year:*** **1995** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** HAM-D (primary), HAM-A, Covi scale, Raskin scale, CGI-I, CGI-S, Hopkins symptom checklist: baseline, weeks 1, 2, 3, 5, 7, MSSI and clinical laboratory evaluation at week 7 only
RESULTS:	• Both treatment groups resulted in significant improvements of depression scores compared to baseline • Mean decrease in HAMD: sertraline: -10.98, fluvoxamine: -10.61 • There was no significant difference in efficacy between the treatment groups
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 30.9%; fluvoxamine: 42.9%, sertraline: 18.5% ***Withdrawals due to adverse events:*** fluvoxamine: 18.4%, sertraline: 2.2% (p-value not reported) ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Significantly more patients withdrew due to adverse events in the fluvoxamine group (n = 9) than in the sertraline group (n = 1) (p = 0.016) • Significantly greater sexual dysfunction was reported in the sertraline group (28%) than in the fluvoxamine group (10%); p = 0.047 • Most common adverse events: sertraline: insomnia (34.8%), headache (32.6%), diarrhea (23.9%), ejaculatory abnormality (22.2%); fluvoxamine: nausea (30.6%), headache (26.5%), insomnia (26.5%), somnolence (24.5%)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Newhouse PA, et al.**[37] ***Year:*** **2000** ***Country:*** US			
FUNDING:	Pfizer, Inc.			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 236			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** (Doses could be doubled after 4 weeks)	Sertraline 50-100 mg/d 12 weeks	Fluoxetine 20-40 mg/d 12 weeks		
INCLUSION:	≥ 60 years of age; DSM-III-R criteria for major depression; ≥ 18 on 24 item HAM-D			
EXCLUSION:	Other psychiatric disorder; significant physical illness; non-responders to antidepressants or ECT therapy			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate, temazepam for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 68, fluoxetine: 67 ***Gender*** (% female): sertraline: 63.2%, fluoxetine: 51.3% ***Ethnicity:*** sertraline: 95.7% white, 3.4% black, other 0.9%, fluoxetine: 100% white ***Other population characteristics:*** Not reported			

Authors: **Newhouse PA, et al.** ***Year:*** **2000** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** 24 item HAM-D, HAM-A, CGI-S, CGI-I, BDI, MADRS, POMS, Q-LES-Q, digit symbol substitution test, SLT ***Timing of assessments:*** Baseline, week 1, 2, 3, 4, 6, 8, 10, 12
RESULTS:	• Sertraline and fluoxetine were effective in the relief of depressive symptoms • There were no significant differences between sertraline and fluoxetine on the primary efficacy measures (HAM-D and CGI) HAMD Responders: sertraline: 73%, fluoxetine: 71% • HAMD remitters: sertraline: 45%, fluoxetine: 46% • Overall there was no significant differences between sertraline and fluoxetine on cognitive measures (SLT and digit symbol substitution test)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 32.2%; sertraline: 31.6%, fluoxetine: 32.8% ***Withdrawals due to adverse events:*** sertraline: 18.8%, fluoxetine: 24.4% (p = 0.5) ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Weight reduction: sertraline: -1.7lb, fluoxetine: -3.2lb (p = 0.018) • Otherwise no statistically significant differences between groups • Headache: sertraline: 33.6%, fluoxetine: 31.4% • Dizziness: sertraline: 7.8%, fluoxetine: 10.2% • Dry mouth: sertraline: 15.5%, fluoxetine: 7.6% • Nausea: sertraline: 14.7%, fluoxetine: 18.6% • Diarrhea: sertraline: 22.4%, fluoxetine: 16.1%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Nieuwstraten C, et al.**[67] ***Year:*** **2001** ***Country:*** Canada
FUNDING:	Not reported
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 1332
AIMS OF REVIEW:	To assess the benefits and risks of bupropion vs. SSRIs in major depression
STUDIES INCLUDED IN META-ANALYSIS	Kavoussi RJ et al. 1997, Segraves RT, et al. 2000, Weihs KL, et al. 2000, Croft H, et al. 1999, ColemanCC, et al. 1999, Feighner JP, et al. 1991
TIME PERIOD COVERED:	1966-1999
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs, study durations: 6-16 weeks, median 7 weeks
CHARACTERISTICS OF INCLUDED POPULATIONS:	Age: 36 to 70 yrs; proportion of females: 48.0% to 61.8%

Authors **Nieuwstraten C, et al.** ***Year:*** **2001** ***Country:*** Canada	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	Bupropion vs. sertraline (3 trials), bupropion vs. paroxetine (1 trial), bupropion vs. fluoxetine (1 trial)
MAIN RESULTS:	Results of HAM-D scores and CGI-I scores could not be pooled due to the unavailability of data; the weighted mean differences of CGI-S and HAM-A scores were not significantly different between bupropion and SSRIs
ADVERSE EVENTS:	Nausea, diarrhea, and somnolence occurred significantly less frequently in the bupropion group compared to the SSRI group RR: nausea: 0.6 (95%CI: 0.41-0.89), diarrhea: 0.31 (95%CI: 0.16-0.57), somnolence: 0.27 (95%CI: 0.15-0.48). Satisfaction with sexual function was significantly less in the SSRI group RR: 1.28 (95%CI: 1.16-1.41)
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 1 Major Depressive Disorder

STUDY:	***Authors:*** **Panzer MJ**[81] ***Year:*** **2005** ***Country*****:** Multinational
FUNDING:	GSK
DESIGN:	***Study design:*** Systematic review ***Number of patients:*** 7299
AIMS OF REVIEW:	To assess medication response of SSRIs to other ADs in patients suffering from MDD with secondary anxious feature
STUDIES INCLUDED IN REVIEW	28 studies
TIME PERIOD COVERED:	Not reported
CHARACTERISTICS OF INCLUDED STUDIES:	Double blinded, comparative trials of SSRIs to other types of ADs
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adult in- and outpatients with MDD as the primary diagnosis with anxious tendencies but not anxiety as a comorbidity

Authors: Panzer MJ **Year: 2005**	
CHARACTERISTICS OF INTERVENTIONS:	SSRIs vs. bupropion (7 studies); mirtazapine vs. SSRIs or amitriptyline (5 studies including 1 meta-analysis); TCAs vs. SSRIs (3 studies); SSRIs vs. SSRIs (2 studies); bupropion vs. TCAs (3 studies); nefazadone vs. TCAs or SSRIs (4 studies); venlafaxine vs. trazadone or SSRIs (4 studies)
MAIN RESULTS:	• SSRIs have not been shown to be more effective than TCAs in the treatment of anxious depression • Limited evidence that mirtazapine, bupropion and nefazadone may be superior to SSRIs
ADVERSE EVENTS:	Not reported
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes- MedLine and PsychInfo
STANDARD METHOD OF APPRAISAL OF STUDIES:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors :*** **Patris M, et al.**[26] ***Year:*** **1996** ***Country:*** France			
FUNDING:	Not specifically stated, one author is an employee of Lundbeck			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (general practices) ***Sample size:*** 357			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Citalopram 20 mg/d 8 weeks	 Fluoxetine 20 mg/d 8 weeks		
INCLUSION:	Ages 21-73; met DSM III R criteria for unipolar depression with a score on MADRS of 22 or more			
EXCLUSION:	Dysthymia; cyclothymia; decrease in MADRS > 20% from baseline during the run-in period; pregnancy; lactation; failure to use contraception; alcohol or drug abuse within the past year; MAOI use within 2 weeks; severe somatic disease; organic brain syndrome; schizophrenia; epilepsy; other neurological diseases; suicide risk; known hypersensitivity			
OTHER MEDICATIONS/ INTERVENTIONS:	Benzos allowed; no other psychotropics allowed; “Drug treatment for concurrent somatic illness was limited as much as possible”; high percentages of patients in both groups (83% and 81%) received concomitant medications; the use of non-psychotropic medication was similar in the 2 groups			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 43.5 years; citalopram: 44, fluoxetine: 43 ***Gender*** (female%): citalopram: 79%, fluoxetine: 76% ***Ethnicity:*** Not reported ***Other population characteristics:*** Major depression single episode: citalopram: 42%, fluoxetine: 46%; recurrent episodes: citalopram: 58%, fluoxetine: 54%			

Authors: **Patris M, et al.** ***Year:*** **1996** ***Country:*** France	
OUTCOME ASSESSMENT:	***Measures:*** Primary outcome: MADRS, secondary outcomes: HAM-D_{17}, CGI ***Timing of assessments:*** Baseline, 1, 2, 4, 6, 8 weeks
RESULTS:	No difference in mean MADRS score at endpoint or in mean change from baseline; mean change: citalopram: -20.7, fluoxetine: -19.4; responders (reduction in score from baseline > 50%) at endpoint: citalopram: 78 %, fluoxetine: 76 %; no statistical difference
ANALYSIS:	***ITT:*** No ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 12.6; citalopram: 13.9%, fluoxetine: 11.4% ***Withdrawals due to adverse events:*** citalopram: 5.7%, fluoxetine: 2.2% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• No significant differences • Reported at least one adverse event: citalopram: 50%, fluoxetine: 52% • No difference in the global evaluation of the interference of adverse events with the patient's daily functioning: citalopram: 34%, fluoxetine: 33%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Rapaport ME, et. al.**[28] ***Year:*** **1996** ***Country:*** US			
FUNDING:	Solvay Pharmaceuticals, Upjohn			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (6 sites) ***Sample size:*** 100			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Fluvoxamine 100-150 mg/d 7 weeks	 Fluoxetine 20-80 mg/d 7 weeks		
INCLUSION:	Male and female outpatients; 18-65 years; met DSM-III-R criteria for MDD; minimum HAM-D (21-item) score of 20; minimum score of 2 on the depressed mood item			
EXCLUSION:	Any primary DSM-IV Axis I disorder diagnosis other than MDD; acute suicidality; unstable medical conditions; history of seizure; had been treated with study medications; history of substance abuse or dependence; pregnancy and lack of appropriate birth control for women of child-bearing age			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** fluoxetine: 38.6; fluvoxamine: 40.0 ***Gender*** (% female): fluoxetine: 63.2; fluvoxamine: 62 ***Ethnicity:*** 95% white; 5% other; fluoxamine 98% white, fluvoxamine 92% white ***Other population characteristics:*** NR			

Authors: **Rapaport ME, et al.** ***Year:*** **1996** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-21, HAM-A, CGI-S, Raskin–Covi Scale, Hopkins Symptom Checklist, TESS (Specific treatment-emergent signs and symptoms) Barnes Akathisia Scale, Modified Scale for Suicidal Ideation ***Timing of assessments:*** Primary outcome measures weekly; secondary outcome measures at baseline and endpoint
RESULTS:	• No statistically significant differences between fluvoxamine and fluoxetine in all outcome measures • Both drugs significantly improved scores on HAM-D (<10 for both groups at endpoint)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes (7)
ATTRITION:	***Loss to follow-up:*** 16% ***Withdrawals due to adverse events:*** 4% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Overall, no difference in the rate of adverse events were reported between fluvoxamine and fluoxetine and there were no differences in the average event severity (1.12 vs. 1.13; p = NR) • Significantly more patients on fluoxetine than on fluvoxamine reported nausea (42.5% vs. NR; p = 0.03) • Other frequent adverse events: headache: fluoxetine 53%, fluvoxamine 50% (p not significant) vomiting: fluoxetine 13%, fluvoxamine 4% (p not significant) daytime agitation: fluoxetine 47%, fluvoxamine 32% (p not significant)
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Rudolph RL, et al.**[56] ***Year:*** **1999** ***Country:*** US			
FUNDING:	Wyeth-Ayerst Research			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 301			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine XR 75-225 mg/d 8 weeks	Fluoxetine 20-60 mg/d 8 weeks	Placebo N/A 8 weeks	Initial dosage could be increased after 2 weeks
INCLUSION:	≥ 18 years of age; met DSM-IV criteria for MDD; symptoms of depression for one month or more before study; pre-study and baseline score of ≥ 20 on the 21 item HAM-D			
EXCLUSION:	Known hypersensitivity to either drug; specified medical conditions; bipolar disorder; psychotic disorder not associated with depression; drug or alcohol abuse; pregnant or lactating			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep			
POPULATION CHARACTERISTICS: For ITT population (not reported for whole population)	***Groups similar at baseline:*** Yes ***Mean age:*** 40 ***Gender*** (female%): venlafaxine: 73%, fluoxetine: 69%, placebo: 64% ***Ethnicity:*** Not reported ***Other population characteristics:*** No statistically significant differences between groups in baseline mean 21-HAMD scores, mean MADRS scores, or duration of the current episode of depression; 24% used fluoxetine in past and 2% used venlafaxine in past			

Authors: **Rudolph RL, et al.** ***Year:*** **1999** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAMD-21, MADRS, CGI, HAM-A) ***Timing of assessments:*** Weeks 1, 2, 3, 4, 6, 8
RESULTS:	• No significant difference between venlafaxine and fluoxetine treatment on the 21-HAMD or MADRS at endpoint in the LOCF analysis • At endpoint in the LOCF analysis, venlafaxine patients showed a significant difference from placebo in the MADRS, CGI, and HAM-D depressed mood item • Fluoxetine patients only showed a significant difference in the HAM-D depressed mood item
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 23%; venlafaxine: 19%, fluoxetine: 28%, placebo: 21% ***Withdrawals due to adverse events:*** venlafaxine: 6%, fluoxetine: 9% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Venlafaxine patients experienced significantly more dizziness and nausea than fluoxetine or placebo patients ($p < 0.05$) • Venlafaxine and fluoxetine patients experienced significantly more asthenia and tremor than placebo patients
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Rush AJ, et al.**[77] ***Year:*** **1998** ***Country:*** US and Canada			
FUNDING:	Bristol Myers Squibb, Seay Center for Research (UT Southwestern), NIMH			
DESIGN:	***Study design:*** Pooled analysis from 3 RCTs: Gillin 1997,[75] Armitage 1997,[76] Rush 1998[77] ***Setting:*** Multi-center ***Sample size:*** 125			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Nefazodone 200-500 mg/d 8 weeks	Fluoxetine 20-40 mg/d 8 weeks		
INCLUSION:	Outpatient; ages 19-55; non-psychotic moderate to severe MDD by DSM-III-R criteria; minimum score of 18 on HAM-D_{17}; at least one of the following sleep disturbances as part of their depression symptoms: difficulty falling asleep on a nightly basis; waking up during the night inability to fall asleep again after getting out of bed			
EXCLUSION:	Engaged in shift work; independent sleep/wake disorders on polysomnography; significant concurrent general medical conditions; DSM IIIR criteria for substance abuse disorders within the year prior to study; other major Axis I disorders; pregnant, lactating or not using contraception			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** No; more people in their second or more depressive episode in fluoxetine group ***Age:*** 36.5; nefazodone: 36, fluoxetine: 37 ***Gender*** (% female) nefazodone: 59%, fluoxetine: 70% ***Ethnicity:*** nefazodone: 78% white, 9% black, 0% Asian, fluoxetine: 85% white, 7% black, 5% Asian ***Other population characteristics:*** Not reported			

Authors: **Rush AJ, et al.** ***Year:*** **1998** ***Country:*** US and Canada	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D_{17}, IDS-C and IDS-R, CGI, sleep quality as measured by HDRS Sleep Disturbance Factor and IDS-C and IDS-SR sleep factors and EEG measures ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8
RESULTS:	• No difference in efficacy between groups as measured by change in HAM-D17 • Response (< 10 on HAMD17): nefazodone: 47%, fluoxetine: 45% • On EEG: increased sleep efficiency, decreased awakenings and decreased % AMT (awake and moving time) for nefazodone as compared to fluoxetine • Also significant differences on sleep disturbance factors of the HAM-D and IDS-C and IDS-SR favoring nefazodone over fluoxetine
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 17% ***Withdrawals due to adverse events:*** nefazodone 9%, fluoxetine 8% ***Loss to follow-up differential high:*** Not reported
ADVERSE EVENTS:	No statistical comparisons reported
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Schatzberg et al.**[48] ***Year:*** **2002** ***Country:*** US			
FUNDING:	Organon Pharma			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 255			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Mirtazapine 15-45 mg/d 8 weeks	Paroxetine 20-40 mg/d 8weeks		(there was extension phase to 16 weeks but only included subjects who had favorable response during the first part of the study)
INCLUSION:	Minimum age of 65 years; DSM IV criteria for single or recurrent MDD; MMSE score > 25% for age and education; minimum score of 18 on HAM-D_{17}			
EXCLUSION:	HAMD decrease > 20% between screening and baseline; untreated or unstable clinically significant medical condition or lab/physical exam abnormality; history of seizures; recent drug or alcohol abuse or any principal psychiatric condition other than MDD; presence of psychotic features; suicide attempt in current episode; use of MAOI within 2 weeks, or other psychotropics or herbal treatments within 1 week; use of paroxetine or mirtazpine for the current episode; ECT therapy within 6 months; use of treatment for memory deficits; prior intolerance or lack of efficacy to mirtazapine or paroxetine in the past; patients who failed more than one adequate trial of an antidepressant for the current episode			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate or zolpidem for sleep induction; therapy for conditions like DM, hypothyroidism, high blood pressure, chronic respiratory conditions was allowed if they had been receiving for at least 1 month prior to screening visit			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 72 ***Gender*** (% female): mirtazapine: 50%, paroxetine: 53% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Schatzberg et al.** ***Year:*** **2002** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D 17, CGI-S, CGI-I ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8
RESULTS:	• Mean Ham-D17 scores significantly lower with mirtazapine at weeks 1, 2, 3, 6 but no difference at 8 week endpoint • Trend towards higher response and remission rates with mirtazapine but only significant difference at 2 weeks (response) and 6 weeks (remission) • Time to response: mirtazapine mean 26 days, paroxetine 40 days, p = -.016 for Kaplan-Meier plot comparing the two • No difference in CGI Improvement response
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 26.8% ***Withdrawals due to adverse events:*** 20.4%; mirtazapine 14.8%, paroxetine 26.2% (p < 0.05) ***Loss to follow-up differential high:*** Moderate
ADVERSE EVENTS:	• Frequency of treatment related adverse events: mirtazapine: 79.7%, paroxetine: 82.5% • Significant differences: dry mouth: mirtazapine 26.6%, paroxetine 10.3%; weight gain: mirtazapine 10.9%, paroxetine 0%; nausea: mirtazapine 6.3%, paroxetine19.0%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Schöne W, et al.**[32] ***Year:*** **1993** ***Country:*** Austria and Germany			
FUNDING:	SmithKline, Beecham			
DESIGN:	***Study design:*** RCT ***Setting:*** Geriatric outpatients at 6 centers in Austria and Germany ***Sample size:*** 108			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20-40 mg/d 6 weeks	Fluoxetine 20-60 mg/d 6 weeks		
INCLUSION:	Age 65 or greater; met DSM-IIR for MDD; HAM-D_{21} score $\geq$ 18 at baseline			
EXCLUSION:	Severe physical illness (not specified further); senile dementia; schizophrenia or organic brain syndrome; known abusers of alcohol; receipt of ECT within prior 3 mos.; MAOI or oral neuroleptics within 14 days; depot neuroleptics with 4 wks.; patients whose baseline HAM-D improved by > 20% or whose score was < 18 after placebo run-in were also excluded			
OTHER MEDICATIONS/ INTERVENTIONS:	Prohibited psychotropic meds except temazapam for sleep. Other allowed nonpsychotropic medications not specifically reported.			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 74; paroxetine: 74.3, fluoxetine: 73.7 ***Gender*** (% female): 87%, paroxetine: 83%, fluoxetine: 90% ***Ethnicity:*** Not reported ***Other population characteristics:*** History of prior depression: paroxetine: 94%, fluoxetine: 88%; duration of present episode > 12 months: paroxetine: 24%, fluoxetine: 27%			

Authors: **Schöne W, et al.** ***Year:*** **1993** ***Country:*** Germany	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D 21, MADRS, CGI ***Timing of assessments:*** Days 7, 21, 42
RESULTS:	• No significant difference in mean changes on HAM-D score • HAM-D responders at week 6 (i.e. reduction > 50% from baseline HAM-D_{21}): paroxetine: 37.5%, fluoxetine: 16% (p = 0.03) MADRS: no significant difference in mean change scores between groups • MADRS responders at week 6 (i.e. reduction > 50% from baseline MADRS): paroxetine 37.5%, fluoxetine 17.5%, (p = 0.04)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** Not reported ***Withdrawals due to adverse events:*** 12%; paroxetine: 11.1%, fluoxetine: 13.5% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	No significant differences between paroxetine and fluoxetine on overall incidence of adverse events or of any specific adverse event
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Sechter D, et al.**[18] ***Year:*** **1999** ***Country:*** France			
FUNDING:	Pfizer France			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (45 private psychiatrists) ***Sample size:*** 234			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Sertraline 50-150 mg/d 24 weeks	 Fluoxetine 20-60 mg/d 24 weeks	 <u>Mean daily dose:</u> Sertraline: 76.5 mg/d Fluoxetine: 33.6 mg/d	
INCLUSION:	≥ 18-65 yrs; DSM-III criteria for major depression; HAM-D-17 ≥ 20			
EXCLUSION:	History of psychosis; organic mental disorder; bipolar disorder; personality disorder; suicidal; psychoactive drugs; ECT within 1 month; drug/alcohol dependence; pregnancy/lactation; clinically significant medical diseases/abnormalities; anticoagulant; serotonergic drugs; MAOI; lithium; alpha methyldopa; drug sensitivity or lactose intolerance; previous failure on three or more antidepressants			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 43.4, fluoxetine: 42.5 ***Gender*** (% female): sertraline: 66.7%, fluoxetine: 68.1% ***Ethnicity:*** Not reported ***Other population characteristics:*** Patients with first depressive episode: sertraline: 27.4%, fluoxetine: 21.0%			

Authors: **Sechter D, et al.** ***Year:*** **1999** ***Country:*** France	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D, CGI-I, CGI-S, Covi, Sickness Impact Profile, HAD scores, Leeds Sleep Evaluation ***Timing of assessments:*** Baseline, weeks 2, 4, 8, 12, 18, 24
RESULTS:	• At study endpoint both treatment groups had significant improvements over baseline on all efficacy variables ($p < 0.001$) • There were no significant differences between study groups in outcome measures (HAM-D, CGI, Covi) at any point in time; the magnitude of changes was higher for sertraline. • Response was observed in 74% in sertraline patients versus 64% in fluoxetine patients on HAM-D • The Leeds Sleep Evaluation Scale showed a trend favoring sertraline but no significant difference compared to fluoxetine • Both treatments showed significant improvements in SIP • SIP sub scores showed significant greater improvements for sertraline relating to sleep and rest ($p = 0.04$), emotional behavior ($p = 0.04$), and ambulation ($p = 0.05$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 29.2%; sertraline: 24.7%, fluoxetine: 33.6% ***Withdrawals due to adverse events:*** sertraline: 6%, fluoxetine: 10% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• There were no significant differences in the incidence of adverse events between treatment groups • Most common adverse event: nausea: sertraline: 23%, fluoxetine: 17%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Segraves, et al.**[85] **Year: 2000** ***Country:*** US			
FUNDING:	Glaxo Wellcome Inc			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 248			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/d 16 weeks	Bupropion SR 100-300 mg/d 16 weeks		
INCLUSION:	DSM-IV diagnosis of moderate to severe depression with minimum duration of 4 weeks and max duration of 24 months; ≥ 18 years of age; in a stable relationship, have normal sexual functioning and sexual activity at least once every 2 weeks			
EXCLUSION:	Predisposition to seizure or taking med that lowers seizure threshold; history or current diagnosis of anorexia or bulimia; pregnant, lactating or unwilling to take contraceptives; history of alcohol or substance abuse; eating disorder; suicidal tendencies; prior treatment with bupropion or sertraline; used any psychoactive drug within 1 week of study (2 weeks for MAOI or protriptyline or 4 weeks for fluoxetine or any investigational drug); prior treatment with bupropion or sertraline			
OTHER MEDICATIONS/ INTERVENTIONS:	None reported			

Authors: **Segraves et al.** ***Year:*** **2000** ***Country:*** US	
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 40 bupropion: 39 ***Gender*** (% female): sertraline: 48%, bupropion SR: 48% ***Ethnicity:*** (% white) sertraline: 94%, bupropion SR: 93% ***Other population characteristics:*** No significant differences in diagnosis
OUTCOME ASSESSMENT:	***Measures:*** Sexual function assessment, Sexual desire disorder, Sexual arousal disorder, Orgasm dysfunction, Premature ejaculation (men only), patient rated overall sexual satisfaction on 6 point Likert scale ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8, 12, 16
RESULTS:	▪ Significantly more sertraline patients developed one of the following sexual dysfunctions compared to bupropion SR patients: sexual arousal disorder, orgasm dysfunction, or premature ejaculation (men only); (men: 63% and 15%, respectively, $p < 0.001$; women: 41% and 7%, respectively, $p < 0.001$) ▪ Beginning on day 21 and continuing throughout the study, significantly more bupropion SR-treated patients were satisfied with their overall sexual functioning compared with sertraline-treated patients
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 31.5%; bupropion SR: 29%, sertraline: 34% ***Withdrawals due to adverse events:*** 1.6%; bupropion SR: 0%, sertraline: 1.6% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Silverstone PH et al.**[57, 58] ***Year:*** **1999, 2001** (subgroup analysis) ***Country:*** Canada			
FUNDING:	Wyeth-Ayerst Research			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 368			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine XR 75-225 mg/d (Could be increased to 150 mg/d on day 14 and 225 mg/d on day 28) 12 weeks	Fluoxetine 20-60 mg/d (Could be increased to 40 mg/d on day 14 and 60 mg/d on day 28) 12 weeks	Placebo N/A 12 weeks	
INCLUSION:	18 years or older; met DSM-IV criteria for major depression; score of 20 on first 17 items of the 21 item HAM-D; score of 8 on the COVI scale; depression for 1 month before the study			
EXCLUSION:	Pregnant women; history of significant illness; suicidal tendencies; other psychiatric or psychotic disorders not associated with depression; history of drug or alcohol abuse; use of investigational drug or ECT therapy within 30 days; history of seizures; taken other antidepressant or antipsychotic within 7 days of baseline			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate or zoplicone for sleep; cisapride for nausea.			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** placebo: 41.6, venlafaxine: 41.1, fluoxetine: 43.2 ***Gender*** (female%): venlafaxine: 64%, fluoxetine: 60%; placebo: 57.6 ***Ethnicity:*** Not reported ***Other population characteristics:*** *Subgroup analysis:* Patients with GAD (n = 92)			

Authors: **Silverstone PH, et al.** ***Year:*** **1999, 2001** ***Country:*** Canada	
OUTCOME ASSESSMENT: Response: 50% decrease in HAMD or HAMA score of 1 or 2 on CGII Remission Score ≤ 8 on HAMD	***Measures:*** 21 item HAM-D, HAM-A, the Covi Scale, Hospital Anxiety and Depression scale, CGI scale ***Timing of assessments:*** Baseline, days 7, 14, 21, 28, 42, 56, 84
RESULTS:	No statistical comparisons between fluoxetine and venlafaxine (just placebo) • HAM-D scores in the venlafaxine and fluoxetine groups dropped significantly when compared with placebo • Venlafaxine had significantly more HAM-A responders at week 12 than fluoxetine • The HAM-D remission rate in the venlafaxine group was significant compared to placebo at weeks 3, 4, 6, 8, 12 & final • The HAM-D remission rate in the fluoxetine group was significant compared to placebo at weeks 8, 12, & final *Subgroup analysis:* • There were no significant differences in outcome measures between the active treatment groups (compared to placebo) • Patients in the venlafaxine group but not in the fluoxetine group showed a significant decrease in HAM-D and HAM-A scores compared to placebo ($p < 0.05$) • Onset of action seemed to be slower in patients with GAD compared to patients without
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 32%; venlafaxine xr: 29%, fluoxetine: 26%, placebo: 40% ***Withdrawals due to adverse events:*** venlafaxine xr: 10%, fluoxetine: 7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Significantly more dizziness ($p < 0.001$) and sweating ($p < 0.05$) occurred with venlafaxine than with fluoxetine
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder

STUDY:	**Authors: Sir A, et al.**[65] **Year: 2005** **Country:** Australia and Turkey		
FUNDING:	Pfizer, Inc.		
OBJECTIVE:	Test for differences between sertraline and venlafaxine XR on measures of QOL and test for efficacy differences on measures of depressive symptoms and tolerability, including discontinuation symptoms		
DESIGN:	**Study design:** RCT: 8 weeks on study drug, then up to 2 weeks discontinuation **Setting:** Clinics (Turkey 7 and Australia 6) **Sample size:** 163		
INTERVENTION: **Drug:** **Dose-mean(range):** **Duration:** **Sample size:**	Sertraline 105.4(50-150)mg/day 8 weeks 79	Venlafaxine XR* 161.4(75-225)mg/day 8 weeks 84	
INCLUSION:	Outpatients; 18 years or older; HAM-D $\geq$ 18; MDD single or recurrent according to the DSM-IV		
EXCLUSION:	History of bipolar disorder; any psychotic disorder; delirium; dementia; pregnancy; alcohol/drug abuse/dependence in past 6 months; schizoid, schizotypal or borderline personality disorders; additional DSM IV axis I disorders were allowed if they were secondary diagnoses; history of non-response to sertraline, venlafaxine or 2 anti-depressants in the current episode		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes, but there was a small differences obvious in family member diagnosis of affective disorder. **Mean age:** 37 **Gender (% female):** sertraline: 72.2%, venlafaxine: 66.7% **Ethnicity (% white):** sertraline: 96.2%, venlafaxine: 100% **Other population characteristics:** **Baseline Q-LES-Q:** sertraline: 55.3 +/- 9.4, venlafaxine: 52.7 +/- 11.2 **Baseline HAM-D:** sertraline: 23.4 +/-4.4, venlafaxine: 23.5 +/-4.4 **Baseline CGI-S:** sertraline: 4.5 +/- 0.8, venlafaxine: 4.6 +/- 0.8 **Family member diagnosed with affective disorder:** sertraline: 42 (53.2%), venlafaxine: 34 (40.5%)		

*Note: From here on venlafaxine refers to venlafaxine XR

<table>
<tr><td colspan="4">Authors: Sir A, et al.
Year: 2005</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Q-LES-Q
Secondary Outcome Measures:
• HAM-D, HAM-A, CGI-S, CGI-I, VAS for pain and depression, Endicott Work Productivity Scale (EWPS), Antidepressant Discontinuation Scale (ADDS)
• Discontinuation emergence: any symptom present in week 9 or 10 not present in first 8 weeks or that increased in severity during weeks 9 or 10.
Timing of assessments: Baseline and every week thereafter.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Efficacy
• Change in Q-LES-Q: Ser 16.8 ± 1.77 Ven 17.5 ± 14.5 p = 0.74
• Change in HAM-D: Ser -15.9 ± 0.95 Ven -14.3 ± 0.94 p = 0.17
• Change in HAM-A: Ser -14.1 ± 0.99 Ven -12.9 ± 0.99 p = 0.32
• Mean CGI-S: Ser 2.0 ± 1.22 Ven 2.2 ± 1.25 p = 0.45
• No significant difference exists in terms of efficacy between venlafaxine and sertraline.
Discontinuation
• Number of discontinuation-emergent symptoms with frequency of >10% vs. other drug: venlafaxine 4, sertraline 0
• Number of discontinuation-emergent symptoms of at least moderate intensity that were more than twice as common as for the other drug: venlafaxine 8, sertraline 1
• Discontinuation of sertraline associated with fewer discontinuation-emergent symptoms than for discontinuation of venlafaxine. (Although not all differences achieved statistical significance, there is a clear trend.)</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions: No</td></tr>
<tr><td>ATTRITION:
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:
Loss to follow-up differential high:</td><td><u>Overall</u>
23%
6%
NR
No</td><td><u>Sertraline</u>
16.5%
3.8%
NR</td><td><u>Venlafaxine</u>
29.8%
8.4%
NR</td></tr>
<tr><td>ADVERSE EVENTS:</td><td colspan="3">• AE rates (n(%)) include those that were evident in taper- off period (2 additional weeks following initial 8 weeks) which results in higher rates than normally found.
• Asthenia: Ser 21(26.6) Ven 21(25.6)
• Headache: Ser 35(44.3) Ven 27(32.1)
• Dry mouth: Ser 32(40.5) Ven 20(23.8)
• Nausea: Ser 41(51.9) Ven 40(47.6)
• Dizziness: Ser 26(32.9) Ven 22(26.2)
• Insomnia: Ser 28(35.4) Ven 23(27.4)
• Somnolence: Ser 17(21.5) Ven 22(26.2)
• Yawning: Ser 24(30.4) Ven 24(28.6)
• Sweating: Ser 25(31.6) Ven 18(21.4)</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Good</td></tr>
</table>

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Tylee A, et al.**[61] ***Year:*** **1997** ***Country:*** UK			
FUNDING:	Wyeth			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (34 UK general practices) ***Sample size:*** 341			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine 75 mg/day, fixed dose 12 weeks + 7day post follow-up	Fluoxetine 20 mg/day, fixed dose 12 weeks + 7day post follow-up		
INCLUSION:	≥18 yrs; DSM-IV criteria for major depression; MADRS ≥ 19; depressive symptoms for more than 2 weeks			
EXCLUSION:	Use of study drugs within 1 month; history of psychosis; organic mental disorder; bipolar disorder; suicidal; psychoactive drugs ECT therapy within 1 month; drug/alcohol dependence; pregnancy/lactation; clinically significant medical diseases/abnormalities			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** venlafaxine: 43.5, fluoxetine: 45.5 ***Gender*** (% female): venlafaxine: 67.8%, fluoxetine: 74.7% ***Ethnicity:*** Not reported ***Other population characteristics:*** CGI severity: Mildly ill: venlafaxine: 8%, fluoxetine: 6%. Moderately ill: venlafaxine: 66%, fluoxetine: 62%. Markedly ill: venlafaxine: 21%, fluoxetine: 28%. Severely ill: venlafaxine: 4%, fluoxetine: 4%			

Authors: **Tylee A, et al.** ***Year:*** **1997** ***Country:*** UK	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** MADRS, baseline, weeks 1, 3, 6, 8, 12, HAM-D, CGI: weeks 3, 6, 8, 12, Hospital Anxiety and Depression (HAD): weeks 3, 6, 12, patient sleep diary: first 3 weeks
RESULTS:	• MADRS, HAM-D, and CGI scores decreased significantly for both treatment groups • There were no significant differences between treatment groups • Remission rate: (MADRS ≤ 6) venlafaxine: 35.4 %, fluoxetine: 34.1% • Response rates: venlafaxine: 55.1%, fluoxetine: 62.8% • No significant differences in effects on sleep
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 27%; venlafaxine: 27%, fluoxetine: 27% ***Withdrawals due to adverse events:*** venlafaxine: 21%, fluoxetine: 14% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• No significant differences between study groups • At least 1 adverse event: venlafaxine: 80.7%, fluoxetine: 71.8% • Nausea: venlafaxine: 34.5%, fluoxetine: 18.2% • Vomiting: venlafaxine: 12.9%, fluoxetine: 5.3% • Headache: venlafaxine: 11.1%, fluoxetine: 17.1% • Dizziness: venlafaxine: 11.1%, fluoxetine: 6.5%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Weihs KL, et al., Doraiswamy PM, et al.**[70, 71] ***Year:*** **2000, 2001** ***Country:*** US			
FUNDING:	Glaxo Wellcome			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 100			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Bupropion SR 100-300 mg/d Mean daily dose: 197 mg/d 6 weeks	 Paroxetine 10-40 mg/d Mean daily dose: 22 mg/d 6 weeks		
INCLUSION:	60 yrs or older; DSM-IV criteria for major depression; recurrent episode of non-psychotic depression; ≥ 18 on HAM-D-21; duration at least 8 weeks not more than 24 months			
EXCLUSION:	History of seizures; dementia; alcohol or substance abuse; existing suicidal risk; clinically relevant; unstable medical disorder; psychoactive drugs within 1 week or investigational drugs within 4 weeks; taking other drugs known to lower seizure threshold; anorexia or bulimia; previous treatment with buproprion or paroxetine			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** bupropion sr: 69.2, paroxetine: 71.0 ***Gender*** (% female): bupropion sr: 54, paroxetine: 60 ***Ethnicity:*** (% white) bupropion sr: 98, paroxetine: 90 ***Other population characteristics:*** Prior antidepressant use for current episode: buproprion sr: 17%, paroxetine: 12%			

Authors: **Weihs KL, et al., Doraiswamy PM et al** ***Year:*** **2000, 2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** HAM-D, CGI-S, CGI-I, HAM-A weekly for 6 weeks, Short Form 36 Health Survey (SF-36), Quality of Life Depression Scale (QLDS) at baseline and week 6
RESULTS:	• No significant differences in any outcome measures between the treatment groups (LOCF and observed) • Response rates (≥ 50% reduction in HAM-D) were similar in both groups: bupropion sr: 71%, paroxetine: 77% • CGIS, CGII, and HAMA were all similar at each week of the study • No significant differences in the Quality of Life scales (QLDS, SF-36) between treatment groups at the endpoint • Overall significant improvement in QLDS and QOL at day 42 ($p < 0.0001$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 16%; bupropion sr: 16.6%, paroxetine: 15.4% ***Withdrawals due to adverse events:*** bupropion sr: 8.3%, paroxetine: 5.8% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Significantly more patients treated with paroxetine reported somnolence (27% vs. 6%; $p < 0.05$), diarrhea (21% vs. 6%; $p < 0.05$), and constipation (15% vs. 4%; $p < 0.05$) • More than 10% in both groups reported headache, insomnia, dry mouth, nausea, dizziness, and agitation • Neither group showed clinically significant changes in weight or clinically significant cardiovascular effects
QUALITY RATING:	**Fair**

Evidence Table 2: Dysthymia

STUDY:	***Authors:*** **Barrett, et. al.**[90] ***Year:*** **2001** ***Country:*** US			
FUNDING:	Hartford Foundation, MacArthur Foundation			
DESIGN:	***Study design:*** RCT (also used a behavior therapy arm) ***Setting:*** Primary care settings ***Sample size:*** 241			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 10-40 mg/d 11 weeks	Placebo N/A 11 weeks	Behavior Therapy N/A 11 weeks	
INCLUSION:	Age 18-59; met DSM II-R criteria for dysthymia or minor depression and score 10 or higher on HAM-D-17; illness at least 4 weeks with at least 3 symptoms; diagnosis made by research psychiatrist using PRIME-MD			
EXCLUSION:	(from Williams et al., 2000) major depression; psychosis; schizophrenia or schizoaffective disorder; bipolar disorder; alcohol or other substance abuse within the past 6 months; borderline or antisocial personality disorder; serious suicidal risk; moderate or severe cognitive impairment (MMSE $\leq$ 23); medical illness with prognosis $\leq$ 6 months to live; patients in current treatment excluded unless willing to discontinue and dose $\leq$ 50 mg of amitriptylline			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Age:*** Mean 44.1 ***Gender*** (% female): 63.9% ***Ethnicity:*** Non-Hispanic white: 90%, Asian Pacific: 3%, African American: 3%, Native American: 3%, Hispanic: < 1% ***Other population characteristics:*** Comorbid anxiety disorders: 25%, employed FT: 61.3%, mean # of chronic medical conditions: 2.1, Duke Severity of Illness mean 13.3			

Authors: **Barrett et al.** ***Year:*** **2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** Primary Outcome was 13 items from the Hopkins Symptom Check list Depression Scale (HSCL-D-20) plus 7 additional items. Timing: baseline and each treatment visit (1, 2, 4, 6, 8, 11), also measured: Ham-D-17 and SF36, mental health component and physical health component timing: baseline, 6 and 11 weeks
RESULTS:	• ITT analysis: mean decrease in HSCL-D-20; paroxetine: 0.88 (0.08), placebo: 0.85 (0.09); behavior therapy: 0.79 (0.09), no significant differences between arms; • remission by HAM-D-17 score $\leq$ 6: paroxetine: 80%, placebo: 44.4%; behavior therapy: 56.8% (p = 0.008 for difference among all three arms) • minor depression: paroxetine 60.7%, placebo 65.6%; behavior therapy 65.5%(p = 0.906 for difference among all three arms) • SF 36 results were not compared head to head, they seem to only be compared within groups over time
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** No
ATTRITION:	***Loss to follow-up:*** 20.7 ***Withdrawals due to adverse events:*** PAR: 7.5 ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 2 Dysthymia

STUDY:	**Authors: Devanand DP, et al.**[92] **Year: 2005** **Country:** US		
FUNDING:	NIMH and capsules provided by Eli Lilly		
OBJECTIVE:	To determine efficacy and side effects of fluoxetine in elderly patients with dysthymia		
DESIGN:	**Study design:** RCT **Setting:** Depression clinic **Sample size:** 90		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Fluoxetine 10-60 mg/day 12 weeks 44	Placebo N/A 12 weeks 46	
INCLUSION:	Outpatients with a primary diagnosis dysthymia following DSM-IV criteria; at least 60 years of age; HAM-D score 8-25; and, CGI-S severity score of 3 or more		
EXCLUSION:	MDD; allergy to fluoxetine; previous lack of response to SSRI; suicide ideation or plan; Mini-Mental State exam less than 23 out of 30; alcohol or substance abuse in last 6 months; bipolar disorder, schizophrenia or other psychotic disorder; stroke, dementia or other major neurological disorder or insult		
OTHER MEDICATIONS/ INTERVENTIONS:	Zolpidem (up to 10 mg/day) for insomnia and lorazepam (up to 2 mg/day) for anxiety		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Uncertain; fluoxetine group more likely to be unmarried males with comorbid anxiety disorder and have a family history of affective disorder. **Mean age:** fluoxetine: 69.0, placebo: 70.8 **Gender (% female):** fluoxetine: 32.5%, placebo: 40.9% **Ethnicity (% white):** fluoxetine: 86.4%, placebo 89.1% **Other population characteristics:** **Married:** fluoxetine: 29.6%, placebo: 37% **Family history of affective disorder:** fluoxetine: 38.6%, placebo 21.7% **Comorbid anxiety disorder:** fluoxetine: 11.4%, placebo 6.5% **HAM-D:** fluoxetine: 15.3 (+/- 5.1), placebo: 14.4 (+/- 3.0) **CGI-S:** fluoxetine: 3.4 (+/- 0.5), placebo 3.2 (+/- 0.5) **CDRS:** fluoxetine: 28.0 (+/- 8.8), placebo 25.2 (+/- 11.5)		

Authors: Devanand DP, et al. **Year: 2005**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** • HAM-D and CDRS • Responders classified as having a ≥ 50% decrease in Ham-D scores at final assessment relative to baseline and have a CGI improvement score of 1 or 2 **Timing of assessments:**		
RESULTS:	• Response rates: fluoxetine: 27.3%, placebo: 19.6% ($p < 0.4$) • No differences between treatment groups in quality of life • Only the CDRS scores demonstrated a significant effect for treatment group in regression analysis: fluoxetine 26.2%, placebo 4.6% ($p < 0.04$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ATTRITION: **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy**: **Loss to follow-up differential high:**	Overall 21 4 4 No	Fluoxetine 12 3 2	Placebo 7 1 2
ADVERSE EVENTS:	• The only side effect that differed significantly between the 2 groups was yawning: fluoxetine baseline 2.5%, endpoint 20% vs. placebo baseline 6.3%, endpoint 7.5% (% change $p < 0.03$)		
QUALITY RATING:	**Good**		

Evidence Table 2 Dysthymia

STUDY:	***Authors:*** **Ravindran et. al.**[89] ***Year:*** **2000** ***Country:*** Canada and Europe			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 310			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Sertraline 50-200 mg/day 12 weeks	 Placebo N/A 12 weeks		
INCLUSION:	18 yrs or older; DSM-III-R criteria for dysthymia disorder; duration ≥ 5yrs; ≥ 12 on HAM-D seasonal affective disorders version			
EXCLUSION:	Pregnancy, lactation or lack of adequate contraception; major depression; history of psychotic disorders; bipolar disorder; previous use of sertraline; clinically relevant disease; unstable medical conditions; use of psychotropic meds			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 46.0; placebo: 44.2 ***Gender*** (% female): sertraline: 65.8, placebo: 67.8 ***Ethnicity:*** Not reported ***Other population characteristics:*** Early onset (before 21 yrs): sertraline: 38.0%, placebo: 40.8% Duration of illness: sertraline: 17 years, placebo: 15.9 years			

Authors: **Ravindran et al.** ***Year:*** **2000** ***Country:*** Canada and Europe	
OUTCOME ASSESSMENT:	***Measures:*** SIGH-SAD (Hamilton Depression Rating Scale, Seasonal Affective Disorders Version), HAM-A, CGI-I, CGI-S, MADRS, HAD-A, HAD-D (Hospital Anxiety and Depression scale), BQOLS (Batelle Quality of Life Scale) ***Timing of assessments:*** Weeks 1, 2, 4, 6, 8, 12
RESULTS:	• Patients in the sertraline group had significantly greater reductions in SIGH-SAD (p = 0.03), MADRS (p = 0.02), CGI-S (p = 0.02), CGI-I (p = 0.02), HAD-A (p = 0.003), and HAD-D (p = 0.004) scores compared to placebo • The number of responders was significantly higher in the sertraline group • HAM-A: sertraline: 51.9%, placebo: 33.8%, p = 0.001 • MADRS: sertraline: 53.2%, placebo: 37.5%, p =0.006 • CGI-I: sertraline: 60.1%, placebo: 39.5%, p < 0.001 • The number of remitters was also significantly higher in the sertraline group 33.8% vs. 21.6%, p = 0.02 • BQOLS showed significantly greater improvements in 8 of 9 domains in the sertraline group
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 24.2%; sertraline: 23.4%, placebo: 25.0% ***Withdrawals due to adverse events:*** sertraline: 13.3%, placebo: 7.9% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• More patients in the sertraline group experienced adverse events: 75.3% vs. 64.5% (p = 0.047) • Increased sweating: sertraline: 13.9%, placebo: 2% • Tremor: sertraline: 13.9%, placebo: 0.7% • Nausea: sertraline: 20.9%, placebo: 17.8% • Ejaculation disorder: sertraline: 9.3%, placebo: 0
QUALITY RATING:	**Fair**

Evidence Table 2 Dysthymia

STUDY:	***Authors:*** **Thase et. al.,[86] Kocsis et. al.,[87] Hellerstein et. al.[88]** ***Year:*** **1996, 1997, 2000** ***Country:*** US			
FUNDING:	Not reported			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (17 US centers) ***Sample size:*** 416			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/day 12 weeks	Imipramine 50-300 mg/day 12 weeks	Placebo N/A 12 weeks	
INCLUSION:	Dysthymia for more than 5 years without depression-free period exceeding 2 consecutive months; HAM-D score ≥ 12; age 25-65 yrs.			
EXCLUSION:	Other Axis I disorders; pregnancy, lactation; failed to respond in previous trials; drug/alcohol dependency; suicidal risk			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** 42 ***Gender*** (% female): 65% ***Ethnicity:*** Caucasian: 95%, black: 2%, Asian: 0.5%, other: 2% ***Other population characteristics:*** Not reported			

Authors: **Thase, Kocsis, Hellerstein** ***Year:*** **1996, 1997, 2000** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures and timing of assessment:*** CGI weekly, HAM-D, MADRS biweekly, DSM-IV, Hopkins Symptom Checklist, Inventory for Depression Symptomatology, Social Adjustment Scale, Quality of Life Enjoyment and Satisfaction Questionnaire weeks 8 and 12
RESULTS:	• Sertraline group showed significantly more responders than placebo (59.0% vs. 44.3%; p < 0.02) • No significant differences in responders between sertraline and imipramine-treated patients • A significantly greater proportion of patients in the sertraline group increased in psychosocial functioning compared to placebo (61% vs. 45%; p = 0.01) as measured by the Global Assessment of Functioning Score of 71 or more • Significant improvements in family relationships, marital relationships, and parental role functioning • The harm avoidance scores (from the Tri-dimensional Personality Questionnaire) were significantly decreased in all treatment groups • Significantly more sertraline patients than placebo patients were classified as harm avoidance responders (p = 0.001) •
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 24.3%; sertraline: 15.7%; imipramine: 33.1%; placebo: 24.3% ***Withdrawals due to adverse events:*** sertraline: 6.0%; imipramine: 18.4%; placebo: 3.6% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 2 Dysthymia

STUDY:	**Authors: Vanelle et al.**[93] **Year:** 1997 **Country:** France		
FUNDING:	NR		
DESIGN:	**Study design:** RCT **Setting:** Psychiatric centers **Sample size:** 140		
INTERVENTION: **Drug:** **Dose:** **Duration:**	fluoxetine 20-40 mg phase I: 3 months phase II: 6 months	placebo N/A phase 1: 3 months phase 2: 6 months	
INCLUSION:	Adults ≥ 18; minimum HAM-D score of 16; dysthymia not secondary to any other axis I disorder		
EXCLUSION:	Additional mental illnesses or organic mental disorder; MDD or other type of depression; secondary-type dysthymia; uncontrolled serious somatic disease; fluoxetine for a depressive disorder which had not been effective; received a psychotropic drug during the previous week (except for authorized benzodiazepines); requiring one of the following during the study: neuroleptic, lithium, or other mood regulator		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** NR **Gender (% female):** fluoxetine: 76.9%, placebo: 73.5% **Ethnicity:** NR **Other population characteristics:** Early onset of dysthymia: 22.9%, late onset: 77.1%		

Authors: Vanelle et al. **Year: 1997** **Country:** France	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** HDRS, CGI **Secondary Outcome Measures:** HDRS, HARS, CGI, GAF-S, Paykel Life Event Questionnaire, HSCL-58, AMDP-5 **Timing of assessments:**
RESULTS:	• # of responders at month 3 (>50% decrease in HAM-D associated with a score of 1 (very much improved) or 2 (much improved) on the CGI-I): fluoxetine = 42, placebo = 14 (p = 0.03) • Remission n at month 3 (HAM-D ≤ 7): fluoxetine = 32, placebo = 10 (p = 0.07) # of responders at month 6: fluoxetine =33, placebo = 9 (p = 0.48) • Remission n at month 6: fluoxetine = 29, placebo = 4 (p = 0.01) • Increase in GAF scores by month 3 significantly greater in fluoxetine (p = 0.02); mean score indicated return to functioning level compatible with normal social & relational life (mean GAF score = 70) • No significant change in GAF scores from month 3 to 6 for either treatment group
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR
ATTRITION:	**Loss to follow-up:** Phase I: fluoxetine: 13.2%; placebo: 26.5% Phase II: fluoxetine: 7%; placebo: 31% **Withdrawals due to adverse events:** NR **Loss to follow-up differential high:** Yes (16.2%)
ADVERSE EVENTS:	• Phase I: reported at least one adverse event: 38.5% (fluoxetine) vs. 44.9% (placebo) • Phase II (responders who continued from month 3 to 6): reported at least one adverse event: 18.6% (fluoxetine) vs. 28.6% (placebo)
QUALITY RATING:	**Fair**

Evidence Table 2 Dysthymia

STUDY:	***Authors:*** **Williams JW, et. al.**[91] ***Year:*** **2000** ***Country:*** US			
FUNDING:	Hartford Foundation, MacArthur Foundation, Smith Kline Beecham supplied meds and placebo, VA (career award to lead author)			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (Community, VA, and academic primary care clinics) ***Sample size:*** 415			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 10-40 mg/d 11 weeks	Placebo N/A 11 weeks	Behavior Therapy N/A 11 weeks	
INCLUSION:	Age 60 or older; met DSM II-R criteria for dysthymia or minor depression and score 10 or higher on HAM-D-17; symptoms for at least 4 weeks with 3-4 symptoms			
EXCLUSION:	Major depression; psychosis; schizophrenia or schizoaffective disorder; bipolar disorder; alcohol or other substance abuse within the past 6 months; borderline or antisocial personality disorder; serious suicidal risk; moderate or severe cognitive impairment (MMSE $\leq$ 23); medical illness with prognosis $\leq$ 6 months to live; patients in current treatment excluded unless willing to discontinue and dose $\leq$ 50 mg of amitriptylline			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 71 ***Ethnicity:*** paroxetine: 82.5% white, 11.0% Latino, 6.0% black, placebo: 75.7% white, 12.1% Latino, 10.0% black ***Gender*** (% female): paroxetine: 39%, placebo: 45% ***Other population characteristics:*** Mean of 3.4 medical conditions per patient			

Authors: **Williams JW, et al.** ***Year:*** **2000** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Hopkins Symptom Checklist Depression Scale (HSCL-D-20), HDRS, and functional status, by the Medical Outcomes Study Short-Form 36 (SF-36) physical and mental components ***Timing of assessments:***
RESULTS:	• Mean (SE) decrease in HSCL-D-20: Paroxetine: 0.61 (p =0.05) Placebo: 0.40 (p = 0.05) Behavior Therapy 0.52 (p = 0.05) p = 0.004 for paroxetine vs. placebo • Paroxetine only statistically and clinically significantly better than placebo for subjects with dysthymia and high baseline mental health function. • HAM-D results not reported for the ITT population
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 25.1% (for all 3 arms, including behavioral tx) ***Withdrawals due to adverse events:*** Paroxetine: 8.8%, Placebo: 5.7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 3: Major Depressive Disorder Pediatrics

STUDY:	***Authors:*** **Keller, et. al.**[99] ***Year:*** **2001** ***Country:*** US			
FUNDING:	Glaxo Smith Kline			
DESIGN:	***Study design:*** RCT ***Setting:*** 10 US and 2 Canadian centers ***Sample size:*** 275			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20-40 mg/d 8 weeks	Imipramine 200-300 mg/d 8 weeks	Placebo N/A 8 weeks	
INCLUSION:	Ages 12-18; met DSM-IV criteria for current MDD of at least 8 weeks duration; minimum score of 12 on HAM-D17; score < 60 on Children's Global Assessment Scale and score of ≥ 80 on Peabody Picture Vocabulary Test			
EXCLUSION:	Current or past history of bipolar disorder; schizoaffective disorder; eating disorder; alcohol or substance use disorder; OCD; autism/pervasive developmental disorder; organic brain disorder; diagnosis of PTSD within 12 months; suicidal ideation with intent or specific plan; history of suicide attempt by drug overdoses; current psychotropic drug use; adequate trial of antidepressant medication within 6 months; exposure to investigational drug use either within 30 days or 5 half-lives of the drug; pregnant, breastfeeding or lactating or sexually active non-contraceptive using females			
ALLOWED OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** paroxetine: 14.8, placebo: 15.1 ***Gender*** (% female): paroxetine: 62.4%; placebo: 65.5% ***Ethnicity:*** paroxetine: white: 82.8%, African American: 5.4%, Asian: 1.1%, other: 10.8%, placebo: white: 80.5%, African American: 6.9%, Asian: 2.3%, other: 10.3% ***Other population characteristics:*** Anxiety: 19-28%, externalizing disorder: 20-26%			

Authors: **Keller et. al.** ***Year:*** **2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Remission (HAM-D ≤ 8), Response (HAM-D ≥ 50% reduction from baseline), mean HAM-D change from baseline, CGI, K-SADS-L, individual HAM-D factors, SIP self-perception profile ***Timing of assessments:*** at baseline and weekly intervals weeks 1-8
RESULTS:	• ***Mean HAM-D change: paroxetine: 10.74 (p = 0.13 vs. placebo), imipramine: 8.91 (p = 0.81 vs. placebo), placebo: 9.09;*** • ***HAM-D remission: paroxetine: 63.3% (p = 0.02 vs. placebo), imipramine: 50% (p = 0.57 vs. placebo), placebo: 46 %;*** • ***HAM-D response: paroxetine: 66.7% (p = 0.11 vs. placebo), imipramine: 58.5% (p = 0.61 vs. placebo), placebo: 55.2%;*** • ***Mean CGI: paroxetine: 2.37 (p = 0.09 vs. placebo), imipramine 2.70 (p = 0.90 vs. placebo), placebo: 2.73*** • CGI score of 1 or 2: paroxetine: 65.6% (p = 0.02 vs. placebo), imipramine: 52.1% (p = 0.64 vs. placebo), placebo: 48.3%
ANALYSIS:	***ITT:*** Not reported ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 31% ***Withdrawals due to adverse events:*** paroxetine: 9.7% (p = 0.5 vs. placebo) imipramine: 31.5% (p < 0.01 vs. placebo) placebo: 6.9% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	No p-values given for comparison • Side effects with > 5 % difference from placebo: paroxetine: dry mouth (20.4% vs. 13.8% in placebo); nausea (23.7% vs. 19.5% in placebo); dizziness (23.7% vs. 18.4% in placebo); emotional lability (6.5% vs. 1.1% in placebo), hostility (7.5% vs. 0 in placebo); insomnia (15.1% vs. 4.6% in placebo); somnolence (17.2% vs. 3.4% in placebo); tremor (10.8% vs. 2.3% in placebo); back pain (4.3% vs. 11.5% in placebo) • Serious adverse effects: paroxetine: 11 (only 1 deemed to be related to medication), imipramine: 5 (2 deemed related to medication), placebo: 2 (related to medication)
QUALITY RATING:	**Fair**

Evidence Table 3 Major Depressive Disorder Pediatrics

STUDY:	***Authors:*** **Mandoki MW**, **et al.**[101] ***Year:*** **1997** ***Country:*** US			
FUNDING:	Not reported			
DESIGN:	***Study design:*** RCT ***Setting:*** Single center ***Sample size:*** 40			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Venlafaxine Age 8-12: 12.5-37.5 mg/d Age 13-17: 25-75 mg/d 6 weeks	 Placebo N/A 6 weeks		
INCLUSION:	Children and adolescents 8-18 years old; DSM-IV criteria for Major Depression			
EXCLUSION:	Female patients of childbearing age had to use oral contraceptives or depo-provera injection; Tourrette's syndrome; mental retardation; seizures; schizophrenia; suicidal; medical illness			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean Age:*** 12.8 ***Gender*** (% female): 24% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Mandoki MW, et al.** ***Year:*** **1997** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Children's Depression Inventory (CDI), Child Behavior Checklist (CBCL), 17 item HAM-D, Children's Depression Rating Scale (CDRS) ***Timing of assessments:*** Weekly
RESULTS:	• Both venlafaxine and placebo patients showed significant improvement. • There was no difference between venlafaxine and placebo.
ANALYSIS:	***ITT:*** No ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 7 (17.5%) ***Withdrawals due to adverse events:*** 1 (2.5%) venlafaxine: 1 (5%), placebo: 0 (0%) ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• A higher percentage of patients in the venlafaxine group experienced side effects than in the placebo group at almost every week. • At week 2 more statistically more venlafaxine patients reported nausea. • At week 6 statistically more venlafaxine patients reported increased appetite.
QUALITY RATING:	**Fair**

Evidence Table 3 Major Depressive Disorder Pediatrics

STUDY:	***Authors:*** **March JS**[98] ***Year:*** **2004** ***Country:*** US ***Trial name:*** TADS			
FUNDING:	NIMH			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (13 sites-academic and community clinics) ***Sample size:*** 439			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** ***Sample Size:***	[blinded] Placebo N/A 12 weeks 112	[blinded] Fluoxetine 10-40 mg/d 12 weeks 109	[unblinded] Fluoxetine and CBT 10-40 mg/d 12 weeks 107	[unblinded] CBT alone N/A 12 weeks 111
INCLUSION:	Ages 12-17; ability to receive care as an outpatient; a DSM-IV diagnosis of MDD at consent and again at baseline; a CDRS-R total score of 45 or higher at baseline; a full scale IQ of 80 or higher; not taking antidepressants prior to consent; depressive mood present in at least 2 or 3 contexts (home, school, among peers) for a least 6 wks prior to consent			
EXCLUSION:	Current or past diagnosis of bipolar disorder, severe conduct disorder, current substance abuse or dependence; pervasive developmental disorders, thought disorder; concurrent treatment with psychotropic medication or psychotherapy outside the study; 2 failed SSRI trials; a poor response to clinical treatment containing CBT for depression; intolerance to fluoxetine; confounding medical condition, non-English speaking patient or parent; pregnancy or refusal to use birth control; suicidal in the past 6 months; patients considered to be a danger to themselves or others			
OTHER MEDICATIONS/ INTERVENTIONS:	Concurrent stable psychostimulant treatment (methylphenidate or mixed amphetamine salts) for attention deficit hyperactivity disorder permitted			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 14.6 (treatment-specific numbers not reported) ***Gender*** (% female): 54.4% (treatment-specific numbers not reported) ***Ethnicity:*** White: 73.8%; black: 12.5%; Hispanic: 8.9% (treatment-specific numbers not reported) ***Other population characteristics:*** None significant			

Authors: March JS **Year: 2004** **Country:** US	
OUTCOME ASSESSMENT:	***Measures:*** CDRS-R total score; CGI-I; RADS; SIQ-Jr ***Timing of assessments:*** Baseline and weeks 6 and 12
RESULTS:	• Fluoxetine with CBT was statistically significantly better than placebo (p = 0.001) on the CDRS-R • Compared to fluoxetine alone (p = 0.02) and CBT alone (p = 0.01), treatment with fluoxetine and CBT was statistically significantly superior on the CDRS-R • Fluoxetine alone was superior to CBT alone (p = 0.01) on the CDRS-R • Fluoxetine with CBT (p < 0.001) and fluoxetine alone (p < 0.001) demonstrated significant improvement on the CGI-I compared to placebo; CBT alone was not significantly better than placebo (p = 0.20) • Fluoxetine plus CBT were significantly better than placebo, fluoxetine alone, or CBT alone (p < 0.01) on the RADS • Clinically significant suicidal thinking improved significantly in all four treatment groups (SIQ-Jr), with fluoxetine plus CBT showing the greatest reduction (p = 0.02)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 18.2%; fluoxetine+CBT: 14%; fluoxetine: 17%; CBT: 22%; placebo: 21% ***Withdrawals due to adverse events:*** Not reported ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Adverse events reported as harm-related, psychiatric, or other • 7.5% of patients had a harm-related adverse event; by FDA definition 69.7% of these had a serious adverse event : fluoxetine alone : 11.9% ; fluoxetine with CBT : 8.4% ; CBT alone : 4.5%] ; placebo :5.4% • Psychiatric adverse events : fluoxetine+CBT : 15% ; fluoxetine alone : 21% ; CBT alone : 1% ; placebo : 9.8% • Headache was most common : fluoxetine+CBT 5.6%, fluoxetine alone 12%, CBT alone 0%, placebo 9%
QUALITY RATING:	**Good**

Evidence Table 3 Major Depressive Disorder Pediatrics

STUDY:	***Authors:*** **Wagner, et. al.**[100] ***Year:*** **2003** ***Country:*** Multinational			
FUNDING:	Pfizer, Inc.			
DESIGN:	***Study design:*** Pooled analysis of 2 multi-center, double-blind, placebo-controlled trials ***Setting:*** 53 hospital, general practice, academic centers in the US, India, Canada, Costa Rica and Mexico. ***Sample size:*** 376			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Sertraline 50-200 mg/d 10 weeks	 Placebo N/A 10 weeks		
INCLUSION:	Ages 6-17 years; met DSM-IV criteria for MDD (as determined by Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, present and lifetime version); current episode of at least 6 weeks duration; minimum score on CDRS-R of 45 and CGI of 4			
EXCLUSION:	Current and primary diagnoses of ADHD; conduct disorder; OCD; panic disorder; history of bipolar disorder; current psychotic features; history of psychotic disorder or autistic spectrum disorder; previous suicide attempts or high suicidal or homicidal risk; abnormal screening EKG, labs, vital signs or body weight; pregnancy; prior enrollment in a sertraline study; medical contraindications to SSRI; history of failure on SSRI; no other psychotropic meds for at least 2 weeks (4 weeks for fluoxetine)			
ALLOWED OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate, diphenhydramine as sleep aids			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Not reported ***Gender*** (% female): sertraline: 57.1%, placebo: 44.9% (p = 0.02) ***Ethnicity:*** sertraline: white, 71.4%; Asian, 13.8%; Hispanic, 7.9%; black, 3.7%; other, 3.2% placebo: white, 69.5%; Asian, 12.3%; Hispanic, 10.2%; black, 4.8%; other, 3.2% ***Other population characteristics:*** Comorbid psychiatric diagnosis: 38 %			

Authors: **Wagner et. al.** ***Year:*** **2003** ***Country:*** Multinational	
OUTCOME ASSESSMENT:	***Measures:*** Change in CDRS-R, CDRS-R response ≥ 40% change from baseline, CGI-S score, CGI-I score, and CGI-response (score of 1 or 2), MASC, CGAS, PQ-LES-Q ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8, 10
RESULTS:	• ***Mean CDRS-R change (ITT): sertraline: 22.84, placebo: 20.19 (p = 0.007)*** • ***Mean CDRS-R change (completers): sertraline: 30.24, placebo: 25.83 (p = 0.001)*** • ***CDRS-responder: sertraline: 69%, placebo: 59% (p = 0.05)*** • ***Mean CGI: sertraline: 2.56, placebo: 2.75 (p = 0.009)*** • ***CGI responder: sertraline: 63%, placebo: 53% (p = 0.05)*** • ***Change in CGI-S: sertraline: 1.22, placebo: 1.01 (p = 0.005)***
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 20%; sertraline: 24.4%; placebo: 16.6% ***Withdrawals due to adverse events:*** 5.9%; sertraline: 9%; placebo: 2.7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Adverse events that occurred in at least 5% of sertraline treated patients with an incidence at least twice that of placebo: insomnia (19.8% vs. 8%), diarrhea (15.1% vs. 4.5%), vomiting (9.3% vs. 4.5%), anorexia (10.5% vs. 2.3%), agitation (8.1% vs. 2.3%) • Serious adverse events (based on pre-defined criteria): sertraline: 7, placebo: 6 • Mean change in body weight: sertraline: -0.38 kg, placebo: 0.78 kg (p = 0.001)
QUALITY RATING:	**Fair**

Evidence Table 3 Major Depressive Disorder Pediatrics

STUDY:	***Authors:*** **Wagner KD, et al.**[97] ***Year:*** **2004** ***Country:*** US		
FUNDING:	Forest Pharmaceuticals		
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (21) ***Sample size:*** 178		
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** ***Sample size:***	 Citalopram 20-40 mg/d 8 weeks 93	 Placebo N/A 8 weeks 85	
INCLUSION:	Children (7-11) and adolescents (12-17) who met DSM-IV criteria for major depression; current depressive episode of 4 weeks or greater; score of at least 40 on the Children's Depression Rating Scale; normal physical exam, laboratory tests, and ECG results.		
EXCLUSION:	Primary psychiatric diagnosis other than MDD; DSM-IV diagnosis of ADHD; PTSD; bipolar disorder; pervasive development disorder; mental retardation; conduct disorder; any psychotic features; history of alcohol or substance abuse; anorexia or bulimia within the past year; suicidal risk		
OTHER MEDICATIONS/ INTERVENTIONS:	Certain prescription and over the counter medications prohibited (e.g., antipsychotics, anticonvulsants, sedatives, hypnotics, cardiovascular agents, among others)		
POPULATION CHARACTERISTICS:	***Groups similar at baseline*****:** Yes ***Mean age:*** Citalopram: 12.1; placebo: 12.1 ***Gender*** (% female): Citalopram: 52.8%; placebo: 54.1% ***Ethnicity:*** Citalopram: white: 80.9%; placebo: 72.9% white ***Other population characteristics:*** Baseline mean Children's Depression Rating Scale: 58.8 citalopram; 57.8 placebo		

Authors: **Wagner KD, et al.** ***Year:*** **2004** ***Country:*** US	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** Children's Depression Rating Scale-Revised ***Secondary Outcome Measures:*** CGI-I; CGI-S ***Timing of assessments:*** Baseline and weeks 1,2,4,6, and 8.
RESULTS:	• Compared to placebo, citalopram showed significantly more improvement on the Children's Depression Rating Scale-Revised ($p < 0.05$) • 47% of citalopram-treated patients had a CGI-I rating ≤ 2 compared to 47% of placebo-treated patients (p =not reported) • Mean change in CGI-S was -1.3 for citalopram and -1 for placebo (p = not reported)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 22% (40); citalopram: 24% (22); placebo: 21% (18) ***Withdrawals due to adverse events:*** 5.7%; citalopram: 5.6%; placebo: 5.9% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Events occurring in greater than 10% of patients (p = NR): • Rhinitis: Citalopram: 13.5%; placebo: 5.9% • Nausea: Citalopram: 13.5%; placebo: 3.5% • Abdominal Pain: Citalopram: 11.2%; placebo: 7.1%
QUALITY RATING:	**Fair**

Evidence Table 3 Major Depressive Disorder Pediatrics

STUDY:	***Authors:*** **Whittington CJ, et. al.**[96] ***Year:*** **2004** ***Country:*** UK
FUNDING:	NICE (National Institute for Clinical Excellence)
DESIGN:	***Study design:*** Systematic review, SSRI versus placebo ***Number of patients:*** 2145
AIMS OF REVIEW:	To evaluate the risk versus benefit of SSRI's when used to treat childhood depression
STUDIES INCLUDED IN META-ANALYSIS	Emslie GJ et al., 1997, Emslie GJ etal., 2002, Keller MB etal., 2001, Wagner, KD etal., 2003 ; unpublished results included in a report by the Committee on Safety of Medicines (UK)
TIME PERIOD COVERED:	All studies up to 2003
CHARACTERISTICS OF INCLUDED STUDIES:	Patients randomized to either an SSRI or placebo
CHARACTERISTICS OF INCLUDED POPULATIONS:	Included trials had patients aged 5-18 years old; no other population information given

Authors: **Whittington CJ, et. al.** ***Year:*** **2004** ***Country:*** UK	
CHARACTERISTICS OF INCLUDED IINTERVENTIONS:	Fluoxetine vs. placebo (2 trials); paroxetine vs. placebo (3 trials); sertraline vs. placebo (2 trials); citalopram vs. placebo (1 trial); venlafaxine vs. placebo (3 trials)
MAIN RESULTS:	• Both published and unpublished data demonstrated fluoxetine has a favorable risk-benefit profile • Published and unpublished data combined on paroxetine demonstrated it does not improve depressive symptoms and has little effect on response • One paroxetine study reported an increased risk of serious adverse events (11.8% vs 2.3%; NNTH 10 [95% CI 6-50]) and suicidal ideation or attempting suicide (5.4% vs 0%; NNTH 20 [10 to ∞]) • Unpublished data on sertraline in children indicate it is not as effective as reported in published trials • One unpublished study of citalopram suggested a negative risk-benefit profile • Combined, published and unpublished data of venlafaxine suggested a negative risk-benefit profile
ADVERSE EVENTS:	Paroxetine, sertraline, citalopram, and venlafaxine all indicated an increased risk of adverse events
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Fair**

Evidence Table 4: General Anxiety Disorder

STUDY:	***Authors*: Allgulander et. al.**[114] ***Year:* 2004** ***Country:*** Australia, Canada, Denmark, Norway, and Sweden		
FUNDING:	Not reported		
DESIGN:	***Study design:*** Meta-analysis ***Setting:*** Multi-center (21) ***Sample size:*** 378		
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** ***Sample size:***	 Sertraline 50-150 mg/d (mean 95 mg/d) 12 weeks 190	 Placebo N/A 12 weeks 188	
INCLUSION:	Outpatients (18 years or older) with a primary diagnosis of DSM-IV defined anxiety disorder based on clinical assessments and structured interview; screening and baseline scores $\geq$ 18 on the Hamilton Anxiety Rating Scale and scores $\geq$ 2 on Hamilton Anxiety Scale item 1 and item 2		
EXCLUSION:	No current use of medically accepted contraception in fertile women; current or past history of bipolar, schizophrenic, psychotic, or OCD; current history of MDD; score $\geq$ 16 on MADRS; concurrent psychotherapy for GAD; unstable medical condition; positive drug test; suicidal risk; previous failure to respond to adequate trial on antidepressant drug treatment		
OTHER MEDICATIONS/ INTERVENTIONS:	Drugs with psychotropic activity		
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Sertraline: 40.3; placebo 42.4 ***Gender* (% female):** Sertraline 59% female; placebo 51% female ***Ethnicity (% white):*** Sertraline 98%; placebo 97% ***Other population characteristics:*** 44% of sertraline patients had partial/full high school education vs. 40% for placebo		

Authors: Allgulander, et al. **Year: 2004** **Country:** Multi-country (Australia, Canada, Denmark, Norway, and Sweden)	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** HAM-A ***Secondary Outcome Measures:*** CGI-I, CGI-S, MADRS, HADS, QoL enjoyment and satisfaction questionnaire, Endicott Work Productivity Scale, VAS for perceived health ***Timing of assessments:*** Baseline, weeks 1, 2, 4, 6, 8, and 12
RESULTS:	• Mean change in HAM-A total score significantly greater among sertraline-treated patients (-11.7) compared to placebo-treated patients (-8.0); ($p < 0.0001$) • Significantly greater improvement for sertraline in the anxiety and depression component of the HADS ($p < 0.0001$) • Sertraline significantly better than placebo as assessed by change in the MADRS, CGI-I, CGI-S, QoL, and Endicott Work Productivity Scales • VAS not reported
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 23%; sertraline: 20%; placebo: 26% ***Withdrawals due to adverse events:*** 9%; sertraline: 8%; placebo: 10% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Discontinuations due to adverse events were 8% for sertraline and 10% for placebo; the incidence of severe adverse events was $\geq$ 3% with sertraline for the following: sweating (3.8% vs 0.0% for placebo), headache (3.3% vs 4.8%), nausea (4.3% vs 1.6%), insomnia (4.3% vs 3.7%), anxiety (3.3% vs 4.2%), and decreased libido in women (4.6% vs 0.0%); Significantly more nausea (28% vs. 13%), insomnia (20% vs. 15%), decreased libido in men (17% vs. 5%), diarrhea (11% vs. 5%), and fatigue (10% vs. 5%)
QUALITY RATING:	**Fair**

Evidence Table 4 General Anxiety Disorder

STUDY:	**Authors: Ball SG, et al.**[104] **Year: 2005** **Country:** US		
FUNDING:	Pfizer Inc, NY		
OBJECTIVE:	To test hypothesis that paroxetine and sertraline are similar in their effectiveness and tolerability for the treatment of adult GAD		
DESIGN:	**Study design:** RCT **Setting:** Single center **Sample size:** 55		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Paroxetine 10-40 mg/d 8 weeks 25	Sertraline 25-100 mg/d 8 weeks 28	
INCLUSION:	18 years or older; primary DSM-IV diagnosis of GAD; HAM-A score of 18 or greater; good physical health		
EXCLUSION:	HAM-D score greater than 20 at baseline; history of substance abuse/dependence within 6 months of baseline; history of psychotic or bipolar disorders; prior non-response to sertraline or paroxetine; pregnancy		
OTHER MEDICATIONS/ INTERVENTIONS:	Concomitant medication for sleep disturbance was not allowed		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Mean age:** paroxetine: 35.6, sertraline: 42.9 **Gender (% female):** paroxetine: 84%, sertraline: 71% **Ethnicity:** paroxetine: 84% white, 12% black, 4% Asian; sertraline: 93% white, 7% black, 0% Asian **Other population characteristics:** Baseline HAM-A: paroxetine: 20.8, sertraline: 21.4 Baseline: CGI-S: paroxetine: 4.2, sertraline: 4.4 Baseline Q-LES-Q: paroxetine: 62, sertraline: 64		

Authors: Ball SG, et al. **Year: 2005** **Country:** US			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** HAM-A; Remission rate (defined as CGI-S score of 1) **Secondary Outcome Measures:** IU-GAMS (Indiana University Generalized Anxiety Measurement Scale); BAI (Beck Anxiety Inventory); Q-LES-Q **Timing of assessments:** Baseline and weekly during the study		
RESULTS:	• There was no significant difference between SR and PX patients in HAM-A score reduction (F= 0.37, df=1,51) • There was no significant difference between SR and PX patients in remission rate (χ^2= 0.22, df=1) • Quality of life scores did not differ significantly between treatment groups		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (2)		
ATTRITION: **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy**: **Loss to follow-up differential high:**	Overall 12 (22%) 6 (11%) 1 (2%) No	Paroxetine 5 (20%) NR NR	Sertraline 5 (18%) NR NR
ADVERSE EVENTS:	• Paroxetine: dizziness, nausea, sexual dysfunction, and constipation • Sertraline: sexual dysfunction, diarrhea		
QUALITY RATING:	**Fair**		

Evidence Table 4 General Anxiety Disorder

STUDY:	**Authors: Bielski RJ, et al.**[105] **Year: 2005** **Country:** US		
FUNDING:	Forest Laboratories, Inc		
DESIGN:	**Study design:** 24-wk randomized, double-blind, flexible dose, head-to-head trial (with1-wk single blind placebo lead-in period and 2-wk double blind down-titration period) **Setting:** Multi-center, outpatient **Sample size:** 123		
INTERVENTION: only for RCT **Drug:** **Dose:** **Duration:** **Sample size:**	Escitalopram 10-20 mg/d 24 wks 61	Paroxetine 20-50 mg/d 24 wks 62	
INCLUSION:	Male/female outpatients aged 18-65 years; DSM-IV criteria for generalized anxiety disorder (GAD); screening and baseline HAM-A $\geq$ 18, HAM-D $\leq$ 17, and Covi Anxiety Scale score greater than Raskin Depression Scale score.		
EXCLUSION:	DSM-IV criteria of any Axis I disorder other than GAD or history of DSM-IV defined psychotic disorders; any psychotic features; personality disorder; substance abuse / dependency; suicidal tendency; pregnant or breastfeeding; nonreliable contraception if female of childbearing age.		
OTHER MEDICATIONS/ INTERVENTIONS:	N/A		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes, with exception of gender **Mean age:** 36.8 +/- 10.9 (escitalopram); 37.4 +/- 9.6 (paroxetine) **Gender:** 55.7% female (escitalopram); 67.7% female (paroxetine) **Ethnicity:** 72.1% white (escitalopram); 79.0% white (paroxetine) **Other population characteristics:** Mean weight 168.7 +/- 37.1 lbs (escitalopram) vs. 167.9 +/- 39.5 lbs (paroxetine)		

Authors: Bielski RJ, et al. **Year: 2005** **Country:** US	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** HAM-A total score change from baseline to wk 24. **Secondary Outcome Measures:** CGI-I, CGI-S, short form of Quality of Life (QOL) **Timing of assessments:** HAM-A and safety assessed at week 1,2,4,6,8,12,16,20, and 24. Secondary outcome measures assessed at baseline (except CGI-I), week 8, & week 24.
RESULTS:	• Both drugs led to improvement in all efficacy measures over time. • Efficacy analyses at weeks 8 & 24 showed no statistically significant difference b/w treatment groups. • Response rates = 78.3% (escitalopram) and 62.3% (paroxetine) at week 24 • Week 24 HAM-A total score: -15.3+/-0.8 (escitalopram) vs. -13.3+/-1.0(paroxetine) • Baseline CGI-S score: 4.3+/-0.1 (escitalopram) vs. 4.3+/-0.1 (paroxetine) • Week 24 CGI-S score: -2.1+/-0.2 (escitalopram) vs. -1.8+/-0.2(paroxetine) • Baseline QOL score: 47.1+/-1.3 (escitalopram) vs. 48.9+/-1.3 (paroxetine) • Week 24 QOL score: 10.2+/-1.4 (escitalopram) vs. 7.5+/-1.7(paroxetine) • Week 24 CGI-I score: 1.8+/-0.1 (escitalopram) vs. 2.1+/-0.2(paroxetine)
	ITT: Yes **Post randomization exclusions:** Cannot tell
ATTRITION:	**Loss to follow-up:** Overall: 11% **Attrition:** Escitalopram: 36%, paroxetine: 47% **Withdrawals due to adverse events:** Escitalopram: 6.6%, paroxetine: 22.6% **Withdrawals due to lack of efficacy**: Not reported **Loss to follow-up differential high:** Not reported
ADVERSE EVENTS:	• Significantly more withdrawals due to adverse events (AEs) in paroxetine group (p = 0.02) • Overall incidence of AEs = 77.0% (escitalopram) vs. 88.7% (paroxetine) • Ejaculation disorder = 14.8% (escitalopram); 30.0% (paroxetine) • Anorgasmia = 5.9% (escitalopram); 26.2% (paroxetine) • Insomnia = 14.8% (escitalopram); 25.8% (paroxetine) • Decreased libido = 4.9% (escitalopram); 22.6% (paroxetine) • Headache = 11.5% (escitalopram); 21.0% (paroxetine) • Somnolence = 13.1% (escitalopram); 16.1% (paroxetine) • Dry mouth = 13.1% (escitalopram); 16.1% (paroxetine) • Constipation = 1.6% (escitalopram); 14.5% (paroxetine) • Nausea = 14.8% (escitalopram); 12.9% (paroxetine) • Inflicted injury = 4.9% (escitalopram); 11.3% (paroxetine) • Increased sweating = 3.3% (escitalopram); 11.3% (paroxetine) • Diarrhea = 21.3% (escitalopram); 8.1% (paroxetine) • Fatigue = 11.5% (escitalopram); 8.1% (paroxetine) • Upper respiratory tract infection = 14.8% (escitalopram); 4.8% (paroxetine)
QUALITY RATING:	**Poor**

Evidence Table 4 General Anxiety Disorder

STUDY:	**Authors: Dahl AA, et al.**[115] **Year: 2005** **Country:** Multinational		
FUNDING:	Pfizer, Inc.		
DESIGN:	**Study design:** RCT **Setting:** Multinational, outpatient "investigational sites" **Sample size:** 373		
INTERVENTION: only for RCT **Drug:** **Dose:** **Duration:** **Sample size:**	Sertraline 50-150 mg/d 12 wks 184	Placebo N/A 12 wks 189	
INCLUSION:	Adult outpatients; DSM-IV diagnosis of GAD; screening & baseline HAM-A scores $\geq$ 18; score $\geq$ 2 on HAM-A item 1 (anxious mood) & item 2 (tension) at baseline		
EXCLUSION:	Current or history of bipolar, schizophrenia, or OCD; dysthymia, social anxiety, substance abuse or major depressive / panic / eating / body dysmorphic / or post-traumatic stress disorders within last 6 months; MADRS score >16; psychotropic drug treatment within 2 wks of randomization		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes, except significantly later mean onset of GAD symptoms in placebo (25.6y) vs. sertraline (22.9y) (p = 0.04). **Mean age (sd):** sertraline: 40.3 (11.1), placebo: 42.4 (11.5) placebo **Gender (% female):** sertraline: 59%, placebo: 51% **Ethnicity(% white):** sertraline: 98%, placebo: 97% **Other population characteristics:** Both groups similar in highest education level achieved, current marital status, and current employment status		

Authors: Dahl AA, et al. **Year: 2005** **Country:** Mulitnational	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** HAM-A **Secondary Outcome Measures:** CGI-S & CGI-I, MADRS, Q-LES-Q **Timing of assessments:** Screening, baseline, and weeks 1, 2, 4, 6, 8, and 12
RESULTS:	• Sertraline group improved significantly more than placebo group across both primary & secondary measures, including HAM-A somatic and psychic anxiety factors. • From week 4 to endpoint, HAM-A psychic factor improved at somewhat faster rate (slope -0.39+/- 0.05 [95% CI: -0.48 to -0.29]) than somatic factor (slope -0.25+/- 0.05 [95% CI: -0.34 to -0.15]) (F=12.51; d.f = 1,170;p = 0.005) • LOCF endpoint mean HAM-A total score (sd) = -11.7(0.6) in sertraline vs. -8.0(0.6) in placebo; p < 0.001 • LOCF endpoint mean CGI-S score (sd) = -1.6(0.1) in sertraline vs. -0.9(0.1) in placebo; p < 0.001 • LOCF endpoint mean CGI-I score (sd) = 2.3(0.1) in sertraline vs. 3.0(0.1) in placebo; p < 0.001 • LOCF endpoint mean MADRS score (sd) = -4.8(0.4) in sertraline vs. -1.1(0.4) in placebo; p < 0.001 • 51% of sertraline group compared to 35% of placebo group had a QLESQ score within normal range. • LOCF endpoint mean QLESQ score (sd) = 9.1(1.0) in sertraline vs. 2.4(0.9) in placebo; p < 0.001
ANALYSIS:	**ITT:** yes (defined as patients who took at least one dose of double-blind medication and had a baseline and at least 1 post-baseline HAM-A assessment) **Post randomization exclusions:** Cannot tell
ATTRITION:	**Loss to follow-up:** NR **Withdrawals due to adverse events:** NR **Withdrawals due to lack of efficacy**: NR **Loss to follow-up differential high:** NR
ADVERSE EVENTS:	• NR
QUALITY RATING:	**Fair**

Evidence Table 4 General Anxiety Disorder

STUDY:	***Authors:*** **Davidson JR, et al.**[106] ***Year:*** **2004** ***Country:*** US		
FUNDING:	Forest Laboratories		
DESIGN:	***Study design*****:** RCT ***Setting:*** Multi-center (number of centers NR) ***Sample size:*** 315		
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** ***Sample size:***	 Escitalopram 10-20 mg/d (mean 12.3 mg/d) 8 weeks 158	 Placebo N/A 8 weeks 157	
INCLUSION:	Male/female outpatients 18-80 yrs old who met DMS-IV criteria for GAD and had normal physical and laboratory exams and ECG results at screening visit; patients required to have a minimum score of 18 on the HAMA and minimum score of 2 on HAM-A tension and anxiety items		
EXCLUSION:	HAM-D scores of >17; lower scores on the Covi Anxiety Scale than the Raskin Depression Scale; current bipolar disorder, schizophrenia or any psychotic disorder, OCD, mental retardation or any pervasive developmental disorder or cognitive disorder; principal diagnosis for any DSM-IV defined Axis I disorder other than GAD; substance abuse or dependence within the past 6 months; depot neuroleptics within 6 months; any neuroleptic, antidepressant, or anxiolytic within 2 weeks (5 weeks for fluoxetine); daily benzodiazepine therapy within 1 month, and concomitant treatment with any psychotropic drug (except zolpidem for sleep) or any drug with a psychotropic component; pregnant, breastfeeding, and not practicing a reliable method of birth control		
OTHER MEDICATIONS/ INTERVENTIONS:	Not Reported		
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Escitalopram: 39.5; placebo: 39.5 ***Gender*** (% female): Escitalopram: 52.5%; placebo: 52.9% ***Ethnicity*****:** Escitalopram: 70.9% white; placebo: 71.3% white ***Other population characteristics:*** HAM-A total score 23.4; HAM-D score 12.15; CGI severity score 4.25		

Authors: Davidson JR, et al. **Year: 2004** **Country:** US	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** HAM-A total score ***Secondary Outcome Measures:*** CGI-S; CGI-I; HAD; Covi and Raskin scales; Q-LES-Q ***Timing of assessments:*** screening, baseline and visits at weeks 1, 2, 4, 6, and 8
RESULTS:	• Mean change in HAM-A total score –11.3 for escitalopram and –7.4 for placebo ($p < 0.001$) • Significantly greater improvement for escitalopram compared to placebo on all secondary outcome measures ($p < 0.001$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 23%; escitalopram: 25%; placebo: 22% ***Withdrawals due to adverse events:*** 7%; escitalopram: 8.9%; placebo: 5.1% ***Loss to follow-up differential high:*** *No*
ADVERSE EVENTS:	• Only four adverse events were reported with an incidence exceeding 10%: headache, nausea, somnolence, and upper respiratory tract infection ($p = NR$); rate of discontinuation due to adverse events not significantly different (escitalopram 8.9% vs. placebo 5.1%, $p = 0.27$)
QUALITY RATING:	**Fair**

Evidence Table 4 General Anxiety Disorder

STUDY:	**Authors: Meoni P, et al.[113]** **Year: 2004** **Country: UK and France**
FUNDING:	Wyeth
DESIGN:	**Study design:** RCT **Number of patients:** 1,841
AIMS OF REVIEW:	To examine the relative efficacy of venlafaxine XR on the somatic and psychic factors of HAM-A
STUDIES INCLUDED IN META-ANALYSIS	Pooled data from five placebo-controlled studies available at the time of this review (Kelsey, 2000)
TIME PERIOD COVERED:	8 weeks to 6 months
CHARACTERISTICS OF INCLUDED STUDIES:	DSM-IV criteria for GAD; RCT-double blind with a 4-10 day washout period
CHARACTERISTICS OF INCLUDED POPULATIONS:	$\geq$ 18 yrs old and met DSM-IV criteria for GAD; HAM-A baseline score $\geq$ 18 or 20 and baseline scores for items 1 and 2 of at least 2; total score on Covi Anxiety Scale greater than total score on the Raskin Depression scale, where the latter score was not >9

Authors: Meoni P, et al. **Year: 2004**	
CHARACTERISTICS OF INTERVENTIONS:	Venlafaxine XR 37.5 to 225 mg/d vs. placebo
MAIN RESULTS:	Mean scores of HAM-A somatic and psychic factors showed different baseline scores of 11.3 and 14.4 respectively, after adjusted by treatment groups; differences in response rates between treatments were greater for the psychic factor of the HAM-A (66.6% vs 35% for venlafaxine and placebo respectively ($p < 0.001$) than for the somatic factor of HAM-A (67% vs 47% for venlafaxine and placebo respectively ($p < 0.001$); comparison within treatments of response rates for the two factors of HAM-A by treatment revealed a significant interaction between treatment and factors ($p = 0.027$).
ADVERSE EVENTS:	Not reported
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Not reported
STANDARD METHOD OF APPRAISAL OF STUDIES:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 4 General Anxiety Disorder

STUDY:	***Authors:*** **Pollack MH, et. al.**[110] ***Year:*** **2001** ***Country:*** US			
FUNDING:	GlaxoSmithKline			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 331			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Paroxetine 10-50 mg/d 8 weeks	 Placebo N/A 8 weeks		
INCLUSION:	DSM-IV criteria for GAD; score ≥ 20 on the 14 item HAM-A; ≥ 18 years of age			
EXCLUSION:	Any other Axis-I diagnosis; MADRS ≥ 17 at baseline; substance abuse; taking psychotropic medications; pregnancy; psychotherapy; untreated illness			
OTHER MEDICATIONS/ INTERVENTIONS:	None allowed			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** No; significant age difference between the paroxetine and placebo groups (p = 0.001) ***Mean age:*** Paroxetine: 39.7; placebo: 41.3 ***Gender*** (% female): Paroxetine: 60.9%, placebo: 66.3% ***Ethnicity:*** Paroxetine: African American: 3.2%, Asian: 0.6%, white: 85.7%, other: 10.5 %; placebo: African American: 4.3%, Asian: 0.6%, white: 81.6%, other: 13.5% ***Other population characteristics:*** No other significant differences			

Authors: **Pollack MH, et. al.** ***Year:*** **2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Change from baseline on HAM-A, change in anxious mood and tension scales of HAM-A, anxiety subscale of HAD, CGI-I responders (score of 1 or 2), CGI-S, Sheenan Disability Scale ***Timing of assessments:*** Weeks 1, 2, 3, 4, 5, 6, 8
RESULTS:	• There was a significantly greater reduction in the total HAM-A score, the anxious mood item, and the tension item in the paroxetine group compared to placebo group at week-6 ($p < 0.05$) and week-8 ($p < 0.01$) • CGI-I responders LOCF: paroxetine: 62%, placebo: 36% ($p = 0.007$) • CGI-I responders (completers): paroxetine: 70%, placebo: 40% ($p = 0.005$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 21% ***Withdrawals due to adverse events:*** Paroxetine: 10.5%; placebo: 3.7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Asthenia; constipation; abnormal ejaculation; decreased libido; nausea; somnolence (> 10% and at least twice placebo rate) • All adverse effects were experienced by more paroxetine than placebo patients
QUALITY RATING:	**Fair**

Evidence Table 4 General Anxiety Disorder

STUDY:	***Authors:*** **Rickels K, et al.**[109] ***Year:*** **2003** ***Country:*** US and Canada			
FUNDING:	GSK			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 566			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20 mg/d 8 weeks	Paroxetine 40 mg/d 8 weeks	Placebo N/A 8 weeks	
INCLUSION:	DSM-IV criteria for GAD; HAM-A score $\geq$ 20; score of 2 or more on item 1 & 2 (anxious mood, tension); mean age $\geq$ 18 years			
EXCLUSION:	Subjects had another primary Axis I disorder; recent use of an SSRI; anti-anxiety, psychotropic medications; recent cognitive behavior therapy; treatment with beta blockers or clonidine; pregnant, lactating; major life event in past 3 months; positive urine screen for BZD			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Paroxetine 20mg/d: 40.2; paroxetine 40 mg/d: 40.5; placebo: 40.8 ***Gender*** (% female): Paroxetine 20 mg/d: 54%; paroxetine 40 mg/d: 56%; placebo: 56% ***Ethnicity:*** Paroxetine 20 mg/d: black: 5%, Asian: 3%, white: 82%, other: 5%, Hispanic: 5%; paroxetine 40 mg/d: black: 4%, Asian: 1%, white: 89%, other: 4%; Hispanic: 3%; placebo: black: 6%, Asian: 2%, white: 82%, other: 5%, Hispanic: 6% ***Other population characteristics:*** Not reported			

Authors: **Rickels K, et al.** ***Year:*** **2003** ***Country:*** US and Canada	
OUTCOME ASSESSMENT:	***Measures:*** HAM-A, HADS, CGI-S, Remission = HAM-A ≤ 7, Sheehan disability scale ***Timing of assessments:*** Weeks 1, 2, 3, 4, 6, 8
RESULTS:	• Paroxetine as a group (20 mg/d and 40 mg/d) had a significantly greater mean change from baseline on all outcome measures except the HAM-A somatic anxiety subscale • Statistically more subjects on sertraline (53% vs. 29% on placebo) were much or very much improved at the end of treatment based on the CGI-I
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 24.7%; paroxetine 20mg: 24% (143); paroxetine 40mg: 27% (143); placebo: 22% (140) ***Withdrawals due to adverse events:*** Paroxetine 20mg: 10.1%; paroxetine 40mg: 12.2%; placebo: 6.7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• At least one adverse event: placebo: 74%, paroxetine: 20mg 88%, paroxetine 40mg: 86% • Paroxetine: nausea: 32.6%, insomnia: 30.4%, dyspepsia: 25.2%, diarrhea: 20.7% • Placebo: diarrhea: 15.9%, nausea: 14.5%, insomnia: 14.5%, asthenia: 11.6% • Significantly more subjects in the Paroxetine group reported nausea: (32.6% vs. 14.55), insomnia: (30.4% vs. 14.5%), dyspepsia: (25.2% vs. 7.2%), flu syndrome (17.8% vs. 5.5%), delayed ejaculation (11.4% vs. 4.3%), sweating (11.1% vs. 5.9%)
QUALITY RATING:	**Fair**

Evidence Table 5: Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Ackerman, et al.**[123] ***Year:*** **2002** ***Country:*** US
FUNDING:	NIMH
DESIGN:	***Study design:*** Meta-analysis (meta regression)
AIMS OF REVIEW:	Meta-analysis with meta regression for treatment of OCD to explain the apparent discrepancy in the literature that makes it seem that CMI is superior to SSRI's in placebo trials vs. in head/head comparison
STUDIES INCLUDED IN META-ANALYSIS	Goodman et al., 1989, Jenike et al., 1990, Mallya et al., 1992, Goodman et al., 1996, Montgomery et al., 1993, Tollefson et al., 1994, Chouinard et al., 1990, Greist et al., 1995, Kronig et al., 1999, Zohar and Judge, 1996
TIME PERIOD COVERED:	Not explicitly reported, studies included spanned 1992-1997 for head to head comparisons and 1989-1999 for placebo comparisons
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs, double-blinded; 8 weeks or longer; efficacy assessed with Y-BOCS; point estimates and SD(or SE) provided or calculable from report
CHARACTERISTICS OF INCLUDED POPULATIONS:	Not reported

Authors: **Ackerman, et al.** ***Year:*** **2002**	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	Clomipramine, fluvoxamine, fluoxetine, sertraline, paroxetine, placebo
MAIN RESULTS:	• Result reported as mean difference in change from baseline on Y-BOCS scale support equal efficacy for clomipramine and all SSRIs; pooled difference between clomipramine and all SSRIs was 0.15 (95% CI -8.86, 9.16), where a number significantly greater than 1.00 would represent greater efficacy for the SSRIs • Effect size was estimated as the difference in improvement (decrease in Y-BOCS) between active drug and placebo. Negative pooled difference represents greater improvement (greater decrease in Y-BOCS) across studies for the active drug compared to placebo • Pooled Difference: Fluvoxamine vs. placebo (4 studies): -4.84 (-7.78, -1.83) Fluoxetine vs. placebo (3 studies): -1.61 (-2.18, -1.04) Sertraline vs. placebo (4 studies): -2.47 (-6.13, 1.20) Paroxetine vs. placebo (1 study): -3.00 (-4.91, -1.09)
ADVERSE EVENTS:	None reported
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	No
QUALITY RATING:	**Fair**

Evidence Table 5 Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Bergeron, et al.**[125] ***Year:*** **2002** ***Country:*** Canada			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 150			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/d 24 weeks	Fluoxetine 20-80 mg/d 24 weeks		
INCLUSION:	Ages 18-65; primary diagnosis of OCD for at least 6 months using Structured Clinical Interview based on DSM-IV criteria; baseline minimum scores of $\geq$ 17 on Y-BOCS; $\geq$ 7 on NIMH-OC; and CGI-S $\geq$ 4 and HAM-D17 $\leq$ 17; females had to have negative pregnancy test at baseline and using medically acceptable form of contraception for at least 3 months			
EXCLUSION:	Primary Axis I disorder other than OCD including presence of major depressive episode; >25% reduction in Y-BOCS or NIMH-OC or > 2 point improvement in CGI-S during washout; suicidal; history of seizure disorder; organic brain disorder; anorexia; bulimia; purgative abuse; drug or alcohol abuse or dependence within 6 months prior; psychotropic medication within the previous week; 2 weeks for antidepressants requiring concomitant treatment with any psychotropic (other than exception as previously noted); requiring concurrent ECT, cognitive-behavioral therapy or formal structured psychotherapy or a likelihood that such therapy might be required; acute or unstable medical condition or used any meds known to interact with either study drug; reported previous adequate treatment > 4 weeks with either study drug or known or suspected intolerance or allergy; participated in a clinical research study within the prior 4 months; pregnancy or lactation			
OTHER MEDICATIONS/ INTERVENTIONS:	Zopiclone or chloral hydrate as hypnotics			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean age:*** 36; sertraline: 36.6; fluoxetine: 36.5 ***Gender*** (female%): 54% ***Ethnicity:*** Not reported ***Other population characteristics:*** Approximately 20% of the sample had a history of a prior episode of depression; OCD > 10 years in 79% of patients			

Authors: **Bergeron** ***Year:*** **2002** ***Country:*** Canada	
OUTCOME ASSESSMENT:	***Measures:*** Primary efficacy measures: Y-BOCS, NIMH-OC, CGI-S, response (CGI-I ≤ 2), remission (CGI-I ≤ 2 and YBOCS ≤ 11); Secondary measures: HAM-D, CAS, Yale schedule for multiple tics and tourettes, Battelle QOL ***Timing of assessments:*** Screening, baseline, weeks 1, 2, 4, 6, 8, 12, 16, 20, 24 or final visit if patients withdrew before study end
RESULTS:	• No significant differences in mean Y-BOCS change at endpoint • Sertraline showed statistically significant improvement at some of the early assessment times (weeks 4, 8, 12) • No difference in CGI-S or CGI-I between groups at week 24 • Median time to response not significantly different Sertraline: 16 weeks Fluoxetine: 20 weeks (p = 0.703) • ***Remission (combined CGI and YBOCS):*** Week 12: Sertraline: 20%, Fluoxetine: 8% (p = 0.045) Week 24: Sertraline: 36%, Fluoxetine: 22% (p = 0.075)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 29.3%; sertraline: 29%; fluoxetine: 30% ***Withdrawals due to adverse events:*** Sertraline: 19%; fluoxetine: 14% (p = 0.342) ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• No significant differences in incidence of side effects between groups • Effects with a 5% or more difference between groups (no p-values given): nausea: sertraline: 41%, fluoxetine: 28%; fatigue: sertraline: 28%, fluoxetine: 22%; flu-like symptoms: sertraline: 25% fluoxetine: 19%; dyspepsia: sertraline: 24%, fluoxetine: 17%; tremor: sertraline: 12%, fluoxetine: 4%; somnolence: sertraline: 13%, fluoxetine: 21% • No significant differences in body weight change between groups
QUALITY RATING:	**Fair**

Obsessive-compulsive Disorder

Evidence Table 5

STUDY:	***Authors:*** **Denys D, et al.**[126, 140] ***Year:*** **2003** ***Country:*** US			
FUNDING:	Wyeth and Glaxo-Smith-Kline			
DESIGN:	***Study design:*** RCT ***Setting:*** Single center ***Sample size:*** 150			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine 75-300 mg/d 12 weeks	Paroxetine 15-60 mg/d 12 weeks		
INCLUSION:	DSM-IV criteria for OCD; ≥ 18 on the Y-BOCS or ≥ 12 if only obsessions or compulsions were present; 18-65 years of age			
EXCLUSION:	Organic mental disorders; epilepsy; CNS disorder; DSM-IV diagnosis of major depression; psychotic illness or bipolar disorder; personality disorder; severe somatic symptoms; pregnancy; suicidal; use of antidepressants 1 month before study			
OTHER MEDICATIONS/ INTERVENTIONS:	Oxazepam, maximum of 30 mg/d, was permitted on an intermittent basis			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes **Mean age:** 35; venlafaxine: 36, paroxetine: 34 **Gender** (female%): venlafaxine: 63%, paroxetine: 61% ***Ethnicity:*** Not reported ***Other population characteristics:*** Patients assigned to venlafaxine had a significantly greater number of previous medication trials			

Authors: **Denys D, et al.** ***Year:*** **2003** ***Country:*** Canada	
OUTCOME ASSESSMENT:	***Measures:*** Yale-Brown Obsessive Compulsive scale (Y-BOCS), Hamilton Anxiety Scale (HAS), HAM-D-17, Global Assessment of Functioning, Lancashire Quality of Life Profile (LQoLP) ***Timing of assessments:*** Baseline, weeks 1, 3, 5, 8, 10, 12
RESULTS:	• Paroxetine showed significantly greater improvement in HAM-D at endpoint ($p < 0.05$) • Both treatment groups had a significant improvement in Y-BOCS score but there was no significant difference between treatment groups; no differences in HAS • Paroxetine and venlafaxine groups improved on all QoL measures • Paroxetine and venlafaxine were equally effective based on LQoLP improvement scores
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 16 (11%) ***Withdrawals due to adverse events:*** 5%; venlafaxine: 2%, paroxetine: 6% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Somnolence, sweating, insomnia, nausea, dry mouth, dizziness, constipation, sexual dysfunction • No differences reported
QUALITY RATING:	**Fair**

Evidence Table 5 Obsessive-compulsive Disorder

STUDY:	**Authors: Denys D, et al.**[120] **Year: 2004** **Country:** The Netherlands			
FUNDING:	Wyeth and GlaxoSmithKline			
DESIGN:	**Study design:** RCT **Setting:** Single center **Sample size:** 43 (of 150) continued in switch study			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** ***Sample Size:***	 Paroxetine 60 mg/d 12 weeks (switch study) 27	 Venlafaxine XR 300 mg/d 12 weeks (switch study) 16		
INCLUSION:	Outpatients ages 18-65 with a primary OCD according to DSM-IV criteria; only patients with a score of at least 18 on the Y-BOCS or at least 12 if only obsessions or compulsions were included; nonresponse in the first phase of the study defined as less than a 25% decrease in Y-BOCS			
EXCLUSION:	Patients with significant depression as determined by a total score of 15 or more on the HAM-D on admission were excluded; pregnant women, childbearing potential not using adequate methods of contraception; patients with organic mental disorders, epilepsy, any structural central nervous system disorder or stroke within the last year; primary DSM–IV diagnoses of major depression, bipolar disorder, schizophrenia, or any other psychotic condition; substance-related disorders within the past 6 months; primary anxiety disorders or obvious personality disorders; use of antidepressants or antipsychotics 1 month before screening visit; use of a concomitant psychotropic drug, behavioral or cognitive therapy 3 months prior to the screening visit			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 35 ***Gender*** (% female): 54.5% ***Ethnicity:*** Not reported ***Other population characteristics:*** YBOCS total score 27.7; HAM-A score 11.0; HAM-D score 7.6			

Authors: Denys D, et al. **Year: 2004** **Country:** The Netherlands	
OUTCOME ASSESSMENT:	***Measures:*** Y-BOCS; HAM-D; HAM-A; GAF ***Timing of assessments:*** 0, 1, 3, 5, 8, 10, 12 weeks
RESULTS:	• LOCF analysis demonstrated a mean decrease of 1.8 (+/-3.5) in the venlafaxine XR group and 6.5 (+/-7.1) in the paroxetine group as measured by the reduction in total Y-BOCS scores; significant decrease in total Y-BOCS score from baseline was found in the paroxetine group ($t=4.7$, $df=26$, $p < 0.0001$) but not in the venlafaxine group ($t = 2.0$, $df = 15$, $p = .065$) • No significant differences between baseline and endpoint for venlafaxine XR- or paroxetine-treated patients on the HAM-D or HAM-A • GAF not reported
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** Paroxetine 0 (0%); Venlafaxine XR 1 (6%) (numbers reported for 43 patients switching) ***Withdrawals due to adverse events:*** Yes ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• 98% of patients reported adverse events; • Paroxetine: somnolence 54%, sweating 25%, headache 21%, constipation 21%, insomnia 18%, nausea 18%, change in mood 18%, loss of libido 18% • Venlafaxine: somnolence 38%, sweating 31%, constipation 31%, dry mouth 19%, headache 13%, insomnia 13%, nausea 13%, loss of libido 13% • p-values not reported
QUALITY RATING:	**Fair**

Evidence Table 5 Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Montgomery SA, et. al.**[128] ***Year:*** **2001** ***Country:*** Europe, South Africa			
FUNDING:	Lundbeck A/S			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 401			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Citalopram 20 mg/d 12 weeks	Citalopram 40 mg/d 12 weeks	Citalopram 60 mg/d 12 weeks	Placebo N/A 12 weeks
INCLUSION:	18-65 years; DSM-IV criteria for OCD; Y-BOCS ≥ 20; symptoms stable for the preceding 6 months			
EXCLUSION:	MADRS ≥ 22; other Axis I disorders; suicidal risk; recent treatment with fluoxetine or MAOI; hypersensitivity to SSRIs; hepatic impairment; drug/alcohol dependence; pregnancy/lactation; Tourette's syndrome in family; concomitant therapy with anticonvulsive and psychoactive drugs			
OTHER MEDICATIONS/ INTERVENTIONS:	55.4% received concomitant medication			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** 38; citalopram: 37.6, placebo: 38.6 ***Gender*** (% female): citalopram: 55%, placebo: 50.1% ***Ethnicity:*** Not reported ***Other population characteristics:*** Mean duration of illness greater than 15 years for all groups			

Authors: **Montgomery SA, et al.** ***Year:*** **2001** ***Country:*** Europe, South Africa	
OUTCOME ASSESSMENT:	***Measures:*** Y-BOCS, MADRS, CGI-I, NIMH-OC ***Timing of assessments:*** Baseline, weeks 1, 3, 5, 7, 9, 12
RESULTS:	• A significant reduction in Y-BOCS scores for all 3 citalopram groups ($p < 0.01$) compared to placebo • Citalopram 60 mg reached statistical significance at week 3, citalopram 20 mg and 40 mg at week 7 • Changes in NIMH-OC scores were also significantly greater in the citalopram groups ($p < 0.001$) • All 3 treatment groups had significantly more responders than placebo
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 16%; citalopram 20 mg: 16%; citalopram 40 mg: 15%; citalopram 60 mg: 15%; placebo: 17% ***Withdrawals due to adverse events:*** 4%; citalopram 20 mg: 4%; citalopram 40 mg: 6%; citalopram 60 mg: 4%; placebo: 2% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Treatment emergent adverse events: citalopram 20 mg: 73%; citalopram 40 mg: 68%; citalopram 60 mg: 72%; placebo: 58% • The incidence of nausea, insomnia, fatigue, increased sweating, dry mouth, ejaculation failure, and diarrhea was significantly higher in one or more citalopram groups compared to placebo
QUALITY RATING:	**Fair**

Evidence Table 5 Obsessive-compulsive Disorder

STUDY:	**Authors: Pallanti S, et al.**[121] **Year: 2004** **Country:** Italy		
FUNDING:	Not reported		
DESIGN:	***Study design:*** RCT ***Setting:*** Single center ***Sample size:*** 49		
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** ***Sample size:***	Citalopram and placebo citalopram 20-80 mg/d and N/A 12 weeks 28	Citalopram and Mirtazapine citalopram and mirtrazapine 20-80 mg/d and 15-30 mg/d 12 weeks 21	
INCLUSION:	Diagnosis of OCD with co-morbid depression by structured clinical interview for DSM-IV Axis I and II disorders; OCD symptoms for 1 year; at least moderate severity on the CGI; SRI naive		
EXCLUSION:	Any of the following conditions: organic mental disorder, psychotic mental disorders, mental retardation, current depressive episode; substance or alcohol abuse; history of bipolar disorder; personality disorders; pregnant or nursing women		
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported		
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** citalopram/placebo 30.4; citalopram/mirtazapine 28.1 ***Gender*** (% female): citalopram/placebo 43%; citalopram/mirtazapine 43% ***Ethnicity:*** Not reported ***Other population characteristics:*** HAM-D total score: 8.7; CGI-S score: 5.4		

Authors: Pallanti S, et al. **Year: 2004** **Country:** Italy	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** Yale-Brown Obsessive Compulsive Scale (YBOCS) ***Secondary Outcome Measures:*** HAM-D19; CGI-I, Arizona Sexual Experience Scale ***Timing of assessments:*** At baseline and weekly thereafter.
RESULTS:	• The citalopram/mirtazapine group showed an earlier response than the citalopram/placebo on reduction in mean YBOCS score; a significant between group difference was observed during weeks 2 through 6 ($p < 0.05$) • No significant between group difference in YBOCS score observed at endpoint. • No differences in CGI-I at endpoint • HAM-D not reported
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions*:** No
ATTRITION:	***Loss to follow-up:*** 8.2% (4): Citalopram/placebo: 7.1% (2); citalopram/mirtazapine: 9.5% (2) ***Withdrawals due to adverse events:*** *2% (1); citalopram/placebo: 3.6% (1); citalopram/mirtrazapine: 0%* ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Mean Arizona Sexual Experience Scale score at endpoint was significantly worse in citalopram/placebo group than the citalopram/mirtrazapine ($p < 0.01$) • Significantly greater weight gain among citalopram/mirtrazapine group.
QUALITY RATING:	**Fair**

Evidence Table 5 Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Piccinelli M, et. al.**[122] ***Year:*** **1995** ***Country:*** Italy
FUNDING:	University of Verona
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 1076
AIMS OF REVIEW:	Efficacy of drug treatment in OCD; subgroup analysis: SSRIs vs. placebo
STUDIES INCLUDED IN META-ANALYSIS	Perse et al., 1987, Goodman et al., 1989a, Cottreaux et al., 1990, Jenike et al., 1990a, Rasmussen et al., (in press), Chouinard et al., 1990, Jenike et al., 1990b, Greist et al., (in press), Montgomery et al., 1993, Wood et al., 1993
TIME PERIOD COVERED:	1975-1994
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs, double-blind placebo-controlled
CHARACTERISTICS OF INCLUDED POPULATIONS:	DSM-III-R diagnosis of OCD; adult patients not refractory to standard treatments with OCD; no comorbid Tourette's syndrome, phobia, depression or obsessive compulsive neurosis

Authors: **Piccinelli M, et al.** ***Year:*** **1995** ***Country:*** Italy	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	13 trials of SSRI vs. placebo (fluoxetine, fluvoxamine, sertraline)
MAIN RESULTS:	• Effect size calculated using Hedge's g; a measure of the difference between the means of active treatment and placebo control; difference measures (Y-BOCS and NIMH-OC) abstracted from trials as the weighted mean g; positive values for Hedge's g indicate greater improvement in the active treatment group, compared to placebo • Fluvoxamine vs. placebo: Y-BOCS: 0.57 (95% CI: 0.37-0.77) NIMH-OC: 0.29 (95% CI 0.07-0.51) • Fluoxetine vs. placebo: Y-BOCS: 0.57 (95% CI: 0.33-0.81) NIMH-OC: N/A • Sertraline vs. placebo: Y-BOCS: 0.52 (95% CI: 0.27-0.77) NIMH-OC: 0.55 (95% CI: 0.30-0.80) • Improvement rate over placebo (binominal effect size display, Rosenthal 1984): Fluvoxamine: 28.2% Fluoxetine: 28.5% Sertraline: 21.6% • No statistically significant differences between study drugs
ADVERSE EVENTS:	Not reported
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 5 Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Stein DJ, et al.**[124] ***Year:*** **1995** ***Country:*** South Africa and US
FUNDING:	Not reported
DESIGN:	***Study design:*** Meta-analysis (SSRI vs. placebo only) ***Number of patients:*** 516
AIMS OF REVIEW:	Assess and integrate data from multiple clinical trials on drug treatment in OCD
STUDIES INCLUDED IN META-ANALYSIS	This review addressed placebo-controlled trials, active control, and open label; we focus on SSRI vs. placebo. Perse et al. 1987, Chouinard et al. 1990, Jenike et al. 1990, Montgomery et al. 1993
TIME PERIOD COVERED:	1980-1993
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs; placebo-controlled SSRI trials detected by MedLine & PsychLit search; subjects rated with YBOCS or NIMH obsessive-compulsive global rating scale; trials at least six weeks in length; no specification on sample size
CHARACTERISTICS OF INCLUDED POPULATIONS:	Diagnosis of OCD; adults; single medication without concomitant therapy

Authors: **Stein DJ, et al.** ***Year:*** **1995** ***Country:*** South Africa, US	
CHARACTERISTICS OF INCLUDED IINTERVENTIONS:	Fluvoxamine (2 studies), fluoxetine (1 study), sertraline (2 studies)
MAIN RESULTS:	• There were no differences in effect sizes between the SSRIs. • Effect size was calculated in comparison to placebo: Fluvoxamine: 0.69 +- 0.47 Sertraline: 0.55 Fluoxetine: 0.51 +- 0.12
ADVERSE EVENTS:	N/A
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	No
QUALITY RATING:	**Fair**

Evidence Table 6: Panic Disorder

STUDY:	***Authors:*** **Asnis G, et al.**[146] ***Year:*** **2001** ***Country:*** US			
FUNDING:	Not reported			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 188			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Fluvoxamine 50-300 mg/d 8 weeks	 Placebo N/A 8 weeks		
INCLUSION:	DSM-III-R diagnosis; age 18-65; at least 1 panic attack per week for at least 4 weeks prior to study			
EXCLUSION:	Concurrent systematic illness; other Axis I psychiatric disorder; clinical significant lab abnormalities or ECG; pregnant or lactatins women without adequate birth control			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate or lorazepam for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean Age:*** Fluvoxamine: 34.2, placebo: 36.7 ***Gender*** (% female): fluvoxamine 64.4%, placebo 64.1% ***Ethnicity:*** Not reported ***Other population characteristics:*** Number of full panic attacks per week at baseline: fluvoxamine: 2.7, paroxetine: 3.3			

Authors: **Asnis G, et al.** ***Year:*** **2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Primary daily panic attack inventory (DPAI), CAS, SDS, CGI-I, CGI ***Timing of assessments:*** Baseline, weekly intervals thereafter for a maximum of 8 weeks of treatment
RESULTS:	• Significantly more fluvoxamine patients were free from full panic attacks (p = 0.002) • Reduction of panic disorder severity was significantly greater in the fluvoxamine group (p = 0.003) • Significantly more fluvoxamine patients were CGI-I responders at endpoint (64% vs. 42%; p = 0.002)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** fluoxetine 37.6%, placebo 33.6% ***Withdrawals due to adverse events:*** fluvoxamine: 9.6%; placebo: 5.9% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Fluvoxamine: nausea: 43%, insomnia: 25%, somnolence: 24%, asthenia: 22% • Placebo: nausea: 33%, headache: 22%, anxiety: 16% • No significant difference in the number of withdrawals due to adverse events
QUALITY RATING:	**Fair**

Evidence Table 6 Panic Disorder

STUDY:	***Authors:*** **Bandelow B, et al.**[143] ***Year:*** **2004** ***Country:*** Germany		
FUNDING:	Pfizer		
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 225		
INTERVENTION: **Drug:** **Dose:** **Duration:**	 Sertraline 50 – 150 mg/d 12 weeks	 Paroxetine 40 – 60 mg/d 12 weeks	
INCLUSION:	Male or female outpatients; aged 18-65; primary DSM-IV and ICD-10 disease of PD with or without agoraphobia; minimum of 4 panic attacks during the 4 weeks prior to screening; total score > 18 at baseline on the PAS (clinician-rated)		
EXCLUSION:	Primary disease other than panic disorder; MADRS rating scale total score > 14; clinically significant and unstable medical illness; current diagnosis of bipolar disorder, schizophrenic disorder, delusional disorder, epilepsy, MDD, OCD, social phobia; history of alcoholism or drug abuse within the past three years; serious risk for suicide; pregnancy or lactation or not using reliable contraceptive methods		
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate; zolpidem; zopiclone could be given for severe insomnia on limited basis (≤ 3 times/wk)		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** 38.6 **Gender** (% female): sertraline: 60%; paroxetine: 66% **Ethnicity:** Not reported **Other population characteristics:** Patients with agoraphobia subtype: sertraline, 68%; paroxetine, 63%; patients with non-agoraphobia subtype: sertraline, 32%; paroxetine, 66%		

Authors: **Bandelow B, et al.** ***Year:*** **2004** ***Country:*** Germany	
OUTCOME ASSESSMENT:	**Measures:** Safety and efficacy assessments, primary efficacy measure was clinician rated PAS **Timing of assessments:** Weeks 1, 2, 4, 6, 8, 12, 15
RESULTS:	• Treatment with sertraline and paroxetine resulted in the same level of improvement on the PAS total score (p = 0.749) • For both groups 35% reduction from baseline PAS total score had been achieved by week 6 • No significant differences in secondary outcome measures (PAS subscales, CGI-S, HAM-A, Sertraline Quality of Life Scale) • Mean improvement on individual PAS subscales was similar at endpoint in both treatment groups stratified by agoraphobia subtype
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No
ATTRITION:	**Loss to follow-up:** sertraline: 28%, paroxetine: 33% **Withdrawals due to adverse events:** sertraline: 12%, paroxetine: 18% **Loss to follow-up differential high:** No
ADVERSE EVENTS:	• Sexual dysfunctional, diarrhea and sedation occurred at a rate less than 10% (data not reported) • Weight gain (> 7% increase in baseline body weight) sertraline: < 1%, paroxetine: 7% (p < 0.05)
QUALITY RATING:	**Fair**

Evidence Table 6 Panic Disorder

STUDY:	***Authors:*** **Black DW, et al.**[149] ***Year:*** **1993** ***Country:*** US			
FUNDING:	Reid Rowell Pharma			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 75			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluvoxamine Up to 300 mg/d 8 weeks	Cognitive therapy Arm 2 8 weeks	Placebo N/A 8 weeks	
INCLUSION:	Age 18-65 yrs; DSM III-R criteria for panic disorder; in good physical health			
EXCLUSION:	Pregnant, lactating; psychotic; suicidal or demented subjects excluded			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean Age:*** 36.5 ***Gender*** (% female): Not reported ***Ethnicity:*** Not reported ***Other population characteristics:*** No prior psychiatric treatment: fluvoxamine: 40%, cognitive therapy: 32%, placebo: 20%			

Authors: **Black DW, et al.** ***Year:*** **1993** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Number of panic attacks and severity as estimated from a patient log, Clinical Anxiety Scale (CAS), CGI-S, CGI-I, Sheehan Disability Scale, MADRS ***Timing of assessments:*** Baseline, during treatment and at endpoint (some were assessed weekly)
RESULTS:	• Significantly greater improvement for fluvoxamine on CAS (p = 0.003) and CGI (p = 0.004), Panic Severity Score (p = 0.003) than placebo • Sheehan Disability Ratings: work (p = 0.01) and social/leisure (p = 0.02) components were significantly better with fluvoxamine than placebo • MADRS score was significantly more improved with fluvoxamine than placebo
ANALYSIS:	***ITT:*** No ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** fluvoxamine: 16%, cognitive therapy: 36%, placebo: 28% ***Withdrawals due to adverse events:*** fluvoxamine: 8%, cognitive therapy: 0%, placebo: 0% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Fluvoxamine-treated patients reported significantly more adverse events than placebo–treated patients (p = 0.005) • 1 person in the fluvoxamine group attempted suicide
QUALITY RATING:	**Fair**

Evidence Table 6 Panic Disorder

STUDY:	**Authors: Bradwejn J, et al.**[148] **Year: 2005** **Country:** Multinational		
FUNDING:	Wyeth		
DESIGN:	**Study design:** RCT **Setting:** Outpatient **Sample size:** 361		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Venlafaxine ER 75-225 mg/d 10 wks 181	Placebo N/A 10 wks 180	
INCLUSION:	Adults ≥ age 18 w/ DSM-IV panic disorder (w/ w/o agoraphobia) for ≥ 6 months before study; CGI-S ≥4; minimum of 4 full-symptom panic attacks during the 4 wks before screening; minimum of 2 full-symptom panic attacks during the 14+/-3 day placebo lead-in period wks before screening		
EXCLUSION:	Any clinically important Axis I or II disorder, current or predominant, within 6 months of study day 1; alcohol dependence or misuse within 1 year; HRSD (Hamilton) ≥15 or item 1 (depressed mood) >2; Covi Anxiety Scale total score ≤ Raskin Depression Scale total score; Raskin Depression Scale total score >9 or single item score >3; treatment w/ venlafaxine ER or IR in last 6 months; investigational drugs, antipsychotics or fluoxetine; regular use of benzodiazepines or triptans within last 30 days; use of other psychopharmacological drugs in last 14 days; investigational procedures within 30 days; ECT within 60 days; non-psychopharmacological drugs w/ psychotropic effects unless at stable dose for ≥ 3 months; formal psychotherapy or cognitive-behavioral therapy within 30 days; clinically significant lab abnormalities; clinically important medical conditions; pregnant, lactating, or inadequate contraception		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes, but mean frequency of panic attacks at baseline (venalfaxine 7; placebo: 5) **Mean age (s.d):** venlafaxine: 38.9 (12.4), placebo: 38.8 (12.1) **Gender (% female):** venlafaxine: 62%, placebo: 59% **Ethnicity:** Not reported **Other population characteristics:** Current panic disorder episode duration; full-symptom panic attacks at baseline(venlafaxine: 12.5 vs. placebo: 9.5, p = 0.078)		

Authors: Bradwejn J, et al. **Year: 2005** **Country:** Multinational			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Percentage of participants who were free from full-symptom panic attacks (≥ 4 symptoms) based on Panic and Anticipatory Anxiety Scale (PAAS) **Secondary Outcome Measures:** change from baseline in full-symptom panic attack frequency; response; remission; CGI-I, CGI-S, Phobia scale, Sheehan Disability Scale, Q-LES-Q **Timing of assessments:** screening visit & study days -1,7,14,21,28,42,56,and 70		
RESULTS:	ITT: • No significant differences in number of patients free from panic attacks between treatment groups (data NR) • Significantly more venlafaxine ER – treated patients responded (data NR; $p < 0.05$) and remitted (data NR; $p < 0.05$) compared to placebo group. On therapy evaluation: • At final evaluations, 55% (venlafaxine) vs. 52.4% (placebo) of patients were free from full-symptom panic attacks (statistically non significant) • Significantly more venlafaxine ER – treated patients responded (68.1% vs. 55.4%; $p = 0.023$) and remitted 35.6% vs. 24.4%; $p = 0.030$) compared to placebo group. • Venlafaxine ER also associated with lower mean panic attack frequency, improvement in fear and avoidance factors of the Phobia Scale, and higher proportion free from limited-symptom panic attacks.		
	ITT: Yes **Post randomization exclusions:** Yes, 9%		
ATTRITION: **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy**: **Loss to follow-up differential high:**	Overall 26.6% attrition NR NR Cannot determine	Venlafaxine NR 9% NR	Placebo NR NR 10%
ADVERSE EVENTS:	• No significant differences b/w treatment groups in primary reasons for withdrawal during the double-blind period. • Overall, adverse events were reported by 86% of venlafaxine ER group and 78% placebo group. • Most frequent AEs causing discontinuation in venlafaxine ER group were anorexia, nausea, insomnia, and sweating.		
QUALITY RATING:	**Fair**		

Evidence Table 6 Panic Disorder

STUDY:	***Authors:*** **Hoehn-Saric R, et al.**[145] ***Year:*** **1993** ***Country:*** US			
FUNDING:	Not reported			
DESIGN:	***Study design:*** RCT ***Setting:*** Single center ***Sample size:*** 50			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Fluvoxamine 50–300 mg/day 8 weeks	 Placebo N/A 8 weeks		
INCLUSION:	Diagnosis by DMS III-R and the SCID; 1 panic attack per week for at least 4 weeks; severity score of 25 or greater on diary (during run in) to enter randomization phase as well as at least one major panic attack (major panic attack = attack with at least 4 symptoms) one week before randomization			
EXCLUSION:	No medication that could affect the CNS for past 3 weeks before study; abnormal lab values; ECG and hypertension; history of major mental illness; depression; OCD; substance abuse			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean Age:*** 38.0 ***Gender*** (% female): 55.6% ***Ethnicity:*** Not reported ***Other population characteristics:*** Education 13.7 yr, 78% with mild agoraphobia, age of onset 26.2 years			

Authors: **Hoehn-Saric R, et al.** ***Year:*** **1993** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Number of panic attacks per week and severity of attacks, MADRS, Clinical Anxiety Scale (CAS), Sheehan Disability Scale, symptoms from diary ***Timing of assessments:*** Weekly for 8 weeks
RESULTS:	• Fluvoxamine group had significantly fewer major panic attacks than placebo group • Significantly more fluvoxamine treated patients were free of panic attacks at endpoint ($p < 0.02$) • Significantly lower scores in the fluvoxamine group on CAS and MADRS (CAS significant at week 6; MADRS significant at week 7) • There was no difference between groups in terms of minor panic attacks or Sheehan Disability Scale
ANALYSIS:	***ITT:*** No ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 24%; fluvoxamine: 24%, placebo: 24% ***Withdrawals due to adverse events:*** 12%; fluvoxamine: 16%, placebo: 8 % ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Fluvoxamine: drowsiness: 28%, dyspepsia: 17%, headache: 11% • Fewer side effects at week 8 than week 3
QUALITY RATING:	**Fair**

Evidence Table 6 Panic Disorder

STUDY:	***Authors:*** **Pohl RB, et al.**[147] ***Year:*** **1998** ***Country:*** US			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 168			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Sertraline 50-200 mg/day 10 weeks	 Placebo N/A 10 weeks		
INCLUSION:	≥ 18 yrs; DSM-III criteria for panic disorder; minimum of 4, but not more than 100, panic attacks during past 4 weeks; HAM-D ≤ 17; HAM-A ≥18			
EXCLUSION:	Other Axis I disorders; substance abuse; use of benzodiazepines in the past month			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** 37.5 ***Gender*** (% female): 57% ***Ethnicity:*** White: 88% ***Other population characteristics:*** Mean length of illness: 9.5 years			

Authors: **Pohl RB, et al.** ***Year:*** **1998** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Multi-center Panic Anxiety Scale, HAM-A, CGI ***Timing of assessments:*** Weekly for 4 weeks then biweekly
RESULTS:	• The number of panic attacks decreased significantly for sertraline treated patients compared to placebo (77% vs. 51%; p = 0.03) • Sertraline treated patients showed significantly greater improvements in the HAM-A scale than placebo treated patients (p = 0.03) • Quality of life and CGI scales had significantly higher ratings in the sertraline group (p = 0.006; p < 0.001)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 21.4%; sertraline: 26%, placebo: 17% ***Withdrawals due to adverse events:*** sertraline: 9%, placebo: 1% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Nausea (33% vs. 17%), diarrhea (24% vs. 11%), dry mouth (19% vs. 8%), ejaculation failure (11% vs. 0%), and decreased libido (10% vs. 0%) were significantly more frequent in the sertraline than in the placebo group
QUALITY RATING:	**Fair**

Evidence Table 6 Panic Disorder

STUDY:	***Authors:*** **Stahl SM, et al.**[141] ***Year:*** **2003** ***Country:*** US			
FUNDING:	Forest Laboratories			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 366			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Escitalopram 5-20 mg/d 10 weeks	Citalopram 10-40 mg/d 10 weeks	Placebo N/A 10 weeks	
INCLUSION:	DSM-IV criteria for panic disorder with or without agoraphobia; minimum of 4 DSM-IV defined panic attacks during the 4 weeks prior to the screening visit; 3 panic attacks during the 2 week placebo lead in; 18-80 years of age			
EXCLUSION:	Score > 17 HAM-D; bipolar disorder; schizophrenia; OCD or other psychotic disorders; pregnancy; clinically significant abnormalities			
OTHER MEDICATIONS/ INTERVENTIONS:	Zolpidem as needed for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean Age:*** Escitalopram: 37.5, citalopram: 37.1, placebo: 38.6 ***Gender*** (% female): Escitalopram: 57.6 %, citalopram: 61.6%, placebo: 55.3% ***Ethnicity:*** Escitalopram: 70.4 % white, citalopram: 75.9% white, placebo: 71.1% white ***Other population characteristics:*** No significant population differences; mean 5 panic attacks per week and estimated 44% of waking hours worrying about future attacks			

Authors: **Stahl SM, et al.** ***Year:*** **2003** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Frequency of panic attacks based on the Modified Sheehan Panic and Anticipatory Anxiety Scale (PAAS), Panic and Agoraphobia Scale, HAM-A, CGI-I, CGI-S, Q-LES-Q, PGE, anticipatory anxiety duration (derived from PAAS) ***Timing of assessments:*** Screening, baseline, weeks 1, 2, 4, 6, 8, 10
RESULTS:	• The frequency of panic attacks was statistically improved in the escitalopram group relative to placebo ($p = 0.04$) • There was no statistical difference in the frequency of panic attacks in citalopram patients relative to placebo; both escitalopram and citalopram significantly reduced panic disorder symptoms and severity versus placebo at endpoint ($p < 0.05$) • Escitalopram was not compared to citalopram
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 32% ***Withdrawals due to adverse events:*** 7.4%; escitalopram: 6.3%, citalopram: 8.4%, placebo: 7.6% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	No significant differences between study groups
QUALITY RATING:	**Fair**

Evidence Table 7: Post-Traumatic Stress Disorder

STUDY:	***Authors:*** **Brady K, et al., 2000, (1 of 2 acute phase)**[152] **Londborg PD, et al., 2001 (24 week open label)**[157] **Rapaport MH, et al., 2002 (64 weeks qol)**[154] **Davidson JRT, Pearlstein T, et al., 2001 (28 week continuation)**[158] ***Country:*** US			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** 1) 2 RCTs (Brady 2000, Davidson 2001; acute phase); NOTE: Davidson 2001 for acute phase in different evidence table 2) Open label (continuation) 3) RCT (maintenance) 4) QOL study over full 64 weeks ***Setting:*** Multi-center ***Sample size:*** Brady 187, continuation 252, maintenance 96, Rapaport 359			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/d 12 weeks Open-label continuation treatment: 24 weeks Maintenance: 28 weeks	Placebo N/A 12 weeks Open-label continuation treatment: 24 weeks Maintenance: 28 weeks		

Authors: **Brady K, et al. 2000,** **Londberg PD, et al., 2001** **Rapaport MH, et al., 2002** **Davidson JRT, Pearlstein T, 2001** ***Country:*** US	
INCLUSION:	18 yrs or older; DSM-III-R criteria for PTSD; minimum of 6 months duration; ≥ 50 on CAPS-2 (Clinician Administered PTSD Scale); free of psychotropic medication for at least 2 weeks Open-label continuation treatment: patients who completed acute phase trials (Brady 2000 or Davidson 2001) (only results from sertraline group reported in article) Maintenance: patients who completed acute and continuation study
EXCLUSION:	Other psychiatric diseases; hepatic or renal disease; current psychotherapy; alcohol or substance abuse; pregnancy or lactation; previously failed to respond to SSRI therapy; clinically relevant progressive disease
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate (not more than 2 nights per week)
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Brady et al: sertraline: 40.2, placebo: 39.5 ***Gender:*** (% female) sertraline: 75.5%, placebo: 71.0% ***Ethnicity:*** (white) sertraline: 80.9%, placebo: 88.2%; (black) sertraline: 14.9%, placebo: 8.6%; (other) sertraline: 4.3%, placebo: 3.2% ***Other population characteristics:*** Brady et al: current major depression: sertraline: 36%, placebo: 30%; current anxiety disorder: sertraline: 18%, placebo: 14%; history of alcohol abuse: sertraline: 22%, placebo: 30%; history of drug abuse: sertraline: 14%, placebo: 14%
OUTCOME ASSESSMENT:	***Measures and timing of assessment*** CAPS-2, CGI-I, IES weeks 1, 2, 3, 4, 6, 8, 10, 12 Open-label continuation treatment: weekly for 4 weeks, then biweekly Maintenance: rate of relapse measured by: CGI $\underline{\geq}$ 3, PTSD increase > 30%, investigator judged clinical worsening, biweekly QOL measures: Q-LES-Q, SF36, occupational & social impairment items of CAPS-2

Authors: **Brady K, et al. 2000,** **Londberg PD, et al., 2001** **Rapaport MH, et al., 2002** **Davidson JRT, Pearlstein T, 2001** ***Country:*** US	
RESULTS:	• Brady et al. (acute) treatment with sertraline yielded statistically significantly greater efficacy on 3 of 4 primary outcome measures: CAPS-2: p = 0.02, CGI-S: p = 0.01, CGI-I: p = 0.02, IES: p = 0.07 • 53% of patients were much or very much improved in sertraline group (p = 0.008 vs. placebo) Quality of life (pooled data from Brady 2000 and Davidson 2001) • Sertraline treated patients showed a significantly greater improvement in Q-LES-Q total scores (p = 0.01) and SF-36 emotional role functioning subscale scores (p = 0.002) than placebo • Sertraline treated patients also showed a significantly greater improvement in social and occupational functioning on CAPS-2 compared to placebo (p = 0.038) Open-label continuation treatment • 92% of acute phase responders sustained treatment response, 54% of acute phase non-responders become responders • There was a modest overall improvement of Quality of Life scores during continuation treatment Maintenance • Continued treatment with sertraline yielded lower PTSD relapse rates (5% vs. 26%; p < 0.02) than placebo, lower acute exacerbation rates (15.8% vs. 52.2%; p < 0.01) and lower discontinuation due to clinical deterioration rates (15.8% vs. 45.7%; p = 0.005) • Placebo led to a significant clinical deterioration of quality of life scores. Kaplan Meier analysis showed a highly significant relapse prevention for sertraline (p = 0.0002)

Authors: **Brady K, et al. 2000, Londberg PD, et al., 2001, Rapaport MH, et al., 2002, Davidson JRT, Pearlstein T, 2001** ***Country:*** US	
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** Brady et al. (acute): 28.9%, sertraline: 30.9%, placebo: 27.2%. Open-label continuation treatment: Not reported Maintenance: 50% ***Withdrawals due to adverse events:*** Brady et al.: sertraline: 5.3%, placebo: 5.4% Open-label continuation treatment: sertraline: 8.6%. Maintenance: sertraline: 8.7%, placebo: 6.0% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• There were no statistically significant differences in adverse events between study groups except: Brady et al. insomnia (p = 0.01), sertraline: 16%, placebo: 4.3% Open-label continuation treatment: • No serious abnormalities in ECG, lab tests, or vital signs were attributed to sertraline treatment Maintenance: • 6.8% gained 7% or more in body weight, no treatment-emergent or treatment-related adverse events reported at 10% or higher
QUALITY RATING:	**Fair**

Evidence Table 7 Post-Traumatic Stress Disorder

STUDY:	***Authors:*** **Connor K, et al.**[156] ***Year:*** **1999** ***Country:*** US			
FUNDING:	NIMH			
DESIGN:	***Study design:*** RCT; 12 week acute with 12 week continuation ***Setting:*** Not reported ***Sample size:*** 54			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluoxetine 10-60 mg/d 12 weeks for acute treatment; 12 weeks for continuation phase	Placebo N/A 12 weeks for acute treatment; 12 weeks for continuation phase		
INCLUSION:	Age 18-55; DSM-III-R criteria for PTSD according to the SCI for DSM-III-R and were civilians			
EXCLUSION:	Determined by SCID: history of psychosis; bipolar disorder; antisocial personality disorder; current/recurrent/recent risk of suicide; homicide; and drug or alcohol abuse within previous 6 months			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 37; fluoxetine: 36, placebo: 38 ***Gender*** (% female): 91%, fluoxetine: 89%, placebo: 93% ***Ethnicity:*** 93% white; fluoxetine: 100%, placebo: 85% ***Other population characteristics:*** 41% married; 93% high school graduates; 43% employed out of home; median age of PTSD onset 25.5; median years of PTSD 6			

Authors: **Connor K, et al.** ***Year:*** **1999** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Duke Global Rating for PTSD, SIP (Structured Interview for PTSD), self-rating sales: DTS (Davidson Trauma Scale), SDS (Sheehan Disability Scale), VS (Vulnerability to Effects of Stress Scale) ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8, 10, 12
RESULTS:	• Using Duke cut off score of 1 (no symptoms) to define responders, the fluoxetine group had significantly more responders than the placebo group (59% vs.19%; $p < 0.005$) • Using Duke cut off score of 1 (no symptoms) or 2 (minimal symptoms) to define responders, no statistically significant difference could be seen (85% vs. 62%; $p < 0.06$) • The SIP showed significant improvements for fluoxetine: SIP: $p < 0.005$ • Fluoxetine subjects responded in significantly less time than placebo treated subjects; Kaplan Meier: $p < 0.005$ • Fluoxetine was also associated with significantly greater effects on the disability and stress subscales (SDS, VS, DTS) at 12 weeks ($p < 0.05$; $p < 0.01$; $p < 0.005$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 31.5%; fluoxetine: 22.2%, placebo: 40.7 % ***Withdrawals due to adverse events:*** 0% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 7 Post-Traumatic Stress Disorder

STUDY:	***Authors:*** **Davidson JRT, et al.**[153] ***Year:*** **2001** ***Country:*** US			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 208			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/d 12 weeks	Placebo N/A 12 weeks		
INCLUSION:	18 yrs or older; DSM-III-R criteria for PTSD; minimum of 6 months duration; ≥ 50 on CAPS-2 (Clinician Administered PTSD Scale); free of psychotropic medication for at least 2 weeks			
EXCLUSION:	Other psychiatric diseases; hepatic or renal disease; current psychotherapy; alcohol or substance abuse; pregnancy or lactation; previously failed to respond to SSRI therapy; clinically relevant progressive disease; hypersensitivity to study drug; current use of any medication			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate; use of concomitant medications was recorded			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Sertraline: 37.6, placebo: 36.6 ***Gender*** (% female): sertraline: 84%, placebo: 72% ***Ethnicity:*** White: sertraline: 83%, placebo: 84%; black: sertraline: 13%, placebo: 11%; other: sertraline: 4%, placebo: 5% ***Other population characteristics:*** Current major depression: sertraline: 40%, placebo: 40%; current anxiety disorder: sertraline: 23%, placebo: 18%; history of alcohol abuse: sertraline: 24%, placebo: 27%; history of substance abuse: sertraline: 14%, placebo: 18%			

Authors: **Davidson JRT, et al.** ***Year:*** **2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures and timing of assessment:*** CAPS-2, CGI-I, CGI-S, IES (Impact of Event Scale) weeks 1, 2, 3, 4, 6, 8, 10, 12, Davidson Trauma Scale, HAM-D, HAM-A weeks 2, 4, 6, 8, 10, 12
RESULTS:	• Treatment with sertraline yielded statistically significantly greater efficacy in all 4 primary outcome measures: CAPS-2: p = 0.04, CGI-S: p = 0.01, CGI-I: p = 0.04, IES: p = 0.02 • Kaplan-Meier analysis showed that significantly more sertraline-treated patients were responders at endpoint than placebo treated patients (p = 0.004) • Mixed effects analysis showed a significantly steeper improvement slope for sertraline compared to placebo (p = 0.003) • Sertraline treated patients showed a significantly greater improvement in social and occupational functioning compared to placebo (p = 0.01; p = 0.02) • No significant differences between treatment groups were found on changes in HAM-A and HAM-D scores or Pittsburgh Sleep Questionnaire
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 32.3% ***Withdrawals due to adverse events:*** sertraline: 9.1%, placebo: 4.7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Adverse events that were significantly more common in sertraline subjects compared with placebo consisted of insomnia (35% vs. 22%), diarrhea (28% vs. 11%), nausea (23% vs 11%0, fatigue (13% vs. 5%), and decreased appetite (12% vs. 1%)
QUALITY RATING:	**Fair**

Evidence Table 7 Post-Traumatic Stress Disorder

STUDY:	***Authors:*** **Marshall RD, et al.**[155] ***Year:*** **2001** ***Country:*** US			
FUNDING:	Glaxo and NIMH			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 563			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20 mg/d 12 weeks	Paroxetine 40 mg/d 12 weeks	Placebo N/A 12 weeks	
INCLUSION:	Age 18 yrs or more; met DSM-IV criteria for chronic PTSD; CAPS part 2 score of 50 or more; negative pregnancy test and use of contraception			
EXCLUSION:	Other primary Axis I disorders within 6 months of screening; receiving disability payments or involvement in litigation related to PTSD or other psychiatric illness; alcohol or substance abuse or dependence within 6 months of screening; homicidal or suicidal risk; intolerance to paroxetine or any other SSRI or having a serious medical condition			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate only during placebo run in and week 1 of active treatment			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 41.8 Years ***Gender*** (% female): 67% ***Ethnicity:*** White: > 90% ***Other population characteristics:*** Physical or sexual assault: 48-54%; witnessing injury, death: 17-18%; serious accident or injury: 6-12%; combat: 5-8%; 45% had comorbid major depression, 28-32% with GAD			

Authors: **Marshall** ***Year:*** **2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Change in CAPS-2, CGI-I, both measured at study endpoint which was 12 weeks, secondary outcomes: change in Davidson Trauma Scale symptom clusters and Treatment Outcome PTSD Scale, Sheehan Disability Scale ***Timing of assessments:*** Weeks 1, 2, 4, 6, 8, 12
RESULTS:	• Paroxetine patients in both treatment groups demonstrated significantly greater improvement on primary outcome measures compared to placebo (CAPS, CGI-I) • Treatment response did not vary by trauma type, time since trauma, or severity of baseline PTSD
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 11.2% ***Withdrawals due to adverse events:*** 12.2%; paroxetine (20mg): 11.2%, paroxetine (40 mg): 15 %, placebo: 9.6% ***Loss to follow-up differential high:*** Not reported
ADVERSE EVENTS:	• Side effects reported at least 10% and twice that of placebo: asthenia, diarrhea, abnormal ejaculation, impotence, nausea, somnolence • 9 serious adverse experiences in paroxetine treated subjects; 7 of 9 rated by investigators as unrelated or probably unrelated to treatment
QUALITY RATING:	**Fair**

Evidence Table 7 Post-Traumatic Stress Disorder

STUDY:	**Authors: McRae A, et al.**[151] **Year: 2004** **Country:** US		
FUNDING:	Bristol-Myers Squibb		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (2 medical centers) **Sample size:** 37		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Nefazodone 463 mg/d (mean) 12 weeks 18	 Sertraline 153 mg/d (mean) 12 weeks 19	
INCLUSION:	Male and female outpatients aged 18-65; met DSM-IV criteria for PTSD; minimum of 3 months duration of PTSD; severity of at least 50 on the CAPS-2		
EXCLUSION:	Any clinically significant medical condition or laboratory abnormality; history of seizure disorder or organic brain disease; pregnancy or breastfeeding; psychotic, eating disorder, or OCD; substance abuse; current diagnosis of major depression; psychotropic medication; drug hypersensitivity; history of non-responsiveness to treatment drugs		
OTHER MEDICATIONS/ INTERVENTIONS:	No other psychotropic medications allowed		
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 40 **Gender** (% female): 77% ***Ethnicity:*** Not reported ***Other population characteristics:*** Time since trauma: 22 years		

Authors: McRae A, et al. **Year: 2004** **Country:** US	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** 17 item PTSD scale; Part 2 CAPS-2; CGI-I ***Secondary Outcome Measures:*** 17 item Davidson Trauma Scale; MADRS; HAM-A; Pittsburg Sleep Quality Index; Sheehan Disability Scale ***Timing of assessments:*** Baseline, weeks 4, 8, and 12
RESULTS:	• No statistically significant differences between the sertraline and the nefazodone treatment groups on any of the outcome measures. • Both treatment groups had statistically significant within-group improvements on all outcome measures from baseline to endpoint CAPS-2: sertraline: 29.08 ($p < 0.001$); nefazodone: 28.77 ($p < 0.001$) CGI: sertraline 2 ($p < 0.001$); nefazodone: 2 ($p < 0.001$)
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes
ATTRITION:	***Loss to follow-up:*** 38%; nefazadone: not reported; sertraline: not reported ***Withdrawals due to adverse events:*** 11%; nefazadone: 11%; sertraline: 10.5% ***Loss to follow-up differential high:*** not reported
ADVERSE EVENTS:	No significant differences in adverse events reported between treatment groups: • Drowsiness: Nefazadone: 26.3%; sertraline: 27.8% • Headache: Nefazadone: 26.3%; sertraline: 22.2% • Insomnia: Nefazadone: 21.1%; sertraline: 16.7% • Dizziness: Nefazadone: 21.1%; sertraline: 0% • Fatigue: Nefazadone: 5.3%; sertraline: 16.7% • Anorgasmia: Nefazadone: 0%; sertraline: 16.7%
QUALITY RATING:	**Fair**

Evidence Table 7 Post Traumatic Stress Disorder

STUDY:	**Authors: Tucker P, et al.**[150] **Year: 2005** **Country:** US		
FUNDING:	Forest Pharmaceuticals		
DESIGN:	**Study design:** RCT **Setting:** University hospital outpatient **Sample size:** 59		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Citalopram 36.2 mg/day 10 weeks 25	Sertraline 134.1 mg/day 10 weeks 23	Placebo N/A 10 weeks 10
INCLUSION:	18-64 years old; PTSD symptoms		
EXCLUSION:	Medical condition precluded use of an SSRI; previous intolerance or lack of response to an adequate trial of citalopram or sertraline; possible placebo treatment was unsafe; psychotherapy was indicated; current alcohol or substance abuse		
OTHER MEDICATIONS/ INTERVENTIONS:	Diphenhydramine for sleep		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** citalopram: 39.2, sertraline: 39.1, placebo: 36.8 **Gender (% female):** citaloparam: 68%, sertraline: 78.3%, placebo: 80% **Ethnicity (% white):** citalopram: 76%, sertraline: 91.3%, placebo 100% **Other population characteristics:** Not reported		

<table>
<tr><td colspan="5">Authors: Tucker P, et al.
Year: 2003
Country: US</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">Primary Outcome Measures: Clinician administered PTSD scale (CAPS) and BDI

Timing of assessments: CAPS: Baseline and weeks 1, 6,and 10; BDI: baseline and weeks 1, 2, 3, 4, 6, 8, and 10</td></tr>
<tr><td>RESULTS:</td><td colspan="4">• No differences in efficacy between sertraline and citalopram treated patients
• No differences in efficacy between active treatments and placebo</td></tr>
<tr><td>ANALYSIS:</td><td colspan="4">ITT: Yes
Post randomization exclusions: No</td></tr>
<tr><td>ATTRITION:</td><td><u>Overall</u></td><td><u>Citalopram</u></td><td><u>Sertraline</u></td><td><u>Placebo</u></td></tr>
<tr><td>Loss to follow-up:</td><td>14</td><td>5</td><td>6</td><td>3</td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>2 known</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Loss to follow-up differential high:</td><td>No</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
<tr><td>ADVERSE EVENTS:</td><td colspan="4">• Fatigue: citalopram: 44%, sertraline: 29%, placebo: 30%
• GI distress: citalopram: 16%, sertraline: 38%, placebo: 30%
• Insomnia: citalopram: 60%, sertraline: 33%, placebo: 70%
• Sexual dysfunction: citalopram: 16%, sertraline: 4%, placebo: 20%</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="4">Fair</td></tr>
</table>

Evidence Table 8: Social Anxiety Disorder

STUDY:	**Authors: Allgulander C, et al.**[159] **Year: 2004** **Country:** Multinational (Sweden, Denmark, Germany, Norway, France, Finland)		
FUNDING:	Wyeth Research		
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size**: 436		
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** ***Sample size:***	 Venlafaxine ER 75-225 mg/d 12 weeks 129	 Paroxetine 20-50mg/d 12 weeks 128	 Placebo N/A 12 weeks 132
INCLUSION:	Over 18 years old with DSM-IV criteria for SAD for at least 6 months prior to study; score of ≥ 4 on CGI-S; 50 on LSAS, with 30% decrease between pre-study and baseline visits; pre-study Raskin depression total score ≤9, and a 17-item HAM-D score <15		
EXCLUSION:	Previous treatment with venlafaxine or venlafaxine ER within 6 months of study day 1; concurrent disorders that confounded the evaluation of treatment: substance disorders, personality disorders (except avoidant personality disorder), depression or other primary anxiety disorders		
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported		
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** No (differences in gender) ***Mean age:*** Venlafaxine ER: 38.7; paroxetine: 38.8; placebo: 38.9 ***Gender*** (% female): Venlafaxine ER: 46%; paroxetine: 52%; placebo: 62% ***Ethnicity:*** Not reported ***Other population characteristics:*** Baseline LSAS score 86.6 for placebo, 83.2 for venlafaxine ER, 83.9 for paroxetine		

Authors: Allgulander C, et al. **Year: 2004** **Country:** Multi-country	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** LSAS ***Secondary Outcome Measures:*** CGI-S; CGI-IM; SPIN; SDI ***Timing of assessments:*** Baseline, and days 7, 14, 21, 28, 42, 56, 70 and 84
RESULTS:	• No significant differences in any outcome measures between venlafaxine ER and paroxetine • Treatment with venlafaxine ER and paroxetine was associated with significantly greater improvement than treatment with placebo for all primary and secondary efficacy variables ($p < 0.05$) • LSAS total scores significantly improved for venlafaxine ER or paroxetine vs. placebo –primary endpoint, the baseline adjusted mean change in LSAS total score was –36.0 (SE 2.35) for venlafaxine, –35.4 (SE 2.46) for paroxetine and –19.1 (SE 2.40) for the placebo group • SPIN scores significantly improved for venlafaxine ER and paroxetine groups than for placebo group at weeks 3-12 (both $p < 0.05$ week 3; both $p < 0.01$ week 4; both $p < 0.001$ weeks 6-12)
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes
ATTRITION:	***Loss to follow-up:*** 16.8%; venlafaxine ER: 16%; paroxetine: 16%; placebo: 18.5% ***Withdrawals due to adverse events:*** 7.6% , venlafaxine: not reported; paroxetine: not reported ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• During the double-blind treatment period, 90% venlafaxine ER, 89% paroxetine, and 82% placebo treated patients reported treatment emergent adverse events; the most common (incidence $\geq$5%) adverse events among venlafaxine ER treated patients were headache (10%), nausea (7%), dizziness (14%), insomnia (6%), and vertigo (10%); among paroxetine-treated patients were headache (12%), dizziness (13%), and insomnia (6%); among placebo treated patients, no taper/post study emergent adverse event occurred at an incidence of $\geq$5% and the differences between groups were not statistically significant
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	***Authors:*** **Baldwin et. al.**[170] ***Year:*** **1999** ***Country:*** Belgium, France, Germany, Ireland, South Africa, Spain, United Kingdom			
FUNDING:	Smith Kline Beecham			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (39) ***Sample size:*** 290			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Paroxetine 20-50 mg/d 12-weeks	 Placebo N/A 12 weeks		
INCLUSION:	Aged 18 or older; DSM-IV diagnosis of social anxiety disorder			
EXCLUSION:	≥ 15 on HAM-D; CGI-I score of 1 or 2 during 1 week run-in; other axis I disorders; body dysmorphic disorder, schizophrenia, or bipolar affective disorder; concomitant use of beta-blockers, MAO-I, benzodiazepines, or other psychoactive medications; previous lack of response or intolerance to paroxetine or other SSRI; alcohol or substance abuse; suicidal or homicidal risk; pregnancy, lactation, or not using acceptable form of contraception			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** 36 ***Gender*** (% female): 53% ***Ethnicity:*** White: 89% ***Other population characteristics:*** Mean HAM-D = 6.5			

Authors: **Baldwin D, et. al.** ***Year:*** **1999** ***Country:*** Belgium, France, Germany, Ireland, South Africa, Spain, United Kingdom	
OUTCOME ASSESSMENT:	***Measures:*** (Primary) mean change from baseline in LSAS; CGI-I responders (Secondary) SADS; SDS; CGI-S ***Timing of assessments:*** Weeks 1, 2, 3, 4, 6, 8, 12
RESULTS:	• Mean change from baseline in LSAS: paroxetine -29.4 vs. placebo -15.6 ($p < 0.001$from week-4 through week-12) • CGI-I responders: paroxetine 65.7% vs. placebo 32.4% ($p < 0.001$ from week-4 through week-12) • Paroxetine was statistically superior to placebo on all secondary outcome measures (SADS; SDS; CGI-S) ($p < 0.05$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** No
ATTRITION:	***Loss to follow-up:*** 27%; paroxetine 25%; placebo 28% ***Withdrawals due to adverse events:*** 6%; paroxetine 7%; placebo 4% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Any adverse event: paroxetine 74.1% vs. placebo 68.2% • Nausea: paroxetine 28.1% vs. placebo 7.9% • Abnormal ejaculation: paroxetine 14.1% vs. placebo 1.4% • Dizziness: paroxetine 12.9% vs. placebo 5.3% • Sweating: paroxetine 12.2% vs. placebo 2.6%
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	***Authors:*** **Blomhoff S, et. al.**[175] ***Year:*** **2001** ***Country:*** Norway and Sweden			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 387			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-150 mg/d 24 weeks	Placebo N/A 24 weeks		Patients also were randomized to receive either exposure therapy or general care
INCLUSION:	18-65 years of age; DSM-IV criteria for generalized social phobia; duration of at least one year; ≥ 4 on the CGI-SP scale			
EXCLUSION:	Panic disorder; current anxiety; major depressive; substance use; eating disorder; lifetime history of bipolar disorder or psychosis			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 40.4 ***Gender*** (% female): 60.5% ***Ethnicity:*** Not reported ***Other population characteristics:*** No significant population differences reported			

Authors: **Blomhoff S, et. al.** ***Year:*** **2001** ***Country:*** Norway and Sweden	
OUTCOME ASSESSMENT:	***Measures:*** CGI-Social Phobia scale (CGI-SP), social phobia scale, brief social phobia scale, social phobia subscale of the Marks Fear Questionnaire, Sheenan Disability Inventory, Fear of Negative Evaluation Scale, MOS 36 Short-Form Health Survey ***Timing of assessments:*** Weeks 4, 8, 12, 16, 24
RESULTS:	• Significantly more sertraline than placebo patients responded to therapy based on a 50% or greater reduction in SPS symptoms ($p < 0.001$) • No significant difference was observed between exposure therapy and non-exposure therapy treated patients
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 35% ***Withdrawals due to adverse events:*** 2.6% ***Loss to follow-up differential high:*** Not reported
ADVERSE EVENTS:	Nausea ($p = 0.002$), malaise ($p = 0.022$), and sexual dysfunction ($p = 0.002$) were observed significantly more in the sertraline group than in the placebo group
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	**Authors: Kasper S, et al.**[164] **Year: 2005** **Country:** Multinational	
FUNDING:	H. Lundbeck A/S	
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 358	
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Escitalopram 10-20 12 weeks 181	 Placebo N/A 12 weeks 177
INCLUSION:	Outpatients with a primary diagnosis GSAD following DSM-IV criteria; 18-65 years old; a score of at least 70 on the LSAS; evidence of fear or avoidance traits in at least 4 social situations; otherwise healthy	
EXCLUSION:	Primary diagnosis of other Axis 1 disorders or a history of within the past 6 months; diagnosis of any Axis II cluster; substance abuse within 12 months; if investigator diagnosed a serious risk of suicide; MADRS >19; use of a depot antipsychotic within 6 months or any antipsychotic, anxiolytic or anticonvulsant within 2 weeks before start; known drug allergy or previous lack of therapeutic response to citalopram	
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No – escitalopram group older (39 vs. 36) with greater duration of disease (24 vs. 21 years) **Mean age:** 38 **Gender (% female):** 45% **Ethnicity:** NR **Other population characteristics:** **Baseline LSAS:** placebo: 95.4, escitalopram: 96.3 **Baseline CGI-S**: placebo: 4.8, escitalopram: 4.8	

Authors: Kasper S, et al. **Year: 2005** **Country:** Multinational			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** LSAS total score **Secondary Outcome Measures:** LSAS subscales; CGI-S; CGI-I; SDS; MADRS **Timing of assessments:** Baseline and weeks 1, 2, 3, 4, 6, 8,12		
RESULTS:	• LSAS at 12 weeks: placebo 68.8, escitalopram 62.2 with a treatment difference of 7.3 ($p < 0.01$) • Mean reduction in LSAS fear/anxiety subscale: escitalopram -16.9, placebo -12.7 ($p < 0.001$) • Mean reduction in LSAS avoidance subscale: escitalopram -17.6, placebo -14.4 ($p < 0.05$) • Escitalopram showed significant improvements over placebo in CGI-S ($p < 0.01$); CGI-I responders 39% for placebo and 54% for escitalopram ($p < 0.01$) • Significantly more improvement in SDS work ($p < 0.001$) and social ($p < 0.05$) subscales • MADRS not reported		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes- 5 had no post-baseline assessment		
ATTRITION: **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy**: **Loss to follow-up differential high:**	Overall 19% 6.8% 4.2% No	Placebo 18% 4.5% 6.2%	Escitalopram 20% 8.8% 2.2%
ADVERSE EVENTS:	• Headache: placebo: 25%, escitalopram: 25% • Nausea: placebo: 12%, escitalopram: 22% • Fatigue: placebo: 9%, escitalopram: 14% • Somnolence: placebo: 5%, escitalopram: 10% • Diarrhea: placebo: 5%, escitalopram: 9% • Insomnia: placebo: 6%, escitalopram: 9%		
QUALITY RATING:	**Fair**		

Evidence Table 8 Social Anxiety Disorder

STUDY:	***Authors:*** **Kobak KA, et. al.**[165] ***Year:*** **2002** ***Country:*** US			
FUNDING:	Eli Lilly & Co.			
DESIGN:	***Study design:*** RCT ***Setting:*** Single center ***Sample size:*** 60			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluoxetine 20-60 mg/d 14 weeks	Placebo N/A 14 weeks		
INCLUSION:	DSM-IV criteria for social phobia for at least 6 months; a score of at least 50 on the Liebowitz Social Anxiety Scale (LSAS) before and after the lead–in; score could not decrease by more than 20%			
EXCLUSION:	Non-response to fluoxetine treatment; pregnancy; previous participation in a fluoxetine study; concurrent use of psychotropic or centrally acting drugs, anticonvulsants, corticosteroids, or tryptophan; serious illness; suicidal; concurrent Axis I disorders in past 12 months; psychotherapy; seizure disorder			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean age:*** 39.5 ***Gender*** (% female): 58% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Kobak KA, et. al.** ***Year:*** **2002** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Liebowitz Social Anxiety Scale (LSAS) (primary), Social Phobia Subscale of Fear Questionnaire, CGI-S, CGI-I, Patient Global Improvement Scales, HAM-A, Brief Social Phobia Scale, HAM-D (did not report which scale), Global Assessment of Functioning Scale, QOL ***Timing of assessments:*** Weeks 1, 2, 4, 6, 8, 10, 12, 14
RESULTS:	• Fluoxetine was not significantly different from placebo on the LSAS score (p = 0.901) • Similar results in secondary outcome measures with no significant difference between fluoxetine and placebo • A significant change was found on all outcome measures from baseline to endpoint with both fluoxetine (p < 0.001) and placebo (p < 0.001)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** No
ATTRITION:	***Loss to follow-up:*** 20%; fluoxetine 16%; placebo 23% ***Withdrawals due to adverse events:*** 7%; fluoxetine 3%, placebo 10% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• For fluoxetine: headache, insomnia, asthenia, and nervousness • For placebo: headache, insomnia, nervousness, and myalgia • Significantly more fluoxetine than placebo patients had asthenia (p = 0.02) • Significantly more placebo than fluoxetine patients had myalgia (p = 0.04)
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	**Authors: Lader M, et al.**[160] **Year: 2004** **Country:** Multinational (11 countries)				
FUNDING:	H. Lundbeck A/S				
DESIGN:	**Study design:** RCT **Setting:** Multi-center (47 centers) **Sample size:** 839				
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** ***Sample size:***	 Escitalopram 5 5 mg/d 24 weeks 167	 Escitalopram 10 10 mg/d 24 weeks 167	 Escitalopram 20 20 mg/d 24 weeks 170	 Paroxetine 20 20 mg/d 24 weeks 169	 Placebo N/A 24 weeks 166
INCLUSION:	Healthy female and male outpatients 18-65 years of age; primary diagnosis of generalized SAD according to DSM-IV criteria; score $\geq$ 70 on the Liebowitz Social Anxiety Scale (LSAS); score $\geq$ 5 on one or more of the Sheehan Disability Scale (SDS) subscales				
EXCLUSION:	Another Axis I disorder primary diagnosis within 6 months; MADRS total score $\geq$ 18; DSM-IV diagnosis of schizophrenia/ other psychotic disorder; Axis II Cluster B diagnosis; learning difficulties or other cognitive disorder; suicidal tendencies; no therapeutic response to SSRIs; drug hypersensitivities; taken a psychoactive drug within 2 weeks of screening; receiving formal psychotherapy				
OTHER MEDICATIONS/ INTERVENTIONS:	NR				
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Escitalopram 5: 36.3; escitalopram 10: 37.2; escitalopram 20: 37; paroxetine 20: 37.4; placebo: 37 ***Gender* (%** female): Escitalopram 5: 50%; escitalopram 10: 57%; escitalopram 20: 53%; paroxetine: 54%; placebo: 49% ***Ethnicity:*** 99.3% white ***Other population characteristics:*** Mean duration of disorder (yrs): 19.5				

Authors: Lader M, et al. **Year: 2004** **Country:** Multinational	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** Mean change from baseline to week 12 in LSAS total score (LOCF) ***Secondary Outcome Measures:*** LSAS subscale scores; CGI-S; CGI-I; change in SDS ***Timing of assessments:*** Baseline and after weeks 1,2,4,6,8,10,12,16,20,24,25, and 26.
RESULTS:	• No significant difference observed between any escitalopram treatment groups and the paroxetine group in the LOCF analysis of LSAS total score. • At weeks 16, 20, and 24 (observed case analysis), compared to the paroxetine group ($p < 0.05$)the 20 mg/d escitalopram group had significantly superior LSAS scores • Escitalopram 20mg/d was superior to paroxetine 20mg/d on CGI-S at week 24 • Escitalopram 20mg/d was superior to paroxetine 20mg/d on some SDS subscales during weeks 16 and 20, but no significant differences were noted at week 24
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 29%; escitalopram 5: 25.1%; escitalopram 10: 33.5%; escitalopram 20: 28.8%; paroxetine: 26.6%; placebo: 30.1% ***Withdrawals due to adverse events:*** 9%; escitalopram 5: 4.8%; escitalopram 10: 9.6%; escitalopram 20: 11.8%; paroxetine: 13.6%; placebo: 6% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Percentage patients experiencing any adverse effect: Escitalopram 5: 68.9%; escitalopram 10: 72.5%; escitalopram 20: 78.2%; paroxetine 20: 79.3%; placebo: 60.8% • Nausea: Escitalopram 5: 20.4%; escitalopram 10: 19.8%; escitalopram 20: 28.8%; paroxetine 20: 29%; placebo: 10.2% • Fatigue: 9% placebo; Escitalopram 5: 11.4%; escitalopram 10: 12%; escitalopram 20: 14.1%; paroxetine 20: 17.8%; placebo: 9% • Increased sweating: Escitalopram 5: 5.4%; escitalopram 10: 10.8%; escitalopram 20: 11.8%; paroxetine 20: 14.2%; placebo: 1.8%
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	**Authors: Lepola et al.**[172] **Year: 2004** **Country:** Multinational		
FUNDING:	GlaxoSmithKline		
DESIGN:	***Study design:*** RCT ***Setting*****:** Multinational (35 academic centers and private clinics in Europe and South Africa) ***Sample size:*** 375		
INTERVENTION: **Drug:** **Dose:** **Duration:**	 Paroxetine CR 12.5-37.5 mg/d 12 weeks	 Placebo N/A 12 weeks	
INCLUSION:	Outpatients with DSM-IV primary diagnosis SAD; ≥ 18 years of age; patients older than 65 included if they did not have renal or hepatic impairment		
EXCLUSION:	CGI score of 1 or 2 or score of ≥ 15 on 17-item HAM-D at baseline; other Axis I disorders currently or within 6 months prior to screening; substance abuse; current homicidal or suicidal risk; history of seizures (except febrile seizures); schizophrenia or bipolar disorder or current diagnosis of body dismorphic disorder or serious medical disorder; treatment with psychotropic medications or antidepressants within 14 days of screening; monoamine oxidase inhibitors or fluoxetine within 4 weeks of screening; depot neuroleptics within 12 weeks of screening or electroconvulsive therapy within past 3 months; patients requiring concomitant therapy with beta-adrenergic blockers, monoamine oxidase inhibitors, benzodiazepines or other psychoactive medications; pregnant, lactating or of childbearing potential and not practicing clinically accepted contraceptive method		
OTHER MEDICATIONS/ INTERVENTIONS:	Concomitant use of other psychotropic medications prohibited except for chloral betaine (up to 828 mg) or chloral hydrate (up to 1000 mg) for insomnia		
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** paroxetine CR: 38.7, placebo: 39.0 ***Gender*** (% female): paroxetine CR: 53%, placebo: 47% ***Ethnicity:*** (% white) paroxetine CR: 93.5%, placebo: 95.1%		

Authors: Lepola U, et al. **Year: 2003** **Country:** Multinational	
OUTCOME ASSESSMENT:	***Measures:*** Liebowitz Social Anxiety Scale (LSAS), CGI-Global Improvement, CGI-S, Social Avoidance and Distress Scale, Sheenan Disability Scale (SDS) ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8, 12 (or at time of early withdrawal)
RESULTS:	• Statistically significant differences were demonstrated in favor of paroxetine CR in change from baseline to week 12 LOCF in LSAS total score (adjusted mean difference = -13.33, 95% CI: -18.25 to -8.41, p < 0.001) • Significant difference in LSAS total score was maintained from week 6 to end of 12-week study • Proportion of patients achieving remission (≥ 70% decrease in LSAS total score from baseline to endpoint) was significantly greater in paroxetine CR group compared with placebo group (24.3% vs. 8.2% ; OR = 3.63, 95% CI: 1.92 to 6.85, p < 0.001) • CGI-I responder analysis reported 57.0% paroxetine CR patients achieved response, compared with 30.4% placebo patients at week 12 LOCF (OR = 3.12, 95% CI: 2.01 to 4.83, p < 0.001) • Proportion of patients who were rated "much improved" (CGI remission) was 28% in paroxetine CR group compared to 12% in placebo group (O R = 2.95, 95% CI: 1.67 to 5.20, p < 0.001) • Paroxetine significantly superior to placebo on LSAS fear or anxiety and avoidance subscales (p < 0.001), social avoidance distress scale (p < 0.001), and SDS total score (p < 0.001)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 21.9%; paroxetine CR: 16.1%, placebo: 25.5% ***Withdrawals due to adverse events:*** paroxetine CR: 2.7%, placebo: 1.6% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Treatment-emergent associated with paroxetine CR (incidence of ≥ 5% in paroxetine CR) were mild to moderate in intensity with incidence greater during first 14 days of treatment • Headache, nausea, diarrhea reported in paroxetine CR patients that stopped treatment • Serious adverse events were reported during treatment phase in 2 patients in paroxetine CR group and 2 in placebo group
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	***Authors:*** **Liebowitz MR, et al.**[174] ***Year:*** **2003** ***Country:*** US			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 415			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/day 12 weeks	Placebo N/A 12 weeks		
INCLUSION:	Age ≥18 yrs; primary diagnosis of social phobia for at least 2 years (meeting DSM criteria plus fear/avoidance of at least 4 social situations (2 involving interpersonal interactions)); Liebowitz Social Anxiety Scale (LSAS) score $\geq$ 68 at baseline			
EXCLUSION:	Met DSM criteria within the past 6 months for substance abuse or dependence, body dysmorphic disorder; MDD; dysthymia; panic disorder; PTSD; eating disorder; any current or past diagnosis of schizophrenia, psychotic disorder, bipolar disorder, or OCD; primary diagnosis of GAD; HAM-D-17 $\geq$ 14 or item 1 rating moderate or greater in severity; serious suicidal or homicidal risk; currently receiving behavioral therapy for social phobia or another anxiety disorder; history of seizure disorder; serous medical illness; pregnant, nursing or lactating; concomitant pyschotropics			
OTHER MEDICATIONS/ INTERVENTIONS:	Zolpidem for insomnia			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 35 ***Gender*** (% female): 40% ***Ethnicity:*** White: sertraline: 66.8%, placebo 76.5%; black: sertraline: 12.8%, placebo 11.3%; Hispanic: sertraline: 13.3%, placebo: 5.4%; other: sertraline: 7.1%, placebo 6.9% ***Other population characteristics:*** Prior history of depression: sertraline 15%, placebo 20%; prior history of anxiety: sertraline 3%, placebo 3%			

Authors: **Liebowitz MR, et al.** ***Year:*** **2003**	
OUTCOME ASSESSMENT:	***Measures:*** Primary Efficacy measures: CGI-I, LSAS, CGI-S, HAM-A, Duke brief social phobia scale, Sheehan Disability Scale, Endicott Work Productivity Scale, Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8, 12
RESULTS:	• CGI-I responders at 12 weeks: sertraline: 47%, placebo: 26% ($p < 0.001$) • Mean change on LSAS at 12 weeks: sertraline mean change: 31, placebo mean change: 21.7 ($p = 0.001$, corresponds to effects size of 0.43) • Sertraline demonstrated significant improvement on all secondary outcome measures (except the Endicott): Mean change Duke BSPS: $p = 0.001$ Mean change HAM-A: $p = 0.041$ Mean change CGI-S: p: = 0.004 Mean CGI-I at endpoint: $p = 0.001$ Mean change Q-LES-Q: $p = 0.001$ Mean change SDS: $p = 0.002$ work Mean change Endicott Work: $p = 0.07$
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** overall: 29%; sertraline: 28%, placebo: 31% ***Withdrawals due to adverse events:*** 5.3%, sertraline: 7.6%, placebo: 2.9% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Insomnia: sertraline 24.4%, placebo 10.1% • Loose stools: sertraline 20.6%, placebo 4% • Nausea: sertraline 16.7%, placebo 6.5% • Dizziness: sertraline 16.7%, placebo 5.5% • Dry mouth: sertraline 14.4%, placebo 3.5% • Ejaculatory dysfunction: sertraline 14.3% placebo 0% • No differences in laboratory parameters, ECG, vital signs, or weight change
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	**Authors: Liebowitz MR, et al.**[161] **Year: 2005** **Country:** US		
FUNDING:	Wyeth Research, Collegeville PA		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (26 centers) **Sample size:** 440		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Venlafaxine 75-225 mg/d 12 weeks 146	Paroxetine 20-50 mg/d 12 weeks 147	Placebo N/A 12 weeks 147
INCLUSION:	Outpatients ≥ 18 years who fulfilled DSM-IV criteria for SAD for ≥ 6 months at screening; LSAS ≥ 50 at screening and baseline with ≤ 30% decrease between prestudy and baseline; ≥ 4 on the CGI-S; Covi Anxiety Score total > Raskin Depression Scale total score; HAM-D < 15 with ≤ 2 on depressed mood item.		
EXCLUSION:	Patients with a clinically important Axis I or Axis II disorder other than SAD or avoidant personality disorder; history or current psychotic illness; Suicidal; history of drug or alcohol dependence within 1 year of the study; used anti-depressants (other than fluoxetine), anxiolytics, or herbal products within 14 days of the study; ECT within 6 months of the study; used antipsychotic medications or fluoxetine treatment within 30 days of the study; clinically significant abnormal findings on laboratory tests; pregnant or breastfeeding		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** venlafaxine: 35.7, paroxetine: 35.8, placebo: 37.3 **Gender (% female):** venlafaxine: 46.6%, paroxetine: 45.6%, placebo: 47.2% **Ethnicity:** White: VX: 71.4% PX: 72.8% Placebo: 70.1% African American: VX: 11.3% PX: 8.8% Placebo: 8.3% Hispanic: VX: 15.0% PX: 12.5% Placebo: 13.2% **Other population characteristics:** Baseline LSAS: VX: 86.2 PX: 87.2 Placebo: 86.1		

Authors: Liebowitz MR, et al. **Year: 2005** **Country:** US				
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Reduction in Liebowitz Social Anxiety Scale (LSAS) total score **Secondary Outcome Measures:** CGI-I; CGI-S; Social Phobia Inventory Scores, SDS **Timing of assessments:** Weekly			
RESULTS:	• No significant difference in LSAS improvement was observed between the venlafaxine and paroxetine groups at endpoint. Both were significantly improved from placebo ($p < 0.05$). • No significant difference in CGI-I improvement was observed between the venlafaxine and paroxetine groups at endpoint. Both were significantly improved from placebo ($p < 0.05$) • No significant difference in Social Phobia Inventory improvement was observed between the venlafaxine and paroxetine groups at endpoint; both significantly improved from placebo ($p < 0.05$) • No significant difference in CGI-S improvement was observed between the venlafaxine and paroxetine groups at endpoint. Both were significantly improved from placebo ($p < 0.05$) • No significant differences in SDS domains between venlafaxine and placebo			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes			
ATTRITION:	Overall	Venlafaxine	Paroxetine	Placebo
Loss to follow-up:	26%	27.0%	28.2%	22.6%
Withdrawals due to adverse events:	10.4%	14.2%	13.4%	4.1%
Withdrawals due to lack of efficacy:	2.3%	0.7%	0.7%	5.5%
Loss to follow-up differential high:	No			

ADVERSE EVENTS:	Venlafaxine	Paroxetine	Placebo
Nausea	32.6%	26.1%	11.0%
Insomnia	27.7%	18.3%	8.2%
Somnolence	27%	26.8%	8.9%
Asthenia	20.6%	23.9%	10.3%
Dry Mouth	17.7%	16.2%	4.8%
Anorexia	14.2%	10.6%	3.4%
Abnormal ejaculation (men)	10.5%	20.8%	0%

QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	**Authors: Montgomery SA, et al.**[163] **Year: 2005** **Country:** Multinational		
FUNDING:	H. Lundbeck A/S		
DESIGN:	**Study design:** Open label followed by randomized, double-blind, parallel group, placebo-controlled, fixed dose relapse prevention comparison **Setting:** 76 private/hospital outpatient clinics & specialized clinical research centers (11 countries) **Sample size:** 517 (open label); 372 (RCT)		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Escitalopram 10 or 20 mg/d 24 wks 191	 Placebo N/A 24 wks 181	
INCLUSION:	Outpatients between 18 and 80 yrs old; primary DSM-IV diagnosis of generalized social anxiety disorder (GSAD); total Liebowitz Social Anxiety Scale (LSAS) score ≥70 w/ exhibited fear or avoidance traits in ≥ 4 social situations; and score ≥ 5 on 1 or more Sheehan Disability Scale (SDS) subscales; RCT required CGI-I score of 1 or 2 after open-label treatment		
EXCLUSION:	Other Axis I diagnosis in previous 6 months; MADRS total score ≥ 18; score ≥ 5 on MADRS item 10 (suicidal thoughts); DSM-IV diagnosis of alcohol/drug abuse, eating disorder, major depressive disorder, panic disorder, obsessive-compulsive disorder, body dysmorphic disorder, schizophrenia, other psychotic disorder, mania or hypomania, or any Axis II diagnosis; known lack of response to SSRI; treatment with psychoactive drug in last 2 wks (or 5 wks if fluoxetine); formal psychotherapy in last 2 weeks.		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** Escitalopram: 36, Placebo: 37 **Gender(% female):** Escitalopram: 46%, placebo: 49% **Ethnicity:** 95% white (both groups) **Other population characteristics:** Mean BMI = 24.2; Mean age at GSAD onset = 17; Mean duration of GSAD = 19y (escitalopram) and 20y (placebo)		

Authors: Montgomery, et al. **Year: 2005** **Country:** Multinational	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** survival analysis estimate of time to relapse in the double-blind period. (Relapse defined as LSAS score increase $\geq$ 10 or withdrawal of patient due to lack of efficacy.) **Secondary Outcome Measures:** LSAS total score; LSAS avoidance and fear/anxiety subscale; SDS **Timing of assessments:** 1,2,4,8,12,16,20,& 24 weeks after randomization; also safety follow-up at 4 weeks after last dose of double-blind treatment
RESULTS:	• Significant advantage in survival for escitalopram vs. placebo in primary efficacy analysis (log rank test $p < 0.001$) • Relapse rates = 22% (escitalopram) vs. 50% (placebo) • Risk of relapse was 2.8 times higher w/ placebo than escitalopram • Median time to relapse = 407 days (escitalopram) vs. 144 days (placebo) • Significant advantage for escitalopram on all secondary measures (LSAS, CGI-S, SDS, and MADRS) • Improvement on LSAS in escitalopram group (8.3 points), deterioration in placebo group (4.5 points) • Mean MADRS score change = +0.8 (escitalopram) and +2.6 (placebo) • Mean CGI-S score change = -0.3 (escitalopram) and +0.3 (placebo)
ANALYSIS:	**ITT:** Yes, defined as all randomized patients who took at least 1 dose of double-blind medication and had at least 1 valid post baseline assessment of LSAS total score **Post randomization exclusions:**
ATTRITION:	**Loss to follow-up:** Escitalopram: 25 (13%), placebo: 15 (8.3%) **Withdrawals due to adverse events:** Escitalopram: 5 (2.6%), placebo: 6 (3.3%) **Withdrawals due to lack of efficacy:** N/A **Loss to follow-up differential high:** No
ADVERSE EVENTS:	• Assessed via spontaneous report, various clinical exam/lab reports, and 43-item Discontinuation Emergent Signs and Symptoms (DESS) checklist at randomization and 1 and 2 wks after. • Treatment emergent adverse events (TEAEs) with incidence $\geq$ 5 % in either group were: headache, dizziness, increased sweating, nervousness, fatigue, insomnia, nausea, rhinitis, and influenza-like symptoms • Incidence of TEAEs was lower in escitalopram group (62.6%) vs. placebo group (71.8%) • Dizziness, increased sweating, and nervousness were significantly higher in placebo group in 1st 2 weeks following discontinuation of escitalopram ($p < 0.05$). Excluding these TEAEs in 1st 2 weeks post-randomization, adverse events were similar in both treatment groups • After 1 and 2 weeks of double-blind treatment, mean total DESS score was significantly lower in -escitalopram group (week 1: escitalopram =1.17 vs. placebo = 2.61; week 2: escitalopram =1.02 vs. placebo = 1.78) ($p < 0.01$)
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	**Authors: Muehlbacher M, et al.**[168] **Year: 2005** **Country:** Multinational		
FUNDING:	NR		
DESIGN:	**Study design:** Randomized, double-blind, placebo controlled **Setting:** Clinics **Sample size:** 66		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Mirtazapine 30 mg/d 10 wks 33	 Placebo N/A 10 wks 33	
INCLUSION:	Women aged 18 or older with DSM-IV diagnosed social phobia		
EXCLUSION:	Psychotic symptoms; use of mirtazapine or other psychotropic drug; psychotherapy; currently or planning to be pregnant (or no contraception use); severe somatic illness; currently suicidal; current drug / alcohol abuse; severe major depressive disorder.		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Cannot tell **Mean age:** NR **Gender:** NR **Ethnicity:** NR **Other population characteristics:** Both groups similar in percentage currently living in partnership, and with personality, panic, general anxiety disorders, OCDs		

Authors: Muehlbacher M, et al. **Year: 2005** **Country:** Multinational	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Change in social anxiety measured w/ social phobia inventory (SPIN) and LSAS **Secondary Outcome Measures:** SF-36 Health Survey **Timing of assessments:** Weekly for 10 weeks, although intermediate results were not analyzed
RESULTS:	• Mirtazapine group experienced significantly greater rate of change on both SPIN and LSAS scales • Initial SPIN scores = 32.5 +/- 4.7 (mirtazapine) vs. 29.0 +/- 4.6 (placebo) • Final SPIN scores = 24.1 +/- 4.3 (mirtazapine) vs. 28.7 +/- 5.1 (placebo) • SPIN: Difference in change b/w both groups = -8.1 (95% CI -9.6 to 4.1; $p < 0.001$) • Initial LSAS scores = 71.9 +/- 8.3 (mirtazapine) vs. 72.5 +/- 8.0 (placebo) • Final LSAS scores= 46.3 +/- 7.0 (mirtazapine) vs. 67.1 +/- 7.4 (placebo) • LSAS: Difference in change b/w both groups = -20.2 (95% CI -27.5 to -4.1; $p < 0.001$) • Mirtazapine group experienced significantly greater rate of change on SF-36 (on general health perceptions, vitality, social functioning, role-emotional, and mental health scales)
ANALYSIS:	**ITT:** No **Post randomization exclusions:** Cannot tell
ATTRITION:	**Loss to follow-up:** NR **Withdrawals due to adverse events:** NR **Withdrawals due to lack of efficacy:** NR **Loss to follow-up differential high:** NR
ADVERSE EVENTS:	• Most frequently reported adverse events in mirtazapine vs. placebo were: dry mouth (21.2% vs. 12.1%), drowsiness (18.2% vs. 9.1%), sedation (18.2% vs. 6.1%), increased appetite (12.1% vs. 3.0%), and weight gain (21.2% vs. 6.1%)
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	***Authors:*** **Stein MB, et. al.**[166] ***Year:*** **1999** ***Country:*** US			
FUNDING:	Solvay Pharmaceuticals Inc. and The Pharmacia and Upjohn Co.			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 92			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Fluvoxamine 50-300 mg/d 12 weeks	 Placebo N/A 12 weeks		
INCLUSION:	DSM-IV criteria for social phobia; score of at least 20 on the Brief Social Phobia Scale; 18-65 years of age			
EXCLUSION:	Patients taking psychotropic medications within 7 days of the study; pregnancy; other primary psychiatric disorder; psychotherapy; serious illness; suicidal or homicidal			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** No (see gender %) ***Mean age:*** Fluvoxamine: 39.1, placebo: 39.7 ***Gender*** (% female): Fluvoxamine: 25%, placebo: 47.7%; significantly more men in fluvoxamine than placebo group (p = 0.04) ***Ethnicity:*** Not reported ***Other population characteristics:*** No other significant population differences reported			

Authors: **Stein MB, et. al.** ***Year:*** **1999**	
OUTCOME ASSESSMENT:	***Measures:*** Proportion of CGI-I responders (1 or 2), Brief Social Phobia Scale, Social Phobia Inventory, Liebowitz Social Anxiety Scale, Sheenan Disability Scale ***Timing of assessments:*** Weeks 1, 2, 3, 4, 6, 8, 10, 12
RESULTS:	• Significantly higher proportion of responders in the fluvoxamine than the placebo group (fluvoxamine: 42.9%, placebo: 22.7%; p = 0.04) • Fluvoxamine better than placebo on all social anxiety scales from week 8 to endpoint
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** Not reported ***Withdrawals due to adverse events:*** 17%; fluvoxamine: 25%, placebo: 9.1% ***Loss to follow-up differential high:*** Not reported
ADVERSE EVENTS:	Difference between fluvoxamine and placebo greater than 10 percentage points: nausea, insomnia, dizziness, reduced libido, nervousness, and somnolence
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	***Authors:*** **Stein MB, et. al.**[171] ***Year:*** **1998** ***Country:*** US, Canada			
FUNDING:	SmithKline Beecham			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (13 US, 1 Canada) ***Sample size:*** 187			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Paroxetine 20-50 mg/d 12 weeks	 Placebo N/A 12 weeks		
INCLUSION:	Age 18 or older; DSM-IV diagnosis of social anxiety disorder; exhibit fear and/or avoidance of at least 4 social situations			
EXCLUSION:	Concurrent use of psychoactive medications (except chloral hydrate); concurrent use of narcotic analgesics, warfarin, digoxin, phenytoin, cimetidine, or sulfonylureas; psychotropic agent or beta-blocker within 14 days; depot neuroleptics within 12 weeks; other Axis I diagnosis; substance abuse or dependence; suicidal or homicidal risk; dysmorphic disorder, schizophrenia, bipolar affective disorder, uncontrolled medical illness; other clinical trial within 12 months; pregnant, lactating, or no clinically acceptable method of birth control			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** 36 ***Gender*** (% female): 53% ***Ethnicity:*** 81% white ***Other population characteristics:*** Not reported			

Authors: **Stein MB, et. al**. ***Year:*** **1998** ***Country:*** US, Canada	
OUTCOME ASSESSMENT:	***Measures:*** (Primary) Percentage of CGI-I responders; mean change from baseline on LSAS (Secondary) Mean change from baseline on SADS; SDI; fear, anxiety and avoidance subscale of the LSAS ***Timing of assessments:*** Weeks 1, 2, 3, 4, 6, 8, 12
RESULTS:	• CGI-I Responders: paroxetine 55%; placebo 24% ($p < 0.001$ from week 4 through week 12) • Mean change from baseline in LSAS: paroxetine -30.5; placebo -14.5 ($p < 0.001$ from week 2 through week 12) • Paroxetine superior to placebo on all secondary efficacy measures except family life item of SDI ($p < 0.05$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 28.3%; paroxetine 34%, placebo 23% ***Withdrawals due to adverse events:*** 9%; paroxetine 14.9%, placebo 5.45% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Abnormal ejaculation: paroxetine 36% vs. placebo 0% • Somnolence: paroxetine 27% vs. placebo 10% • Nausea: paroxetine 26% vs. placebo 12%
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	***Authors:*** **Stein D, et. al.**[169] ***Year:*** **2002** ***Country:*** Multinational			
FUNDING:	SKB			
DESIGN:	***Study design:*** Controlled trial, single blinded (acute phase); RCT (maintenance phase 24 weeks) ***Setting:*** Outpatient clinics ***Sample size:*** 323			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Paroxetine 20-50 mg/day 36 weeks	 Placebo N/A 36 weeks		
INCLUSION:	DSM-IV diagnosis for social anxiety disorder; HAM-A score at least 20 with a score of 2 or more on item 1 & 2 (anxious mood, tension); age 18 yrs & older Maintenance phase: eligible if CGI-S decreased by 2 points during the acute phase			
EXCLUSION:	Elderly not able to tolerate paroxetine 20mg; elderly with renal or hepatic impairment; other Axis I disorders in the past 6 months; primary diagnosis of panic disorder; history of schizophrenia or bipolar; substance abuse in past 3 months; substance dependence in past 6 months; use of beta blockers; MAOI; BDZ; psychoactive agent (except chloral hydrate); psychotropic or antidepressant 14 days before study; having received a therapeutic dose of SSRI for SAD; received paroxetine and did not respond			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Paroxetine 38.1, placebo 38.2 ***Gender*** (% female): Paroxetine: 60.5%, placebo: 60.2% ***Ethnicity:*** Paroxetine: white: 93.8%, other: 6.2%; placebo: white: 93.2%, other: 6.8% ***Other population characteristics:*** Not reported			

Authors: **Stein D, et. al.** ***Year:*** **2002** ***Country:*** Multinational	
OUTCOME ASSESSMENT:	***Measures:*** Proportion of patients relapsing during maintenance stage (increase in CGI-S of 2 points from week 12, score of 4 or >, or withdrawal because of lack of efficacy). Time to relapse % of improvers, CGI-I, Liebowitz Social anxiety Scale (LSAS), social phobia inventory scale, Sheehan disability scale, Symptom checklist-90 (SCL-90), EQ-5D ***Timing of assessments:*** Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36
RESULTS:	• Significantly fewer patients relapsed on paroxetine; OR = 2.78 ($p < 0.001$) • Time to relapse was significantly longer in paroxetine group • Hazard ratio for relapse time = 3.29 • Significantly more paroxetine subjects were much improved or very much improved on the CGI-I • Significantly greater improvement with paroxetine on LSAS, Sheehan, SCL-90, EQ-5D, VAS
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** No
ATTRITION:	***Loss to follow-up:*** 20.5%; paroxetine: 16%, placebo: 25% ***Withdrawals due to adverse events:*** Paroxetine: 2%, placebo: 5% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Paroxetine during acute phase (all patients): nausea 24%, somnolence 17%, insomnia 17%, abnormal ejaculation 26%, headache 20%. • Continuation phase: paroxetine: headache 11%; placebo: headache 16%, dizziness 15% • Significantly more subjects in the paroxetine group experienced weight gain (23% vs. 9%)
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	***Authors:*** **Van Ameringen R, et. al.**[173] ***Year:*** **2001** ***Country:*** Canada			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 204			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Sertraline 50–200 mg/day 20 weeks	 Placebo N/A 20 weeks		
INCLUSION:	DSM-IV criteria for primary, generalized social phobia (GSP); CGI-S score of 4 or less; age 18-60 yrs; if subject also had a diagnosis of major depression, MADRS 19 or less & diagnosis of GSP predated current episode of depression by 5 years			
EXCLUSION:	Other primary Axis I disorder; recent use of SSRI, anti-anxiety or psychotropic medications; recent cognitive behavior therapy; treatment with beta blockers or clonidine; pregnant or lactating; major life event in past 3 months; positive urine screen for BZD			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate, zopidone			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Sertraline: 35.7; placebo: 35.6 ***Gender*** (% female): Sertraline: 42%, placebo: 49% ***Ethnicity:*** Sertraline: black: 2%, Asian: 3%, white: 92%, other: 3%; placebo: black: 0%, Asian: 3%, white: 96%, other: 1% ***Other population characteristics:*** Concomitant DSM-IV diagnosis: avoidant personality disorder: sertraline 55%, placebo 61%; MDD: sertraline 2%, placebo 1%			

Authors: **Van Ameringen R, et. al.** ***Year:*** **2001** ***Country:*** Canada	
OUTCOME ASSESSMENT:	***Measures:*** CGI-S, CGI-I, MADRS, Liebowitz Panic & Social Phobic Disorders Rating Scale; Social Phobia & Anxiety Inventory Social Phobia Subscale; Social Avoidance & Distress Scale; Fear of Negative Evaluation Scale, Clinical Anxiety Scale, Sheehan Disability Scale ***Timing of assessments:*** Weeks 1, 2, 4, 7, 10, 13, 16, 20
RESULTS:	• Difference in change from baseline to end of treatment was significantly better for sertraline on all scales measured • Statistically more subjects on sertraline (53% vs. 29% on placebo) were much or very much improved at the end of treatment based on the CGI-I
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** Sertraline: 23%, placebo: 22% ***Withdrawals due to adverse events:*** sertraline: 12%; placebo: 1% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Sertraline: nausea 32.6%, insomnia 30.4%, dyspesia 25.2%, diarrhea 20.7%. • Placebo: diarrhea 15.9%, nausea 14.5%, insomnia 14.5%, asthenia: 11.6%. • Significantly more subjects in the sertraline group reported nausea (32.6% vs. 14.55), insomnia (30.4% vs. 14.5%), dyspepsia (25.2% vs. 7.2%), flu syndrome (17.8% vs. 5.5%), delayed ejaculation (11.4% vs. 4.3%), sweating (11.1% vs. 5.9%)
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	***Authors:*** **van der Linden et. al.**[162] ***Year:*** **2000** ***Country:*** South Africa, the Netherlands
FUNDING:	MRC Research Unit on Anxiety and Stress Disorders; Harry Crossley Trust; Cochrane review collaborators
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 1482
AIMS OF REVIEW:	To review all available SSRI studies for social anxiety disorder
STUDIES INCLUDED IN META-ANALYSIS	Van Vliet et al., 1994, Katzelnick et al., 1995, Stein et al., 1998, Stein et al., 1999, Baldwin et al., 1999, Pfizer Pharmaceutical Group data on file, 1999, SmithKlineBeecham data on file, 1998
TIME PERIOD COVERED:	Not reported (included studies for dates 1994 to 2000)
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs (placebo controlled); 18 trials; 2 unpublished
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients with social anxiety disorder

Authors: **van der Linden, et. al.** ***Year:*** **2000** ***Country:***	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	RCT data were analyzed for fluvoxamine, paroxetine, and sertraline
MAIN RESULTS:	• Odds ratio of responder status for SSRI vs. placebo varied between 2.1 and 26.2 • The NNT varied from 1.6 to 4.2 • LSAS effect size varied from 0.3 to 2.2 • No difference in efficacy between SSRIs was reported
ADVERSE EVENTS:	Not reported
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Not defined in article but described to be consistent with methods of a Cochrane review
STANDARD METHOD OF APPRAISAL OF STUDIES:	Not defined in article but described to be consistent with methods of a Cochrane review
QUALITY RATING:	**Fair**

Evidence Table 8 Social Anxiety Disorder

STUDY:	**Authors: Westenberg H, et al.**[167] **Year: 2004** **Country:** Multinational	
FUNDING:	Solvay Pharmaceuticals Inc	
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 300	
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Fluvoxamine 100-300 mg/day 12 weeks 149	 Placebo N/A 12 weeks 151
INCLUSION:	Outpatients with a primary diagnosis GSAD following DSM-IV criteria and minimum score of 60 on the LSAS; 18- 70 years old	
EXCLUSION:	Pregnancy or lactation; psychiatric disorders other than GSAD that are predominant in the previous 6 months; MADRS of 18 or more; substance abuse in last 6 months; positive urine test; serious suicide risk; serious medical conditions, patients requiring formal CBT	
OTHER MEDICATIONS/ INTERVENTIONS:	NR	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** fluvoxamine: 38.6, placebo: 37.3 **Gender (% female):** fluvoxamine: 54%, placebo: 50% **Ethnicity:** NR **Other population characteristics:** Mean LSAS: fluvoxamine: 94.8(1.5), placebo: 94.8(1.8) CGI-S: fluvoxamine: 4.8(0.1), placebo: 4.7(0.1)	

Authors: Westenberg H, et al. **Year: 2004** **Country:** Multinational			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** LSAS **Secondary Outcome Measures:** CGI-S, SDS, CGI-I, PGI **Timing of assessments:** Screening, baseline and weeks 2,4,6,8,10,12		
RESULTS:	LSAS- mean change from baseline fluvoxamine -36.1 (± 2.7) placebo -27.3 (± 2.4) (p = 0.02) CGI-S- mean change from baseline fluvoxamine -1.5 (± 0.1) placebo -1.0 (± 0.1) (p = 0.022) SDS- mean change from baseline fluvoxamine -7.8 (± 0.7) placebo -5.8 (± 0.6) (p = 0.036) CGI-I- endpoint score fluvoxamine 2.5 (± 0.1) placebo 2.9 (± 0.1) (p = 0.026) Responders – CGI-I of very much or much improved fluvoxamine 48% placebo 44% (p = 0.078) PGI- endpoint score fluvoxamine 2.6 (± 0.1) placebo 3.0 (± 0.1) (p = 0.051)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes- 6 had no post baseline assessments		
ATTRITION: **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy**: **Loss to follow-up differential high:**	Overall 32% 15% 5% No	Fluvoxamine 38% 26% 0%	Placebo 29% 5% 9%
ADVERSE EVENTS:	• All AEs: fluvoxamine 92%, placebo 83% • Nausea: fluvoxamine 47%, placebo 15% • Headache: fluvoxamine 35%, placebo 32% • Insomnia: fluvoxamine 32%, placebo 15% • Asthenia: fluvoxamine 28%, placebo 13% • Somnolence: fluvoxamine 22%, placebo 7%		
QUALITY RATING:	**Fair**		

Evidence Table 9: Premenstrual Dysphoric Disorder

STUDY:	***Authors:*** **Dimmock PW, et al.**[177] ***Year:*** **2000** ***Country:***
FUNDING:	No external funding
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 904
AIMS OF REVIEW:	To determine the efficacy of SSRIs in severe premenstrual syndrome
STUDIES INCLUDED IN META-ANALYSIS	Pearlstein et al., 1997, Ozeren et al., 1997, Su et al., 1997, Steiner et al., 1995, Menkes et al., 1999, Wood et al., 1992, Stone et al., 1991, Halbreich et al, 1997, Yonkers et al., 1997, Young et al., 1998, Eriksson et al., 1995, Jermain et al., 1999, Freeman et al., 1999, Veeninga et al., 1990, Wilkander et al., 1998
TIME PERIOD COVERED:	1966-1999
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs; 1 head-to-head; all placebo controlled
CHARACTERISTICS OF INCLUDED POPULATIONS:	Women with PMS

Authors: **Dimmock PW, et al.** ***Year:*** **2000**	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	Fluoxetine, sertraline, citalopram, paroxetine, fluvoxamine
MAIN RESULTS:	• Overall standardized mean difference showed a significant reduction of PMS symptoms in SSRI group compared to placebo • -1.066 (95% CI -1.381 to -0.750) = OR 6.91 (3.90-12.2) • SSRIs were effective in physical and behavioral symptoms; there was no significant variation in the overall standardized mean differences (p = 0.386)
ADVERSE EVENTS:	Insufficient data; some trials did not quote a complete breakdown
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 9 Premenstrual Dysphoric Disorder

STUDY:	***Authors:*** **Freeman EW, et al.**[178] ***Year:*** **2001** ***Country:*** US			
FUNDING:	Wyeth-Ayerst			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 157			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine 50-200 mg/d Four menstrual cycles	Placebo N/A Four menstrual cycles		(Dosage increased at the beginning of each menstrual cycle if no improvement)
INCLUSION:	18-45 years of age; regular menstrual cycles lasting 22-35 days for the last 6 months; evidence of ovulation; meets DSM-III-R criteria for PMDD; general good health			
EXCLUSION:	Prescription or non-prescription medication for PMDD; breastfeeding, pregnancy; hysterectomy; symptomatic endometriosis; irregular menstrual cycles; not using medically approved nonhormonal contraception; serious health problems; Axis I psychiatric diagnosis; suicidal; drug or alcohol dependence			
OTHER MEDICATIONS/ INTERVENTIONS:	No other psycho-pharmalogical medications			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** No; premenstrual severity lower in placebo group at baseline ***Mean Age:*** venlafaxine: 35, placebo: 35 ***Gender*** (% female): 100% ***Ethnicity:*** Venlafaxine: 89% white, 10% black, 1% Hispanic; placebo: 91% white, 7% black, 3% Hispanic ***Other population characteristics:*** Premenstrual daily symptom report was significantly lower at baseline in placebo group (p = 0.032)			

Authors: **Freeman EW, et al.** ***Year:*** **2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Premenstrual daily symptom report (maintained by subject), 21 item HAM-D, CGI scale ***Timing of assessments:*** Scales administered twice a cycle: once during the premenstrual phase and once during the postmenstrual phase
RESULTS:	• Premenstrual Daily Symptom Report scores were significantly more improved in the venlafaxine group than in the placebo group at each time point and at endpoint ($p < 0.001$) • Venlafaxine showed significantly greater improvement than placebo in four of the factors of the DSR: emotion ($p < 0.001$), function ($p = 0.011$), pain ($p = 0.016$), and physical symptoms ($p = 0.003$) • The venlafaxine group was significantly more improved on the 21 item HAM-D ($p = 0.001$) • DSR response (> 50% reduction): venlafaxine 60%, placebo: 35% ($p = 0.003$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 36%; venlafaxine: 35%, placebo: 36% ***Withdrawals due to adverse events:*** 12.8%; venlafaxine: 9%, placebo: 6.25% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Nausea 45% vs. 13% (venlafaxine vs. placebo $p < 0.001$) • Insomnia 34 % vs. 16% (venlafaxine vs. placebo $p = 0.05$) • Dizziness 32% vs. 5% (venlafaxine vs. placebo $p < 0.001$) • Decreased libido (venlafaxine vs. placebo $p < 0.001$) • Fatigue (not significant) • Headache (not significant) • Dry mouth (not significant) • Dysmenorrhea (not significant) •
QUALITY RATING:	**Fair**

Evidence Table 9 Premenstrual Dysphoric Disorder

STUDY:	**Authors: Freeman EW, et al.**[181] **Year: 2004** **Country:** US		
FUNDING:	NIH-Institute of Child Health and Human Development Pfizer		
DESIGN:	**Study design:** RCT **Setting:** Single center (University of Pennsylvania Medical Center) **Sample size:** 167		
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:*** ***Sample size:***	 Sertraline 50-100 mg/d (full cycle dosing) 3 menstrual cycles 56	 Sertraline 50-100 mg/d (Luteal phase dosing) 3 menstrual cycles 56	 Placebo N/A 3 menstrual cycles 55
INCLUSION:	Women aged 18-45 years; diagnosis of severe PMS based on symptoms reported over three screening cycles; regular menstrual cycles; positive urine test for probable ovulation; persistent premenstrual symptoms for at least 6 months; moderate to severe impairment in work, family life, or social activity; general good health		
EXCLUSION:	Any major Axis I psychiatric diagnosis currently or within the past year; use of psychotropic medications; pregnancy, lactation, not using medically-approved contraception; hysterectomy; symptomatic endometriosis; irregular menstrual cycles; serious health problems; risk of suicide; alcohol or drug abuse		
OTHER MEDICATIONS/ INTERVENTIONS:	No other prescription, over-the-counter, or herbal therapies for PMS allowed		
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 33.6 ***Gender*** (% female): 100% ***Ethnicity:*** 81% white ***Other population characteristics:*** Mean Baseline Daily Symptom Report Scores MBDSRS): Premenstrual: 153 full cycle; 153 luteal phase; 142 placebo Postmenstrual: 25 full cycle; 28 luteal phase; 23 placebo		

Authors: Freeman EW, et al. **Year: 2004** **Country:** US	
OUTCOME ASSESSMENT:	***Primary Outcome Measures:*** Total score on the premenstrual Daily Symptom Rating Form ***Secondary Outcome Measures:*** Subject Global Ratings of Functioning ***Timing of assessments:*** Symptoms were recorded daily and patients were seen at the start of each cycle
RESULTS:	• Both sertraline treatment groups showed greater improvement than placebo on the Premenstrual Daily Symptom Scores: full cycle dosing (p = 0.055); Luteal phase dosing (p = 0.009) • Clinical response rate (>50% reduction on Daily Symptom Rating Form): continuous: 63%; intermittent: 51%; placebo: 36% (p = 0.03) • No significant difference was observed between the two sertraline groups (p = 0.44)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** yes
ATTRITION:	***Loss to follow-up:*** 49%; full cycle dosing: 28.6%; luteal phase dosing: 37.5% ***Withdrawals due to adverse events:*** 13%; full cycle dosing: 12/5%; luteal phase dosing: 9% ***Loss to follow-up differential high:*** N/A
ADVERSE EVENTS:	• Most frequent adverse events for sertraline: gastrointestinal (19%), decreased libido or orgasm (15%), headache (14%), insomnia (13%), dry mouth (13%), nausea (13%), nightmares (12%) • Adverse event reporting in the third cycle did not differ between the full-cycle dosing group and placebo (p = 0.38), but did differ between the luteal phase dosing group and placebo (p = 0.03).
QUALITY RATING:	**Fair**

Evidence Table 9 Premenstrual Dysphoric Disorder

STUDY:	***Authors:*** **Halbreich U, et al.**[180] ***Year:*** **2002** ***Country:*** US and Canada			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 281			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Sertraline 50-100 mg/d (taken only during the luteal phase) Three menstrual cycles	 Placebo N/A Three menstrual cycles		
INCLUSION:	24-45 years of age (inclusive); regular menstrual cycles lasting 24-36 days; 2 year self-reported history of PMDD; meets DSM-IV criteria for PMDD			
EXCLUSION:	Marked level of functional impairment for at least 2 days (daily record of severity of problems) use of oral contraceptives; follicular phase HAM-D >10; other major psychotic disorder; depression not associated with PMDD; over 38 years old with abnormal LH or FSH levels; hysterectomy; failure to respond to antidepressants; current use of psychotropic medication			
OTHER MEDICATIONS/ INTERVENTIONS:	Other medications for PMS symptomatology not allowed			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** Sertraline: 35.9, placebo: 36.5 ***Gender*** (% female): 100% ***Ethnicity:*** White: 91% ***Other population characteristics:*** Comparable clinical characteristics at baseline			

Authors: **Halbreich U, et al.** ***Year:*** **2002** ***Country:*** US and Canada	
OUTCOME ASSESSMENT:	***Measures:*** CGI-S, CGI-I, total score from the Daily Record of Severity of Problems, Patient Global Evaluation, Social Adjustment Scale, Quality of Life Enjoyment and Satisfaction questionnaire ***Timing of assessments:*** Not reported
RESULTS:	At endpoint, sertraline had significantly lower scores than placebo on the CGI-I scale ($p < 0.001$), the CGI-S scale ($p < .001$) , and the Daily Record of Severity of Problems ($p < 0.002$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 21% ***Withdrawals due to adverse events:*** 4%; sertraline: 7.7%, placebo: 0.7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Headache, nausea (sertraline vs. placebo; $p = 0.006$) • Insomnia, diarrhea, dry mouth (sertraline vs. placebo; $p = 0.027$) • More patients experienced severe adverse events with sertraline (16.9%) than placebo (7.1%); $p = 0.022$
QUALITY RATING:	**Fair**

Evidence Table 9 Premenstrual Dysphoric Disorder

STUDY:	***Authors:*** **Landen M, et al.**[179] ***Year:*** **2001** ***Country:*** Sweden			
FUNDING:	Swedish Medical Research Council, the Professor Bror Gadelius Foundation, Fredrik and Ingrid Thuring's Foundation, and Bristol-Myers Squibb			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 69			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Nefazodone 100-400 mg/d (four menstrual cycles, 2 cycles of intermittent drug treatment during the luteal phase, 2 cycles of continuous treatment)	Buspirone 10-40mg/d (four menstrual cycles, 2 cycles of intermittent drug treatment during the luteal phase, 2 cycles of continuous treatment)	Placebo N/A (four menstrual cycles, 2 cycles of intermittent drug treatment during the luteal phase, 2 cycles of continuous treatment)	
INCLUSION:	Fulfilled diagnostic criteria A-C of DSM-IV criteria for PMDD (modified to use 2 of 11 criteria); confirmed cyclicity of at least irritability or depressed mood; 18-45 years old; menstrual cycles 22-35 days			
EXCLUSION:	Psychiatric illness; pregnancy; irregular menstrual cycles; previous antidepressant treatment for menstrual symptoms; ongoing somatic illness; MDD; suicidal; continuous medications; hormonal therapy; other condition that could pose risk; MARDS > 14			
OTHER MEDICATIONS/ INTERVENTIONS:	No continuous medication or hormonal medication			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** Nefazodone: 37, buspirone: 37, placebo: 33 ***Gender*** (% female): 100% ***Ethnicity:*** Not reported ***Other population characteristics:*** No differences reported			

Authors: **Landen M, et al.** ***Year:*** **2001** ***Country:*** Sweden	
OUTCOME ASSESSMENT:	***Measures:*** Daily symptom ratings using a visual analogue scale for the following symptoms: irritability, depressed mood, tension, affect lability, food craving, bloating, breast tenderness. CGI scale after last treatment cycle or after dropout ***Timing of assessments:*** Daily
RESULTS:	• Nefazodone was not significantly different from placebo on the CGI score (p = 0.22) • Nefazodone did not significantly improve irritability, depressed mood, or tension at any time point • After the second cycle of the intermittent phase, nefazodone was significantly better than placebo for affect lability (p = 0.05); significance was not maintained after the continuous treatment
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 22% ***Withdrawals due to adverse events:*** 14.5% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Dizziness, blurred vision, insomnia, abnormal dreams, somnolence, and flu-like symptoms were reported more often in nefazodone than placebo (p < 0.05)
QUALITY RATING:	**Fair**

Evidence Table 9 Premenstrual Dysphoric Disorder

STUDY:	**Authors: Steiner M, et al.**[182] **Year: 2005** **Country:** Multinational		
FUNDING:	NR		
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 373		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Paroxetine CR 12.5 mg 3 months 131	Paroxetine CR 25 mg 3 months 119	Placebo N/A 3 months 123
INCLUSION:	Female outpatients; 18 to 45 years; regular menstrual cycles; PMDD as outlined in the DSM-IV; have had the condition for at least 1 year, during which symptoms of the disorder needed to have been present in at least 9 of 12 menstrual cycles; baseline rating of at least "mildly ill" according to the CGI-S		
EXCLUSION:	Other Axis I disorders (except specific phobias) within 6 months; gynecologic or other clinically significant disease; clinically significant depressive symptomatology during the follicular phase; significant risk for suicide; medications that could interfere with their PMDD symptoms or with the assessment of their symptoms; oral or systemic contraceptives; previous adequate treatment for PMDD, had participated in a clinical trial with an SSRI for PMDD; pregnant or breastfeeding		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Mean age:** paroxetine (25 mg): 37.2; paroxetine (12.5 mg): 35.9; placebo: 36.9 **Gender (% female):** 100% **Ethnicity (% white):** paroxetine (25 mg): 100%; paroxetine (12.5 mg): 96.2%; placebo: 98.3% **Duration of PMDD (years):** paroxetine (25mg): 10.5; paroxetine (12.5 mg): 10.5; placebo: 10.4		

Authors: Steiner M, et al. **Year: 2005**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** VAS-Mood score at treatment cycle 3 **Secondary Outcome Measures:** Premenstrual Tension Scale (PMTS-O); CGI-S and CGI-I; patient global evaluation (PGE); SDS **Timing of assessments:** First 3 days of the onset of menses for up to 3 treatment cycles		
RESULTS:	• **VAS- Mood score** paroxextine CR 25 mg vs. placebo −10.79 (95% CI−16.46 to −5.12) p < 0.001 paroxetine CR 12.5 mg vs. placebo −7.66 (95% CI −13.25 to −2.08) p = 0.007 • **VAS-total** paroxextine CR 25 mg vs placebo −77.82 (95% CI −133.47 to −22.16) p = 0.006 paroxetine CR 12.5 mg vs placebo −73.13 (95% CI −127.91 to −18.36) p = 0.009 • **PMTS-O total score** paroxextine CR 25 mg vs placebo −3.21 (95% CI −5.42 to −0.99) p = 0.005 paroxetine CR 12.5 mg vs placebo −1.78 (95% CI −3.86 to 0.30) p = 0.093 • **CGI-S** paroxetine CR 25 mg vs placebo −0.61 (95% CI −1.03 to −0.20) p = 0.004 paroxetube CR 12.5 mg vs placebo −0.27 (95% CI −0.67 to 0.12) p = 0.177 • **SDS total** paroxetine CR 25 mg vs placebo −2.74 (95% CI −4.97 to −0.51) p = 0.016 paroxextube CR 12.5 mg vs placebo −2.33 (95% CI −4.40 to −0.26) p = 0.028		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes -7		
ATTRITION:	Paroxetine 12.5 mg	Paroxetine 25 mg	Placebo
Loss to follow-up:	26 (19.8%)	29 (24.4%)	19 (15.4%)
Withdrawals due to adverse events:	13 (9.9%)	16 (13.4%)	5 (4.1%)
Withdrawals due to lack of efficacy:	2 (1.7%)	2 (1.5%)	6 (5%)
Loss to follow-up differential high:	No	No	
ADVERSE EVENTS:	• 9 AEs occurred at a frequency ≥ 5% and at an incidence in either paroxetine CR group of at least twice that of placebo: nausea, asthenia, libido decreased, sweating, diarrhea, dizziness, tremor, insomnia, and sinusitis; all but insomnia and sinusitis were observed more frequently in the 25 mg paroxetine CR- than in the 12.5-mg paroxetine CR treatment group; the majority were rated as mild or moderate in severity		
QUALITY RATING:	**Fair**		

Evidence Table 9 Premenstrual Dysphoric Disorder

STUDY:	***Authors:*** **Wyatt KM, et al.**[176] ***Year:*** **2004** ***Country:*** UK
FUNDING:	Cochrane Collaboration
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 844
AIMS OF REVIEW:	To evaluate the effectiveness of SSRIs in reducing symptoms in women diagnosed with severe premenstrual syndrome
STUDIES INCLUDED IN META-ANALYSIS	Pearstein, 1997, Ozeren, 1997, Su, 1997, Steiner, 1995a, Menkes, 1993, Wood, 1992, Stone, 1991, Halbreich, 1997, Yonkers, 1997, Young, 1998, Erikkson, 1995, Jermain, 1999, Freeman, 1999a, Veeninga, 1990, Wikander,1998a
TIME PERIOD COVERED:	Not reported
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs; quasi-randomized controlled trials; controlled trials
CHARACTERISTICS OF INCLUDED POPULATIONS:	Women of any age who met the diagnostic criteria for premenstrual syndrome, premenstrual dysphoria, PMDD, or LLPDD; diagnosis must have been established by a clinician prior to inclusion in the trial

Authors: **Wyatt KM, et al.** ***Year:*** **2004** ***Country:*** UK	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	SSRIs at any dosage and any dosing regimen for any duration longer than one menstrual cycle versus placebo
MAIN RESULTS:	Main outcome measure: reduction in overall symptomatology: SSRIs were found to be highly effective in treating premenstrual symptoms compared to placebo; SMD: -0.75 (95% CI=-0.98 to -0.51); equivalent to: OR 4.51 (95%CI=7.49-2.71)
ADVERSE EVENTS:	Withdrawals: higher drop-out rate in SSRI group due to side effects: OR 2.42 (95% CI = 1.59 to 3.67)
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 10: Adverse Events

STUDY:	***Authors:*** **Benkert O, et al.**[49] ***Year:*** **2000** ***Country:*** Germany			
FUNDING:	Organon, GmBH, Munich, Germany			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (50 centers) ***Sample size:*** 275			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Mirtazapine 15-45 mg/d 6 weeks	Paroxetine 20-40 mg/d 6 weeks		
INCLUSION:	18-70 years of age; DSM-IV criteria for major depression; ≥ 18 on HAM-D-17			
EXCLUSION:	Depressive episode longer than 12 months; other psychiatric or psychotic disorder; alcohol or substance abuse; suicidal risk; significant physical illness; non-responders to antidepressants; recent medication with similar drugs; pregnancy			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Mirtazapine: 47.2, paroxetine: 47.3 ***Gender*** (% female): Mirtazapine: 63%, paroxetine: 65% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Benkert O, et al.** ***Year:*** **2000** ***Country:*** Germany	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-17, HAM-A, CGI-S, CGI-I, BDI-II, Welzel-Kohnen Colored Scales, Short Form 36 ***Timing of assessments:*** Screening, baseline, weeks 1, 2, 3, 4, 6
RESULTS:	• Mirtazapine and paroxetine were equally effective in reducing mean HAM-D-17 score (58.3% vs. 53.7%) • Significantly more mirtazapine patients responded at weeks 1 & 4 on the HAM-D-17 than paroxetine patients; week 1 response: mirtazapine: 23.2%, paroxetine: 8.9% ($p < 0.002$).
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 23%; mirtazapine: 21.6%, paroxetine: 24.2% ***Withdrawals due to adverse events:*** 8%; mirtazapine: 8.6%, paroxetine: 7.4% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Significantly more mirtazapine patients experienced weight increase ($p < 0.05$) • At least one adverse event reported: mirtazapine: 68.1%, paroxetine: 63.4% • Dry mouth: mirtazapine: 14.1%, paroxetine: 8.2% • Headache: mirtazapine: 9.6%, paroxetine: 10.4% • Nausea: mirtazapine: 4.4%, paroxetine: 11.2% • Flu-like symptoms: mirtazapine: 9.6%, paroxetine: 3.7% • Differences all $p < 0.1$
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Brambilla P, et al.**[187] ***Year:*** **2005** ***Country*****:** Multinational
FUNDING:	NR
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 15,920
AIMS OF REVIEW:	To assess the frequency of side-effects in fluoxetine compared to other SSRIs, TCAs and other anti-depressants
STUDIES INCLUDED IN META-ANALYSIS	131 studies
TIME PERIOD COVERED:	Not reported
CHARACTERISTICS OF INCLUDED STUDIES:	All studies with random assigned patients that received fluoxetine or any other anti-depressant. Cross-over studies and those with patients with concomitant medical illness were excluded.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients with MDD

Authors: Brambilla P, et al. **Year: 2005** **Country:** Multinational	
CHARACTERISTICS OF INTERVENTIONS:	Fluoxetine vs. TCA (65 studies); fluoxetine vs. SSRI (22 studies); fluoxetine vs. another AD (44 studies)
MAIN RESULTS:	• Fluoxetine less withdrawals due to side effects than TCAs and other related Ads RR 0.61 95%CI 0.52, 0.71 but not in comparison to other SSRIs RR 1.04 95% CI 0.84, 1.29 • Fluoxetine less side effects (50.9%) than TCAs (60.3%) RR= 0.84 95% CI 0.76 to 0.94(p = 0.03) but not in comparison to other SSRIs RR 1.00 95% CI 0.95, 1.04 • Fluoxetine patients had more activating and GI adverse effects and less cholinergic side effects than other ADs
ADVERSE EVENTS:	N/A
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Buckley NA, et al.**[210] **Year: 2002** **Country:** UK		
FUNDING:	None		
DESIGN:	**Study design:** Retrospective database analysis **Setting:** General practice **Sample size:** 121,927		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	TCAs and related drugs Varied N/A 74,598	Serotoninergic drugs Varied N/A 47,329	
INCLUSION:	Used TCAs or SSRIs		
EXCLUSION:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Mean age:** NR **Gender (% female):** NR **Ethnicity:** NR **Other population characteristics:** NR		

Authors: Buckley NA, et al. **Year: 2002** **Country:** UK	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Death due to acute poisoning by a single drug w/ or w/o co-ingestion of alcohol **Timing of assessments:**
RESULTS:	▪ Among second generation antidepressants, venlafaxine had the highest fatal toxicity index (deaths/million prescriptions): Venlafaxine: 13.2 (9.2-18.5) Fluvoxamine: 3.0 (0.3-10.9) Citalopram: 1.9 (0.6-4.5) Sertraline: 1.2 (0.5-2.4) Fluoxetine: 0.9 (0.5-1.4) Paroxetine: 0.7 (0.4-1.3) Nefazodone: 0 (0-6.4)
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION:	**Loss to follow-up:** N/A **Withdrawals due to adverse events:** N/A **Withdrawals due to lack of efficacy**: N/A **Loss to follow-up differential high:** N/A
ADVERSE EVENTS:	• See above
QUALITY RATING:	**N/A**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Clayton AH, et al.**[200] ***Year:*** **2002** ***Country:*** US			
FUNDING:	Glaxo Wellcome Inc.			
DESIGN:	***Study design:*** Cross sectional survey ***Setting:*** Multi-center ***Sample size:*** 6297			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Second generation antidepressants Variable Variable			
INCLUSION:	≥ 18 years of age; receiving antidepressant monotherapy for depression; sexually active; using one of the newer antidepressants: buproprion IR, buproprion SR, citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine, venlafaxine XR			
EXCLUSION:	Taking an antidepressant for an illness other than depression			
OTHER MEDICATIONS/ INTERVENTIONS:	None			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** N/A ***Mean age:*** Overall clinical population: 42.7; target population: 32.0 (target population consisted of patients free of other probable causes of sexual dysfunction (e.g., age, comorbid illness) ***Gender*** (% female): overall clinical population: 28%; target population: 22.8% ***Ethnicity:*** overall clinical population: white: 93.5%, black: 2.7%, Asian: 0.5%, Hispanic: 2.7%, other: 0.6%; target population: white: 93.1%, black: 2%, Asian: 0.6%, Hispanic: 3.7%, other: 0.5% ***Other population characteristics:*** Not reported			

Authors: **Clayton AH, et al.** **Y*ear:*** **2002**	
OUTCOME ASSESSMENT:	***Measures:*** Changes in sexual functioning questionnaire ***Timing of assessments:*** Completed at one visit
RESULTS:	In the overall clinical population: • Patients taking buproprion SR or nefazodone had a lower prevalence of sexual dysfunction than patients taking fluoxetine, paroxetine, sertraline, or venlafaxine XR • Patients taking buproprion IR had a lower prevalence of sexual dysfunction than patients taking paroxetine, sertraline, or venlafaxine XR • Patients taking fluoxetine had a lower prevalence of sexual dysfunction than patients taking paroxetine In the target population: • Patients taking buproprion SR or nefazodone had a lower prevalence of sexual dysfunction than patients taking citalopram, paroxetine, sertraline, or venlafaxine XR
ANALYSIS:	***ITT:*** N/A ***Post randomization exclusions:*** N/A
ATTRITION:	***Loss to follow-up:*** N/A ***Withdrawals due to adverse events:*** N/A ***Loss to follow-up differential high:*** N/A
ADVERSE EVENTS:	N/A
QUALITY RATING:	**N/A**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Coleman CC, et al.**[74] ***Year:*** **1999** ***Country:*** US			
FUNDING:	Glaxo Wellcome			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (9 centers) ***Sample size:*** 364			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/d 8 weeks	Buproprion 150-400 mg/d 8 weeks	Placebo N/A 8 weeks	
INCLUSION:	DSM-IV criteria for major depression; minimum score of 18 on the first 21 items of the 31 item HAM-D; 18 years of age or older; be in a stable relationship, have normal sexual functioning, and sexual activity at least once every 2 weeks; currently experiencing recurrent major episode of duration 2-24 months			
EXCLUSION:	Predisposition to seizure or taking med that lowers seizure threshold; anorexia or bulimia; pregnancy; alcohol or substance abuse; eating disorder; suicidal tendencies; prior treatment with buproprion or sertraline; used any psychoactive drug within 1 week of study (2 weeks for MAOI or 4 weeks for fluoxetine)			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep (first 2 weeks only)			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Sertraline: 38.3 , buproprion: 38.1, placebo: 38.5 ***Gender*** (% female): 59%; sertraline: 54%, buproprion: 56%, placebo: 59% ***Ethnicity:*** Sertraline: white: 92%, black: 8%,other: < 1%; buproprion: white: 87%, black: 11%, other: 2%; placebo: white: 88%, black: 9%, other: 3% ***Other population characteristics:*** No significant differences at diagnosis			

Authors: **Coleman CC, et al.** ***Year:*** **1999** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual functioning by investigator questions: sexual desire disorder, sexual arousal disorder, orgasm dysfunction, premature ejaculation, patient rated overall sexual function ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8
RESULTS:	• Mean HAM-D scores in the buproprion but not the sertraline group were statistically better than placebo (by day 28 $p < 0.05$) • There was no significant difference between the buproprion and sertraline groups • CGI-I and CGI-S for buproprion significantly better than placebo but not better than sertraline • Sertraline not statistically better than placebo • No differences in HAM-A; significantly fewer buproprion patients had sexual desire disorder than sertraline patients ($p < 0.05$) • There was no significant difference between either active treatment group and placebo • Orgasm dysfunction occurred significantly more in sertraline patients compared with placebo or buproprion patients ($p < 0.05$) • Diagnosed with at least one sexual dysfunction: sertraline: 39%, buproprion: 13%, placebo: 17%
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 30%; sertraline: 36%, buproprion sr: 22%, placebo: 32% ***Withdrawals due to adverse events:*** 18:5%; sertraline: 8%, buproprion: 6%, placebo: 2% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Headache was the most commonly reported event in all treatment groups • Nausea, diarrhea, dyspepsia occurred more frequently in sertraline patients than buproprion or placebo • Insomnia and agitation were reported more frequently in buproprion patients than sertraline or placebo
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Coleman CC, et al.**[69] ***Year:*** **2001** ***Country:*** US			
FUNDING:	Glaxo Wellcome			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (15 centers) ***Sample size:*** 456			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Buproprion 150-400 mg/d 8 weeks	Fluoxetine 150-400 mg/d 8 weeks	Placebo N/A 8 weeks	
INCLUSION:	DSM-IV criteria for major depression; minimum score of 20 on the 21 item HAM-D; ≥18 years of age; have sexual activity at least once every 2 weeks; currently experiencing episode lasting 2-24 months			
EXCLUSION:	Predisposition to seizure; pregnancy; alcohol or substance abuse; eating disorder; suicidal; treatment with buproprion or fluoxetine in the past year; used any psychoactive drug within 1 week of study; non-responders to antidepressant treatment; anorexia or bulimia			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Fluoxetine: 37.1, buproprion sr: 36.6 , placebo: 36.7 ***Gender:*** (% female) Fluoxetine: 66%, buproprion: 63%, placebo: 61% ***Ethnicity:*** Fuoxetine: white 82%, black 11%, other 7%; buproprion: white 83%, black 11%, other 5%; placebo: white 82%, black 14%, other 4% ***Other population characteristics:*** At baseline more patients in the fluoxetine and buproprion goups than the placebo group had sexual desire disorder			

Authors: **Coleman CC, et al.** ***Year:*** **2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** 21item HAM-D, sexual function assessment, substance-induced arousal disorder and orgasm dysfunction. Assessed: orgasm dysfunction, sexual desire disorder, sexual arousal disorder, overall patient sexual functioning (1-6 scale) ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 5, 6, 7, 8
RESULTS:	• Mean HAM-D scores were not statistically different between the three groups (in ITT analysis) • No difference in responders (≥ 50 decrease in HAM-D), remitters (HAMD < 8) • More buproprion remitters (47%) compared to placebo (32%). • Orgasm dysfunction occurred significantly more in fluoxetine patients compared with placebo or buproprion patients ($p < 0.001$) • At endpoint more fluoxetine treated patients had sexual desire disorder than buproprion-treated patients ($p < 0.05$). • More fluoxetine-treated patients dissatisfied with sexual function beginning at week 1 ($p < 0.05$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 34% ***Withdrawals due to adverse events:*** fluoxetine: 4%, buproprion: 9%, placebo: 3% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Headache was the most commonly reported event in all treatment groups • Headache, diarrhea, and somnolence occurred more frequently in fluoxetine than buproprion or placebo groups • Dry mouth, nausea, and insomnia were reported more frequently in buproprion than fluoxetine or placebo groups • Buproprion group had mean increases in DBP and heart rate, authors state these were not clinically significant • Fluoxetine treated patients had a mean decrease in both DBP and heart rate
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Coogan PF, et al.**[164] **Year: 2005** **Country:** US		
FUNDING:	NR		
DESIGN:	**Study design:** Case-control **Setting:** 3 centers **Sample size:** 4996		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Cases SSRIs Various N/A 2138	Controls None N/A N/A 2858	
INCLUSION:	Cases: women with a first occurrence of primary invasive breast cancer diagnosed within the last year and no concurrent or previous cancer other than nonmelanoma skin cancer Controls: women admitted for nonmalignant diagnoses, unrelated to the use of SSRIs and no history of cancer other than nonmelnoma skin cancer		
EXCLUSION:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS:	N/A		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Range of age:** 24-73 **Gender (% female):** 100% **Ethnicity:** NR		

Authors: Coogan PF, et al. **Year: 2005**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Increased risk of breast cancer due to use of SSRIs Risk factors other than SSRI use that were taken into account include alcohol consumption, religion, family history of breast cancer, center, age and race **Secondary Outcome Measures:** **Timing of Assessments:**
RESULTS:	• Regular use of SSRIs was not associated with breast cancer risk after adjustment for other risk factors OR 1.1 95% 0.8, 1.7
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION:	**Loss to follow-up:** N/A **Withdrawals due to adverse events:** N/A **Withdrawals due to lack of efficacy**: N/A **Loss to follow-up differential high:** N/A
ADVERSE EVENTS:	• N/A
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Croft H, et al.**[73] ***Year:*** **1999** ***Country:*** US			
FUNDING:	Glaxo Wellcome			
DESIGN:	***Study design:*** RCT (active and placebo control) ***Setting:*** Multi-center (8 centers) ***Sample size:*** 360			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/d 8 weeks	Buproprion 150-400 mg/d 8 weeks	Placebo N/A 8 weeks	
INCLUSION:	DSM-IV criteria for major depression; minimum score of 18 on the first 21 items of the 31 item HAM-D; ≥ 18 years of age; in a stable relationship; have normal sexual functioning and sexual activity at least once every 2 weeks; current depressive episode of 8 weeks to 24 months			
EXCLUSION:	Predisposition to seizure; pregnancy; alcohol or substance abuse; eating disorder; suicidal tendencies; prior treatment with buproprion or sertraline; used any psychoactive drug within 1 week of study			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Sertraline: 36.0, buproprion: 35.9, placebo: 37.4 ***Gender*** (% female)***:*** Sertraline: 50%, buproprion: 51%, placebo: 50% ***Ethnicity:*** Sertraline: white: 87%, black: 8%, other: 4%; buproprion: white: 86%, black: 9%, other: 5%; placebo: white: 88%, black: 8%, other: 3% ***Other population characteristics:*** Not reported			

Authors: **Croft H, et al.** ***Year:*** **1999** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual function assessment by investigator interview-sexual desire disorder, sexual arousal disorder, orgasmic dysfunction, premature ejaculation (men only), overall patient satisfaction with sexual functioning, vital signs ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8
RESULTS:	• Mean HAM-D scores in both the buproprion and sertraline group were statistically better than placebo ($p < 0.05$) • No significant difference in HAM-D scores between the buproprion and sertraline groups • CGI-S and CGI-I improvement compared to placebo but no differences between drugs at any week • No difference in changes of HAM-A scores for any group • By day 42 significantly fewer buproprion sr-treated patients had sexual desire disorder than sertraline- or placebo-treated patients ($p < 0.05$) • At day 56 both buproprion and sertraline groups had higher sexual arousal disorder ($p < 0.05$) than placebo • Orgasmic dysfunction occurred significantly more in sertraline group compared with placebo or buproprion groups ($p < 0.001$) • At day 56 no difference in overall satisfaction with sexual function between treatment groups
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 32% ***Withdrawals due to adverse events:*** sertraline: 3%, buproprion sr: 3%, placebo: 7% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Headache was the most commonly reported event in all treatment groups • Somnolence and insomnia occurred more frequently in sertraline group than buproprion goup • Nausea and diarrhea occurred more frequently with sertraline than buproprion or placebo
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Didham RC, et al.**[195] **Year: 2005** **Country:** New Zealand		
FUNDING:	The Royal NZ College of General Practitioners Research Unit which receives funding from the NZ government		
DESIGN:	**Study design:** Retrospective cohort and nested case control study **Setting:** General practice **Sample size:** 57,361		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Cases:**	SSRIs and other ADS Varied 120 days Suicides: 26 Self-harms: 330		
INCLUSION:	Patients that received a prescription for an anti-depressant from 1996 to 2001		
EXCLUSION:	Patients under 10 years old; additional concurrent anti-depressants		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Median age:** 46 **Gender (% female):** 68.1% **Ethnicity:** NR		

Authors: Didham RC, et al. **Year: 2005**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Suicides or self-harm within 120 days of a prescription **Timing of assessments:** N/A
RESULTS:	• No significant increase in suicides for SSRIs as a group: OR 1.28; 95% CI 0.38-4.35 • No significant difference in suicides between drugs Fluoxetine: 0.80 (0.22-2.89) Paroxetine: 2.25 (0.47-10.72) • Self-harm SSRIs vs. TCAs incidence rate 2.57 95% CI 2.03-3.28 • Increased risk of self-harm for SSRIs as a group OR 1.66 95% CI 1.23-2.23 • No significant differences in self-harm between drugs Fluoxetine; 1.30 (0.96-1.75) Paroxetine 1.21 (0.84-1.72)
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION:	**Loss to follow-up:** N/A **Withdrawals due to adverse events:** N/A **Withdrawals due to lack of efficacy**: N/A **Loss to follow-up differential high:** N/A
ADVERSE EVENTS:	• N/A
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Dunner et al.**[204] **Year: 1998** **Country:** US		
FUNDING:	Glaxo Wellcome Inc., Research Triangle Park, NC		
DESIGN:	**Study design:** Observational prospective **Setting:** Multi-center (105 sites) **Sample size:** 3100		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Bupropion 100-300 mg/d 8 weeks 3100		
INCLUSION:	Male or female patients at least 18 years of age; met DSM-III-R criteria for MDD, dysthymia, bipolar I or II)		
EXCLUSION:	Previous treatment with bupropion; patients with a history of bulimia or anorexia or with a known predisposition to seizures; pregnant; lactating; suicidal		
OTHER MEDICATIONS/ INTERVENTIONS:	Benzodiazepines		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Mean age:** 42 **Gender (% female):** 62.4 **Ethnicity:** white: 89.5%, black: 7%, other: 3.5% **Other population characteristics:** NR		

Authors: Dunner et al. **Year: 1998** **Country:** US			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Number of seizures; seizure rate **Secondary Outcome Measures:** N/A **Timing of assessments:** Biweekly during the study		
RESULTS:	• During the 8 week acute phase of the trial, 2 patients (0.06% -- Upper 1-sided CL of 0.14%) experienced seizures out of 3094 patients.		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ATTRITION: **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy**: **Loss to follow-up differential high:**	<u>Overall</u> 34% NR NR N/A		
ADVERSE EVENTS:	• 54 serious adverse events (other than seizure) occurred during the study. Suicide attempt or overdose: 9 patients; accidental injury: 4 patients; myocardial function: 3 patients		
QUALITY RATING:	**Fair**		

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Ekselius, et al.**[197] ***Year:*** **2001** ***Country:*** Sweden			
FUNDING:	Swedish Medical Research Council and Pfizer AB			
DESIGN:	***Study design:*** Subgroup analysis of RCT ***Setting:*** Multi-center ***Sample size:*** 400			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-150 mg/d 24 weeks	Citalopram 20-60 mg/d 24 weeks		
INCLUSION:	DSM-III-R criteria for major depression; MADRS score ≥ 21			
EXCLUSION:	Pregnancy; alcohol or substance abuse; suicidal tendencies; significant physical illness; bipolar disorder; known intolerance or allergic reactions to SSRIs; severe depression or psychotic dimension; previous adequate treatment with citalopram or sertraline; lithium within past month			
OTHER MEDICATIONS/ INTERVENTIONS:	Hypnotics for insomnia or daytime anxiolytics			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Gender*** (% female): Sertraline: 72%, citalopram: 71% ***Ethnicity:*** Not reported ***Mean age:*** Sertraline: 47.3, citalopram: 48.1 ***Other population characteristics:*** No significant population differences			

Authors: **Ekselius, et al.** ***Year:*** **2001**	
OUTCOME ASSESSMENT:	***Measures:*** MADRS, CGI-S, CGI-I, sexual function assessed by five items in the Utvalg for Kliniske Undersogelser Side Effect Scale (UKU-SES); increased or decreased sexual desire, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction ***Timing of assessments:*** Not reported
RESULTS:	• No statistically significant differences between sertraline and citalopram in the magnitude or frequency of adverse sexual side effects • For both groups sexual desire and mean total score of UKU significantly improved in women; sexual desire improved in men, but not mean score of UKU. • In female patients reporting no sexual dysfunction at baseline, 11.8% reported decreased sexual desire and 14.3% reported orgasmic dysfunction • In male patients reporting no sexual dysfunction at baseline, 16.7% reported decreased sexual desire, 18.9% reported orgasmic dysfunction, 25% experienced ejaculatory dysfunction
ANALYSIS:	***ITT:*** Not reported ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 23%; sertraline: not reported, citalopram: not reported ***Withdrawals due to adverse events:*** 11%; sertraline: not reported, citalopram: not reported ***Loss to follow-up differential high:*** Not reported
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Fava M, et al.**[34] ***Year:*** **2002** ***Country:*** US			
FUNDING:	Eli Lilly Research			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 284			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluoxetine 20-60 mg/day 10-16 weeks	Sertraline 50-200 mg/day 10-16 weeks	Paroxetine 20-60 mg/day 10-16 weeks	
INCLUSION:	≥ 18 years of age; DSM-V criteria for major depression; DSM-IV for atypical MDD; HAM-D-17 ≥ 16; episode ≥ 1month			
EXCLUSION:	Pregnancy or lactation, lack of adequate contraception; history of psychotic disorders, bipolar disorder; alcohol or substance abuse; existing suicidal risk; previously failed to respond to antidepressant therapies; clinically relevant progressive disease; hypersensitivity to study medication; serious comorbid illness not stabilized; anxiolytic or psychotropic within 7 days; MAOI within 2 weeks			
OTHER MEDICATIONS/ INTERVENTIONS:	Thyroid medications, chloral hydrate			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Fluoxetine: 42.1, sertraline: 44.0, paroxetine: 42.5 ***Gender*** (female%): Fluoxetine: 63.0, sertraline: 57.3, paroxetine: 58.3 ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Fava M, et al.** ***Year:*** **2002** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-17, CGI-S, HAM-D sleep disturbance ***Timing of assessments:*** Not reported
RESULTS:	• No statistical differences between fluoxetine, sertraline and paroxetine in all outcome measures • Response rate: 64.8%, 72.9%, and 68.8% respectively • Remission rates: 54.4%, 59.4%, and 57.0% respectively • No statistical differences in sleep disturbance factor scores; no significant differences of treatment groups in patients with high or low insomnia Subgroup analysis (Fava 2000): Anxious depression • No significant differences between treatment groups and changes over time • Response: fluoxetine: 73%, sertraline: 86%, paroxetine: 77%, overall p = 0.405 • Remission: fluoxetine: 53%, sertraline: 62%, paroxetine: 50%, overall p = 0.588 • Fluoxetine and sertraline had a significantly greater improvement than paroxetine in week 1 on the HAM-D anxiety score
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 27.1%; fluoxetine: 26.1%, sertraline: 27.1%, paroxetine: 28.1% ***Withdrawals due to adverse events:*** Fuoxetine: 8.7%, sertraline: 6.3%, paroxetine: 11.5% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Pairwise comparisons indicated that the paroxetine-treated patients reported more constipation than the fluoxetine-treated patients; the fluoxetine-treated patients reported more twitching and cough increase than the sertraline-treated patients • Most common adverse events: Fluoxetine: headache (25%); sertraline: headache (28.1%), diarrhea (26.0%), insomnia (26%), nausea (20.8%); paroxetine: nausea (25.0%), headache (21.9%), insomnia (20.8%), abnormal ejaculation (20.8%) • There was a significant increase in weight for the paroxetine group; fluoxetine treated patients showed a significant decrease in weight and the sertraline group a non-significant decrease in weight from baseline to endpoint Subgroup analysis (Fava 1999) • Adverse events were similar among treatments; only flu-like syndrome was significantly higher in the sertraline treated group overall (p = 0.021)
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Fergusson D, et al.**[191] ***Year:*** **2005** ***Country:*** Canada
FUNDING:	Canadian Institutes of Health Research
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 36,445
AIMS OF REVIEW:	To establish if an association exists between SSRI use and suicide attempts.
STUDIES INCLUDED IN META-ANALYSIS	345 trials included in analysis
TIME PERIOD COVERED:	1967 – June 2003
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs comparing an SSRI with either placebo or an active non-SSRI control
CHARACTERISTICS OF INCLUDED POPULATIONS:	All patients included in trials comparing SSRIs to either placebo or non-SSRI control; no age, gender, or diagnosis restrictions

Authors: Fergusson D, et al. **Year: 2005**	
CHARACTERISTICS OF INTERVENTIONS:	Patients randomized to either an SSRI, placebo, or non-SSRI control
MAIN RESULTS:	• A significant increase in the odds of suicide attempts was found in patients receiving SSRIs compared to patients receiving placebo (OR: 2.28; CI: 1.144 to 4.55; p = 0.02) • No significant difference found in the odds of suicide attempts between patients receiving SSRIs and patients receiving TCAs (OR: 0.88 (CI: 0.54 to 1.42)
ADVERSE EVENTS:	• No other adverse events reported.
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Greist J, et al.**[183] ***Year:*** 2004 ***Country*****:** US
FUNDING:	Eli Lilly
DESIGN:	***Study design:*** Pooled analysis ***Number of patients:*** 2,345
AIMS OF REVIEW:	To assess the incidence, severity and onset of nausea among MDD patients treated with duloxetine
STUDIES INCLUDED IN META-ANALYSIS	Detke et al. 2002; Detke et al. 2002; Goldstein et al 2002; Goldstein et al. 2004; 4 unpublished studies submitted for FDA approval of duloxetine
TIME PERIOD COVERED:	Not reported
CHARACTERISTICS OF INCLUDED STUDIES:	Double blinded, placebo or active controlled trials of duloxetine
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adult outpatients with MDD

Authors: Greist J, et al. **Year: 2004** **Country:** US	
CHARACTERISTICS OF INTERVENTIONS:	Duloxetine vs. placebo (8 studies); duloxetine vs. paroxetine (4 studies); duloxetine vs. fluoxetine (2 studies)
MAIN RESULTS:	• No significant differences in nausea between duloxetine (40-120mg/d) and paroxetine (20mg/d) (14.4% vs. 12%; p = not reported) • No significant differences between duloxetine (120mg/d) and fluoxetine (20mg/d) (17.1% vs. 15.7%; p = not reported) • Significantly more patients on duloxetine than on placebo reported nausea (19% vs. 6.9%; p < 0.001)
ADVERSE EVENTS:	N/A
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No; analysis of published and unpublished trials
STANDARD METHOD OF APPRAISAL OF STUDIES:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Gunnell D, et al.**[189] **Year: 2005** **Country:** UK
FUNDING:	Not Reported
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 40,826
AIMS OF REVIEW:	To investigate whether SSRIs are associated with an increased risk of suicide related outcomes in adults.
STUDIES INCLUDED IN META-ANALYSIS	Published and unpublished data submitted by pharmaceutical companies to the Medicine and Healthcare Products Regulatory Agency (MHRA) (2004) 342 placebo controlled trials included in report – citations not given in bibliography
TIME PERIOD COVERED:	NR
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized, placebo controlled trials of SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) submitted by pharmaceutical companies
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adult patients with various indications included in trials comparing SSRIs to placebo.

Authors: Gunnell, et al. **Year: 2005**	
CHARACTERISTICS OF INTERVENTIONS:	Patients randomized to either SSRI or placebo.
MAIN RESULTS:	• No significant difference was found between SSRI treatment and placebo treatment in the odds ratios for suicide (OR: 0.85 CI: 0.2 to 3.4), non-fatal self harm (OR: 1.57 CI: 0.99 to 2.55), or suicidal thought (OR: 0.77 CI: 0.37 to 1.55). • For non-fatal self-harm the NNT to harm is 759
ADVERSE EVENTS:	• No other adverse events reported.
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No (published and unpublished data submitted by pharmaceutical companies; review does not include studies from sources other than pharmaceutical companies)
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Haffmans, et al.**[186] ***Year:*** **1996** ***Country:*** The Netherlands			
FUNDING:	Lundbeck			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 217			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Citalopram 20-40 mg/d 6 weeks	Fluvoaxamine 100–200 mg/d 6 weeks		
INCLUSION:	Ages 18-70 years; met DSM III-R criteria for major depression (single episode or recurrent) or bipolar disorder; score of ≥ 16 on HAM-D-17; reasonable knowledge of the Dutch language			
EXCLUSION:	MAOI or fluoxetine use within 3 weeks or other psychotropic drugs within 1 week (except for benzos); other primary psychiatric diagnosis (other than MDD); history of epilepsy, alcohol or drug abuse; pregnancy, lactation, or not using contraception; renal, hepatic, cardiovascular, neurological or somatic disorders and/or significant abnormal lab findings			
OTHER MEDICATIONS/ INTERVENTIONS:	Selected benzodiazepines; oxazepam, lormetazepam, temazepam, lorazepam, or flurazepam, all non-psychotropic medications were allowed, domperidone for nausea/vomiting allowed			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** No ***Mean age:*** Citalopram: 44.2, fluvoxamine: 40.2 ***Gender*** (% female): 58%; citalopram: 58%, fluvoxamine: 60% ***Ethnicity:*** Not reported ***Other population characteristics:*** Previous depressive disorder: citalopram: 43%; fluvoxamine: 54%; previous antidepressant therapy (within 3 weeks of starting trial): citalopram: 65%, fluvoxamine: 73%			

Authors: **Haffmans, et al.** ***Year:*** **1996** ***Country:*** The Netherlands	
OUTCOME ASSESSMENT:	***Measures:*** Primary: HAM-D-17; secondary: CGI, UKU side effect rating scale, Zung self-rating depression scale ***Timing of assessments:*** Baseline, weeks 1, 2, 4, 6
RESULTS:	• No difference in mean HAM-D-17 scores after 6 weeks • Complete Response (HAM-D17) ≤ 7: citalopram: 14%, fluvoxamine: 18%; no significant difference • Mean % reduction in score at week 6: citalopram: 33%, fluvoxamine: 26% • Responders (reduction in score from baseline > 50%): citalopram: 30.5%, fluvoxamine: 28.4%
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 23%; citalopram: 19.4%, fluvoxamine: 26.6% ***Withdrawals due to adverse events:*** Citalopram: 13.9%, fluvoxamine: 21.1% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• No differences between groups in laboratory values or vital signs • 10 serious adverse events (4 in citalopram and 6 in fluvoxamine) none of which were deemed to be causally related to treatment • Similar UKU side effect scale measured impact on functioning between groups • Fluvoxamine had the following excess incidence of adverse events as compared to citalopram: Diarrhea: 13.6% (p = 0.026) Nausea: 16.0% (p = 0.017) Vomiting: 9.1% (p = 0.052) Suicide attempt: 4.6% • Citalopram had the following excess incidence of adverse events as compared to fluoxamine: paraesthesia: 10.4%
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Jick H, et al.**[211] ***Year:*** **2004** ***Country:*** UK
FUNDING:	Boston Collaborative Drug Surveillance Program
DESIGN:	***Study design:*** Matched case-control; post-hoc database analysis ***Setting:*** General practices in the UK using VAMP database (General Practice Research Database) ***Sample size:*** 159,810 (555 cases, 2062 controls)
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Dothiepin, amitryptyline, fluoxetine, paroxetine Not reported Not reported
INCLUSION:	Received a prescription for at least 1 antidepressant in the VAMP database during the 1993-1999 years; all patients who had a first-time recorded diagnosis of nonfatal suicidal ideation or attempted suicide at age 10-69 years during the 1993-1999 time period; had received at least 1 prescription for a study drug within 90 days before their index date
EXCLUSION:	Received prescription for another antidepressant or more than one study drug prior to their index date; history of psychosis, panic disorders, phobias, obsessive-compulsive neurosis, manic-depressive disease, drug abuse, alcohol abuse, epilepsy, anorexia, bulimia, and attention-deficit disorder
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** not reported ***Gender*** (% female): 65.4% female (cases only) ***Ethnicity:*** Not reported ***Other population characteristics:*** ~85% of cases had attempted suicide while 15% had suicidal ideation

Authors: **Jick H, et al.** ***Year:*** **2004** ***Country:*** UK	
OUTCOME ASSESSMENT:	***Measures:*** Frequency of first-time exposure to amitriptyline, fluoxetine, paroxetine and dothiepin of patients with a recorded diagnosis of first-time nonfatal suicidal behavior or suicide compared with matched patients who did not exhibit suicidal behavior ***Timing of assessments:*** N/A
RESULTS:	• Risk of suicidal behavior was similar among users of amitryptyline (RR: 0.83; 95% CI 0.61 – 1.13), fluoxetine (RR 1.16; 95% CI 0.90 – 1.50), and paroxetine (RR 1.29; 95% CI 0.97 – 1.70) compared to dotiepin • Suicide risk was increased in the first month after starting antidepressants, especially during the first 1 – 9 days (RR 4.07; 95% CI 2.89 – 5.74)
ANALYSIS:	***ITT:*** N/A ***Post randomization exclusions:*** N/A
ATTRITION:	***Loss to follow-up:*** N/A ***Withdrawals due to adverse events:*** N/A ***Loss to follow-up differential high:*** N/A
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**N/A**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Jick, et al.**[192] ***Year:*** **1995** ***Country:*** UK
FUNDING:	Various pharmaceutical companies (Berlex, Boots, Burroughs Wellcome, Ciba-Geigy, Hoeschst, Hoffman-LaRoche, RW Johnson, Pfizer, Proctor and Gamble, Sanofi Winthrop
DESIGN:	***Study design:*** Cohort study with nested case-control analysis ***Setting:*** General practices in the UK using VAMP database ***Sample size:*** 172,598
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Drugs studies in this cohort: dothiepin, amitryptyline, climipramine, imipramine, flupenthixol, lofepramine, mianserin, fluoxetine, doxepin, trazodone, maprotiline, desipramine Not reported Not reported
INCLUSION:	Received a prescription for 1 or more antidepressant in the VAMP database (General Practice Research Database); all patients who committed suicide identified in the cohort evaluation were included as cases
EXCLUSION:	Not reported
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean age:*** Not reported ***Gender:*** Not reported ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported

Authors: **Jick, et al.** ***Year:*** **1995** ***Country:*** UK	
OUTCOME ASSESSMENT:	***Measures:*** Suicide completion rate, suicides/person time at risk, relative risks of suicide reported with dothiepin as reference group ***Timing of assessments:*** N/A
RESULTS:	• From cohort analysis: Suicide rate/10,000 person years: fluoxetine: 19.0, adjusted RR: 2.1 (95% CI 1.1-4.1) relative to dothiepin • From case control analysis: Adjusted RR 3.8 (95% CI 1.7- 8.6), analysis restricted to those prescribed antidepressants for the first time and who had no history of suicidal behavior, adjusted RR: 2.1 (95% CI 0.6 - 7.9)
ANALYSIS:	***ITT:*** N/A ***Post randomization exclusions:*** N/A
ATTRITION:	***Loss to follow-up:*** Not reported ***Withdrawals due to adverse events:*** N/A ***Loss to follow-up differential high:*** N/A
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Johnston et al.**[203] **Year: 1991** **Country:** US
FUNDING:	Burroughs Wellcome Co., RTP, NC
DESIGN:	**Study design:** Prospective observational **Setting:** Multi-center (102 sites) **Sample size:** 3341
INTERVENTION: **Dose:** **Duration:** **Sample size:**	Buproprion 225-450 mg/d 8 weeks with a one year continuation 3341
INCLUSION:	Patients 18 years of age or older with a diagnosis of depression for which antidepressant treatment was appropriate
EXCLUSION:	Previous use of bupropion; pregnant; lactating: anorexic or bulimic; known predisposition to seizures; received an MAO inhibitor within 14 days of the study or an investigational drug within 30 days of the study
OTHER MEDICATIONS/ INTERVENTIONS:	Other antidepressant medications, neuroleptic drugs, or amphetamine-type drugs were not allowed
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Mean age:** 43.5 **Gender (% female):** 59.4 **Ethnicity:** 96% white; 3% black; 1% other **Other population characteristics:** **Psychiatric diagnosis:** Major depression: 73% Dysthymic disorder: 10% Bipolar depression: 8% Atypical depression: 6% Atypical bipolar: 2% Other: 1%

Authors: Johnston et al. **Year: 1991** **Country:** US	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Number of seizures **Secondary Outcome Measures:** N/A **Timing of assessments:** Biweekly
RESULTS:	• Eight seizures were reported in the 3277 patients analyzed during the treatment phase. This is a seizure rate of 0.24%. A survival analysis showed a cumulative seizure rate of 0.36% during the 8 week trial.
ANALYSIS:	**ITT:** No **Post randomization exclusions:** N/A
ATTRITION: **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy**: **Loss to follow-up differential high:**	Overall NR 613 (19%) NR N/A
ADVERSE EVENTS:	• 82 (2.5%) patients experienced major adverse events (life threatening or requiring hospitalization) • Most common adverse events were nausea (3.6%), agitation (2.4%), anxiety (1.7%), headache (1.5%), insomnia (1.3%), and rash (1.3%)
QUALITY RATING:	**N/A**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Khan, et al.**[194] ***Year:*** **2003** ***Country:*** US
FUNDING:	Not reported
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 48,277
AIMS OF REVIEW:	Compare suicide rates among depressed patients
STUDIES INCLUDED IN META-ANALYSIS	Pooled analysis of FDA clinical trial data from 1985-2000 for 9 SSRIs 2000 publication reports on 1987 to 1997 (same data)
TIME PERIOD COVERED:	1985-2000
CHARACTERISTICS OF INCLUDED STUDIES:	FDA clinical trial data
CHARACTERISTICS OF INCLUDED POPULATIONS:	Major depression according to DSM-II-R criteria; minimum score of 18 or 20 on HAM-D-17 or HAM-D-21

Authors: **Khan, et al.** ***Year:*** **2003** ***Country:*** US	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	Fluoxetine, sertaline, paroxetine, citalopram, fluvoxamine, nefazodone, mirtazapine, buproprion, venlafaxine, imipramine, amitrptyline, maprotiline, trazadone, mianserin, dothiepin
MAIN RESULTS:	• Absolute Suicide Rate SSRI: 0.15% (0.10-0.20% 95% CI) "Other": 0.20% (0.09-0.27% 95% CI) Placebo: 0.10% (0.01-0.19% 95% CI) p > 0.05 for difference • Suicide Rate by Patient Exposure Years (PEY) SSRI: 0.59%/PEY (0.31-0.87 95% CI) "Other": 0.76%/PEY (0.49-1.03 95% CI) Placebo: 0.45%/PEY (0.01-0.89 95% CI) p > 0.05 for difference • 2000 study: looked at suicide attempts and completion and found no difference
ADVERSE EVENTS:	N/A
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No
STANDARD METHOD OF APPRAISAL OF STUDIES:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Kiev, et al.**[40] ***Year:*** **1997** ***Country:*** US			
FUNDING:	Solvay Pharma, Upjohn			
DESIGN:	***Study design:*** RCT ***Setting:*** Single center ***Sample size:*** 60			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluvoxamine 50-150 mg/d 7 weeks	Paroxetine 20-50 mg/d 7 weeks		
INCLUSION:	Age 18-65; meet DMS-III-R criteria for single or recurrent MDD; ≥ 20 on HAM-D-21 (including minimum score of 2 on depressed mood item)			
EXCLUSION:	Non-English speakers; history of medication non-compliance; demonstration of placebo response during run-in, history of substance abuse; severe suicide risk or auto-aggressive behavior; used a drug within 30 days with anticipated major organ toxicity; pregnancy, lactation; hypersensitivity to SSRIs; participation in prior drug 1 studies; other significant organic disease; clinically significant lab abnormalities; other primary psychiatric diagnoses; transportation difficulties			
OTHER MEDICATIONS/ INTERVENTIONS:	Antacids, laxatives, acetaminophen, aspirin, ibuprofen, chloral hydrate, other meds only with permission of study physician			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Fluvoxamine: 42.7, paroxetine: 39 ***Gender*** (female%): Fluvoxamine: 53%, paroxetine: 53% ***Ethnicity:*** White: fluvoxamine: 87%, paroxetine: 93% ***Other population characteristics:*** Not reported			

Authors: **Kiev, et al.** ***Year:*** **1997**	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-21, HAM-A, SCL-56, CGI ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 5, 7
RESULTS:	• Mean change in HAM-D score: fluvoxamine: -13.45, paroxetine: -12.86 (p = 0.763) • No significant differences between groups on HAM-D-21, CGI, HAM-A, or SCL56
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 31% ***Withdrawals due to adverse events:*** fluvoxamine: 6.8%, paroxetine: 13.8% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Sweating (p = 0.028); fluvoxamine: 10%, paroxetine: 33% • Headache: fluvoxamine: 40%, paroxetine: 57% • Nausea: fluvoxamine: 37%, paroxetine: 47% • No clinically significant labs or vital sign changes in either group
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Landen M, et al.**[198] **Year: 2005** **Country:** Sweden and Norway		
FUNDING:	Bristol-Myers Squibb, Sweden		
OBJECTIVE:	To determine: 1) concordance of sexual dysfunction adverse event rates between open-ended questioning and directed questioning; 2) the incidence of sexual side effects of citalopram and paroxetine; 3) the correlation between sexual side effects and illness severity, treatment duration and drug/dose combination		
DESIGN:	**Study design:** Non-randomized trial of adverse event elicitation methods embedded in a RCT (Landen et al 1998 – patients who had not responded to CP or PX were randomized to receive buspirone or placebo) **Setting:** Multi-center (13 centers) **Sample size:** 119		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Citalopram at least 40 mg/d 4 weeks 77	Paroxetine at least 30 mg/d 4 weeks 42	
INCLUSION:	Patients 18 years or older; met criteria for a major depressive episode according to DSM-IV criteria; has not responded to CP or PX for a minimum of 4 weeks prior to start of study		
EXCLUSION:	Pregnancy; epilepsy; severe somatic disease; mental disorder due to a general medical condition; substance abuse; highly suicidal status		
OTHER MEDICATIONS/ INTERVENTIONS:	Patients received either buspirone or placebo for 4 week study duration		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** 46 **Gender (% female):** 69% **Ethnicity:** NR **Other population characteristics:** NR		

Authors: Landen M, et al **Year: 2005** **Country:** Sweden and Norway	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Sexual dysfunction score (0-6); Percent patients reporting any sexual side effect based on open and direct questioning **Secondary Outcome Measures:** N/A **Timing of assessments:** Before and after the 4 week trial
RESULTS:	By objective 1. Side effect elicitation method • Significantly more patients (49 versus 6) reported sexual side effects in response to direct questioning than open questioning ($p < 0.001$). 2. Incidence of side effects by drug • There were no statistically significant differences between the paroxetine and paroxetine groups in sexual side effects reported or sexual dysfunction score. • Open-ended questioning: citalopram 5%, paroxetine 7% ($p = 0.98$) • Direct questioning: citalopram 44%, paroxetine 36% ($p = 0.37$) 3. Correlations with illness severity and treatment parameters • Only weak correlation with duration of current depression episode ($p = 0.043$)
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION:	**Loss to follow-up:** N/A **Withdrawals due to adverse events:** N/A **Withdrawals due to lack of efficacy**: N/A **Loss to follow-up differential high:** N/A
ADVERSE EVENTS:	• Decreased desire reported by 43% of men and 32% of women • Orgasmic dysfunction reported by 23% women and 32% men
QUALITY RATING:	**Good**

Evidence Table 10 Adverse Events

STUDY:	***Authors*: Lopez-Ibor JJ**[13] ***Year:* 1993** ***Country*:** Spain		
FUNDING:	N/A		
DESIGN:	***Study design:*** Retrospective database analysis ***Setting:*** Not reported ***Sample size:*** 4,668		
INTERVENTION: **Drug:** **Dose:** **Duration:**	 Paroxetine Not reported Up to 6 weeks	 Placebo N/A Up to 6 weeks	 Active control N/A Up to 6 weeks
INCLUSION:	Depressed patients enrolled in a clinical trial		
EXCLUSION:	Not reported		
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Not reported **Mean age:** Not reported **Gender:** Not reported **Ethnicity:** Not reported **Other population characteristics:** Not reported		

***Authors*: Lopez-Ibor, JJ** ***Year*: 1993** ***Country*:** Spain	
OUTCOME ASSESSMENT:	***Measures:*** Suicide item of HAM-D, emergence of suicidal ideation, assessed by the development of HAM-D suicide item score ***Timing of assessments*:** N/A
RESULTS:	Paroxetine and active control were significantly better than placebo in reducing suicidal thoughts and behavior from week 1 onwards
ANALYSIS:	***ITT:*** N/A ***Post randomization exclusions*:** Not reported
ATTRITION:	***Loss to follow-up:*** N/A ***Withdrawals due to adverse events:*** N/A ***Loss to follow-up differential high:*** N/A
ADVERSE EVENTS:	• There were no differences among the groups with regards to suicidality as an adverse event. • 0.4% of each group reported suicidality. • There were 10 suicides overall and 58 attempts overall.
QUALITY RATING:	**N/A**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Mackay, et al.**[184, 185] ***Year:*** **1997** ***Country:*** UK
FUNDING:	Drug Safety Research Unit, UK, various unnamed pharmaceutical companies
DESIGN:	***Study design:*** Cohort study (prescription event monitoring) ***Setting:*** General practice in the UK ***Sample size:*** Number identified as getting a first prescription" fluvoxamine: 20,504, fluoxetine: 24,738, sertraline: 24,632, paroxetine: 26,194
INTERVENTION: ***Drugs:*** ***Dose:*** ***Duration:***	 Drugs compared: fluvoxamine, fluoxetine, sertraline, paroxetine N/A Outcomes assessed after approximately 6 months for all but fluovoxamine (which was 12 months)
INCLUSION:	Patients who received a first prescription from their GP during the following time periods: fluvoxamine: Feb 1987 - Feb 1988; fluoxetine: Mar 1989 - Mar 1990; sertraline: Jan 1991 - Sep 1992; paroxetine: Mar 1991 - Mar 1992
EXCLUSION:	Not reported
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes; some differences existed between groups as far as indication for prescription ***Mean age:*** 50 ***Gender*** (% female): 70% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported

Authors: **Mackay, et al.**
Year: **1997**
Country: UK

OUTCOME ASSESSMENT:

Measures: GP completion of a simple questionnaire (green form), questions asked: perceived efficacy, reason for stopping, indication for prescribing, duration of therapy, and events during and after treatment. (Event = new diagnosis, reason for referral to a consultant or admission to hospital, unexpected deterioration (or improvement) in a concurrent illness, suspected drug reaction or any complaint which was considered of sufficient importance to enter in patient notes.
Timing of assessments: Mailed 6-12 months after initial prescription written

RESULTS:

- Reasons for discontinuation in 1st month of treatment due to adverse events:

Incidence Densities (Events/1000 patient-months)

	Fluvoxamine	Fluoxetine	Sertraline	Paroxetine
Nausea/vomiting	127.2	26.3	34.6	52.9
Malaise/lassitude	41.5	16.3	12.0	17.8
Drowsiness/sedation*	22.6	8.2	7.3	20.5
Dizziness	25.5	6.7	8.7	11.5
Headache/migraine	25.1	13.5	13.1	13.1
Tremor*	13.2	5.7	6.2	12.4

* ($p < 0.001$ for fluoxetine and sertraline vs. fluvoxamine and paroxetine)

- Adverse Effects Reported:

Incidence Densities (Events/1000 patient-months)

	Fluvoxamine	Fluoxetine	Sertraline	Paroxetine
Nausea/vomiting	42.8	9.0	8.6	13.0
Malaise/lassitude	15.2	5.5	3.7	5.2
Dizziness	9.6	2.7	2.8	4.0
Headache/migraine	10.1	5.7	5.4	4.8
Mean	17.6	7.0	6.2	4.8

- No statistical differences in onset of mania or hypomania with any of the SSRIs
- No serious cardiac events with any of the SSRIs
- No deaths attributed to SSRIs. No difference in the number of suicides with each of the four SSRIs (approx 0.2-0.3% in each arm)

RESULTS:	**SSRIs and nefazodone:** • Most frequent events for all 5 drugs in the first month of treatment: venlafaxine had the highest rate of occurrence per 1,000 patient months: 71.9, fluoxetine: 26.3, sertraline: 34.6, paroxetine: 52.9, nefazodone: 46.1 • Sertraline and fluoxetine had a significantly lower rate ratio of agitation and anxiety than the remaining drugs • Drowsiness and sedation were reported most frequently with nefazodone and paroxetine • Male sexual dysfunction was most frequent with paroxetine and venlafaxine: rate ratios: fluoxetine: 1.0, sertraline: 3.1 (0.9 - 10.9), paroxetine: 11.1 (3.5 - 35.8), venlafaxine: 5.8 (1.9 - 19.3), nefazodone: 2.0 (0.6 - 7.5) • There were more reports of mania during 90 days with fluoxetine than with the other drugs • There was no significant difference in deaths between drugs
ANALYSIS:	***ITT:*** N/A ***Post randomization exclusions:*** N/A
ATTRITION:	***Loss to follow-up:*** *N/A* ***Completion rates of surveys****:* 60% ***Withdrawals due to adverse events:*** N/A ***Loss to follow-up differential high:*** N/A
ADVERSE EVENTS:	N/A
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Maina G, et al.**[201] **Year: 2004** **Country:** Italy					
FUNDING:	None					
DESIGN:	**Study design:** Non-randomized, open-label trial **Setting:** Single center (Department of Neuroscience, University of Turin) **Sample size:** 149 started trial					
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Clomipramine 150-250 mg/d 2.5 years 23	Citalopram 40-80 mg/d 2.5 years 21	Fluoxetine 40-80 mg/d 2.5 years 23	Paroxetine 40-80 mg/d 2.5 years 21	Fluvoxamine 200-300 mg/d 2.5 years 28	Sertraline 150-200 mg/d 2.5 years 22
INCLUSION:	Patients 18 years of age or older; Met DSM-IV criteria for OCD based on the Structured Clinical Interview; YBOCS score greater than or equal to 16; completed 6 month acute treatment phase of trial; gave informed consent					
EXCLUSION:	Pregnant; lactating; current or past diagnosis of eating disorder, schizophrenia, or other psychotic disorders; organic mental disorder; medical illness; met diagnostic criteria for a major depressive episode; had a HAM-D17 score greater than or equal to 15					
OTHER MEDICATIONS/ INTERVENTIONS:	NR					
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** 34.9 years **Gender:** 51% female **Ethnicity:** NR **Other population characteristics:** • Mean duration of illness: 12.1 years					

Authors: Maina G, et al. **Year: 2004** **Country:** Italy	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Percentage weight gain **Secondary Outcome Measures:** Number of patients with extreme weight gain **Timing of assessments:** Weight recorded at the beginning of treatment and at six months intervals thereafter.
RESULTS:	• An ANOVA analysis showed significant between group differences in weight gain ($p = 0.009$). Clomipramine had the highest increase in weight and fluoxetine and sertraline had the lowest increase in weight. • Clomipramine (+2.6 kg; $p < 0.001$), citalopram (+1.5kg; $p = 0.002$), paroxetine (+1.7kg; $p = 0.001$), fluvoxamine (+1.7kg; $p < 0.001$), and sertraline (+ 1.0kg; $p = 0.01$) showed significant increases in weight from baseline. No significant increase in weight was observed in the fluoxetine group (+0.5kg; p = NR). • Patients with significant weight gain ($\geq$ 7%): clomipramine 34.8%; citalopram 14.3%; paroxetine 14.3%; fluvoxamine 10.7%; sertraline 4.5%; fluoxetine 8.7%
ANALYSIS:	**ITT:** No **Post randomization exclusions:** N/A: above results are reported only for patients who completed the 2 year extension phase of the trial
ATTRITION:	***Loss to follow-up:*** 7% ***Withdrawals due to adverse events:*** NR ***Loss to follow-up differential high:*** NR
ADVERSE EVENTS:	• NR
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Martinez C, et al.**[190] **Year: 2005** **Country:** UK		
FUNDING:	Medicines and Healthcare products Regulatory Agency		
DESIGN:	**Study design:** Case control study **Setting:** General Practice Research Database (clinical primary care records in the UK) **Sample size:** 146,095		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size (suicides/self-harm):**	Cases (suicide and non-fatal self-harm) SSRIs/TCAs NR 1995-2001 2037 (69/1968)	Controls SSRIs/TCAs NR 1995-2001 35,615	
INCLUSION:	Individuals 90 years or younger with a first prescription for antidepressants between January 1, 1995 and December 31, 2001 entered in the General Practice Research Database; diagnosed with depression		
EXCLUSION:	None		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** 31% of patients were in the age cohort 31-45 years old **Gender:** 65% female **Ethnicity:** NR **Other population characteristics:** • History of self harm: <1 % patients		

Authors: Martinez C, et al. **Year: 2005** **Country:** UK	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Risk of non-fatal self harm and completed suicide **Secondary Outcome Measures:** none **Timing of assessments:** N/A
RESULTS:	• No difference in risk of non-fatal self harm among the different SSRIs (p =0.35). The greatest risk of self harm was found in patients taking paroxetine. • No difference in the risk of self-harm between SSRIs and TCAs (OR: 0.99 CI: 0.86 to 1.14). • Significantly higher risk of self-harm among SSRI patients younger than 18 years compared to those on TCAs (OR 1.59; 95% CI 1.01-2.50). Among SSRIs, the greatest risk of self harm was found in patients taking paroxetine. • No difference in the risk of suicide between SSRIs and TCAs (OR: 0.57 CI: 0.26 to 1.25).
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION:	***Loss to follow-up:*** N/A ***Withdrawals due to adverse events:*** N/A ***Loss to follow-up differential high:*** N/A
ADVERSE EVENTS:	N/A
QUALITY RATING:	**Good**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Meijer WE, et. al.**[188] ***Year:*** **2002** ***Country:*** The Netherlands
FUNDING:	Pfizer
DESIGN:	***Study design:*** Observational study of adverse effects ***Setting:*** Multi-center (109 psychiatrists) ***Sample size:*** 1,251
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Observed: Sertraline or fluoxetine, fluvoxamine, or paroxetine Any administered dose 12 month observation period
INCLUSION:	All patients with a new sertraline prescription; patients taking fluoxetine, fluvoxamine, or paroxetine were used as controls
EXCLUSION:	None reported
ALLOWED OTHER MEDICATIONS/ INTERVENTIONS:	None reported
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** N/A ***Mean age:*** 41 ***Gender*** (% female): 64.1% ***Ethnicity:*** Not reported ***Other population characteristics:*** Significantly more sertraline patients had a diagnosis of depressive disorder than patients on other SSRIs ($p < 0.001$); anxiety disorder was significantly less in sertraline patients than patients with other SSRIs ($p < 0.001$); MDD: 77.9%, anxiety: 15.5%, multiple diagnoses: 37.8%.

Authors: **Meijer WE, et al.** ***Year:*** **2002**	
OUTCOME ASSESSMENT:	***Measures:*** Physicians recorded adverse events at each patient visit, used WHO coding; serious adverse events (SAEs) recorded according to the International Conference on Harmonization of Good Clinical Practice (ICH-CGP) ***Timing of assessments:*** Not reported
RESULTS:	• 2.2 adverse events per sertraline patient • 2.1 adverse events per SSRI patient • 73.4% of sertraline patients and 75.0% of other SSRI patients reported an adverse event • Diarrhea was reported more frequently by sertraline patients than patients taking other SSRIs ($p < 0.05$) • Abdominal pain was reported more frequently by other SSRI users ($p < 0.05$) • Nausea: sertraline: 24.3%, SSRI: 27% • Headache: sertraline: 19.3%, SSRI: 17.1%
ANALYSIS:	***ITT:*** N/A ***Post randomization exclusions:*** N/A
ATTRITION:	***Loss to follow-up:*** N/A ***Withdrawals due to adverse events:*** N/A ***Loss to follow-up differential high:*** N/A
ADVERSE EVENTS:	N/A
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Montejo et al.**[199] **Year: 2001** **Country:** Spain							
FUNDING:	Bristol-Myers Squibb							
DESIGN:	**Study design:** Observational **Setting:** Multi-center **Sample size:** 1022							
INTERVENTION: **Drug:** **Dose (mean):** **Duration:** **Sample size:**	fluoxetine 24.5 mg NR 279	paroxetine 23.4 mg NR 208	fluvoxamine 115.7 mg NR 77	sertraline 90.4 mg NR 159	citalopram 28.7 mg NR 66	venlafaxine 159.5 mg NR 55	mirtazapine 37.7 mg NR 49	nefazodone 324.6 mg NR 50
INCLUSION:	Normal sexual functioning prior to taking antidepressants; treatment with an antidepressant alone or in combination with a benzodiazepine; previous regular and satisfactory sexual practices; occurrence of sexual dysfunction within the two months after introduction of an antidepressant							
EXCLUSION:	Prior sexual dysfunction; combination of antidepressant and neuroleptic treatment; treatment with hormones or any other drug capable of interfering with sexual intercourse; significant intercurrent diseases affecting sexual function; substance abuse							
OTHER MEDICATIONS/ INTERVENTIONS:	NR							
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR **Mean age:** Overall: 39.8 **Gender (% female):** Overall: 60% **Ethnicity:** NR **Other population characteristics:** MDD: 60.1%; dysthymic disorder: 17.3%; panic disorder: 12.1%; OCD: 5.9%; other disorders: 3.7%							

Authors: Montejo et al. **Year: 2001** **Country:** Spain	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PRSexDQ (Pscychotropic-Related Sexual Dysfunction Questionnaire) **Secondary Outcome Measures:** None **Timing of assessments:** Each clinic visit
RESULTS:	• Overall incidence of sexual dysfunction was 59.1% (604/1022) when all antidepressants were considered as a whole • There were relevant differences when the incidence of any type of sexual dysfunction was compared among different drugs: fluoxetine: 57.7%; sertraline: 62.9%; fluvoxamine: 62.3%; paroxetine: 70.7%; citalopram: 72.7%; venlafaxine: 67.3%; mirtazapine: 24.4%; nefazodone: 8% • Men had a higher frequency of sexual dysfunction (62.4%) than women (56.9%), although women had higher severity
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION:	**Loss to follow-up:** N/A **Withdrawals due to adverse events:** N/A **Withdrawals due to lack of efficacy:** N/A **Loss to follow-up differential high:** N/A
ADVERSE EVENTS:	N/A
QUALITY RATING:	**Fair**

Adverse Events

Evidence Table 10

STUDY:	***Authors:*** **Nieuwstraten C, et al.**[67] ***Year:*** **2001** ***Country:*** Canada
FUNDING:	Not reported
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 1332
AIMS OF REVIEW:	To assess the benefits and risks of bupropion vs. SSRIs in major depression
STUDIES INCLUDED IN META-ANALYSIS	Kavoussi RJ et al. 1997, Segraves RT, et al. 2000, Weihs KL, et al. 2000, Croft H, et al. 1999, ColemanCC, et al. 1999, Feighner JP, et al. 1991
TIME PERIOD COVERED:	1966-1999
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs, study durations: 6-16 weeks, median 7 weeks
CHARACTERISTICS OF INCLUDED POPULATIONS:	Age: 36 to 70 yrs; proportion of females: 48.0% to 61.8%

Authors **Nieuwstraten C, et al.** ***Year:*** **2001** ***Country:*** Canada	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	Bupropion vs. sertraline (3 trials), bupropion vs. paroxetine (1 trial), bupropion vs. fluoxetine (1 trial)
MAIN RESULTS:	Results of HAM-D scores and CGI-I scores could not be pooled due to the unavailability of data; the weighted mean differences of CGI-S and HAM-A scores were not significantly different between bupropion and SSRIs
ADVERSE EVENTS:	Nausea, diarrhea, and somnolence occurred significantly less frequently in the bupropion group compared to the SSRI group RR: nausea: 0.6 (95%CI: 0.41-0.89), diarrhea: 0.31 (95%CI: 0.16-0.57), somnolence: 0.27 (95%CI: 0.15-0.48). Satisfaction with sexual function was significantly less in the SSRI group RR: 1.28 (95%CI: 1.16-1.41)
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Pedersen AG**[212] **Year: 2005** **Country:** Multinational		
FUNDING:	H. Lundbeck A/S		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Clinical trials **Sample size:** 4,091		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Escitalopram 5-20 mg/day 8-24 weeks 2648	 Placebo N/A 8-24 weeks 1443	
INCLUSION:	Adult outpatients with MDD (2277) or anxiety (371)		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR **Mean age:** NR **Gender (% female):** NR **Ethnicity:** NR **Other population characteristics:** NR		

Authors: Pederson AG **Year: 2005** **Country:** Multinational	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Rates of suicide and self-harm **Secondary Outcome Measures:** **Timing of assessments:** N/A
RESULTS:	• MADRS item 10 (suicidal thoughts) escitalopram patients had less suicidal thoughts than placebo from weeks 1 ($p < 0.05$) to 8 ($p < 0.001$). • Suicides in placebo-controlled studies escitalopram n- 0 rate- 0 incidence- 0 Placebo n-1 rate-0.003 incidence- 0.1 • Non-fatal self harm in placebo-controlled studies: escitalopram n- 5 rate- 0.011 incidence- 0.2 Placebo n-1 rate-0.003 incidence- 0.1
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION:	Overall **Loss to follow-up:** NR **Withdrawals due to adverse events:** NR **Withdrawals due to lack of efficacy:** NR **Loss to follow-up differential high:** Not enough information
ADVERSE EVENTS:	• N/A
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Rapaport ME, et. al.**[28] ***Year:*** **1996** ***Country:*** US			
FUNDING:	Solvay Pharmaceuticals, Upjohn			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (6 sites) ***Sample size:*** 100			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluvoxamine 100-150 mg/d 7 weeks	Fluoxetine 20-80 mg/d 7 weeks		
INCLUSION:	Male and female outpatients; 18-65 years; met DSM-III-R criteria for MDD; minimum HAM-D (21-item) score of 20; minimum score of 2 on the depressed mood item			
EXCLUSION:	Any primary DSM-IV Axis I disorder diagnosis other than MDD; acute suicidality; unstable medical conditions; history of seizure; had been treated with study medications; history of substance abuse or dependence; pregnancy and lack of appropriate birth control for women of child-bearing age			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** fluoxetine: 38.6; fluvoxamine: 40.0 ***Gender*** (% female): fluoxetine: 63; fluvoxamine: 61 ***Ethnicity:*** 95% white; 5% other ***Other population characteristics:*** NR			

Authors: **Rapaport ME, et al.** ***Year:*** **1996** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-21, HAM-A, CGI-S, Raskin–Covi Scale, Hopkins Symptom Checklist, TESS (Specific treatment-emergent signs and symptoms) Barnes Akathisia Scale, Modified Scale for Suicidal Ideation ***Timing of assessments:*** Primary outcome measures weekly; secondary outcome measures at baseline and endpoint
RESULTS:	• No statistically significant differences between fluvoxamine and fluoxetine in all outcome measures • Both drugs significantly improved scores on HAM-D (<10 for both groups at endpoint)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes (7)
ATTRITION:	***Loss to follow-up:*** 11% ***Withdrawals due to adverse events:*** 4% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Overall, no difference in the rate of adverse events were reported between fluvoxamine and fluoxetine and there were no differences in the average event severity (1.12 vs. 1.13; p = NR) • Significantly more patients on fluoxetine than on fluvoxamine reported nausea (42.5% vs. NR; p = 0.03) • Other frequent adverse events: headache: fluoxetine 53%, fluvoxamine 50% (p not significant) vomiting: fluoxetine 13%, fluvoxamine 4% (p not significant) daytime agitation: fluoxetine 47%, fluvoxamine 32% (p not significant)
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Schatzberg et al.**[48] ***Year:*** 2002 ***Country:*** US			
FUNDING:	Organon Pharma			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 255			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Mirtazapine 15-45 mg/d 8 weeks	Paroxetine 20-40 mg/d 8weeks		(There was extension phase to 16 weeks but only included subjects who had favorable response during the first part of the study)
INCLUSION:	Min. age of 65 years; DSM IV criteria for single or recurrent MDD; MMSE score > 25% for age and education; min. score of 18 on HAM-D_{17}			
EXCLUSION:	HAMD decrease > 20% between screening and baseline; untreated or unstable clinically significant medical condition or lab/physical exam abnormality; history of seizures; recent drug or alcohol abuse or any principal psych condition other than MDD; presence of psychotic features; suicide attempt in current episode; use of MAOI within 2 weeks, or other psychotropics or herbal treatments within 1 week; use of paroxetine or mirtazpine for the current episode; ECT therapy within 6 months; use of treatment for memory deficits; prior intolerance or lack of efficacy to mirtazapine or paroxetine in the past; patients who failed more than one adequate trial of an antidepressant for the current episode			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate or zolpidem for sleep induction; therapy for conditions like DM, hypothyroidism, high blood pressure, chronic respiratory conditions was allowed if they had been receiving for at least 1 month prior to screening visit.			

Authors: **Schatzberg, et al.** ***Year:*** **2002** ***Country:*** US	
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 72 ***Gender*** (% female): Mirtazapine: 63%, paroxetine: 64% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-17, CGI-S, CGI-I ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8
RESULTS:	• Mean Ham-D-17 scores significantly lower with mirtazapine at week 1, 2, 3, 6 but no difference at 8 week endpoint • Trend towards higher response and remission rates with mirtazapine but only significant difference at 2 weeks (response) and 6 weeks (remission) • Time to response: mirtazapine mean 26 days, paroxetine 40 days; p = -0.016 for Kaplan-Meier plot comparing the two • No difference in CGI Improvement response
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 26.8% ***Withdrawals due to adverse events:*** 20.4%; mirtazapine 14.8%, paroxetine 26.2% (p < 0.05) ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Frequency of treatment related adverse events: mirtazapine: 79.7%, paroxetine: 82.5% • Significant differences: dry mouth: mirtazapine 26.6%, paroxetine 10.3%; weight gain: mirtazapine 10.9%, paroxetine 0%; nausea: mirtazapine 6.3%, paroxetine19.0%
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Segraves, et al.**[85] **Year: 2000** ***Country:*** US			
FUNDING:	Glaxo Wellcome Inc			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 248			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/d 16 weeks	Bupropion 100-300 mg/d 16 weeks		
INCLUSION:	Received a DSM-IV diagnosis of moderate to severe depression with a minimum duration of 4 weeks and a maximum duration of 24 months; ≥ 18 years of age; in a stable relationship, have normal sexual functioning and sexual activity at least once every 2 weeks			
EXCLUSION:	Predisposition to seizure; pregnancy; alcohol or substance abuse; eating disorder; suicidal tendencies; prior treatment with bupropion or sertraline; used any psychoactive drug within 1 week of study			
OTHER MEDICATIONS/ INTERVENTIONS:	None reported			

Authors: **Segraves et al.** ***Year:*** **2000** ***Country:*** US	
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 39 ***Gender*** (% female): Sertraline: 48%, bupropion: 48% ***Ethnicity:*** (% white) Sertraline: 94%, bupropion: 93% ***Other population characteristics:*** No significant differences in diagnosis
OUTCOME ASSESSMENT:	***Measures:*** Sexual function assessment, Sexual desire disorder, Sexual arousal disorder, Orgasm dysfunction, Premature ejaculation, patient rated overall sexual satisfaction on 6 point Likert scale ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8, 12, 16
RESULTS:	▪ Significantly more sertraline patients developed a sexual dysfunction compared to bupropion patients; $p < 0.001$ for men and women $p < 0.05$ for sexual desire disorder • Overall sexual satisfaction (patient-rated) significantly more improved in bupropion treated patients. Men ($p < 0.05$) significant difference at day 21, 28, 42, and 56. Women ($p < 0.01$) beginning at day 56 and continuing to end
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 31.5%; bupropion: 29%, sertraline: 34% ***Withdrawals due to adverse events:*** 1.6%; bupropion 0%, sertraline 1.6% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	***Authors:*** **Thase ME**[206] ***Year:*** **1998** ***Country:*** US
FUNDING:	Wyeth-Ayerst Labs; National Institute of Mental Health
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 3744
AIMS OF REVIEW:	To assess the effects of venlafaxine on blood pressure
STUDIES INCLUDED IN META-ANALYSIS	Original data for the statistical analysis were provided by Wyeth-Ayerst Laboratories.
TIME PERIOD COVERED:	Not reported
CHARACTERISTICS OF INCLUDED STUDIES:	Acute and continuation phase data from randomized controlled trials comparing venlafaxine with placebo and imipramine. (21 outpatient and 6 inpatient trials at 180 different sites)
CHARACTERISTICS OF INCLUDED POPULATIONS:	Meet DSM-III-R criteria for a current principal diagnosis of major depression; score at least 20 on the 21-item HAM-D ; have no poorly controlled or serious medical illness

Authors: **Thase** ***Year:*** **1998** ***Country:*** US	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	Venlfaxine, imipramine, placebo
MAIN RESULTS:	Acute phase results at 6 weeks*:* • Mean supine DBP: venlafaxine: 78mmHg, imipramine: 78 mmHg, placebo: 75 mmHg ($p < 0.001$) • Mean increase in supine DBP: venlafaxine 1.02 mmHG. • Sustained elevation in supine DBP: venlafaxine: 4.8%, imipramine 4.7%, placebo 2.1%, ($p = 0.015$ for crude group comparison and $p = 0.086$ after adjustment for age/sex) • Incidence of supine DBP $\geq$ 90 mmHg: venlafaxine: 11.5%, imipramine 7.9 %, placebo 5.7% ($p < 0.001$ venlafaxine vs imipramine and venlafaxine vs placebo, $p = 0.24$ for imipramine vs placebo) Continuation Phase Results: • Mean supine DBP: no drug effect $p = 0.58$ (actual values not reported) • 4.5% (21 of 467) of subjects with normal supine DBPs developed elevated readings during this phase and it was significantly higher in the venlafaxine group $p = 0.058$ (actual numbers not reported) • A significant dose response effect on BP was seen in the venlafaxine group ($p < 0.001$)
ADVERSE EVENTS:	N/A
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No
STANDARD METHOD OF APPRAISAL OF STUDIES:	No
QUALITY RATING:	**Fair**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Thase ME, et al.**[207] **Year: 2005** **Country:** US and Europe		
FUNDING:	Eli Lilly and Mental Health Intervention Center grant		
DESIGN:	**Study design:** Post hoc analysis **Setting:** Multi-center **Sample size:** 1,568		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Duloxetine 40 mg/d-120 mg/d 8-9 weeks 1139	Paroxetine 20 mg/d 8-9 weeks 359	Fluoxetine 20 mg/d 8-9 weeks 70
INCLUSION:	18 years of age or older; current primary MDD diagnosis as defined in DSM-IV; HAM-D score ≥15; CGI-S score ≥4		
EXCLUSION:	Serious or poorly controlled medical illness or condition		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** duloxetine: 42.7; paroxetine: 43.2; fluoxetine: 39.7 **Gender (% female):** duloxetine: 66.8; paroxetine: 63.8; fluoxetine: 42 **Ethnicity (%):** duloxetine: white: 89.2; black: 4.8; Hispanic: 4.3; Asian: 0.8; other: 0.8 paroxetine: white: 89.1; black: 4.7; Hispanic: 5.0; Asian: 0.8; other: 0.3 fluoxetine: white: 82.9; black: 10; Hispanic: 4.3; Asian: 0; other: 2.9 **Other population characteristics:** **Supine BP systolic (mm Hg):** duloxetine: 121.8; paroxetine: 122.0; fluoxetine: 118.8 **Supine BP diastolic (mm Hg):** duloxetine: 76.6; paroxetine: 76.4; fluoxetine: 75.1 **Supine heart rate (bpm):** duloxetine: 73.0; paroxetine: 73.5; fluoxetine: 72.7		

Authors: Thase et al. **Year: 2005** **Country:** US and Europe	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Supine blood pressure, heart rate and ECG interval **Timing of assessments:** Supine BP and heart rateat each study visit, ECG at baseline and last visit
RESULTS:	• Greater change in heart rate for duloxetine vs. fluoxetine and paroxetine: mean change of 2.8 bpm for duloxetine vs. -1.0 bpm for fluoxetine ($p \leq 0.01$); mean change of 1.0 bpm for duloxetine vs. -1.4 bpm for paroxetine ($p \leq 0.001$) • Duloxetine had slightly lower mean change in systolic BP than fluoxetine (2.3 mm Hg vs. 3.2 mm Hg) • No statistically significant differences in systolic and diastolic BP for duloxetine vs. fluoxetine or paroxetine • Mean changes in QTcF and QRS intervals not significantly different for duloxetine vs. paroxetine
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** at least 7
ATTRITION: **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy**: **Loss to follow-up differential high:**	NR
ADVERSE EVENTS:	N/A
QUALITY RATING:	**N/A**

Evidence Table 10 Adverse Events

STUDY:	**Authors: Whyte et al.**[205] **Year: 2003** **Country:** Australia		
FUNDING:	NR		
DESIGN:	**Study design:** Observational-prospective cohort **Setting:** Hospital (Hunter Area Toxicology Service Database, Australia) **Sample size:** 538 (284 venlafaxine and other SSRI records)		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Venlafaxine overdose N/A 51	 Other SSRIs overdose N/A 284	
INCLUSION:	First time admissions for overdose with an SSRI or TCA		
EXCLUSION:	Patients who ingested multiple drugs of interest		
OTHER MEDICATIONS/ INTERVENTIONS:	N/A		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No, SSRI group was younger and significantly; took more drug; waited longer to present **Mean age:** VX: 36; SSRI: 29 **Gender:** VX: 68.6%; SSRI: 67% female **Ethnicity:** NR **Other population characteristics:** NR		

Authors: Whyte et al. **Year: 2003** **Country:** US	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Incidence of seizures **Secondary Outcome Measures:** Serotonin toxicity; ICU admission; life-threatening arrhythmias; heart rate; blood pressure; coma score; ECG measures; time in hospital **Timing of assessments:** N/A
RESULTS:	• Significantly more patients overdosing on venlafaxine (13.7%) experienced seizures than patients taking other SSRIs (1.3%) $p < 0.001$ • Significantly more patients overdosing on venlafaxine (29.4%) required ICU admission than patients taking other SSRIs (7.3%) $p < 0.01$ • No other significant differences were found between venlafaxine overdoses and SSRI overdoses
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION: **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy**: **Loss to follow-up differential high:**	Overall N/A
ADVERSE EVENTS:	N/A
QUALITY RATING:	**Good**

Evidence Table 11: Subgroups

STUDY:	***Authors:*** **Burt VK, et al.**[215] ***Year:*** **2005** ***Country*****:** US
FUNDING:	Eli Lilly
DESIGN:	***Study design:*** Pooled data analysis ***Number of patients:*** 512 (subgroup analysis 114)
AIMS OF REVIEW:	To assess the efficacy of duloxetine in depressed women during the years in which most women undergo perimenopause (aged 40-55)
STUDIES INCLUDED IN META-ANALYSIS	Two identical but independently conducted double-blinded RCTs
TIME PERIOD COVERED:	NR
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized, double-blind, parallel-group, placebo controlled trials of duloxetine
CHARACTERISTICS OF INCLUDED POPULATIONS:	Women 40-55 years of age; MDD; HAM-D score $\geq$ 15; CGI-S score $\geq$ 4

Authors: Burt et al. **Year: 2005** **Country:** US	
CHARACTERISTICS OF INTERVENTIONS:	Duloxetine 60 mg/d vs. placebo
MAIN RESULTS:	• Significantly greater improvement in HAM-D total scores at endpoint for duloxetine vs. placebo (p = 0.001) • Estimated probability of response significantly greater for duloxetine vs. placebo: 74.7% vs. 47.0% (p = 0.03) • Estimated probabilities of remission were 41.8% vs. 23.4% for duloxetine and placebo, respectively (p < 0.07) • Using LOCF analysis, response rates were 58.2% for duloxetine 60 mg/d vs. 32.2% for placebo (p = 0.008); remission rates were 34.6% for duloxetine vs. 18.6% for placebo (p = 0.06)
ADVERSE EVENTS:	NR
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No; analysis of 2 trials
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Cassano GB, et al.**[29] ***Year:*** **2002** ***Country:*** Italy			
FUNDING:	SmithKline Beecham, Ravizza Farmaceutici			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (38) ***Sample size:*** 242			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20-40 mg/day 1 year	Fluoxetine 20-60 mg/day 1 year		
INCLUSION:	65 yrs or older; ICD-10 criteria for depression; ≥ 18 on HAM-D-17; mini mental state ≥ 22; Raskin score higher than Covi Anxiety score			
EXCLUSION:	History of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; clinically relevant progressive disease; depot neuroleptics within 6 months			
OTHER MEDICATIONS/ INTERVENTIONS:	Treatments for concomitant systemic diseases; short or intermediate half-life benzodiazepines; temazepam for insomnia			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Paroxetine: 75.6, fluoxetine: 74.9 ***Gender*** (% female): Paroxetine: 61%, fluoxetine: 50% ***Ethnicity:*** Not reported ***Other population characteristics:*** Duration of present episode was less than 6 months for 60% of patients and more than 1 year for 25%; 40% had already been treated for present episode			

Authors: **Cassano GB, et al.** ***Year:*** **2002** ***Country:*** Italy	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** HAM-D, CGI, Clinical Anxiety Scale at baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52 HAMD responders = score < 10, anxiety responders = CAS score < 8 Cognitive tests: Buschke Selective Reminding Test, Blessed Information and Memory Test, Clifton Assessment Schedule, Cancellation Task Test, Wechsler Paired Word Test, Mini-mental State Examination, baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52
RESULTS:	Cognitive function: • Both treatment groups showed significant improvement in cognitive performance on all test scales • There were no significant differences between treatment groups and cognitive performance except for the Buschke test at week 3 and 6 where paroxetine showed a significantly greater improvement on a number of tests Depressive symptoms: • Both treatment groups significantly improved the HAM-D total scores • Paroxetine showed a greater improvement of HAM-D scores during the first 6 weeks (week 3: $p < 0.05$; week 6: $p < 0.002$), otherwise there were no differences between the treatment groups • A Kaplan Meier analysis evaluating the percentage of responders (HAM-D ≥ 10) over time showed a significant difference in favor of paroxetine ($p < 0.03$) • No significant differences on CGI scores
ANALYSIS:	***ITT:*** No ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 39.3%; paroxetine: 40.6%, fluoxetine:37.8% ***Withdrawals due to adverse events:*** 15% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• At least 1 adverse event: paroxetine: 27.6%, fluoxetine: 32.8% • Fluoxetine had significantly more severe adverse events than paroxetine (22 vs. 9; $p < 0.02$)
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Cassano P, et al.**[216] ***Year:*** **2004** ***Country:*** US			
FUNDING:	NIMH			
DESIGN:	***Study design:*** Open trial ***Setting:*** Not reported ***Sample size:*** **384**			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Fluoxetine 20 mg/d 8 weeks			
INCLUSION:	Outpatients aged 18-65; met criteria for MDD using the DSM-III-R and HAM-D-17 (score 16 or higher at baseline)			
EXCLUSION:	Pregnancy or lactation, lack of accepted contraceptive method; women of child bearing potential taking a birth control pill; serious suicidal risk; serious and unstable co-morbid illness; seizure disorder with a seizure occurring with the last year; presence of other DSM-III-R diagnoses; schizophrenia; delusional disorder; antisocial personality disorder; mood congruent disorder or mood incongruent disorders			
OTHER MEDICATIONS/ INTERVENTIONS:	Concomitant use of psychotropic drugs			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean age:*** Not reported ***Gender:*** (% female): 54.6% ***Ethnicity:*** Not reported ***Other population characteristics:*** Mean age of onset for MDD was 28.4+/-13.1 yrs			

Authors: Cassano P, et al. **Year: 2004** **Country:** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-17 ***Timing of assessments:*** Baseline and weeks 2, 4, 6, 8
RESULTS:	• No difference in remission rates between older (> 45 years) and younger (<45 years) women (57.1% vs. 50% (p = 0.84) • No difference in remission rates between older (> 45 years) and younger (<45 years) men (57.2% vs. 49.1% (p = 0.96) • Co-morbid anxiety was a significant predictor of a higher burden of residual depressive symptoms (p = 0.047) • Anxious and non-anxious subtypes of depression did not present age or sex-related differences in outcomes
ANALYSIS:	***ITT:*** Not reported ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** Not reported ***Withdrawals due to adverse events:*** Not reported ***Loss to follow-up differential high:*** Not reported
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Clayton AH, et al.**[222] ***Year:*** **2005** ***Country*****:** NR
FUNDING:	Pfizet, Inc.
DESIGN:	***Study design:*** Pooled analysis ***Number of patients:*** 673 (338 women, 335 men)
AIMS OF REVIEW:	To examine the sex differences in efficacy and safety when panic disorder is treated with sertraline or placebo
STUDIES INCLUDED IN POOLED-ANALYSIS	Four double-blinded RCTs (Pohl et al., 1998; Londborg et al, 1998; Pollack and Otto, 1998; and Sheikh et al., 2000)
TIME PERIOD COVERED:	Not reported
CHARACTERISTICS OF INCLUDED STUDIES:	Double blinded, placebo controlled trials of sertraline: all used a 2-week single-blind period
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adult, 18 years or older, outpatients with panic disorder with or without agoraphobia; at baseline males reported an earlier age of onset (28.1 vs. 30.0 years)shorter duration of disease (8.6 vs. 7.3 years), were younger (36 vs. 40 years) and had higher past histories with alcohol/substance abuse/dependence (substance 14% vs.6% alcohol 20% vs. 9%)

Authors: Clayton AH, et al. **Year: 2005**	
CHARACTERISTICS OF INTERVENTIONS:	2 fixed dose studies 12 weeks in length, 2 flexible dose studies 10 weeks in length
MAIN RESULTS:	• Panic attack frequency- change from baseline males -77% females -82% p = 0.02 • PDSS total score- change from baseline males -5.79 (0.61) females -6.99 (0.47) p = 0.42 • Time spent worrying- change from baseline males -61.4% females -72.1% p = 0.01 • HAM-A total score- change from baseline males -10.74 (0.60) females -10.07 (0.58) p = 0.42 • Q-LES-Q total score- change from baseline males +8.45 (1.84) females +8.89 (1.43) p = 0.85
ADVERSE EVENTS:	Excess over placebo rates of more than 5% in nausea (11% male, 11% female), insomnia (10% male, 5% female), sedation (9% male, 2% female) diarrhea (7% male, 14% female) dry mouth (7% male, 3% female) fatigue (5% male, 6% female)
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No; analysis of published trials
STANDARD METHOD OF APPRAISAL OF STUDIES:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Cornelius JR, et. al.**[228-230] ***Year:*** **1997**, Subgroup analysis, **1998***;* Follow up study, **2000** ***Country:*** US			
FUNDING:	Not reported			
DESIGN:	***Study design:*** RCT ***Setting:*** Single-center ***Sample size:*** 51 Subgroup analysis 1998: 17 Follow up study 2000: 31			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluoxetine 20-40 mg/d 12 weeks	Placebo N/A 12 weeks		
INCLUSION:	18-65 years old; DSM-III-R criteria for MDD and alcohol dependence Subgroup analysis 1998: cocaine abuse by DSM-III			
EXCLUSION:	Serious concomitant medical illness; pregnancy; bipolar; schizoaffective; schizophrenia; non-alcohol substance abuse; antidepressant medication within 1 month			
OTHER MEDICATIONS/ INTERVENTIONS:	None reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** No ***Mean Age:*** 34.8 ***Gender*** (female%): 49% ***Ethnicity:*** 47% white, 53% black ***Other population characteristics:*** The fluoxetine group was significantly more depressed on the BDI scale than the placebo group following washout ($p < 0.02$)			

Authors: **Cornelius JR, et. al.** ***Year:*** **1997, 1998, 2000** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** 24 item HAM-D, BDI , Addiction Severity Index, drinking level ***Timing of assessments:*** Assessments performed weekly
RESULTS:	• Change in HAM-D score was significantly better for the fluoxetine group than placebo ($p < 0.05$) • Change in BDI score was not significantly different between groups • Fluoxetine patients had significantly fewer drinks, number of drinking days, and drinks per day ($p < 0.05$) Subgroup analysis 1998 • Cocaine abusers showed a significantly worse outcome on HAM-D ($p = 0.17$) and on BDI ($p = 0.001$) and multiple measures of alcohol consumption ($p = 0.042$) compared to non-cocaine abusing alcoholics Follow up study 2000 • HAM-d scores remained significantly lower in the fluoxetine group during the one year follow-up. No additional improvement was reported. • Number of days intoxicated decreased in fluoxetine group ($p = 0.010$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** No
ATTRITION:	***Loss to follow-up:*** 10% ***Withdrawals due to adverse events:*** 0 ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	No side effects observed
QUALITY RATING:	**Good**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Entsuah AR, et al.**[219] ***Year:*** **2001** ***Country:*** Not reported
FUNDING:	Wyeth
DESIGN:	***Study design:*** Systematic review ***Number of patients:*** 2045
AIMS OF REVIEW:	To detect differences in response and remission rates with respect to age and gender
STUDIES INCLUDED IN META-ANALYSIS	No systematic literature search
TIME PERIOD COVERED:	Not reported
CHARACTERISTICS OF INCLUDED STUDIES:	Double-blind, active-controlled, RCTs
CHARACTERISTICS OF INCLUDED POPULATIONS:	MDD; ≥ 20 on HAM-D; age 18-85

Authors: **Entsuah AR, et. al.** ***Year:*** **2001** ***Country:*** Not reported	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	Venlafaxine, paroxetine, fluoxetine, placebo
MAIN RESULTS:	No significant age by treatment; gender by treatment; or age-by-gender by treatment interactions
ADVERSE EVENTS:	No differences in adverse events for age or gender subgroups
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No
STANDARD METHOD OF APPRAISAL OF STUDIES:	No
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Krishnan KRR, et. al.**[236] ***Year:*** **2001** ***Country:*** US			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** Pooled data of 2 RCTs ***Setting:*** US ***Sample size:*** 220			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Sertraline 50-150 mg/day 12 weeks			
INCLUSION:	Age 60 or older; DSM-III-R criteria for major depression; ≥ 18 on HAM-D-24; minimal improvement on CGII			
EXCLUSION:	Organic mental disorder; other Axis 1 diagnosis; MMSE less than 23; acute or unstable medical condition; concomitant use of psychotropic drugs; suicidal risk; previous history of non-response to adequate treatment			
OTHER MEDICATIONS/ INTERVENTIONS:	Concomitant medications other than psychotropic meds allowed Chloral hydrate, temezapam			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes HTN (hypertension); VAS (vascular disease); NOVASC (no hypertension, no vascular comorbidity) ***Mean Age:*** HTN: 68.6; VASC: 68.9; NOVASC: 67.3 ***Gender:*** (% female) HTN: 69%; VASC: 44%; NOVASC: 62% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Krishnan KRR, et. al.** ***Year:*** **2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D (change from baseline, > 50% response), HAM-A, CGI-I (1 or 2 = responder), CGI-S ***Timing of assessments:*** Weeks 1, 2, 3, 4, 6, 8, 10, 12
RESULTS:	The antidepressant effect of sertraline was not significantly affected by the presence of vascular illness
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** Not reported ***Withdrawals due to adverse events:*** High concomitant medication group: 23.6%; low concomitant medication: 15.7% ***Loss to follow-up differential high:*** Not reported
ADVERSE EVENTS:	• Vascular comorbidity was not associated with an increase in the reported severity of adverse events, or premature discontinuation for patients on sertraline • Sertraline did not have clinically significant effects on blood pressure or heart rate
QUALITY RATING:	**FAIR** (only for subgroup analysis)

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Kroenke K, et al.**[19] ***Year:*** **2001** ***Country:*** ***Trial name:*** ARTIST (A randomized trial investigating SSRI treatment)			
FUNDING:	Eli Lilly			
DESIGN:	***Study design:*** RCT (open label) ***Setting:*** Multi-center (76 primary care physicians) ***Sample size:*** 601			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20 mg/day 9 months	Fluoxetine 20 mg/day 9 months	Sertraline 50 mg/day 9 months	Mean dose at 9 months: Paroxetine: 23.5mg Fluoxetine: 23.4mg Sertraline: 72.8mg
INCLUSION:	18 years or older; depressive disorder as determined by the primary care physician (PCP); had home telephone			
EXCLUSION:	Cognitive impairment; lack of reading/writing skills; terminal illness; nursing home resident; actively suicidal; SSRI within past 2 months; other antidepressant therapy; bipolar disorder; pregnancy; lactation			
OTHER MEDICATIONS/ INTERVENTIONS:	Yes			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Paroxetine: 47.2, fluoxetine: 47.1, sertraline: 44.1 ***Gender*** (% female): Paroxetine: 76%, fluoxetine: 86%, sertraline: 75% ***Ethnicity:*** (white) Paroxetine: 85%, fluoxetine: 88%, sertraline: 79%; (black) paroxetine: 13%, fluoxetine: 9%, sertraline: 17% (other) paroxetine: 2%, fluoxetine: 3%, sertraline: 4% ***Other population characteristics:*** (MDD) total: 74%, paroxetine: 71%, fluoxetine: 74%, sertraline: 73%; (dysthymia) total: 18%, paroxetine: 22%, fluoxetine: 17%, sertraline: 18%; (minor depression) total: 8%, paroxetine: 7%, fluoxetine: 9%, sertraline: 9%			

Authors: **Kroenke K, et al.** ***Year:*** **2001** ***Country:*** ***Trial name:*** ARTIST	
OUTCOME ASSESSMENT:	***Measures:*** Computer assisted telephone interview: SF-36, MSC (mental component summary), SCL-20 (symptoms checklist), PRIME-MD (primary care Evaluation of mental disorders), subscales of: medical outcomes study questionnaire (MOS): patient health questionnaire, health and daily living form, quality of social interaction scale, quality of close relationship scale, work limitations questionnaire ***Timing of assessments:*** Months 1, 3, 6, 9
RESULTS:	• All 3 treatment groups showed significant improvements in depression and other health related quality of life domains (social function, work function, physical function) • There were no significant differences between treatment groups in any of the 3 and 9 months outcome measures • Subgroup analysis showed that there were no differences in treatment effects for patients with MDD and for patients older than 60 years • Switch rate to other medication: paroxetine: 22%, fluoxetine: 14%, sertraline: 17%
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 24.3%**;** paroxetine: 24.8%, fluoxetine: 22.5%, sertraline: 25.7% ***Withdrawals due to adverse events:*** paroxetine: 30%, fluoxetine: 23%, sertraline: 24% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	No significant differences in adverse events between treatment groups
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Linden RD, et al.**[227] ***Year:*** **1994** ***Country:*** US			
FUNDING:	Not reported			
DESIGN:	***Study design:*** Retrospective analysis of two RCTs ***Setting:*** Multi-center ***Sample size:*** 89			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine: 20-50 mg/d 12 weeks	Fluoxetine 20-80 mg/d 12 weeks	Placebo N/A 12 weeks	
INCLUSION:	18-70 yrs; DSM-III-R criteria for major depression; ≥17 on HAM-D-17			
EXCLUSION:	Not reported			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean Age:*** 42 ***Gender*** (female%): 56.6% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Linden RD, et. al.** ***Year:*** **1994**	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D, Raskin, Covi, CGI, SCL-90 ***Timing of assessments:*** Weeks 1, 2, 3, 4, 6, 9, 12
RESULTS:	• Subjects with baseline complaints of gastrointestinal symptoms or more severe depression were not more likely to develop gastrointestinal side effects under SSRI treatment
ANALYSIS:	***ITT:*** No ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** Not reported ***Withdrawals due to adverse events:*** GI withdrawals: fluoxetine: 5.2%, paroxetine: 0% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	For this analysis only gastrointestinal side effects were considered • Nausea: paroxetine: 28%, fluoxetine: 26%, placebo: 0% • Diarrhea: paroxetine: 14%, fluoxetine: 16%, placebo: 7% • Weight loss/loss of appetite: paroxetine: 22%, fluoxetine: 8%, placebo: 7%
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Newhouse PA, et al.**[37] ***Year:*** **2000** ***Country:*** US			
FUNDING:	Pfizer, Inc.			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 236			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-100 mg/d 12 weeks	Fluoxetine 20-40 mg/d 12 weeks		(Doses could be doubled after 4 weeks)
INCLUSION:	≥ 60 years of age; DSM-III-R criteria for major depression; ≥ 18 on 24 item HAM-D			
EXCLUSION:	Other psychiatric disorder; significant physical illness; non-responders to antidepressants or ECT therapy			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate, temazepam for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Sertraline: 68 , fluoxetine: 67 ***Gender*** (% female): Sertraline: 63.2%, fluoxetine: 51.3% ***Ethnicity:*** (white) Sertraline: 95.7%, fluoxetine: 100%; (black) sertraline: 3.4% (other) sertraline: 0.9% ***Other population characteristics:*** Not reported			

Authors: **Newhouse PA, et al.** ***Year:*** **2000** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** 24 item HAM-D, HAM-A, CGI-S, CGI-I, BDI, MADRS, POMS, Q-LES-Q, digit symbol substitution test, SLT ***Timing of assessments:*** Baseline, week 1, 2, 3, 4, 6, 8, 10, 12
RESULTS:	• Sertraline and fluoxetine were effective in the relief of depressive symptoms • There were no significant differences between sertraline and fluoxetine on the primary efficacy measures (HAM-D and CGI) HAM-D Responders: sertraline: 73%, fluoxetine: 71% • HAMD remitters: sertraline: 45%, fluoxetine: 46% • Overall there was no significant differences between sertraline and fluoxetine on cognitive measures (SLT and digit symbol substitution test)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 32.2%; sertraline: 31.6%, fluoxetine: 32.8% ***Withdrawals due to adverse events:*** sertraline: 18.8%, fluoxetine: 24.4%, p = 0.5 ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Weight reduction: sertraline: -1.7lb, fluoxetine: -3.2lb (p = 0.018) • Otherwise no statistically significant differences between groups • Headache: sertraline: 33.6%, fluoxetine: 31.4% • Dizziness: sertraline: 7.8%, fluoxetine: 10.2% • Dry mouth: sertraline: 15.5%, fluoxetine: 7.6% • Nausea: sertraline: 14.7%, fluoxetine: 18.6% • Diarrhea: sertraline: 22.4%, fluoxetine: 16.1%
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Petrakis I, et. al.**[234] ***Year:*** **1998** ***Country:*** US			
FUNDING:	National Institute on Drug Abuse			
DESIGN:	***Study design:*** RCT ***Setting:*** Teaching hospital ***Sample size:*** 44			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Fluoxetine 20-60 mg/d 3 months	 Placebo N/A 3 months		
INCLUSION:	Opoid dependent patients; methadone treatment for at least 3 months; DSM-III-R criteria for major depression; ≥ 14 on HAM-D-17; > 8 on BDI			
EXCLUSION:	MDD independent of drug abuse; history of psychotic disorders; bipolar disorder			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** Fluoxetine: 35.4 years, placebo: 33.3 years ***Gender*** (% female): Fluoxetine: 39.1%, placebo: 33.3% ***Ethnicity:*** White: fluoxetine: 91.3% placebo: 85.7%; African American: fluoxetine: 4.3%, placebo: 4.8%; Hispanic: fluoxetine: 4.3%, placebo: 9.5% ***Other population characteristics:*** MDD: fluoxetine: 47.1%, placebo: 52.9%; dysthymia: fluoxetine: 57.1%, placebo: 42.9%			

Authors: **Petrakis I, et. al.** ***Year:*** **1998** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** BDI, HAM-D (Hamilton Depression Rating Scale), ASI (addiction severity index) ***Timing of assessments:*** Weekly, weeks 4, 8, 12, urine samples weekly
RESULTS:	• BDI and HADRS scores decreased significantly in both groups ($z = 2.37$; $p = 0.01$; $z = 5.85$, $p < 0.01$). There were no significant differences between placebo and fluoxetine treated patients. • Concomitant heroin use and ASI scores decreased significantly for both groups ($z = 2.92$, $p < 0.01$; $z = 2.66$, $p < 0.01$) but there was no significant difference between groups
ANALYSIS:	***ITT:*** No ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 15.9%; fluoxetine: 13%, placebo: 19% ***Withdrawals due to adverse events:*** Not reported ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	All fluoxetine discontinuations due to possible treatment -related adverse events
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Rabkin JG, et al.**[232] ***Year:*** **1999** ***Country:*** US			
FUNDING:	NIMH, Eli Lilly			
DESIGN:	***Study design:*** RCT ***Setting:*** University-affiliated research outpatient clinic ***Sample size:*** 120			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluoxetine mean dose 37 mg/day 8 weeks	Placebo N/A 8 weeks		(Note responders were followed for an additional 18 weeks to assess effect of drug on immune status)
INCLUSION:	Ages 18-70; HIV + for at least 2 months; physically healthy except for HIV; those with an AIDS-defining condition had to be in treatment with a consenting primary care provider; DSM-IV criteria for MDD or dysthymia or both			
EXCLUSION:	History of psychosis; bipolar disorder within past 6 months of substance use; panic disorder; current risk for suicide; significant cognitive impairment; use of other antidepressant within 2 weeks before study entry; initiation of psychotherapy within past 4 weeks; medical exclusions: HIV wasting syndrome; significant diarrhea; unstable health; onset of opportunistic infections within past 6 weeks			
OTHER MEDICATIONS/ INTERVENTIONS:	Concurrent HIV medications allowed			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean Age:*** 39 ***Gender*** (% female): 2.5% ***Ethnicity:*** African American 20%, Latino 15 %, 65% white ***Other population characteristics:*** 36% receiving disability benefits, 46% college graduates, 88% had some post-high school education			

Authors: **Rabkin JG, et al.** ***Year:*** **1999** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D, brief symptom inventory, Beck Hopelessness Scale, Quality of Life Enjoyment and Satisfaction Questionnaire ***Timing of assessments:*** Baseline, weeks 4, 8
RESULTS:	• Significantly more responders on HAM-D in the fluoxetine group (fluoxetine: 57%, placebo: 41%; p = 0.03) • No significant differences in changes of HAM-D scores • No significant difference in CGI responders
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 27.5%; fluoxetine: 29.6%; placebo: 23.1% ***Withdrawals due to adverse events:*** 5%; fluoxetine: 7.4%, placebo: 0 ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Reporting at least 1 treatment emergent side effect during study: fluoxetine: 50%, placebo 50% • Mean number of side effects reported: fluoxetine: 1.4 (2.0 sd), placebo: 1.3 (1.8 sd) • Only headache was reported more significantly more frequently among fluoxetine group as compared to placebo
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	**Authors: Rapaport MH, et al.**[217] **Year: 2003** **Country:** US and Canada		
FUNDING:	GlaxoSmithKline		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (29 US and 2 Canadian sites) **Sample size:** 323		
INTERVENTION: **Drug:** **Dose:** **Duration:**	 Paroxetine CR 12.5-50 mg/d 12 weeks	 Paroxetine IR 10-40 mg/d 12 weeks	 Placebo N/A 12 weeks
INCLUSION:	DSM-IV criteria for MDD; total score of 18 or more on 17-item HAM-D at both screen and baseline visits; at least 60 years of age		
EXCLUSION:	HAM-D total score decreased by 25% or more between screen and baseline visits; concomitant therapy with psychoactive medication; other Axis 1 disorders within 6 months of screen visit; history of brief depressive episodes lasting $\leq$ 8 weeks with spontaneous remission; neurologic disorders contributing to secondary depression; dementia; Mini-Mental State Examination score $\leq$ 24; serious medical conditions that would preclude paroxetine administration; history of seizure disorders; concomitant treatment with warfarin, pheytoin, cimetidine, sumatriptan, type IC antiarrhythmic agents, quinidine; history of substance abuse or dependence within 6 months; electroconvulsive therapy within 3 months; unresolved clinically abnormal laboratory or electrocardiogram (ECG) findings at baseline; suicidal or homicidal tendencies		
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep disturbance		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** paroxetine CR=70.4; paroxetine IR=70.1; placebo=69.4 **Gender:**(% female) paroxetine CR=48.1%; paroxetine IR=56.6%; placebo=63.3% **Ethnicity:**(% white) paroxetine CR=96.2%; paroxetine IR=95.3%; placebo=94.5% (% black) paroxetine CR=1.9%; paroxetine IR=0.9%; placebo=1.8% (% Asian) paroxetine CR=0%; paroxetine IR=1.9%; placebo=0% (% other) paroxetine CR=1.9%; paroxetine IR=1.9%; placebo=3.7% **Other population characteristics:** • % concomitant medications: paroxetine CR=99.0%; paroxetine IR=93.4%; placebo=94.5%		

Authors: Rapaport MH, et al. **Year: 2003** **Country:** US	
OUTCOME ASSESSMENT:	**Measures:** Change from baseline to endpoint in 17-item HAM-D total score; CGI-S; CGI-I all visits except baseline **Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8, 10, 12
RESULTS:	• Both paroxetine IR and paroxetine CR had significantly higher rates of response and remission than placebo • No significant differences in any efficacy measures between paroxetine IR and paroxetine CR (HAM-D, CGI-I)
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (4)
ATTRITION:	**Loss to follow-up:** 24% **Withdrawals due to adverse events:** Paroxetine CR=13 (12.5%); paroxetine IR=17 (16.0%); placebo=9 (8.3%) **Loss to follow-up differential high:** No
ADVERSE EVENTS:	• The most common events reported in > 10% of patients were somnolence, dry mouth, headache, abnormal ejaculation, diarrhea, asthenia, nausea, constipation, dyspepsia and decreased appetite • Reports of hypotension and insomnia were similar in paroxetine CR (4.8% and 9.6%) and placebo (3.7% and 8.3%), as well as in paroxetine IR (12.3% and 14.2%) and placebo
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Razavi D, et. al.**[233] ***Year:*** **1996** ***Country:*** Europe			
FUNDING:	Eli Lilly			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 91			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Fluoxetine 20 mg/day 5 weeks	 Placebo N/A 5 weeks		
INCLUSION:	Cancer patients with MDD or adjustment disorder as defined by DSM-III; 18 yrs or older; cancer diagnosis within 6 weeks to 7 years; ≥ 13 on HADS (Hospital Anxiety and Depression Scale); ≥ 60 on Karnofsky Performance Scale			
EXCLUSION:	MDD with melancholic features; bipolar disorder; alcohol abuse previous year; uncontrolled pain; life expectancy less than 3 months; major somatic comorbidities; abdominal or thoracic surgery in last 6 weeks; > 15 corticosteroid treatment; pregnant or nursing; psychotropic drug within 2 weeks; fluoxetine or MAOI within 6 weeks; ondansetron or granisitron longer than 48 hours			
OTHER MEDICATIONS/ INTERVENTIONS:	Zolpidem, benzodiazepines, other prescription treatment			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** Fuoxetine: 53.2, placebo: 52.6 ***Gender*** (% female): Fluoxetine: 77%, placebo: 82% ***Ethnicity:*** Not reported ***Other population characteristics:*** Metastatic disease: fluoxetine 13%, placebo 5%; 40% had previous psychiatric disorder			

Authors: **Razavi D, et. al.** ***Year:*** **1999** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** MADRS, HAM-D, Hospital Anxiety Scale (HAS), Hospital Anxiety and depression Scale (HADS), Revised Symptom Checklist (SCL90-R), Spitzer Quality of Life Index (SQOLI) ***Timing of assessments:*** Not reported
RESULTS:	• There were no significant differences in efficacy between treatment groups (observer rated scales) • Responders (improvement ≥ 50% on HADS): fluoxetine: 18%, placebo: 20% • Both treatment groups showed significant improvements on all assessment scales compared to baseline • The improvements were greater for the fluoxetine group but only statistically significant for SCL90-R (p = 0.02) • Drop out rate was significantly higher in the fluoxetine group (33% vs. 15%; p = 0.04)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** 24.2%; fluoxetine: 33%, placebo: 15% ***Withdrawals due to adverse events:*** Fluoxetine: 15.6%, placebo: 0 ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	Frequency of adverse events did not differ between treatment groups (p = 0.43)
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	**Authors: Roscoe JA, et al.**[235] **Year: 2005** **Country:** US		
FUNDING:	Department of Defense, SmithKline Beecham provided drug and placebo		
OBJECTIVE:	To evaluate the effect of a serotonin uptake inhibitor on depression and fatigue (both conditions are postulated to share a serotonin link) in a homogeneous sample of breast cancer patients		
DESIGN:	**Study design:** RCT **Setting:** University affiliated hospital and 2 of its affiliated hospitals **Sample size:** 94		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	 Paroxetine 20 mg/day At least 6 weeks 44	 Placebo N/A At least 6 weeks 50	
INCLUSION:	Female patients about to begin or currently undergoing chemotherapy treatment for breast cancer, with at least 4 cycles to be completed		
EXCLUSION:	Concurrent radiation or interferon treatment; history of seizures or mania taking psychotropic medications; treatment cycles of less than 2 weeks apart		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Mean age:** 51.3 **Gender (% female):** 100% **Ethnicity (% white):** paroxetine: 93%, placebo 86% **Other population characteristics:** **Baseline depression (CES-D of 19 or more):** paroxetine: 13 (29%), placebo: 13 (26%)		

Authors: Roscoe JA, et al. **Year: 2005**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Fatigue using the Fatigue Symptom Checklist (FSCL), Multidimensional Assessment of Fatigue (MAF) and the Fatigue/Inertia subscale of the Monopolar Profile of Mood States (POMS-FI) **Secondary Outcome Measures: Depression** using the CES-D and the Depression/Dejection subscale of the Monopolar Profile of Mood States (POMS-DD) **Timing of assessments:** 7th day after each of the 4 chemotherapy treatments
RESULTS:	• Cycle 4 comparisons of paroxetine versus placebo: mean (SE) • CES-D: 8.8 (1.11) vs. 12.6 (1.24) $p < 0.1$ • POMS-DD: 1.2 (0.30) vs. 2.2 (0.34) $p < 0.01$ • MAF (question 1): 4.6 (0.38) vs. 5.9 (0.37) p = NS • POMS-FI: 6.0 (0.70) vs. 7.1 (0.79) p = NS • FSCL: 44.6 (2.41) vs. 48.0 (2.62) p = NS
ANALYSIS:	**ITT:** No- 122 were randomized, analysis was done on 94 that completed at least 2 cycles **Post randomization exclusions:** Yes – 28/122 (23%)
ATTRITION:	**Loss to follow-up:** 14/94 (15%) **Withdrawals due to adverse events:** NR except in non-completers **Withdrawals due to lack of efficacy:** NR **Loss to follow-up differential high:** No
ADVERSE EVENTS:	• 11 patients not in the analysis withdrew because of AEs, primarily headache and nausea (paroxetine: 6, placebo: 5); no other AEs were reported
QUALITY RATING:	**Poor**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Roy-Byrne PP, et al.**[220] ***Year:*** **2005** ***Country*****:** US
FUNDING:	NIMH
DESIGN:	***Study design:*** Pooled analysis ***Number of patients:*** 14,875
AIMS OF REVIEW:	To explore differences in minorities response and tolerability to paroxetine
STUDIES INCLUDED IN ANALYSIS	104 placebo controlled paroxetine trials
TIME PERIOD COVERED:	Not reported
CHARACTERISTICS OF INCLUDED STUDIES:	Double blinded, placebo controlled trials of paroxetine at least 6 weeks in length.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adult outpatients with: MDD (7603), anxiety disorders GAD, SAD, OCD, PTSD (6156) and PMDD (1116); 63% were women, 89% white, 4% black, 3% Hispanic, 0.9% Asian, 3% unknown or other, mean age 42.3 years

Authors: Roy-Byrne PP, et al. **Year: 2005**	
CHARACTERISTICS OF INTERVENTIONS:	Paroxetine vs. placebo (104 studies) 10-40 mg/day
MAIN RESULTS:	• Significant treatment by ethno-racial groups for response (p = 0.014) and full response (p = 0.012) • Response rates white- OR 2.1 95% CI 2.0 to 2.3 (p < 0.001), black- OR 2.1 95% CI 1.5 to 3.0 (p < 0.001), Hispanic- OR 1.1 95% CI 0.5 to 2.4 (p = 0.554), Asian- 1.1 95% CI 0.5 to 2.4 (p = .743) • Hispanics and Asians had a substantially lower response rate than white and black • Full response rates white- OR 2.0 95% CI 1.8 to 2.2 (p < 0.001), black- OR 1.6 95% CI 1.1 to 2.4 (p = 0.016), Hispanic- OR 0.9 95% CI 0.6 to 1.5 (p = 0.554), Asian- 2.7 95% CI 1.0 to 2.0 (p = 0.061) • Asians had the highest rate of "full response'' and Hispanics had the lowest
ADVERSE EVENTS:	Insomnia was the only event to show a significance difference due to a higher rate shown in Asians
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	No; analysis of published and unpublished trials in GSK database
STANDARD METHOD OF APPRAISAL OF STUDIES:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Schatzberg et al.**[48] ***Year:*** **2002** ***Country:*** US			
FUNDING:	Organon Pharma			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 255			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Mirtazapine 15-45 mg/d 8 weeks	Paroxetine 20-40 mg/d 8weeks		(There was extension phase to 16 weeks but only included subjects who had favorable response during the first part of the study)
INCLUSION:	Min. age of 65 years; DSM IV criteria for single or recurrent MDD; MMSE score > 25% for age and education; min. score of 18 on HAM-D_{17}			
EXCLUSION:	HAMD decrease > 20% between screening and baseline; untreated or unstable clinically significant medical condition or lab/physical exam abnormality; H/o seizures; recent drug or alcohol abuse or any principal psych condition other than MDD; presence of psychotic features; suicide attempt in current episode; use of MAOI within 2 weeks, or other psychotropics or herbal treatments within 1 week; use of paroxetine or mirtazpine for the current episode; ECT therapy within 6 months; use of treatment for memory deficits; prior intolerance or lack of efficacy to mirtazapine or paroxetine in the past; patients who failed more than one adequate trial of an antidepressant for the current episode			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate or zolpidem for sleep induction; therapy for conditions like DM, hypothyroidism, high blood pressure, chronic respiratory conditions was allowed if they had been receiving for at least 1 month prior to screening visit			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 72 ***Gender*** (% female): Martazapine: 63%, paroxetine: 64% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Schatzberg et al.** ***Year:*** **2002** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D 17, CGI-S, CGI-I ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8
RESULTS:	• Mean Ham-D17 scores significantly lower with mirtazapine at week 1, 2, 3, 6 but no difference at 8 week endpoint • Trend towards higher response and remission rates with mirtazapine but only significant difference at 2 weeks (response) and 6 weeks (remission) • Time to response: mirtazapine mean 26 days, paroxetine 40 days (p = -.016 for Kaplan-Meier plot comparing the two) • No difference in CGI Improvement response
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 26.8%; mirtazapine 22.7%, paroxetine 31.0% ***Withdrawals due to adverse events:*** 20.4%; mirtazapine 14.8 paroxetine 26.2% (p < 0.05) ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Frequency of treatment related adverse events: mirtazapine: 79.7%, paroxetine: 82.5% • Significant differences: dry mouth: mirtazapine 26.6%, paroxetine 10.3%; weight gain: mirtazapine 10.9%, paroxetine 0%; nausea: mirtazapine 6.3%, paroxetine 19.0%
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Schöne W, et al.**[32] ***Year:*** **1993** ***Country:*** Austria and Germany			
FUNDING:	SmithKline, Beecham			
DESIGN:	***Study design:*** Randomized, double-blind trial ***Setting:*** Geriatric outpatients at 6 centers in Austria and Germany ***Sample size:*** 108			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20-40 mg/d 6 weeks	Fluoxetine 20-60 mg/d 6 weeks		
INCLUSION:	Age 65 or more; met DSM-IIR for MDD; HAM-D_{21} score $\geq$ 18 at baseline			
EXCLUSION:	Severe physical illness (not specified further); senile dementia; schizophrenia or organic brain syndrome; known abusers of alcohol; receipt of ECT within prior 3 mos.; MAOI or oral neuroleptics within 14 days; depot neuroleptics with 4 wks.; patients whose baseline HAM-D improved by > 20% or whose score was < 18 after placebo run-in			
OTHER MEDICATIONS/ INTERVENTIONS:	Prohibited psychotropic meds except temazapam for sleep; other allowed nonpsychotropic medications not specifically reported.			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 74, paroxetine: 74.3, fluoxetine: 73.7 ***Gender*** (% female): 87%, paroxetine: 83%, fluoxetine: 90% ***Ethnicity:*** Not reported ***Other population characteristics:*** History of prior depression: paroxetine: 94%, fluoxetine: 88%; duration of present episode > 12 months: paroxetine: 24%, fluoxetine: 27%			

Authors: **Schöne W, et al.** ***Year:*** **1993** ***Country:*** Germany	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D 21, MADRS, CGI ***Timing of assessments:*** Days 7, 21, 42
RESULTS:	• No significant difference in mean changes on HAM-D score • HAM-D responders at week 6 (i.e. reduction > 50% from baseline HAM-D_{21}): paroxetine: 37.5%, fluoxetine: 16% (p = 0.03) MADRS: no significant difference in mean change scores between groups • MADRS responders at week 6 (i.e. reduction > 50% from baseline MADRS): paroxetine 37.5%, fluoxetine 17.5% (p = 0.04)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** Not reported ***Withdrawals due to adverse events:*** 12%; paroxetine: 11.1%, fluoxetine: 13.5% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	No significant differences between paroxetine and fluoxetine on overall incidence of adverse events or of any specific adverse event
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	**Authors: Thase et al.**[214] **Year: 2005** **Country:** Multinational		
FUNDING:	Not reported		
DESIGN:	**Study design:** Pooled data from 8 randomized, double-blind, placebo controlled trials **Setting:** Various **Sample size:** 2045		
INTERVENTION: **Drug:** **Dose:** **Duration:** **Sample size:**	Venlafaxine 75 - 375mg/d 6-12 wks 851	SSRIs (fluoxetine, paroxetine, fluvoxamine) varying 6-12 wks 748	Placebo N/A 6-12 weeks 446
INCLUSION:	18 years or older with DSM-IV diagnosed MDD; HAM-D $\geq$ 20		
EXCLUSION:	Malignancies; history of significant or unstable cardiovascular, renal, endocrine or hepatic diseases, seizure disorders; alcohol or substance abuse; pregnant or nursing; any investigational or anti-psychotic drugs.		
OTHER MEDICATIONS/ INTERVENTIONS:	As required		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes, except within the older group men receiving placebo were younger than those taking anti-depressants and within younger male placebo group CGIS were significantly lower. **Mean age:** 42 **Gender:** 64% female **Ethnicity:** NR		

Authors: Thase et al. **Year: 2005** **Country:** Multinational			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Remission (HAM-D $\leq$ 7) **Timing of assessments:** Study days 7,14,21,28,42,56		
RESULTS:	• Remission rates on venlafaxine therapy were not affected by age or sex. • Poorer SSRI response in the older age group (Wald chi-square = 4.21, df = 1, p = 0.04) • With SSRIs, older women age > 50 had a 28% chance of remission compared to younger women, 36%		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** Cannot tell		
ATTRITION:	Overall	Mirtazapine	Placebo
Loss to follow-up:	NR	NR	NR
Withdrawals due to adverse events:	NR	NR	NR
Withdrawals due to lack of efficacy:	NR	NR	NR
Loss to follow-up differential high:	NR	NR	NR
ADVERSE EVENTS:	NR		
QUALITY RATING:	**Fair**		

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Wagner GJ, et. al.**[221] ***Year:*** **1998** ***Country:*** US			
FUNDING:	National Institute for Mental Health			
DESIGN:	***Study design:*** RCT ***Setting:*** Not reported ***Sample size:*** 118			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Fluoxetine 20-80 mg/d 8 weeks	 Placebo N/A 8 weeks		
INCLUSION:	HIV pos; DSM-IV diagnosis of major depression; under care of HIV physician			
EXCLUSION:	History of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; unstable medical condition; severe cognitive impairment			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** 39 ***Gender*** (% female): 2% ***Ethnicity:*** White: 67%, black: 19%, Latino: 14% ***Other population characteristics:*** All HIV +			

Authors: **Wagner GJ, et. al.** ***Year:*** **1998**	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D, CGI, BSI (Brief Symptom Inventory) ***Timing of assessments:*** Not reported
RESULTS:	• Responders in the fluoxetine group among patients who completed study: white: 84%, black: 50%, Latino:67% • Dosages did not differ significantly comparing whites/blacks ($p < 0.05$) • Responders among patients who completed the placebo group: white: 43%, black: 36%, Latino:80% • In a direct linear regression model ethnicity was not a significant predictor of study completion ($p = 0.08$) • Attrition rate was significantly higher among Latinos ($p < 0.05$), white: 28%, black: 14%, Latino: 52% • When adjusting for covariates HAM-D score was only predictor of attrition
ANALYSIS:	***ITT:*** No ***Post randomization exclusions:*** Not reported
ATTRITION:	***Loss to follow-up:*** white: 38%, black: 14%, Latino: 52% ($p < 0.05$) ***Withdrawals due to adverse events:*** Not reported ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	There was no significant difference in the frequency of adverse events, white: 53%, black: 50%, Latino: 35%
QUALITY RATING:	**Poor**

Evidence Table 11 Subgroups

STUDY:	***Authors :*** **Wagner, et. al.**[100] ***Year:*** **2003** ***Country:*** Multinational			
FUNDING:	Pfizer, Inc.			
DESIGN:	***Study design:*** Pooled analysis of 2 multi-center, double-blind, placebo-controlled trials ***Setting:*** 53 hospital, general practice, academic centers in the US, India, Canada, Costa Rica and Mexico. ***Sample size:*** 376			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-200 mg/d 10 weeks	Placebo N/A 10 weeks		
INCLUSION:	Ages 6-17 years; met DSM-IV criteria for MDD (as determined by Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, present and lifetime version); current episode of at least 6 weeks duration; minimum score on CDRS-R of 45 and CGI of 4			
EXCLUSION:	Current and primary diagnoses of ADHD; conduct disorder; OCD; panic disorder; history of bipolar disorder; current psychotic features; history of psychotic disorder or autistic spectrum disorder; previous suicide attempts or high suicidal or homicidal risk; abnormal screening EKG, labs, vital signs or body weight; pregnancy; prior enrollment in a sertraline study; medical contraindications to SSRI; history of failure on SSRI; no other psychotropic meds for at least 2 weeks (4 weeks for fluoxetine)			
ALLOWED OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate, diphenhydramine as sleep aids			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Not reported ***Gender*** (% female): sertraline: 57.1%, placebo: 44.9% (p = 0.02) ***Ethnicity:*** sertraline: white, 71.4%; Asian, 13.8%; Hispanic, 7.9%; black, 3.7%; other, 3.2% placebo: white, 69.5%; Asian, 12.3%; Hispanic, 10.2%; black, 4.8%; other, 3.2% ***Other population characteristics:*** Comorbid psychiatric diagnosis: 38 %			

Authors: **Wagner et. al.** ***Year:*** **2003** ***Country:*** Multinational	
OUTCOME ASSESSMENT:	***Measures:*** Change in CDRS-R, CDRS-R response $\geq$ 40% change from baseline, CGI-S score, CGI-I score, and CGI-response (score of 1 or 2), MASC, CGAS, PQ-LES-Q ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 6, 8, 10
RESULTS:	• ***Mean CDRS-R change (ITT): sertraline: 22.84, placebo: 20.19 (p = 0.007)*** • ***Mean CDRS-R change (completers): sertraline: 30.24, placebo: 25.83 (p = 0.001)*** • ***CDRS-responder: sertraline: 69%, placebo: 59% (p = 0.05)*** • ***Mean CGI: sertraline: 2.56, placebo: 2.75 (p = 0.009)*** • ***CGI responder: sertraline: 63%, placebo: 53% (p = 0.05)*** • ***Change in CGI-S: sertraline: 1.22, placebo: 1.01 (p = 0.005)***
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 20%; sertraline: 24.4%; placebo: 16.6% ***Withdrawals due to adverse events:*** 5.9%; sertraline: 9%; placebo: 2.7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Adverse events that occurred in at least 5% of sertraline treated patients with an incidence at least twice that of placebo: insomnia (19.8% vs. 8%), diarrhea (15.1% vs. 4.5%), vomiting (9.3% vs. 4.5%), anorexia (10.5% vs. 2.3%), agitation (8.1% vs. 2.3%) • Serious adverse events (based on pre-defined criteria): sertraline: 7, placebo: 6 • Mean change in body weight: sertraline: -0.38 kg, placebo: 0.78 kg (p = 0.001)
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Weihs KL, et al., Doraiswamy PM, et al.**[70, 71] ***Year:*** **2000, 2001** ***Country:*** US			
FUNDING:	Glaxo Wellcome			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 100			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Bupropion SR 100-300 mg/d (Mean daily dose: 197 mg/d) 6 weeks	 Paroxetine 10-40 mg/d (Mean daily dose: 22 mg/d) 6 weeks		
INCLUSION:	60 yrs or older; DSM-IV criteria for major depression; recurrent episode of non-psychotic depression; ≥ 18 on HAM-D-21; duration at least 8 weeks not more than 24 months			
EXCLUSION:	History of seizures; dementia; alcohol or substance abuse; existing suicidal risk; clinically relevant; unstable medical disorder; psychoactive drugs within 1 week or investigational drugs within 4 weeks; taking other drugs known to lower seizure threshold; anorexia or bulimia; previous treatment with buproprion or paroxetine			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** Bupropion sr: 69.2, paroxetine: 71.0 ***Gender*** (% female): Bupropion sr: 54, paroxetine: 60 ***Ethnicity:*** (white%) Bupropion sr: 98, paroxetine: 90 ***Other population characteristics:*** Prior antidepressant use for current episode: buproprion sr: 17%, paroxetine: 12%			

Authors: **Weihs KL, et al., Doraiswamy PM et al.** ***Year:*** **2000, 2001** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures and timing of assessments:*** HAM-D, CGI-S, CGI-I, HAM-A weekly for 6 weeks, Short Form 36 Health Survey (SF-36), Quality of Life Depression Scale (QLDS) at baseline and week 6
RESULTS:	• No significant differences in any outcome measures between the treatment groups (LOCF and observed) • Response rates (≥ 50% reduction in HAM-D) were similar in both groups: bupropion sr: 71%, paroxetine: 77% • CGIS, CGII, and HAMA were all similar at each week of the study • No significant differences in the Quality of Life scales (QLDS, SF-36) between treatment groups at endpoint • Overall significant improvement in QLDS and QOL at day 42 ($p < 0.0001$)
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 16%; bupropion sr: 16.6%, paroxetine: 15.4% ***Withdrawals due to adverse events:*** Bupropion sr: 8.3%, paroxetine: 5.8% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	• Significantly more patients treated with paroxetine reported somnolence (27% vs. 6%; $p < 0.05$), diarrhea (21% vs. 6%; $p < 0.05$), and constipation (15% vs. 4%; $p < 0.05$) • More than 10% in either group reported headache, insomnia, dry mouth, nausea, dizziness, and agitation • Neither group showed clinically significant changes in weight or clinically significant cardiovascular effects
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Whittington CJ, et. al.**[96] ***Year:*** **2004** ***Country:*** UK
FUNDING:	NICE (National Institute for Clinical Excellence)
DESIGN:	***Study design:*** Systematic review, SSRI versus placebo ***Number of patients:*** 2145
AIMS OF REVIEW:	To evaluate risk versus benefit of SSRI's when used to treat childhood depression
STUDIES INCLUDED IN META-ANALYSIS	Emslie GJ et. al., 1997, Emslie GJ et. al., 2002, Keller MB et. al., 2001, Wagner, KD et. al., 2003. Also unpublished results included in a report by the Committee on Safety of Medicines (UK)
TIME PERIOD COVERED:	All studies up to 2003
CHARACTERISTICS OF INCLUDED STUDIES:	Patients randomized to either an SSRI or placebo
CHARACTERISTICS OF INCLUDED POPULATIONS:	Included trials had patients aged 5-18 years old; no other population information given

Authors: **Whittington CJ, et. al.** ***Year:*** **2004** ***Country:*** UK	
CHARACTERISTICS OF INCLUDED IINTERVENTIONS:	Fluoxetine vs. placebo (2 trials); paroxetine vs. placebo (3 trials); sertraline vs. placebo (2 trials); citalopram vs. placebo (1 trial); venlafaxine vs. placebo (3 trials)
MAIN RESULTS:	• Both published and unpublished data demonstrated fluoxetine has a favorable risk-benefit profile • Published and unpublished data combined on paroxetine demonstrated it does not improve depressive symptoms and has little effect on response • Unpublished data on sertraline in children indicate it is not as effective as reported in published trials • One unpublished study of citalopram a negative risk-benefit profile • Combined published and unpublished data of venlafaxine suggested a negative risk-benefit profile
ADVERSE EVENTS:	Paroxetine, sertraline, citalopram, and venlafaxine all indicated an increased risk of adverse events
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Fair**

Evidence Table 11 Subgroups

STUDY:	***Authors:*** **Williams JW, et. al.**[91] ***Year:*** **2000** ***Country:*** US			
FUNDING:	Hartford Foundation, MacArthur Foundation, Smith Kline Beecham supplied meds and placebo, VA (career award to lead author)			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (Community, VA, and academic primary care clinics) ***Sample size:*** 415			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 10-40 mg/d 11 weeks	Placebo N/A 11 weeks	Behavior Therapy N/A 11 weeks	
INCLUSION:	Age 60 and older; met DSM II-R criteria for dysthymia or minor depression and score 10 or higher on HAM-D-17; symptoms for at least 4 weeks with 3-4 symptoms			
EXCLUSION:	Major depression; psychosis; schizophrenia or schizoaffective disorder; bipolar disorder; alcohol or other substance abuse within the past 6 months; borderline or antisocial personality disorder; serious suicidal risk; moderate or severe cognitive impairment (MMSE $\leq$ 23); medical illness with prognosis $\leq$ 6 months to live; patients in current treatment excluded unless willing to discontinue and dose $\leq$ 50 mg of amitriptylline			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 71 ***Ethnicity:*** (% white) Paroxetine: 82.5%, placebo: 75.7% ***Gender*** (% female): Paroxetine: 39%, placebo: 45% ***Other population characteristics:*** Mean of 3.4 medical conditions per patient			

Authors: **Williams JW, et al.** ***Year:*** **2000** ***Country:*** US	
OUTCOME ASSESSMENT:	***Measures:*** Hopkins Symptom Checklist Depression Scale (HSCL-D-20), HDRS, and functional status, by the Medical Outcomes Study Short-Form 36 (SF-36) physical and mental components ***Timing of assessments:*** Not reported
RESULTS:	• Mean (SE) decrease in HSCL-D-20: Paroxetine: 0.61 (p = 0.05) Placebo: 0.40 (p = 0.05) Behavior Therapy 0.52 (p = 0.05) (p = 0.004 for paroxetine vs. placebo) • Paroxetine only statistically and clinically significantly better than placebo for subjects with dysthymia and high baseline mental health function. • HAM-D results not reported for the ITT population
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** 25.1% (all three arms, including behavioral tx) ***Withdrawals due to adverse events:*** Paroxetine 8.8%, placebo: 5.7% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Appendix A. Search Strategy

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

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

#5 Search #1 OR #4 = 11409

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

#7 Search #5 AND #6 = 4565

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

Adverse Events

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

#11 Search #10 AND #7 = 89

Longitudinal Studies

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

#15 Search #14 AND #7 = 185

Drug Interactions

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

#21 Search #7 AND #20 = 292

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

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

PUBMED = 1480
Cochrane = 105 records = 5 new records

EMBASE = 227 records = 14 new records

International Pharmaceutical Abstracts = 78 records = 24 new records

Psychological Abstracts = 55 records = 7 new records

Total unduplicated records across questions and databases = 1530

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

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

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

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

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

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

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

#7 Search #2 AND #6 = 86

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

15 Search #14 AND #2 = 63

Total unduplicated records for children = 295.

Appendix B: Quality Assessment

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

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

Not reported
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?
2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)
3. Were the events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there non-biased and accurate ascertainment of events (independent ascertainers; validation of ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?
2. How similar is the population to the population to whom the intervention would be applied?
3. How many patients were recruited?
4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or

inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Excluded Studies

Study	Design	Sample size	Intervention	Reason for exclusion
Major depressive disorder				
Aguglia et al., 1993[237]	RCT	108	Sertraline vs. fluoxetine	High loss to follow-up; High differential loss to follow-up
Davidson et al., 2002[238]	Pooled analysis	1097	Venlafaxine vs. fluoxetine	No systematic literature search
Feiger et al., 2003[239]	Pooled analysis	1,088	Sertraline vs. fluoxetine	No systematic literature search
Goldstein et al., 2004[240]	RCT	353	Duloxetine vs. Paroxetine	High loss to follow-up
Gorman et al., 2002[241]	Meta-analysis	1,321	Escitalopram vs. citalopram	No systematic literature search
Llorca et al., 2005[242]	Pooled analysis	506	Escitalopram vs. citalopram	No systematic literature search
Oslin et al., 2003[218]	RCT	52	Venlafaxine vs. sertraline	High loss to follow-up
Schmitz et al., 2001[231]	RCT	68	Fluoxetine vs. placebo	High loss to follow-up
Shelton et al. 2005[243]	Pooled analysis	1,391	Venlafaxine vs. Fluoxetine and paroxetien	No systematic literature search
Stahl et al., 2000[244]	RCT	323	Citalopram vs. sertraline vs. placebo	High loss to follow-up
Stahl et al., 2002[245]	Pooled analysis	1,622	Venlafaxine fluoxetine paroxetine placebo	No systematic literature search
Thase et al., 2001[246]	Pooled analysis	2,117	Venlafaxine vs. SSRI vs. placebo	No systematic literature search
Thase et al, 2005[247]	Meta-analysis	1,975	Bupropion vs. SSRI	No systematic literature search
Wade et al., 2003[248]	RCT	197	Mirtazapine vs. paroxetine	High loss to follow-up
MDD-Ped				
DeVane et al., 1996[249]	Meta-analysis	61	Fluoxetine vs. placebo	No systematic literature search
Emslie et al., 1997, 1998[102, 250]	RCT	96	Fluoxetine vs. placebo	Loss to follow-up differential > 15 percentage points
Emslie et al., 2002[103]	RCT	219	Fluoxetine vs. placebo	Loss to follow-up differential > 15 percentage points
Generalized Anxiety Disorder				
Bielski et al., 2005[105]	RCT	123	Escitalopram vs. paroxetine	High loss to follow-up
Kelsey et al.,	Pooled	2000	Venlafaxine vs.	No systematic literature

2000[112]	analysis		placebo	search
OCD				
Cox et al., 1993[251]	Meta-analysis	Not reported	Clomipramine vs. fluoxetine vs. behavior therapy	Lack of information on included studies
Greist et al., 1995[252]	Meta-analysis	1530	Clomipramine vs. fluoxetine vs. fluvoxamine vs. sertraline	No systematic literature search
Kobak et al., 1998[253]	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[254]	RCT	148	Fluvoxamine vs. placebo	High loss to follow-up
PTSD				
Chung et al. 2004[255]	Open-label trial	113	Mirtazapine vs. Sertraline	Significant differences in patient characteristics at baseline
Davidson et al. 1998[256]	Open-label trial	15	Fluovoxamine	Open-label, high loss to follow-up
Davidson et al., 1998[257]	Open-label trial	17	Nefazodone	Open-label, high loss to follow-up
De Boer et al., 1992[258]	Open-label trial	24	Fluovoxamine	Open-label, high loss to follow-up
Martenyi et al., 2002[259, 260]	RCT	301	Fluoxetine vs. placebo	High loss to follow-up
Smajkic et al., 2001[261]	RCT	40	Sertraline vs. paroxetine vs. venlafaxine	Small sample size, no ITT analysis
Tucker et al., 2001[262]	RCT	323	Paroxetine vs. placebo	High loss to follow-up
Social Anxiety Disorder				
Allgulander et al., 2001[116]	RCT	96	Paroxetine vs. placebo	No ITT analysis, lack of statistical comparisons
PMDD				
Diegoli et al., 1998[263]	RCT	120	Pyridoxine, alprazolam, fluoxetine, propanolol	Important information about study methodology not reported
Carr et al.,2002[264]	Systematic review	NR	fluoxetine	No critical appraisal of study quality; no description of review process
Subgroups				
Beasley et al., 1991[265, 266] and Tollefson et al.,	Meta-analysis	3,065	Fluoxetine vs. placebo	No systematic literature search

1994[267]				
Gülseren et al. 2005[268]	RCT	25	Fluoxetine vs. paroxetine	High rate of post-randomization exclusions
Roy-Byrne et al. 2000[269]	RCT	64	Nefazodone vs. placebo	High loss to follow-up
Wagner et al., 1998[221]	RCT	118	Fluoxetine vs. placebo	No ITT analysis
Adverse Events				
Croft et al., 2002[202]	RCT	432	Buprprion vs. placebo	High loss to follow-up
Demyttenaere et al. 2005[270]	RCT	85	Escitalopram vs. placebo	No ITT analysis
Ferguson et al., 2001[271]	RCT	72	Nefazodone vs. sertraline	Selection bias
Letizia et al., 1996[272]	Systematic review	3,828	Fluvoxamine vs. TCA vs. placebo	Search strategy not reported; no critical appraisal of study quality
Wernicke et al., 1997[224]	Meta-analysis	4016	Fluoxetine, placebo ,TCA	No systematic literature search

Appendix D. Pharmacokinetic Properties and Drug Interactions

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

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

*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]

[a]Decrease in second generation antidepressant plasma levels
[b]Increase in second generation antidepressant plasma levels
[c] Decrease in plasma levels for the interacting drug or its active metabolite
[d] Increase in plasma levels for the interacting drug or its active metabolite

(1) Citalopram package insert
(2) Escitalopram package insert
(3) Fluoxetine package insert

Clinically Significant Drug Interactions: 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
(10) Nefazodone

Appendix E. Placebo-controlled Trials (not included)

1. Ackerman DL, Greenland S, Bystritsky A, Small GW. Characteristics of fluoxetine versus placebo responders in a randomized trial of geriatric depression. Psychopharmacol Bull 1997;33(4):707-14.

2. Agosti V, McGrath PJ. Comparison of the effects of fluoxetine, imipramine and placebo on personality in atypical depression. J Affect Disord 2002;71(1-3):113-20.

3. Albert R, Ebert D. Full efficacy of SSRI treatment in refractory dysthymia is achieved only after 16 weeks. J Clin Psychiatry 1996;57(4):176.

4. Allgulander C. Paroxetine in social anxiety disorder: a randomized placebo-controlled study. Acta Psychiatr Scand 1999;100(3):193-8.

5. Allgulander C, Hackett D, Salinas E. Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. Br J Psychiatry 2001;179:15-22.

6. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. Stroke 1994;25(6):1099-104.

7. Appleby L, Warner R, Whitton A, Faragher B. A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. BMJ 1997;314(7085):932-6.

8. Ballenger JC. Remission rates in patients with anxiety disorders treated with paroxetine. J Clin Psychiatry 2004;65(12):1696-707.

9. Ballenger JC, Wheadon DE, Steiner M, Bushnell W, Gergel IP. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry 1998;155(1):36-42.

10. Barak Y, Kimhi R, Weizman R. Is selectivity for serotonin uptake associated with a reduced emergence of manic episodes in depressed patients? Int Clin Psychopharmacol 2000;15(1):53-6.

11. Beasley CMJ, Masica DN, Heiligenstein JH, Wheadon DE, Zerbe RL. Possible monoamine oxidase inhibitor-serotonin uptake inhibitor interaction: fluoxetine clinical data and preclinical findings. J Clin Psychopharmacol 1993;13(5):312-20.

12. Beasley CMJ, Potvin JH. Fluoxetine: activating and sedating effects. Int Clin Psychopharmacol 1993;8(4):271-5.

13. Beasley CMJ, Potvin JH, Masica DN, Wheadon DE, Dornseif BE, Genduso LA. Fluoxetine: no association with suicidality in obsessive-compulsive disorder. J Affect Disord 1992;24(1):1-10.

14. Beasley CMJ, Sayler ME, Weiss AM, Potvin JH. Fluoxetine: activating and sedating effects at multiple fixed doses. J Clin Psychopharmacol 1992;12(5):328-33.

15. Blumenfield M, Levy NB, Spinowitz B, Charytan C, Beasley CMJ, Dubey AK, et al. Fluoxetine in depressed patients on dialysis. Int J Psychiatry Med 1997;27(1):71-80.

16. Boyer P, Mahe V, Hackett D. Social adjustment in generalised anxiety disorder: a longterm placebocontrolled study of venlafaxine extended release. Eur Psychiatry 2004;19(5):272-9.

17. Brannan SK, Mallinckrodt CH, Brown EB, Wohlreich MM, Watkin JG, Schatzberg AF. Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. J Psychiatr Res 2005;39(1):43-53.

18. Brannan SK, Mallinckrodt CH, Detke MJ, Watkin JG, Tollefson GD. Onset of action for duloxetine 60 mg once daily: double-blind, placebo-controlled studies. J Psychiatr Res 2005;39(2):161-72.

19. Burrows AB, Salzman C, Satlin A, Noble K, Pollock BG, Gersh T. A randomized, placebo-controlled trial of paroxetine in nursing home residents with non-major depression. Depress Anxiety 2002;15(3):102-10.

20. Byerley WF, Reimherr FW, Wood DR, Grosser BI. Fluoxetine, a selective serotonin uptake inhibitor, for the treatment of outpatients with major depression. J Clin Psychopharmacol 1988;8(2):112-5.

21. Chouinard G, Goodman W, Greist J, Jenike M, Rasmussen S, White K, et al. Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive disorder. Psychopharmacol Bull 1990;26(3):279-84.

22. Claghorn J. A double-blind comparison of paroxetine and placebo in the treatment of depressed outpatients. Int Clin Psychopharmacol 1992;6 Suppl 4:25-30.

23. Claghorn JL. The safety and efficacy of paroxetine compared with placebo in a double-blind trial of depressed outpatients. J Clin Psychiatry 1992;53 Suppl:33-5.

24. Claghorn JL, Earl CQ, Walczak DD, Stoner KA, Wong LF, Kanter D, et al. Fluvoxamine maleate in the treatment of depression: a single-center, double-blind, placebo-controlled comparison with imipramine in outpatients. J Clin Psychopharmacol 1996;16(2):113-20.

25. Claghorn JL, Kiev A, Rickels K, Smith WT, Dunbar GC. Paroxetine versus placebo: a double-blind comparison in depressed patients. J Clin Psychiatry 1992;53(12):434-8.

26. Cohen LS, Miner C, Brown E, Freeman EW, Halbreich U, Sundell K, et al. Premenstrual daily fluoxetinefor premenstrual dysphoric disorder: a placebo-controlled, clinical trial using computerized diaries. Obstet Gynecol 2002;100(3):435-444.

27. Cohen LS, Soares CN, Yonkers KA, Bellew KM, Bridges IM, Steiner M. Paroxetine controlled release for premenstrual dysphoric disorder: a double-blind, placebo-controlled trial. Psychosom Med 2004;66(5):707-13.

28. Cohn CK, Robinson DS, Roberts DL, Schwiderski UE, O'Brien K, Ieni JR. Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. J Clin Psychiatry 1996;57 Suppl 2:15-8.

29. Cohn JB, Crowder JE, Wilcox CS, Ryan PJ. A placebo- and imipramine-controlled study of paroxetine. Psychopharmacol Bull 1990;26(2):185-9.

30. Cohn JB, Wilcox C. A comparison of fluoxetine, imipramine, and placebo in patients with major depressive disorder. J Clin Psychiatry 1985;46(3 Pt 2):26-31.

31. Cohn JB, Wilcox CS. Paroxetine in major depression: a double-blind trial with imipramine and placebo. J of Clinical Psychiatry 1992;53 Suppl:52-6.

32. Corrigan MH, Denahan AQ, Wright CE, Ragual RJ, Evans DL. Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress Anxiety 2000;11(2):58-65.

33. Cunningham LA. Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. Venlafaxine XR 208 Study Group. Ann Clin Psychiatry 1997;9(3):157-64.

34. Davidson JR, DuPont RL, Hedges D, Haskins JT. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry 1999;60(8):528-35.

35. Davidson JR, Landerman LR, Farfel GM, Clary CM. Characterizing the effects of sertraline in post-traumatic stress disorder. Psychol Med 2002;32(4):661-70.

36. Davidson JR, Weisler RH, Butterfield MI, Casat CD, Connor KM, Barnett S, et al. Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. Biol Psychiatry 2003;53(2):188-91.

37. Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry 2002;63(4):308-15.

38. Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res 2002;36(6):383-90.

39. Doogan DP, Caillard V. Sertraline in the prevention of depression. Br J Psychiatry 1992;160:217-22.

40. Doogan DP, Langdon CJ. A double-blind, placebo-controlled comparison of sertraline and dothiepin in the treatment of major depression in general practice. Int Clin Psychopharmacol 1994;9(2):95-100.

41. Dubini A, Bosc M, Polin V. Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. J Psychopharmacol 1997;11(4 Suppl):S17-23.

42. Dunbar GC, Claghorn JL, Kiev A, Rickels K, Smith WT. A comparison of paroxetine and placebo in depressed outpatients. Acta Psychiatr Scand 1993;87(5):302-5.

43. Dunbar GC, Cohn JB, Fabre LF, Feighner JP, Fieve RR, Mendels J, et al. A comparison of paroxetine, imipramine and placebo in depressed out-patients. Br J Psychiatry 1991;159:394-8.

44. Dunlop SR, Dornseif BE, Wernicke JF, Potvin JH. Pattern analysis shows beneficial effect of fluoxetine treatment in mild depression. Psychopharmacol Bull 1990;26(2):173-80.

45. Dunner DL, Goldstein DJ, Mallinckrodt C, Lu Y, Detke MJ. Duloxetine in treatment of anxiety symptoms associated with depression. Depress Anxiety 2003;18(2):53-61.

46. Elliott AJ, Russo J, Roy-Byrne PP. The effect of changes in depression on health related quality of life (HRQoL) in HIV infection. Gen Hosp Psychiatry 2002;24(1):43-7.

47. Entsuah AR, Rudolph RL, Chitra R. Effectiveness of venlafaxine treatment in a broad spectrum of depressed patients: a meta-analysis. Psychopharmacol Bull 1995;31(4):759-66.

48. Entsuah AR, Rudolph RL, Hackett D, Miska S. Efficacy of venlafaxine and placebo during long-term treatment of depression: a pooled analysis of relapse rates. Int Clin Psychopharmacol 1996;11(2):137-45.

49. Entsuah R, Derivan A, Kikta D. Early onset of antidepressant action of venlafaxine: pattern analysis in intent-to-treat patients. Clin Ther 1998;20(3):517-26.

50. Eriksson E, Hedberg MA, Andersch B, Sundblad C. The serotonin reuptake inhibitor paroxetin is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. Neuropsychopharm 1995;12(2):167-176.

51. Evans M, Hammond M, Wilson K, Lye M, Copeland J. Placebo-controlled treatment trial of depression in elderly physically ill patients. Int J Geriatr Psychiatry 1997;12(8):817-24.

52. Fabre L, Birkhimer LJ, Zaborny BA, Wong LF, Kapik BM. Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. Int Clin Psychopharmacol 1996;11(2):119-27.

53. Fabre LF. A 6-week, double-blind trial of paroxetine, imipramine, and placebo in depressed outpatients. J Clin Psychiatry 1992;53 Suppl:40-3.

54. Fabre LF, Abuzzahab FS, Amin M, Claghorn JL, Mendels J, Petrie WM, et al. Sertraline safety and efficacy in major depression: a double-blind fixed-dose comparison with placebo. Biol Psychiatry 1995;38(9):592-602.

55. Fabre LF, Brodie HK, Garver D, Zung WW. A multicenter evaluation of bupropion versus placebo in hospitalized depressed patients. J Clin Psychiatry 1983;44(5 Pt 2):88-94.

56. Fava M, Mallinckrodt CH, Detke MJ, Watkin JG, Wohlreich MM. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates? J Clin Psychiatry 2004;65(4):521-30.

57. Fava M, Mulroy R, Alpert J, Nierenberg AA, Rosenbaum JF. Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. Am J Psychiatry 1997;154(12):1760-2.

58. Fava M, Schmidt ME, Zhang S, Gonzales J, Raute NJ, Judge R. Treatment approaches to major depressive disorder relapse. Part 2: reinitiation of antidepressant treatment. Psychother Psychosom 2002;71(4):195-9.

59. Fawcett J, Barkin RL. A meta-analysis of eight randomized, double-blind, controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety. J Clin Psychiatry 1998;59(3):123-7.

60. Feiger AD, Bielski RJ, Bremner J, Heiser JF, Trivedi M, Wilcox CS, et al. Double-blind, placebo-substitution study of nefazodone in the prevention of relapse during continuation treatment of outpatients with major depression. Int Clin Psychopharmacol 1999;14(1):19-28.

61. Feighner JP. A double-blind comparison of paroxetine, imipramine and placebo in depressed outpatients. Int Clin Psychopharmacol 1992;6 Suppl 4:31-5.

62. Feighner JP, Boyer WF. Paroxetine in the treatment of depression: a comparison with imipramine and placebo. J Clin Psychiatry 1992;53 Suppl:44-7.

63. Feighner JP, Boyer WF, Merideth CH, Hendrickson GG. A double-blind comparison of fluoxetine, imipramine and placebo in outpatients with major depression. Int Clin Psychopharmacol 1989;4(2):127-34.

64. Feighner JP, Cohn JB, Fabre LFJ, Fieve RR, Mendels J, Shrivastava RK, et al. A study comparing paroxetine placebo and imipramine in depressed patients. J Affect Disord 1993;28(2):71-9.

65. Feighner JP, Entsuah AR, McPherson MK. Efficacy of once-daily venlafaxine extended release (XR) for symptoms of anxiety in depressed outpatients. J Affect Disord 1998;47(1-3):55-62.

66. Feighner JP, Overo K. Multicenter, placebo-controlled, fixed-dose study of citalopram in moderate-to-severe depression. J Clin Psychiatry 1999;60(12):824-30.

67. Feighner JP, Pambakian R, Fowler RC, Boyer WF, D'Amico MF. A comparison of nefazodone imipramine, and placebo in patients with moderate to severe depression. Psychopharmacol Bull 1989;25(2):219-21.

68. Ferguson JM, Wesnes KA, Schwartz GE. Reboxetine versus paroxetine versus placebo: effects on cognitive functioning in depressed patients. Int Clin Psychopharmacol 2003;18(1):9-14.

69. Fieve RR, Goodnick PJ, Peselow E, Schlegel A. Fluoxetine response: endpoint vs pattern analysis. Int Clin Psychopharmacol 1986;1(4):320-3.

70. Fisch C, Knoebel B. Electrocardiographic findings in sertraline depression trials. Drug Investigation (New Zealand) 1992;4:305-312.

71. Flament MF, Bisserbe JC. Pharmacologic treatment of obsessive-compulsive disorder: comparative studies. J Clin Psychiatry 1997;58 Suppl 12:18-22.

72. Fontaine R, Ontiveros A, Elie R, Kensler TT, Roberts DL, Kaplita S, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry 1994;55:234-41.

73. Freeman EW, Rickels K, Sondheimer SJ, Polansky M. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: A randomized controlled trial. Archives-of-General-Psychiatry 1999;56(10):932-939.

74. Gelenberg AJ, Lydiard RB, Rudolph RL, Aguiar L, Haskins JT, Salinas E. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: A 6-month randomized controlled trial. JAMA 2000;283(23):3082-8.

75. Gelenberg AJ, Trivedi MH, Rush AJ, Thase ME, Howland R, Klein DN, et al. Randomized, placebo-controlled trial of nefazodone maintenance treatment in preventing recurrence in chronic depression. Biol Psychiatry 2003;54(8):806-17.

76. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JTJ, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002;288(6):701-9.

77. Golden RN, Nemeroff CB, McSorley P, Pitts CD, Dube EM. Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. 2002;63(7):577-84.

78. Goldstein DJ, Hamilton SH, Masica DN, Beasley CMJ. Fluoxetine in medically stable, depressed geriatric patients: effects on weight. J Clin Psychopharmacol 1997;17(5):365-9.

79. Goldstein DJ, Lu Y, Detke MJ, Hudson J, Iyengar S, Demitrack MA. Effects of duloxetine on painful physical symptoms associated with depression. Psychosomatics 2004;45(1):17-28.

80. Goodman WK, Kozak MJ, Liebowitz M, White KL. Treatment of obsessive-compulsive disorder with fluvoxamine: a multicentre, double-blind, placebo-controlled trial. Int Clin Psychopharmacol 1996;11(1):21-9.

81. Goodman WK, Price LH, Rasmussen SA, Delgado PL, Heninger GR, Charney DS. Efficacy of fluvoxamine in obsessive-compulsive disorder. A double-blind comparison with placebo. Arch Gen Psychiatry 1989;46(1):36-44.

82. Goodnick PJ, Fieve RR, Peselow ED, Barouche F, Schlegel A. Double-blind treatment of major depression with fluoxetine: use of pattern analysis and relation of HAM-D score to CGI change. Psychopharmacol Bull 1987;23(1):162-3.

83. Green TD, Reynolds CFr, Mulsant BH, Pollock BG, Miller MD, Houck PR, et al. Accelerating antidepressant response in geriatric depression: a post hoc comparison of combined sleep deprivation and paroxetine versus monotherapy with paroxetine, nortriptyline, or placebo. J Geriatr Psychiatry Neurol 1999;12(2):67-71.

84. Greenberg RP, Bornstein RF, Zborowski MJ, Fisher S, Greenberg MD. A meta-analysis of fluoxetine outcome in the treatment of depression. J Nerv Ment Dis 1994;182(10):547-51.

85. Greist J, Chouinard G, DuBoff E, Halaris A, Kim SW, Koran L, et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry 1995;52(4):289-95.

86. Greist JH, Jefferson JW, Kobak KA, Chouinard G, DuBoff E, Halaris A, et al. A 1 year double-blind placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol 1995;10(2):57-65.

87. Greist JH, Jenike MA, Robinson D, Rasmussen SA. Efficacy of fluvoxamine in obsessive-compulsive disorder: results of multicentre, double blind, placebo-controlled trial. Eur J Clin Res 1995;7:195-204.

88. Halaris AE, Stern WC, Van Wyck Fleet J, Reno RM. Evaluation of the safety and efficacy of bupropion in depression. J Clin Psychiatry 1983;44(5 Pt 2):101-3.

89. Halbreich U, Smoller JW. Intermittent luteal phase sertraline treatment of dysphoric premenstrual syndrome. J Clin Psychiatry 1997;58(9):399-402.

90. Halikas JA. Org 3770 (Mirtazapine) versus Trazodone: a placebo controlled trial in depressed elderly patients. Hum Psychopharmacol 1995;10:S125-S133.

91. Heiligenstein JH, Tollefson GD, Faries DE. A double-blind trial of fluoxetine, 20 mg, and placebo in out-patients with DSM-III-R major depression and melancholia. Int Clin Psychopharmacol 1993;8(4):247-51.

92. Heiligenstein JH, Tollefson GD, Faries DE. Response patterns of depressed outpatients with and without melancholia: a double-blind, placebo-controlled trial of fluoxetine versus placebo. J Affect Disord 1994;30(3):163-73.

93. Heiligenstein JH, Ware JEJ, Beusterien KM, Roback PJ, Andrejasich C, Tollefson GD. Acute effects of fluoxetine versus placebo on functional health and well-being in late-life depression. Int Psychogeriatr 1995;7 Suppl:125-37.

94. Hellerstein DJ, Yanowitch P, Rosenthal J, Samstag LW, Maurer M, Kasch K, et al. A randomized double-blind study of fluoxetine versus placebo in the treatment of dysthymia. Am J Psychiatry 1993;150(8):1169-75.

95. Hertzberg MA, Feldman ME, Beckham JC, Kudler HS, Davidson JR. Lack of efficacy for fluoxetine in PTSD: a placebo controlled trial in combat veterans. Ann Clin Psychiatry 2000;12(2):101-5.

96. Hochstrasser B, Isaksen PM, Koponen H, Lauritzen L, Mahnert FA, Rouillon F, et al. Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. Br J Psychiatry 2001;178:304-10.

97. Hollander E, Allen A, Steiner M, Wheadon DE, Oakes R, Burnham DB. Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. J Clin Psychiatry 2003;64(9):1113-1121.

98. Hollander E, Koran LM, Goodman WK, Greist JH, Ninan PT, Yang H, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. J Clin Psychiatry 2003;64(6):640-7.

99. Jamerson BD, Krishnan KR, Roberts J, Krishen A, Modell JG. Effect of bupropion SR on specific symptom clusters of depression: analysis of the 31-item Hamilton Rating Scale for depression. Psychopharmacol Bull 2003;37(2):67-78.

100. Jenike MA, Baer L, Minichiello WE, Rauch SL, Buttolph ML. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. Am J Psychiatry 1997;154(9):1261-4.

101. Jenike MA, Baer L, Summergrad P, Minichiello WE, Holland A, Seymour R. Sertraline in obsessive-compulsive disorder: a double-blind comparison with placebo. Am J Psychiatry 1990;147(7):923-28.

102. Jenike MA, Hyman S, Baer L, Holland A, Minichiello WE, Buttolph L, et al. A controlled trial of fluvoxamine in obsessive-compulsive disorder: implications for a serotonergic theory. Am J Psychiatry 1990;147(9):1209-15.

103. Jermain DM, Preece CK, Sykes RL, Kuehl TJ, Sulak PJ. Luteal phase sertraline treatment for premenstrual dysphoric disorder. Results of a double-blind, placebo-controlled, crossover study. Arch Fam Med 1999;8(4):328-32.

104. Judge R, Plewes JM, Kumar V, Koke SC, Kopp JB. Changes in energy during treatment of depression: an analysis of fluoxetine in double-blind, placebo-controlled trials. J Clin Psychopharmacol 2000;20(6):666-72.

105. Kamijima K, Murasaki M, Asai M, Higuchi T, Nakajima T, Taga C, et al. Paroxetine in the treatment of obsessive-compulsive disorder: randomized, double-blind, placebo-controlled study in Japanese patients. Psychiatry Clin Neurosci 2004;58(4):427-33.

106. Kampman M, Keijsers GP, Hoogduin CA, Hendriks GJ. A randomized, double-blind, placebo-controlled study of the effects of adjunctive paroxetine in panic disorder patients unsuccessfully treated with cognitive-behavioral therapy alone. J Clin Psychiatry 2002;63(9):772-7.

107. Kane JM, Cole K, Sarantakos S, Howard A, Borenstein M. Safety and efficacy of bupropion in elderly patients: preliminary observations. J Clin Psychiatry 1983;44(5 Pt 2):134-6.

108. Kasper S, Moller HJ, Montgomery SA, Zondag E. Antidepressant efficacy in relation to item analysis and severity of depression: a placebo-controlled trial of fluvoxamine versus imipramine. Int Clin Psychopharmacol 1995;9 Suppl 4:3-12.

109. Katz IR, Reynolds CFr, Alexopoulos GS, Hackett D. Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: pooled analysis of five randomized placebo-controlled clinical trials. J Am Geriatr Soc 2002;50(1):18-25.

110. Katzelnick DJ, Kobak KA, Greist JH, Jefferson JW, Mantle JM, Serlin RC. Sertraline for social phobia: a double-blind, placebo-controlled crossover study. Am J Psychiatry 1995;152(9):1368-71.

111. Keller MB, Kocsis JH, Thase ME, Gelenberg AJ, Rush AJ, Koran L, et al. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. JAMA 1998;280(19):1665-72.

112. Kerr JS, Fairweather DB, Hindmarch I. Effects of fluoxetine on psychomotor performance, cognitive function and sleep in depressed patients. Int Clin Psychopharmacol 1993;8(4):341-3.

113. Khan A, Upton GV, Rudolph RL, Entsuah R, Leventer SM. The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-

response study. Venlafaxine Investigator Study Group. J Clin Psychopharmacol 1998;18(1):19-25.

114. Klysner R, Bent-Hansen J, Hansen HL, Lunde M, Pleidrup E, Poulsen DL, et al. Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. Br J Psychiatry 2002;181:29-35.

115. Kocsis JH, Schatzberg A, Rush AJ, Klein DN, Howland R, Gniwesch L, et al. Psychosocial outcomes following long-term, double-blind treatment of chronic depression with sertraline vs placebo. Arch Gen Psychiatry 2002;59(8):723-8.

116. Koran LM, Hackett E, Rubin A, Wolkow R, Robinson D. Efficacy of sertraline in the long-term treatment of obsessive-compulsive disorder. Am J Psychiatry 2002;159(1):88-95.

117. Kronig MH, Apter J, Asnis G, Bystritsky A, Curtis G, Ferguson J, et al. Placebo-controlled, multicenter study of sertraline treatment for obsessive-compulsive disorder. J Clin Psychopharmacol 1999;19(2):172-6.

118. Lam RW, Gorman CP, Michalon M, Steiner M, Levitt AJ, Corral MR, et al. Multicenter, placebo-controlled study of fluoxetine in seasonal affective disorder. Am J Psychiatry 1995;152(12):1765-70.

119. Lapierre YD. Controlling acute episodes of depression. Int Clin Psychopharmacol 1991;6 Suppl 2:23-35.

120. Lecrubier Y, Bakker A, Dunbar G, Judge R. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. Collaborative Paroxetine Panic Study Investigators. Acta Psychiatr Scand 1997;95(2):145-52.

121. Lecrubier Y, Judge R. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Collaborative Paroxetine Panic Study Investigators. Acta Psychiatr Scand 1997;95(2):153-60.

122. Leinonen E, Lepola U, Koponen H, Turtonen J, Wade A, Lehto H. Citalopram controls phobic symptoms in patients with panic disorder: randomized controlled trial. J Psychiatry Neurosci 2000;25(1):25-32.

123. Lenderking WR, Tennen H, Nackley JF, Hale MS, Turner RR, Testa MA. The effects of venlafaxine on social activity level in depressed outpatients. J Clin Psychiatry 1999;60(3):157-63.

124. Lenox-Smith AJ, Reynolds A. A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care. Br J Gen Pract 2003;53(495):772-7.

125. Lepine JP, Caillard V, Bisserbe JC, Troy S, Hotton JM, Boyer P. A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. Am J Psychiatry 2004;161(5):836-42.

126. Lepola UM, Wade AG, Leinonen EV, Koponen HJ, Frazer J, Sjodin I, et al. A controlled, prospective, 1-year trial of citalopram in the treatment of panic disorder. J Clin Psychiatry 1998;59(10):528-34.

127. Levitan RD, Shen JH, Jindal R, Driver HS, Kennedy SH, Shapiro CM. Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects. J Psychiatry Neurosci 2000;25(4):337-46.

128. Liebowitz MR, Mangano RM, Bradwejn J, Asnis G. A randomized controlled trial of venlafaxine extended release in generalized social anxiety disorder. J Clin Psychiatry 2005;66(2):238-47.

129. Liebowitz MR, Stein MB, Tancer M, Carpenter D, Oakes R, Pitts CD. A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. J Clin Psychiatry 2002;63(1):66-74.

130. Lineberry CG, Johnston JA, Raymond RN, Samara B, Feighner JP, Harto NE, et al. A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. J Clin Psychiatry 1990;51(5):194-9.

131. Londborg PD, Wolkow R, Smith WT, DuBoff E, England D, Ferguson J, et al. Sertraline in the treatment of panic disorder. A multi-site, double-blind, placebo-controlled, fixed-dose investigation. Br J Psychiatry 1998;173:54-60.

132. Lydiard RB, Laird LK, Morton WAJ, Steele TE, Kellner C, Laraia MT, et al. Fluvoxamine, imipramine, and placebo in the treatment of depressed outpatients: effects on depression. Psychopharmacol Bull 1989;25(1):68-70.

133. Mallinckrodt CH, Goldstein DJ, Detke MJ, Lu Y, Watkin JG, Tran PV. Duloxetine: A New Treatment for the Emotional and Physical Symptoms of Depression. Prim Care Companion J Clin Psychiatry 2003;5(1):19-28.

134. Mallinckrodt CH, Watkin JG, Liu C, Wohlreich MM, Raskin J. Duloxetine in the treatment of Major Depressive Disorder: a comparison of efficacy in patients with and without melancholic features. BMC Psychiatry 2005;5(1):1.

135. Mallya GK, K. W, C. W, al. e. Short- and long-term treatment of obsessive-compulsive disorder with fluvoxamine. Ann Clin Psychiatry 1992;4:77-80.

136. Marcus RN, Mendels J. Nefazodone in the treatment of severe, melancholic, and recurrent depression. J Clin Psychiatry 1996;57 Suppl 2:19-23.

137. Mendels J, Kiev A, Fabre LF. Double-blind comparison of citalopram and placebo in depressed outpatients with melancholia. Depress Anxiety 1999;9(2):54-60.

138. Menkes DB, Taghavi E, Mason PA, Howard RC. Fluoxetine's spectrum of action in premenstrual syndrome. Int Clin Psychopharmacol 1993;8(2):95-102.

139. Menkes DB, Taghavi E, Mason PA, Spears GF, Howard RC. Fluoxetine treatment of severe premenstrual syndrome. BMJ 1992;305(6849):346-7.

140. Michelson D, Allgulander C, Dantendorfer K, Knezevic A, Maierhofer D, Micev V, et al. Efficacy of usual antidepressant dosing regimens of fluoxetine in panic disorder: randomised, placebo-controlled trial. Br J Psychiatry 2001;179:514-8.

141. Michelson D, Lydiard RB, Pollack MH, Tamura RN, Hoog SL, Tepner R, et al. Outcome assessment and clinical improvement in panic disorder: evidence from a randomized controlled trial of fluoxetine and placebo. The Fluoxetine Panic Disorder Study Group. Am J Psychiatry 1998;155(11):1570-7.

142. Michelson D, Pollack M, Lydiard RB, Tamura R, Tepner R, Tollefson G. Continuing treatment of panic disorder after acute response: randomised, placebo-controlled trial with fluoxetine. The Fluoxetine Panic Disorder Study Group. Br J Psychiatry 1999;174:213-8.

143. Miller SM, Naylor GJ, Murtagh M, Winslow G. A double-blind comparison of paroxetine and placebo in the treatment of depressed patients in a psychiatric outpatient clinic. Acta Psychiatr Scand Suppl 1989;350:143-4.

144. Miner C, Brown E, McCray S, Gonzales J, Wohlreich M. Weekly luteal-phase dosing with enteric-coated fluoxetine 90 mg in premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled clinical trial. Clin Ther 2002;24(3):417-33.

145. Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol 1995;10 Suppl 4:37-45.

146. Montgomery SA. Implications of the severity of social phobia. J Affect Disord 1998;50 Suppl 1:S17-22.

147. Montgomery SA, Dunbar G. Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. Int Clin Psychopharmacol 1993;8(3):189-95.

148. Montgomery SA, Mahe V, Haudiquet V, Hackett D. Effectiveness of venlafaxine, extended release formulation, in the short-term and long-term treatment of generalized anxiety disorder: results of a survival analysis. J Clin Psychopharmacol 2002;22(6):561-7.

149. Montgomery SA, McIntyre A, Osterheider M, Sarteschi P, Zitterl W, Zohar J, et al. A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R

obsessive-compulsive disorder. The Lilly European OCD Study Group. Eur Neuropsychopharmacol 1993;3(2):143-52.

150. Montgomery SA, Pedersen V, Tanghoj P, Rasmussen C, Rioux P. The optimal dosing regimen for citalopram--a meta-analysis of nine placebo-controlled studies. Int Clin Psychopharmacol 1994;9 Suppl 1:35-40.

151. Montgomery SA, Rasmussen JG. Citalopram 20 mg, citalopram 40 mg and placebo in the prevention of relapse of major depression. Int Clin Psychopharmacol 1992;6 Suppl 5:71-3.

152. Montgomery SA, Rasmussen JG, Lyby K, Connor P, Tanghoj P. Dose response relationship of citalopram 20 mg, citalopram 40 mg and placebo in the treatment of moderate and severe depression. Int Clin Psychopharmacol 1992;6 Suppl 5:65-70.

153. Montgomery SA, Sheehan DV, Meoni P, Haudiquet V, Hackett D. Characterization of the longitudinal course of improvement in generalized anxiety disorder during long-term treatment with venlafaxine XR. J Psychiatr Res 2002;36(4):209-17.

154. Narushima K, Kosier JT, Robinson RG. Preventing poststroke depression: a 12-week double-blind randomized treatment trial and 21-month follow-up. J Nerv Ment Dis 2002;190(5):296-303.

155. Nimatoudis I, Zissis NP, Kogeorgos J, Theodoropoulou S, Vidalis A, Kaprinis G. Remission rates with venlafaxine extended release in Greek outpatients with generalized anxiety disorder. A double-blind, randomized, placebo controlled study. Int Clin Psychopharmacol 2004;19(6):331-6.

156. Nyth AL, Gottfries CG, Lyby K, Smedegaard-Andersen L, Gylding-Sabroe J, Kristensen M, et al. A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. Acta Psychiatr Scand 1992;86(2):138-45.

157. Oehrberg S, Christiansen PE, Behnke K, Borup AL, Severin B, Soegaard J, et al. Paroxetine in the treatment of panic disorder. A randomised, double-blind, placebo-controlled study. Br J Psychiatry 1995;167(3):374-9.

158. Ottevanger EA. The efficacy of fluvoxamine in patients with severe depression. Prog Neuropsychopharmacol Biol Psychiatry 1994;18(4):731-40.

159. Oxman TE, Barrett JE, Sengupta A, Katon W, Williams JWJ, Frank E, et al. Status of minor depression or dysthymia in primary care following a randomized controlled treatment. Gen Hosp Psychiatry 2001;23(6):301-10.

160. Ozeren S, Corakci A, Yucesoy I, Mercan R, Erhan G. Fluoxetine in the treatment of premenstrual syndrome. Eur J Obstet Gynecol Reproductive Biol 1997;73:167-70.

161. Pande AC, Sayler ME. Severity of depression and response to fluoxetine. Int Clin Psychopharmacol 1993;8(4):243-5.

162. Pearlstein T, Joliat MJ, Brown EB, Miner CM. Recurrence of symptoms of premenstrual dysphoric disorder after the cessation of luteal-phase fluoxetine treatment. Am J Obstet Gynecol 2003;188(4):887-95.

163. Pearlstein TB, Bellew KM, Endicott J, Steiner M. Paroxetine Controlled Release for Premenstrual Dysphoric Disorder: Remission Analysis Following a Randomized, Double-Blind, Placebo-Controlled Trial. Prim Care Companion J Clin Psychiatry 2005;7(2):53-60.

164. Pearlstein TB, Halbreich U, Batzar ED, Brown CS, Endicott J, Frank E, et al. Psychosocial functioning in women with premenstrual dysphoric disorder before and after treatment with sertraline or placebo. J Clin Psychiatry 2000;61(2):101-9.

165. Perse TL, Greist JH, Jefferson JW, Rosenfeld R, Dar R. Fluvoxamine treatment of obsessive-compulsive disorder. Am J Psychiatry 1987;144(12):1543-48.

166. Pollack MH, Otto MW, Worthington JJ, Manfro GG, Wolkow R. Sertraline in the treatment of panic disorder: a flexible-dose multicenter trial. Arch Gen Psychiatry 1998;55(11):1010-6.

167. Pollack MH, Worthington JJr, Otto MW, Maki KM, Smoller JW, Manfro GG, et al. Venlafaxine for panic disorder: results from a double-blind, placebo-controlled study. Psychopharmacol Bull 1996;32(4):667-70.

168. Pols H, Zandergen J, de Loof C, Fernandez I, Griez E. Clinical effects of fluvoxamine on panic symptomatology. Acta Psychiatr Belg 1993;93(3):169-77.

169. Rapaport MH, Bose A, Zheng H. Escitalopram continuation treatment prevents relapse of depressive episodes. J Clin Psychiatry 2004;65(1):44-9.

170. Rapaport MH, Wolkow R, Rubin A, Hackett E, Pollack M, Ota KY. Sertraline treatment of panic disorder: results of a long-term study. Acta Psychiatr Scand 2001;104(4):289-98.

171. Rasmussen A, Lunde M, Poulsen DL, Sorensen K, Qvitzau S, Bech P. A double-blind, placebo-controlled study of sertraline in the prevention of depression in stroke patients. Psychosomatics 2003;44(3):216-21.

172. Rasmussen S, Hackett E, DuBoff E, Greist J, Halaris A, Koran LM, et al. A 2-year study of sertraline in the treatment of obsessive-compulsive disorder. International Clin Psychopharm 1996;12:309-16.

173. Reimherr FW, Amsterdam JD, Quitkin FM, Rosenbaum JF, Fava M, Zajecka J, et al. Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. Am J Psychiatry 1998;155(9):1247-53.

174. Reimherr FW, Byerley WF, Ward MF, Lebegue BJ, Wender PH. Sertraline, a selective inhibitor of serotonin uptake, for the treatment of outpatients with major depressive disorder. Psychopharmacol Bull 1988;24(1):200-5.

175. Reimherr FW, Chouinard G, Cohn CK, Cole JO, Itil TM, LaPierre YD, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. J Clin Psychiatry 1990;51 Suppl B:18-27.

176. Reimherr FW, Cunningham LA, Batey SR, Johnston JA, Ascher JA. A multicenter evaluation of the efficacy and safety of 150 and 300 mg/d sustained-release bupropion tablets versus placebo in depressed outpatients. Clin Ther 1998;20(3):505-16.

177. Reimherr FW, Strong RE, Marchant BK, Hedges DW, Wender PH. Factors affecting return of symptoms 1 year after treatment in a 62-week controlled study of fluoxetine in major depression. J Clin Psychiatry 2001;62 Suppl 22:16-23.

178. Rickels K, Amsterdam J, Clary C, Fox I, Schweizer E, Weise C. A placebo-controlled, double-blind, clinical trial of paroxetine in depressed outpatients. Acta Psychiatr Scand Suppl 1989;350:117-23.

179. Rickels K, Amsterdam J, Clary C, Fox I, Schweizer E, Weise C. The efficacy and safety of paroxetine compared with placebo in outpatients with major depression. J Clin Psychiatry 1992;53 Suppl:30-2.

180. Rickels K, Mangano R, Khan A. A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder. J Clin Psychopharmacol 2004;24(5):488-96.

181. Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. Am J Psychiatry 2000;157(6):968-74.

182. Robert P, Montgomery SA. Citalopram in doses of 20-60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. Int Clin Psychopharmacol 1995;10 Suppl 1:29-35.

183. Romano S, Goodman W, Tamura R, Gonzales J. Long-term treatment of obsessive-compulsive disorder after an acute response: a comparison of fluoxetine versus placebo. J Clin Psychopharmacol 2001;21(1):46-52.

184. Roose SP, Sackeim HA, Krishnan KR, Pollock BG, Alexopoulos G, Lavretsky H, et al. Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. Am J Psychiatry 2004;161(11):2050-9.

185. Rudolph RL, Entsuah R, Chitra R. A meta-analysis of the effects of venlafaxine on anxiety associated with depression. J Clin Psychopharmacol 1998;18(2):136-44.

186. Rudolph RL, Fabre LF, Feighner JP, Rickels K, Entsuah R, Derivan AT. A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. J Clin Psychiatry 1998;59(3):116-22.

187. Satterlee WG, Faries D. The effects of fluoxetine on symptoms of insomnia in depressed patients. Psychopharmacol Bull 1995;31(2):227-37.

188. Scahill L, Riddle MA, King RA, Hardin MT, Rasmusson A, Makuch RW, et al. Fluoxetine has no marked effect on tic symptoms in patients with Tourette's syndrome: a double-blind placebo-controlled study. J Child Adolesc Psychopharmacol 1997;7(2):75-85.

189. Schmidt ME, Fava M, Robinson JM, Judge R. The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. J Clin Psychiatry 2000;61(11):851-7.

190. Schmidt ME, Fava M, Zhang S, Gonzales J, Raute NJ, Judge R. Treatment approaches to major depressive disorder relapse. Part 1: dose increase. Psychother Psychosom 2002;71(4):190-4.

191. Schneider LS, Nelson JC, Clary CM, Newhouse P, Krishnan KR, Shiovitz T, et al. An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. Am J Psychiatry 2003;160(7):1277-85.

192. Schweizer E, Weise C, Clary C, Fox I, Rickels K. Placebo-controlled trial of venlafaxine for the treatment of major depression. J Clin Psychopharmacol 1991;11:233-36.

193. Sharp DM, Power KG, Simpson RJ, Swanson V, Anstee JA. Global measures of outcome in a controlled comparison of pharmacological and psychological treatment of panic disorder and agoraphobia in primary care. Br J Gen Pract 1997;47(416):150-5.

194. Sheehan D, Dunbar GC, Fuell DL. The effect of paroxetine on anxiety and agitation associated with depression. Psychopharmacol Bull 1992;28(2):139-43.

195. Sheehan DV, Burnham DB, Iyengar MK, Perera P. Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. J Clin Psychiatry 2005;66(1):34-40.

196. Sheikh JI, Londborg P, Clary CM, Fayyad R. The efficacy of sertraline in panic disorder: combined results from two fixed-dose studies. Int Clin Psychopharmacol 2000;15(6):335-42.

197. Shrivastava RK, Shrivastava SH, Overweg N, Blumhardt CL. A double-blind comparison of paroxetine, imipramine, and placebo in major depression. J Clin Psychiatry 1992;53 Suppl:48-51.

198. Simeon D, Stein DJ, Gross S, Islam N, Schmeidler J, Hollander E. A double-blind trial of fluoxetine in pathologic skin picking. J Clin Psychiatry 1997;58(8):341-7.

199. Simeon JG, Dinicola VF, Ferguson HB, Copping W. Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. Prog neuropsychoarmacol Biol Psychiat 1990;14:791-95.

200. Simon JS, Aguiar LM, Kunz NR, Lei D. Extended release venlafaxine in relapse prevention for patients with major depressive disorder. J Psychiatr Res 2004;38(3):249-57.

201. Small GW, Birkett M, Meyers BS, Koran LM, Bystritsky A, Nemeroff CB. Impact of physical illness on quality of life and antidepressant response in geriatric major depression. Fluoxetine Collaborative Study Group. J Am Geriatr Soc 1996;44(10):1220-5.

202. Smith WT, Glaudin V. A placebo-controlled trial of paroxetine in the treatment of major depression. J Clin Psychiatry 1992;53 Suppl:36-9.

203. Stein DJ, Berk M, Els C, Emsley RA, Gittelson L, Wilson D, et al. A double-blind placebo-controlled trial of paroxetine in the management of social phobia (social anxiety disorder) in South Africa. S Afr Med J 1999;89(4):402-6.

204. Stein MB, Chartier MJ, Hazen AL, Kroft CD, Chale RA, Cote D, et al. Paroxetine in the treatment of generalized social phobia: open-label treatment and double-blind placebo-controlled discontinuation. J Clin Psychopharmacol 1996;16(3):218-22.

205. Stein MB, Pollack MH, Bystritsky A, Kelsey JE, Mangano RM. Efficacy of low and higher dose extended-release venlafaxine in generalized social anxiety disorder: a 6-month randomized controlled trial. Psychopharmacology (Berl) 2005;177(3):280-8.

206. Steiner M, Brown E, Trzepacz P, Dillon J, Berger C, Carter D, et al. Fluoxetine improves functional work capacity in women with premenstrual dysphoric disorder. Arch Women Ment Health 2003;6(1):71-7.

207. Steiner M, Lamont J, Steinberg S, Stewart D, Reid R, Streiner D. Effect of fluoxetine on menstrual cycle length in women with premenstrual dysphoria. Obstet Gynecol 1997;90(4 Pt 1):590-5.

208. Steiner M, Romano SJ, Babcock S, Dillon J, Shuler C, Berger C, et al. The efficacy of fluoxetine in improving physical symptoms associated with premenstrual dysphoric disorder. BJOG 2001;108(5):462-8.

209. Steiner M, Steinberg S, Stewart D, Carter D, Berger C, Reid R, et al. Fluoxetine in the treatment of premenstrual dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group. N Engl J Med 1995;332(23):1529-34.

210. Stern WC, Harto-Truax N, Bauer N. Efficacy of bupropion in tricyclic-resistant or intolerant patients. J Clin Psychiatry 1983;44(5 Pt 2):148-52.

211. Stewart JW, Quitkin FM, McGrath PJ, Amsterdam J, Fava M, Fawcett J, et al. Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo. Arch Gen Psychiatry 1998;55(4):334-43.

212. Stocchi F, Nordera G, Jokinen RH, Lepola UM, Hewett K, Bryson H, et al. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. J Clin Psychiatry 2003;64(3):250-8.

213. Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of premenstrual syndrome. Psychopharmacol Bull 1990;26(3):331-5.

214. Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1991;52(7):290-3.

215. Strik JJ, Honig A, Lousberg R, Lousberg AH, Cheriex EC, Tuynman-Qua HG, et al. Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind, placebo-controlled trial. Psychosom Med 2000;62(6):783-9.

216. Su TP, Schmidt PJ, Danaceau MA, Tobin MB, Rosenstein DL, Murphy DL, et al. Fluoxetine in the treatment of premenstrual dysphoria. Neuropsychopharmacology 1997;16(5):346-56.

217. Sullivan MD, Katon WJ, Russo JE, Frank E, Barrett JE, Oxman TE, et al. Patient beliefs predict response to paroxetine among primary care patients with dysthymia and minor depression. J Am Board Fam Pract 2003;16(1):22-31.

218. Terra JL, Montgomery SA. Fluvoxamine prevents recurrence of depression: results of a long-term, double-blind, placebo-controlled study. Int Clin Psychopharmacol 1998;13(2):55-62.

219. Thase ME. Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. The Venlafaxine XR 209 Study Group. J Clin Psychiatry 1997;58(9):393-8.

220. Thase ME, Nierenberg AA, Keller MB, Panagides J. Efficacy of mirtazapine for prevention of depressive relapse: a placebo-controlled double-blind trial of recently remitted high-risk patients. J Clin Psychiatry 2001;62(10):782-8.

221. Thompson C. Management of depression in real-life settings: knowledge gained from large-scale clinical trials. Int Clin Psychopharmacol 1994;9 Suppl 3:21-5.

222. Thorell LH, Kjellman B, Arned M, Lindwall-Sundel K, Walinder J, Wetterberg L. Light treatment of seasonal affective disorder in combination with citalopram or placebo with 1-year follow-up. Int Clin Psychopharmacol 1999;14 Suppl 2:S7-11.

223. Tollefson GD, Birkett M, Koran L, Genduso L. Continuation treatment of OCD: double-blind and open-label experience with fluoxetine. J Clin Psychiatry 1994;55 Suppl:69-76; discussion 77-8.

224. Tollefson GD, Bosomworth JC, Heiligenstein JH, Potvin JH, Holman S. A double-blind, placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. The Fluoxetine Collaborative Study Group. Int Psychogeriatr 1995;7(1):89-104.

225. Tollefson GD, Holman SL. Analysis of the Hamilton Depression Rating Scale factors from a double-blind, placebo-controlled trial of fluoxetine in geriatric major depression. Int Clin Psychopharmacol 1993;8(4):253-9.

226. Tollefson GD, Holman SL, Sayler ME, Potvin JH. Fluoxetine, placebo, and tricyclic antidepressants in major depression with and without anxious features. J Clin Psychiatry 1994;55(2):50-9.

227. Trivedi MH, Pigotti TA, Perera P, Dillingham KE, Carfagno ML, Pitts CD. Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder. J Clin Psychiatry 2004;65(10):1356-64.

228. Turner R. Quality of life: experience with sertraline. Int Clin Psychopharmacol 1994;9 Suppl 3:27-31.

229. van den Brink RH, van Melle JP, Honig A, Schene AH, Crijns HJ, Lambert FP, et al. Treatment of depression after myocardial infarction and the effects on cardiac prognosis and quality of life: rationale and outline of the Myocardial INfarction and Depression-Intervention Trial (MIND-IT). Am Heart J 2002;144(2):219-25.

230. Veeninga AT, Westenberg HGM, Weusten JTN. Fluvoxamine in the treatment of menstrually related mood disorders. Psychopharmacol 1990;102:414-416.

231. Wade A, Michael Lemming O, Bang Hedegaard K. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2002;17(3):95-102.

232. Wade AG, Lepola U, Koponen HJ, Pedersen V, Pedersen T. The effect of citalopram in panic disorder. Br J Psychiatry 1997;170:549-53.

233. Wagstaff AJ, Cheer SM, Matheson AJ, Ormrod D, Goa KL. Spotlight on paroxetine in psychiatric disorders in adults. CNS Drugs 2002;16(6):425-34.

234. Wakelin JS. Fluvoxamine in the treatment of the older depressed patient; double-blind, placebo-controlled data. Int Clin Psychopharmacol 1986;1(3):221-30.

235. Walczak DD, Apter JT, Halikas JA, Borison RL, Carman JS, Post GL, et al. The oral dose-effect relationship for fluvoxamine: a fixed-dose comparison against placebo in depressed outpatients. Ann Clin Psychiatry 1996;8(3):139-51.

236. Walker JR, Van Ameringen MA, Swinson R, Bowen RC, Chokka PR, Goldner E, et al. Prevention of relapse in generalized social phobia: results of a 24-week study in responders to 20 weeks of sertraline treatment. J Clin Psychopharmacol 2000;20(6):636-44.

237. Weihs KL, Houser TL, Batey SR, Ascher JA, Bolden-Watson C, Donahue RM, et al. Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. Biol Psychiatry 2002;51(9):753-61.

238. Wenger TL, Stern WC. The cardiovascular profile of bupropion. J Clin Psychiatry 1983;44(5 Pt 2):176-82.

239. Wernicke JF, Dunlop SR, Dornseif BE, Bosomworth JC, Humbert M. Low-dose fluoxetine therapy for depression. Psychopharmacol Bull 1988;24(1):183-8.

240. Wernicke JF, Dunlop SR, Dornseif BE, Zerbe RL. Fixed-dose fluoxetine therapy for depression. Psychopharmacol Bull 1987;23(1):164-8.

241. Wikander I, Sundblad C, Andersch B, Dagnell I, Zylberstein D, Bengtsson F, et al. Citalopram in premenstrual dysphoria: is intermittent treatment during luteal phases more effective than continuous medication throughout the menstrual cycle? J Clin Psychopharmacol 1998;18(5):390-8.

242. Wilson KC, Mottram PG, Ashworth L, Abou-Saleh MT. Older community residents with depression: long-term treatment with sertraline. Randomised, double-blind, placebo-controlled study. Br J Psychiatry 2003;182:492-7.

243. Wood A, Tollefson GD, Birkett M. Pharmacotherapy of obsessive compulsive disorder--experience with fluoxetine. Int Clin Psychopharmacol 1993;8(4):301-6.

244. Wood SH, Mortola JF, Chan YF, Moossazadeh F, Yen SS. Treatment of premenstrual syndrome with fluoxetine: a double-blind, placebo-controlled, crossover study. Obstet Gynecol 1992;80(3 Pt 1):339-44.

245. Yonkers KA, Halbreich U, Freeman E, Brown C, Endicott J, Frank E, et al. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. A randomized controlled trial. Sertraline Premenstrual Dysphoric Collaborative Study Group. JAMA 1997;278(12):983-8.

246. Yonkers KA, Halbreich U, Freeman E, Brown C, Pearlstein T. Sertraline in the treatment of premenstrual dysphoric disorder. Psychopharmacol Bull 1996;32(1):41-6.

247. Young SA, Hurt PH, Benedek DM, Howard RS. Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: a randomized, double-blind, placebo-controlled crossover trial. J Clin Psychiatry 1998;59(2):76-80.

248. Zajecka J, Fawcett J, Amsterdam J, Quitkin F, Reimherr F, Rosenbaum J, et al. Safety of abrupt discontinuation of fluoxetine: a randomized, placebo-controlled study. J Clin Psychopharmacol 1998;18(3):193-7.

249. Zajecka JM. The effect of nefazodone on comorbid anxiety symptoms associated with depression: experience in family practice and psychiatric outpatient settings. J Clin Psychiatry 1996;57 Suppl 2:10-4.

250. Zohar J, Amital D, Miodownik C, Kotler M, Bleich A, Lane RM, et al. Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. J Clin Psychopharmacol 2002;22(2):190-5.

251. Zohar J, Judge R. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. OCD Paroxetine Study Investigators. Br J Psychiatry 1996;169(4):468-74.

252. Zung WW. Review of placebo-controlled trials with bupropion. J Clin Psychiatry 1983;44(5 Pt 2):104-14.

Appendix F. Abstract-only Studies (not included)

1. Suicidal ideas with paroxetine or venlafaxine. Prescrire Int 2004;13(69):21.

2. Alexopoulos GS, Privitera W, Ventura D, Bose A, Wang Q. Double-blind comparison of escitalopram 10 mg/day and optimally-dosed sertraline 50-200 mg/day in the treatment of major depressive disorder. 2003.

3. Davidson JRT. Escitalopram in the treatment of generalized anxiety disorder: a double-blind, placebo-controlled, flexible dose study. Data on file @ Forest Labs 2004.

4. 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;29:255S.

5. 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;10 (Suppl 3):S252.

6. 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;7 Suppl 2:S147.

7. 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;40(9):568.

8. 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.

9. Gutierrez M. Lack of a pharmacokinetic interaction between escitalopram and the CYP3A4 inhibitor ritonavir. Data on file @ Forest Labs 2004.

10. 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;6 Suppl 3:124.

11. Lydiard B. Effects of escitalopram on anxiety symptoms in depression. Data on file @ Forest Labs 2004.

12. Montgomery SA. Comparative efficacy and tolerability of escitalopram oxalate versus venlafaxine XR. Data on file @ Forest Labs 2004.

13. Rudolph R, Entsuah R, Aguiar L, Derivan A. Early onset of antidepressant activity of venlafaxine compared with placebo and fluoxetine in outpatients in a double-blind study. Eur Neuropsychopharm 1998;8 Suppl 2:S142.

14. Salinas E. Once-daily extended release (XR) venlafaxine versus paroxetine in outpatients with major depression. Biol Psychiatry 1997;42 Suppl 1:244S.

Appendix G: Acknowledgements

Reviewers

We gratefully acknowledge the following individuals who reviewed the initial draft of this report and provided us with valuable and constructive feedback.

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References

1. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51(1):8-19.

2. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289(23):3095-105.

3. Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry 2003;64(12):1465-75.

4. US Food and Drug Administration. Electronic Orange Book. 2004(http://www.fda.gov/cder/ob/default.htm).

5. IMS Health. Press Release: Growth is sustained by new products despite a difficult year. IMS Reports 2004.

6. Williams JW, Mulrow CD, Chiquette E, Noel PH, Augilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Annals Internal Medicine 2000;132(9):743-756.

7. Geddes JR, Freemantle N, Mason J, Eccles MP, Boynton J. Selective serotonin reuptake inhibitors (SSRIs) versus other antidepressants for depression. The Cochrane Library (Cochrane Review) 2004(1).

8. Hoagwood K, Hibbs E, Brent D, Jensen P. Introduction to the special section: efficacy and effectiveness in studies of child and adolescent psychotherapy. J Consult Clin Psychol 1995;63(5):683-7.

9. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354(9193):1896-900.

10. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20(3 Suppl):21-35.

11. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition). 2001.

12. Egger M, Smith GD, Altman DG. Systematic Reviews in Health Care (2nd edition). 2001.

13. Lopez-Ibor JJ. Reduced suicidality with paroxetine. European Psychiatry 1993;8(Suppl 1):17S-19S.

14. Gagiano CA. A double blind comparison of paroxetine and fluoxetine in patients with major depression. British Journal of Clinical Research 1993;4:145-52.

15. Ontiveros A, Garcia-Barriga C. A double-blind, comparative study of paroxetine and fluoxetine in out-patients with depression. British Journal of Clinical Research 1997:23-32.

16. Colonna L, Reines EH, Andersen HF. Escitalopram is well tolerated and more efficacious than citalopram in long-term treatment of moderately depressed patients. Int J Psychiatry Clin Pract 2002;6:243-44.

17. Ekselius L, von Knorring L, Eberhard G. A double-blind multicenter trial comparing sertraline and citalopram in patients with major depression treated in general practice. Int Clin Psychopharmacol 1997;12(6):323-31.

18. Sechter D, Troy S, Paternetti S, Boyer P. A double-blind comparison of sertraline and fluoxetine in the treatment of major depressive episode in outpatients. Eur Psychiatry 1999;14(1):41-8.

19. Kroenke K, West SL, Swindle R, Gilsenan A, Eckert GJ, Dolor R, et al. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. JAMA 2001;286(23):2947-55.

20. Lepola UM, Loft H, Reines EH. Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2003;18(4):211-7.

21. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. 2002;63(4):331-6.

22. Colonna L, Andersen HF, Reines EH. A randomized, double-blind, 24-week study of escitalopram (10 mg/day) versus citalopram (20 mg/day) in primary care patients with major depressive disorder. Curr Med Res Opin 2005;21(10):1659-68.

23. Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. Int Clin Psychopharmacol 2005;20(3):131-7.

24. Lader M, Andersen HF, Baekdal T. The effect of escitalopram on sleep problems in depressed patients. Hum Psychopharmacol 2005;20(5):349-54.

25. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41(5):582-92.

26. Patris M, Bouchard JM, Bougerol T, Charbonnier JF, Chevalier JF, Clerc G, et al. Citalopram versus fluoxetine: a double-blind, controlled, multicentre, phase III trial in patients with unipolar major depression treated in general practice. Int Clin Psychopharmacol 1996;11(2):129-36.

27. Dalery J, Honig A. Fluvoxamine versus fluoxetine in major depressive episode: a double-blind randomised comparison. Hum Psychopharmacol 2003;18(5):379-84.

28. Rapaport M, Coccaro E, Sheline Y, Perse T, Holland P, Fabre L, et al. A comparison of fluvoxamine and fluoxetine in the treatment of major depression. J Clin Psychopharmacol 1996;16(5):373-8.

29. Cassano GB, Puca F, Scapicchio PL, Trabucchi M. Paroxetine and fluoxetine effects on mood and cognitive functions in depressed nondemented elderly patients. J Clin Psychiatry 2002;63(5):396-402.

30. Chouinard G, Saxena B, Belanger MC, Ravindran A, Bakish D, Beauclair L, et al. A Canadian multicenter, double-blind study of paroxetine and fluoxetine in major depressive disorder. J Affect Disord 1999;54(1-2):39-48.

31. De Wilde J, Spiers R, Mertens C, Bartholome F, Schotte G, Leyman S. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. Acta Psychiatr Scand 1993;87(2):141-5.

32. Schone W, Ludwig M. A double-blind study of paroxetine compared with fluoxetine in geriatric patients with major depression. J Clin Psychopharmacol 1993;13(6 Suppl 2):34S-39S.

33. Fava M, Amsterdam JD, Deltito JA, Salzman C, Schwaller M, Dunner DL. A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression. Ann Clin Psychiatry 1998;10(4):145-50.

34. Fava M, Hoog SL, Judge RA, Kopp JB, Nilsson ME, Gonzales JS. Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia. J Clin Psychopharmacol 2002;22(2):137-47.

35. Bennie EH, Mullin JM, Martindale JJ. A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. J Clin Psychiatry 1995;56(6):229-37.

36. Thompson C. Management of depression in real-life settings: knowledge gained from large-scale clinical trials. Int Clin Psychopharmacol 1994;9 Suppl 3:21-5.

37. Newhouse PA, Krishnan KR, Doraiswamy PM, Richter EM, Batzar ED, Clary CM. A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. J Clin Psychiatry 2000;61(8):559-68.

38. Boyer P, Danion JM, Bisserbe JC, Hotton JM, Troy S. Clinical and economic comparison of sertraline and fluoxetine in the treatment of depression. A 6-month double-blind study in a primary-care setting in France. Pharmacoeconomics 1998;13(1 Pt 2):157-69.

39. Finkel SI, Richter EM, Clary CM, Batzar E. Comparative efficacy of sertraline vs. fluoxetine in patients age 70 or over with major depression. Am J Geriatr Psychiatry 1999;7(3):221-7.

40. Kiev A, Feiger A. A double-blind comparison of fluvoxamine and paroxetine in the treatment of depressed outpatients. J Clin Psychiatry 1997;58(4):146-52.

41. Aberg-Wistedt A, Agren H, Ekselius L, Bengtsson F, Akerblad AC. Sertraline versus paroxetine in major depression: clinical outcome after six months of continuous therapy. J Clin Psychopharmacol 2000;20(6):645-52.

42. Nemeroff CB, Ninan PT, Ballenger J, Lydiard RB, Feighner J, Patterson WM, et al. Double-blind multicenter comparison of fluvoxamine versus sertraline in the treatment of depressed outpatients. 1995;3:163-69.

43. Franchini L, Gasperini M, Perez J, Smeraldi E, Zanardi R. A double-blind study of long-term treatment with sertraline or fluvoxamine for prevention of highly recurrent unipolar depression. J Clin Psychiatry 1997;58(3):104-7.

44. Franchini L, Gasperini M, Zanardi R, Smeraldi E. Four-year follow-up study of sertraline and fluvoxamine in long-term treatment of unipolar subjects with high recurrence rate. J Affect Disord 2000;58(3):233-6.

45. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. J Clin Psychiatry 2002;63(3):225-31.

46. Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Neuropsychopharmacol 2004;14(6):457-70.

47. Hong CJ, Hu WH, Chen CC, Hsiao CC, Tsai SJ, Ruwe FJ. A double-blind, randomized, group-comparative study of the tolerability and efficacy of 6 weeks' treatment with mirtazapine or fluoxetine in depressed Chinese patients. J Clin Psychiatry 2003;64(8):921-6.

48. Schatzberg AF, Kremer C, Rodrigues HE, Murphy GMJ. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. Am J Geriatr Psychiatry 2002;10(5):541-50.

49. Benkert O, Szegedi A, Kohnen R. Mirtazapine compared with paroxetine in major depression. J Clin Psychiatry 2000;61(9):656-63.

50. Behnke K, Sogaard J, Martin S, Bauml J, Ravindran AV, Agren H, et al. Mirtazapine orally disintegrating tablet versus sertraline: a prospective onset of action study. J Clin Psychopharmacol 2003;23(4):358-64.

51. Allard P, Gram L, Timdahl K, Behnke K, Hanson M, Sogaard J. Efficacy and tolerability of venlafaxine in geriatric outpatients with major depression: a double-blind, randomised 6-month comparative trial with citalopram. Int J Geriatr Psychiatry 2004;19(12):1123-30.

52. Montgomery SA. Comparative efficacy and tolerability of escitalopram oxalate versus venlafaxine XR. Data on file @ Forest Labs 2004.

53. Bielski RJ, Ventura D, Chang CC. A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. J Clin Psychiatry 2004;65(9):1190-6.

54. Costa e Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. J Clin Psychiatry 1998;59(7):352-357.

55. De Nayer A, Geerts S, Ruelens L, Schittecatte M, De Bleeker E, Van Eeckhoutte I, et al. Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety. Int J Neuropsychopharmacol 2002;5(2):115-20.

56. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J Affect Disord 1999;56(2-3):171-81.

57. Silverstone PH, Ravindran A. Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group. J Clin Psychiatry 1999;60(1):22-8.

58. Silverstone PH, Salinas E. Efficacy of venlafaxine extended release in patients with major depressive disorder and comorbid generalized anxiety disorder. J Clin Psychiatry 2001;62(7):523-9.

59. Alves C, Cachola I, Brandao J. Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. Primary Care Psychiatry 1999;5(2):57-63.

60. Dierick M, Ravizza L, Realini R, Martin A. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. Prog Neuropsychopharmacol Biol Psychiatry 1996;20(1):57-71.

61. Tylee A, Beaumont G, Bowden MW, Reynolds A. A double-blind, randomized, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe depression in general practice. Primary Care Psychiatry 1997;3:51-58.

62. Smith D, Dempster C, Glanville J, Freemantle N, Anderson I. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. Br J Psychiatry 2002;180:396-404.

63. Ballus C, Quiros G, De Flores T, de la Torre J, Palao D, Rojo L, et al. The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder or dysthymia. Int Clin Psychopharmacol 2000;15(1):43-8.

64. McPartlin GM, Reynolds A, Anderson C, Casoy J. A comparison of once-daily venlafaxine XR and paroxetine in depressed outpatients treated in general practice. Primary Care Psychiatry 1998;4(3):127-132.

65. Sir A, D'Souza RF, Uguz S, George T, Vahip S, Hopwood M, et al. Randomized Trial of Sertraline Versus Venlafaxine XR in Major Depression: Efficacy and Discontinuation Symptoms. J Clin Psychiatry 2005;66(10):1312-1320.

66. Mehtonen OP, Sogaard J, Roponen P, Behnke K. Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. Venlafaxine 631 Study Group. J Clin Psychiatry 2000;61(2):95-100.

67. Nieuwstraten CE, Dolovich LR. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. Ann Pharmacother 2001;35(12):1608-13.

68. Feighner JP, Gardner EA, Johnston JA, Batey SR, Khayrallah MA, Ascher JA, et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. J Clin Psychiatry 1991;52(8):329-35.

69. Coleman CC, King BR, Bolden-Watson C, Book MJ, Segraves RT, Richard N, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin Ther 2001;23(7):1040-58.

70. Weihs KL, Settle ECJ, Batey SR, Houser TL, Donahue RM, Ascher JA. Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. J Clin Psychiatry 2000;61(3):196-202.

71. Doraiswamy PM, Khan ZM, Donahue RM, Richard NE. Quality of life in geriatric depression: a comparison of remitters, partial responders, and nonresponders. Am J Geriatr Psychiatry 2001;9(4):423-8.

72. Kavoussi RJ, Segraves RT, Hughes AR, Ascher JA, Johnston JA. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. J Clin Psychiatry 1997;58(12):532-7.

73. Croft H, Settle EJ, Houser T, Batey SR, Donahue RM, Ascher JA. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clin Ther 1999;21(4):643-58.

74. Coleman CC, Cunningham LA, Foster VJ, Batey SR, Donahue RM, Houser TL, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. Ann Clin Psychiatry 1999;11(4):205-15.

75. Gillin JC, Rapaport M, Erman MK, Winokur A, Albala BJ. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial. J Clin Psychiatry 1997;58(5):185-92.

76. Armitage R, Yonkers K, Cole D, Rush AJ. A multicenter, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. J Clin Psychopharmacol 1997;17(3):161-8.

77. Rush AJ, Armitage R, Gillin JC, Yonkers KA, Winokur A, Moldofsky H, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. Biol Psychiatry 1998;44(1):3-14.

78. Baldwin DS, Hawley CJ, Abed RT, Maragakis BP, Cox J, Buckingham SA, et al. A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. J Clin Psychiatry 1996;57 Suppl 2:46-52.

79. Baldwin DS, Hawley CJ, Mellors K. A randomized, double-blind controlled comparison of nefazodone and paroxetine in the treatment of depression: safety, tolerability and efficacy in continuation phase treatment. J Psychopharmacol 2001;15(3):161-5.

80. Feiger A, Kiev A, Shrivastava RK, Wisselink PG, Wilcox CX. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996;57 Suppl 2:53-62.

81. Panzer MJ. Are SSRIs really more effective for anxious depression? Ann Clin Psychiatry 2005;17(1):23-9.

82. Fava M, Judge R, Hoog SL, Nilsson ME, Koke SC. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. J Clin Psychiatry 2000;61(11):863-7.

83. Lepola U, Wade A, Andersen HF. Do equivalent doses of escitalopram and citalopram have similar efficacy? A pooled analysis of two positive placebocontrolled studies in major depressive disorder. Int Clin Psychopharmacol 2004;19(3):149-55.

84. Montgomery SA, Huusom AK, Bothmer J. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. Neuropsychobiology 2004;50(1):57-64.

85. Segraves RT, Kavoussi R, Hughes AR, Batey SR, Johnston JA, Donahue R, et al. Evaluation of sexual functioning in depressed outpatients: a double-blind comparison of sustained-release bupropion and sertraline treatment. J Clin Psychopharmacol 2000;20(2):122-8.

86. Thase ME, Fava M, Halbreich U, Kocsis JH, Koran L, Davidson J, et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. Arch Gen Psychiatry 1996;53(9):777-84.

87. Kocsis JH, Zisook S, Davidson J, Shelton R, Yonkers K, Hellerstein DJ, et al. Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: psychosocial outcomes. Am J Psychiatry 1997;154(3):390-5.

88. Hellerstein DJ, Kocsis JH, Chapman D, Stewart JW, Harrison W. Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: effects on personality. Am J Psychiatry 2000;157(9):1436-44.

89. Ravindran AV, Guelfi JD, Lane RM, Cassano GB. Treatment of dysthymia with sertraline: a double-blind, placebo-controlled trial in dysthymic patients without major depression. J Clin Psychiatry 2000;61(11):821-7.

90. Barrett JE, Williams JWJ, Oxman TE, Frank E, Katon W, Sullivan M, et al. Treatment of dysthymia and minor depression in primary care: a randomized trial in patients aged 18 to 59 years. J Fam Pract 2001;50(5):405-12.

91. Williams JWJ, Barrett J, Oxman T, Frank E, Katon W, Sullivan M, et al. Treatment of dysthymia and minor depression in primary care: A randomized controlled trial in older adults. JAMA 2000;284(12):1519-26.

92. Devanand DP, Nobler MS, Cheng J, Turret N, Pelton GH, Roose SP, et al. Randomized, double-blind, placebo-controlled trial of fluoxetine treatment for elderly patients with dysthymic disorder. Am J Geriatr Psychiatry 2005;13(1):59-68.

93. Vanelle JM, Attar-Levy D, Poirier MF, Bouhassira M, Blin P, Olie JP. Controlled efficacy study of fluoxetine in dysthymia. Br J Psychiatry 1997;170:345-50.

94. Anonymous. Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants. 2004.

95. Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents. BMJ 2004;328:897-83.

96. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 2004;363(9418):1341-5.

97. Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. Am J Psychiatry 2004;161(6):1079-83.

98. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. Jama 2004;292(7):807-20.

99. Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 2001;40(7):762-72.

100. Wagner KD, Ambrosini P, Rynn M, Wohlberg C, Yang R, Greenbaum MS, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. JAMA 2003;290(8):1033-41.

101. Mandoki MW, Tapia MR, Tapia MA, Sumner GS, Parker JL. Venlafaxine in the treatment of children and adolescents with major depression. Psychopharmacol Bull 1997;33(1):149-54.

102. Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997;54(11):1031-7.

103. Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry 2002;41(10):1205-15.

104. Ball SG, Kuhn A, Wall D, Shekhar A, Goddard AW. Selective serotonin reuptake inhibitor treatment for generalized anxiety disorder: a double-blind, prospective comparison between paroxetine and sertraline. J Clin Psychiatry 2005;66(1):94-9.

105. Bielski RJ, Bose A, Chang CC. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Annals of clinical psychiatry: official journal of the American Academy of Clinical Psychiatrists 2005;17(2):65-9.

106. Davidson JR, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. Depress Anxiety 2004;19(4):234-40.

107. Allgulander C, Hackett D, Salinas E. Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. Br J Psychiatry 2001;179:15-22.

108. Boyer P, Mahe V, Hackett D. Social adjustment in generalised anxiety disorder: a longterm placebocontrolled study of venlafaxine extended release. Eur Psychiatry 2004;19(5):272-9.

109. Rickels K, Zaninelli R, McCafferty J, Bellew K, Iyengar M, Sheehan D. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. Am J Psychiatry 2003;160(4):749-56.

110. Pollack MH, Zaninelli R, Goddard A, McCafferty JP, Bellew KM, Burnham DB, et al. Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001;62(5):350-7.

111. Stocchi F, Nordera G, Jokinen RH, Lepola UM, Hewett K, Bryson H, et al. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. J Clin Psychiatry 2003;64(3):250-8.

112. Kelsey JE. Efficacy, safety, and tolerability of venlafaxine XR in generalized anxiety disorder. Depress Anxiety 2000;12 Suppl 1:81-4.

113. Meoni P, Hackett D, Lader M. Pooled analysis of venlafaxine XR efficacy on somatic and psychic symptoms of anxiety in patients with generalized anxiety disorder. Depress Anxiety 2004;19(2):127-32.

114. Allgulander C, Dahl AA, Austin C, Morris PL, Sogaard JA, Fayyad R, et al. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. Am J Psychiatry 2004;161(9):1642-9.

115. Dahl AA, Ravindran A, Allgulander C, Kutcher SP, Justin C, Burt T. Sertraline in generalized anxiety disorder: efficacy in treating the psychic and somatic anxiety factors. Acta psychiatrica Scandinavica 2005;111(6):429-35.

116. Allgulander C, Nilsson B. A prospective study of 86 new patients with social anxiety disorder. Acta Psychiatr Scand 2001;103(6):447-52.

117. Davidson JR, DuPont RL, Hedges D, Haskins JT. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry 1999;60(8):528-35.

118. Gelenberg AJ, Lydiard RB, Rudolph RL, Aguiar L, Haskins JT, Salinas E. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: A 6-month randomized controlled trial. JAMA 2000;283(23):3082-8.

119. Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. Am J Psychiatry 2000;157(6):968-74.

120. Denys D, van Megen HJ, van der Wee N, Westenberg HG. A doubleblind switch study of paroxetine and venlafaxine in obsessivecompulsive disorder. J Clin Psychiatry 2004;65(1):37-43.

121. Pallanti S, Quercioli L, Bruscoli M. Response acceleration with mirtazapine augmentation of citalopram in obsessive-compulsive disorder patients without comorbid depression: a pilot study. J Clin Psychiatry 2004;65(10):1394-9.

122. Piccinelli M, Pini S, Bellantuono C, Wilkinson G. Efficacy of drug treatment in obsessive-compulsive disorder. A meta-analytic review. Br J Psychiatry 1995;166(4):424-43.

123. Ackerman D, Greenland S. Multivariate meta-analysis of controlled drug studies for obsessive-compulsive disorder. Journal of Clinical Psychopharmacology 2002;22:309-317.

124. Stein DJ, Spadaccini E, Hollander E. Meta-analysis of pharmacotherapy trials for obsessive-compulsive disorder. International Clin Psychopharm 1995;10:11-18.

125. Bergeron R, Ravindran AV, Chaput Y, Goldner E, Swinson R, van Ameringen MA, et al. Sertraline and fluoxetine treatment of obsessive-compulsive disorder: results of a double-blind, 6-month treatment study. J Clin Psychopharmacol 2002;22(2):148-54.

126. Denys D, van der Wee N, van Megen HJ, Westenberg HG. A double blind comparison of venlafaxine and paroxetine in obsessive-compulsive disorder. J Clin Psychopharmacol 2003;23(6):568-75.

127. Greist JH, Jenike MA, Robinson D, Rasmussen SA. Efficacy of fluvoxamine in obsessive-compulsive disorder: results of multicentre, double blind, placebo-controlled trial. Eur J Clin Res 1995;7:195-204.

128. Montgomery SA, Kasper S, Stein DJ, Bang Hedegaard K, Lemming OM. Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. Int Clin Psychopharmacol 2001;16(2):75-86.

129. Goodman WK, Price LH, Rasmussen SA, Delgado PL, Heninger GR, Charney DS. Efficacy of fluvoxamine in obsessive-compulsive disorder. A double-blind comparison with placebo. Arch Gen Psychiatry 1989;46(1):36-44.

130. Jenike MA, Hyman S, Baer L, Holland A, Minichiello WE, Buttolph L, et al. A controlled trial of fluvoxamine in obsessive-compulsive disorder: implications for a serotonergic theory. Am J Psychiatry 1990;147(9):1209-15.

131. Mallya GK, K. W, C. W, al. e. Short- and long-term treatment of obsessive-compulsive disorder with fluvoxamine. Ann Clin Psychiatry 1992;4:77-80.

132. Goodman WK, Kozak MJ, Liebowitz M, White KL. Treatment of obsessive-compulsive disorder with fluvoxamine: a multicentre, double-blind, placebo-controlled trial. Int Clin Psychopharmacol 1996;11(1):21-9.

133. Montgomery SA, McIntyre A, Osterheider M, Sarteschi P, Zitterl W, Zohar J, et al. A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. The Lilly European OCD Study Group. Eur Neuropsychopharmacol 1993;3(2):143-52.

134. Tollefson GD, Rampey AHJ, Potvin JH, Jenike MA, Rush AJ, kominguez RA, et al. A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 1994;51(7):559-67.

135. Jenike MA, Baer L, Minichiello WE, Rauch SL, Buttolph ML. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. Am J Psychiatry 1997;154(9):1261-4.

136. Chouinard G, Goodman W, Greist J, Jenike M, Rasmussen S, White K, et al. Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive disorder. Psychopharmacol Bull 1990;26(3):279-84.

137. Jenike MA, Baer L, Summergrad P, Minichiello WE, Holland A, Seymour R. Sertraline in obsessive-compulsive disorder: a double-blind comparison with placebo. Am J Psychiatry 1990;147(7):923-28.

138. Greist J, Chouinard G, DuBoff E, Halaris A, Kim SW, Koran L, et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry 1995;52(4):289-95.

139. Kronig MH, Apter J, Asnis G, Bystritsky A, Curtis G, Ferguson J, et al. Placebo-controlled, multicenter study of sertraline treatment for obsessive-compulsive disorder. J Clin Psychopharmacol 1999;19(2):172-6.

140. Tenney NH, Denys DA, van Megen HJ, Glas G, Westenberg HG. Effect of a pharmacological intervention on quality of life in patients with obsessive-compulsive disorder. Int Clin Psychopharmacol 2003;18(1):29-33.

141. Stahl SM, Gergel I, Li D. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2003;64(11):1322-7.

142. Perna G, Bertani A, Caldirola D, Smeraldi E, Bellodi L. A comparison of citalopram and paroxetine in the treatment of panic disorder: a randomized, single-blind study. Pharmacopsychiatry 2001;34(3):85-90.

143. Bandelow B, Behnke K, Lenoir S, Hendriks GJ, Alkin T, Goebel C, et al. Sertraline versus paroxetine in the treatment of panic disorder: an acute, double-blind noninferiority comparison. J Clin Psychiatry 2004;65(3):405-13.

144. Black DW, Wesner R, Gabel J. The abrupt discontinuation of fluvoxamine in patients with panic disorder. J Clin Psychiatry 1993;54(4):146-9.

145. Hoehn-Saric R, McLeod DR, Hipsley PA. Effect of fluvoxamine on panic disorder. J Clin Psychopharmacol 1993;13(5):321-6.

146. Asnis GM, Hameedi FA, Goddard AW, Potkin SG, Black D, Jameel M, et al. Fluvoxamine in the treatment of panic disorder: a multi-center, double-blind, placebo-controlled study in outpatients. Psychiatry Res 2001;103(1):1-14.

147. Pohl RB, Wolkow RM, Clary CM. Sertraline in the treatment of panic disorder: a double-blind multicenter trial. Am J Psychiatry 1998;155(9):1189-95.

148. Bradwejn J, Ahokas A, Stein DJ, Salinas E, Emilien G, Whitaker T. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. Br J Psychiatry 2005;187:352-9.

149. Black DW, Wesner R, Bowers W, Gabel J. A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder. Arch Gen Psychiatry 1993;50(1):44-50.

150. Tucker P, Potter-Kimball R, Wyatt DB, Parker DE, Burgin C, Jones DE, et al. Can physiologic assessment and side effects tease out differences in PTSD trials? A double-blind comparison of citalopram, sertraline, and placebo. Psychopharmacol Bull 2003;37(3):135-49.

151. McRae AL, Brady KT, Mellman TA, Sonne SC, Killeen TK, Timmerman MA, et al. Comparison of nefazodone and sertraline for the treatment of posttraumatic stress disorder. Depress Anxiety 2004;19(3):190-6.

152. Brady K, Pearlstein T, Asnis GM, Baker D, Rothbaum B, Sikes CR, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA 2000;283(14):1837-44.

153. Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. Arch Gen Psychiatry 2001;58(5):485-92.

154. Rapaport MH, Endicott J, Clary CM. Posttraumatic stress disorder and quality of life: results across 64 weeks of sertraline treatment. J Clin Psychiatry 2002;63(1):59-65.

155. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. Am J Psychiatry 2001;158(12):1982-8.

156. Connor KM, Sutherland SM, Tupler LA, Malik ML, Davidson JR. Fluoxetine in post-traumatic stress disorder. Randomised, double-blind study. Br J Psychiatry 1999;175:17-22.

157. Londborg PD, Hegel MT, Goldstein S, Goldstein D, Himmelhoch JM, Maddock R, et al. Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. J Clin Psychiatry 2001;62(5):325-31.

158. Davidson J, Pearlstein T, Londborg P, Brady KT, Rothbaum B, Bell J, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. Am J Psychiatry 2001;158(12):1974-81.

159. Allgulander C, Mangano R, Zhang J, Dahl AA, Lepola U, Sjodin I, et al. Efficacy of Venlafaxine ER in patients with social anxiety disorder: a double-blind, placebo-controlled, parallel-group comparison with paroxetine. Hum Psychopharmacol 2004;19(6):387-96.

160. Lader M, Stender K, Burger V, Nil R. Efficacy and tolerability of escitalopram in 12 and 24week treatment of social anxiety disorder: randomised, doubleblind, placebo-controlled, fixeddose study. Depress Anxiety 2004;19(4):241-8.

161. Liebowitz MR, Gelenberg AJ, Munjack D. Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. Arch Gen Psychiatry 2005;62(2):190-8.

162. van der Linden GJH, Stein DJ, van Balkom A. The efficacy of the selective serotonin reuptake inhibitors for social anxiety disorder (social phobia): a meta-analysis of randomised controlled trials. Int Clin Psychopharm 2000.

163. Montgomery SA, Nil R, Durr-Pal N, Loft H, Boulenger JP. A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder. J Clin Psychiatry 2005;66(10):1270-8.

164. Kasper S, Stein DJ, Loft H, Nil R. Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study. Br J Psychiatry 2005;186:222-6.

165. Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ. Fluoxetine in social phobia: a double-blind, placebo-controlled pilot study. J Clin Psychopharmacol 2002;22(3):257-62.

166. Stein MB, Fyer AJ, Davidson JR, Pollack MH, Wiita B. Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind, placebo-controlled study. Am J Psychiatry 1999;156(5):756-60.

167. Westenberg H, Stein D, Yang H, Li D, Barbato L. A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. Journal of clinical psychopharmacology 2004;24(1):49-55.

168. Muehlbacher M, Nickel MK, Nickel C, Kettler C, Lahmann C, Pedrosa Gil F, et al. Mirtazapine treatment of social phobia in women: a randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 2005;25(6):580-3.

169. Stein DJ, Versiani M, Hair T, Kumar R. Efficacy of paroxetine for relapse prevention in social anxiety disorder: a 24-week study. Arch Gen Psychiatry 2002;59(12):1111-8.

170. Baldwin D, Bobes J, Stein DJ, Scharwachter I, Faure M. Paroxetine in social phobia/social anxiety disorder. Randomised, double-blind, placebo-controlled study. Paroxetine Study Group. Br J Psychiatry 1999;175:120-6.

171. Stein MB, Liebowitz MR, Lydiard RB, Pitts CD, Bushnell W, Gergel I. Paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial. JAMA 1998;280(8):708-13.

172. Lepola U, Bergtholdt B, St Lambert J, Davy KL, Ruggiero L. Controlled-release paroxetine in the treatment of patients with social anxiety disorder. J Clin Psychiatry 2004;65(2):222-9.

173. Van Ameringen MA, Lane RM, Walker JR, Bowen RC, Chokka PR, Goldner EM, et al. Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. Am J Psychiatry 2001;158(2):275-81.

174. Liebowitz MR, DeMartinis NA, Weihs K, Londborg PD, Smith WT, Chung H, et al. Efficacy of sertraline in severe generalized social anxiety disorder: results of a double-blind, placebo-controlled study. J Clin Psychiatry 2003;64(7):785-92.

175. Blomhoff S, Haug TT, Hellstrom K, Holme I, Humble M, Madsbu HP, et al. Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. Br J Psychiatry 2001;179:23-30.

176. Wyatt KM, Dimmock PW, O'Brien PM. Selective serotonin reuptake inhibitors for premenstrual syndrome. Cochrane Database Syst Rev 2004(4):CD001396.

177. Dimmock PW, Wyatt KM, Jones PW, O' Brian PMS. Efficacy of selective serotonin inhibitors in premenstrual syndrome: a sytematic review. The Lancet 2000;356:1131-1136.

178. Freeman EW, Rickels K, Yonkers KA, Kunz NR, McPherson M, Upton GV. Venlafaxine in the treatment of premenstrual dysphoric disorder. Obstet Gynecol 2001;98(5 Pt 1):737-44.

179. Landen M, Eriksson O, Sundblad C, Andersch B, Naessen T, Eriksson E. Compounds with affinity for serotonergic receptors in the treatment of premenstrual dysphoria: a comparison of buspirone, nefazodone and placebo. Psychopharmacology 2001;155:292-98.

180. Halbreich U, Bergeron R, Yonkers KA, Freeman E, Stout AL, Cohen L. Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. Obstet Gynecol 2002;100(6):1219-29.

181. Freeman EW, Rickels K, Sondheimer SJ, Polansky M, Xiao S. Continuous or intermittent dosing with sertraline for patients with severe premenstrual syndrome or premenstrual dysphoric disorder. Am J Psychiatry 2004;161(2):343-51.

182. Steiner M, Hirschberg AL, Bergeron R, Holland F, Gee MD, Van Erp E. Luteal phase dosing with paroxetine controlled release (CR) in the treatment of premenstrual dysphoric disorder. Am J Obstet Gynecol 2005;193(2):352-60.

183. Greist J, McNamara RK, Mallinckrodt CH, Rayamajhi JN, Raskin J. Incidence and duration of antidepressant-induced nausea: duloxetine compared with paroxetine and fluoxetine. Clin Ther 2004;26(9):1446-55.

184. Mackay FJ, Dunn NR, Wilton LV, Pearce GL, Freemantle SN, Mann RD. A comparison of fluvoxamine, fluoxetine, sertraline and paroxetine examined by observational cohort studies. Pharmacoepid Drug Safety 1997;6:235-46.

185. Mackay FR, Dunn NR, Martin RM, Pearce GL, Freemantle SN, Mann RD. Newer antidepressants: a comparison of tolerability in general practice. Br J Gen Pract 1999;49(448):892-6.

186. Haffmans PM, Timmerman L, Hoogduin CA. Efficacy and tolerability of citalopram in comparison with fluvoxamine in depressed outpatients: a double-blind, multicentre study. The LUCIFER Group. Int Clin Psychopharmacol 1996;11(3):157-64.

187. Brambilla P, Cipriani A, Hotopf M, Barbui C. Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. Pharmacopsychiatry 2005;38(2):69-77.

188. Meijer WE, Heerdink ER, van Eijk JT, Leufkens HG. Adverse events in users of sertraline: results from an observational study in psychiatric practice in The Netherlands. Pharmacoepidemiol Drug Saf 2002;11(8):655-62.

189. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ 2005;330(7488):385-9.

190. Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. Bmj 2005;330(7488):389.

191. Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. Bmj 2005;330(7488):396.

192. Jick SS, Dean AD, Jick H. Antidepressants and suicide. BMJ 1995;310:215-218.

193. Jick H, Ulcickas M, Dean A. Comparison of frequencies of suicidal tendencies among patients receiving fluoxetine, lofepramine, mianserin, or trazodone. Pharmacotherapy 1992;12(6):451-4.

194. Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry 2003;160(4):790-92.

195. Didham RC, McConnell DW, Blair HJ, Reith DM. Suicide and self-harm following prescription of SSRIs and other antidepressants: confounding by indication. Br J Clin Pharmacol 2005;60(5):519-25.

196. Kukoyi O, Argo TR, Carnahan RM. Exacerbation of panic disorder with rifampin therapy in a patient receiving citalopram. Pharmacotherapy 2005;25(3):435-7.

197. Ekselius L, von Knorring L. Effect on sexual function of long-term treatment with selective serotonin reuptake inhibitors in depressed patients treated in primary care. J Clin Psychopharmacol 2001;21(2):154-60.

198. Landen M, Hogberg P, Thase ME. Incidence of sexual side effects in refractory depression during treatment with citalopram or paroxetine. J Clin Psychiatry 2005;66(1):100-6.

199. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. J Clin Psychiatry 2001;62 Suppl 3:10-21.

200. Clayton AH, Pradko JF, Croft HA, Montano CB, Leadbetter RA, Bolden-Watson C, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry 2002;63(4):357-66.

201. Maina G, Albert U, Salvi V, Bogetto F. Weight gain during long-term treatment of obsessive-compulsive disorder: a prospective comparison between serotonin reuptake inhibitors. J Clin Psychiatry 2004;65(10):1365-71.

202. Croft H, Houser TL, Jamerson BD, Leadbetter R, Bolden-Watson C, Donahue R, et al. Effect on body weight of bupropion sustained-release in patients with major depression treated for 52 weeks. Clin Ther 2002;24(4):662-72.

203. Johnston JA, Lineberry CG, Ascher JA, Davidson J, Khayrallah MA, Feighner JP, et al. A 102-center prospective study of seizure in association with bupropion. J Clin Psychiatry 1991;52(11):450-6.

204. Dunner DL, Zisook S, Billow AA, Batey SR, Johnston JA, Ascher JA. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. J Clin Psychiatry 1998;59(7):366-73.

205. Whyte IM, Dawson AH, Buckley NA. Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. QJM 2003;96(5):369-74.

206. Thase ME. Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. J Clin Psychiatry 1998;59(10):502-8.

207. Thase ME, Tran PV, Wiltse C, Pangallo BA, Mallinckrodt C, Detke MJ. Cardiovascular profile of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine. J Clin Psychopharmacol 2005;25(2):132-40.

208. Liu BA, Mittmann N, Knowles SR, Shear NH. Hyponatremia and the syndrome of innappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: a review of spontaneous reports. CMAJ 1996;155(5):519-527.

209. Stewart DE. Hepatic adverse reactions associated with nefazodone. Can J Psychiatry 2002;47(4):375-7.

210. Buckley NA, McManus PR. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. BMJ 2002;325(7376):1332-3.

211. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. Jama 2004;292(3):338-43.

212. Pedersen AG. Escitalopram and suicidality in adult depression and anxiety. Int Clin Psychopharmacol 2005;20(3):139-43.

213. Coogan PF, Palmer JR, Strom BL, Rosenberg L. Use of selective serotonin reuptake inhibitors and the risk of breast cancer. Am J Epidemiol 2005;162(9):835-8.

214. Thase ME, Entsuah R, Cantillon M, Kornstein SG. Relative antidepressant efficacy of venlafaxine and SSRIs: sex-age interactions. J Womens Health (Larchmt) 2005;14(7):609-16.

215. Burt VK, Wohlreich MM, Mallinckrodt CH, Detke MJ, Watkin JG, Stewart DE. Duloxetine for the treatment of major depressive disorder in women ages 40 to 55 years. Psychosomatics 2005;46(4):345-54.

216. Cassano P, Soares CN, Cohen LS, Lyster AK, Fava M. Sex- and age-related differences in major depressive disorder with comorbid anxiety treated with fluoxetine. Arch Women Ment Health 2004;7(3):167-71.

217. Rapaport MH, Schneider LS, Dunner DL, Davies JT, Pitts CD. Efficacy of controlled-release paroxetine in the treatment of late-life depression. J Clin Psychiatry 2003;64(9):1065-74.

218. Oslin DW, Ten Have TR, Streim JE, Datto CJ, Weintraub D, DiFilippo S, et al. Probing the safety of medications in the frail elderly: evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents. J Clin Psychiatry 2003;64(8):875-82.

219. Entsuah AR, Huang H, Thase ME. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. J Clin Psychiatry 2001;62(11):869-77.

220. Roy-Byrne PP, Perera P, Pitts CD, Christi JA. Paroxetine Response and Tolerability Among Ethnic Minority Patients With Mood or Anxiety Disorders: A Pooled Analysis. J Clin Psychiatry 2005;66(10):1228-1233.

221. Wagner GJ, Maguen S, Rabkin JG. Ethnic differences in response to fluoxetine in a controlled trial with depressed HIV-positive patients. Psychiatr Serv 1998;49(2):239-40.

222. Clayton AH, Stewart RS, Fayyad R, Clary CM. Sex differences in clinical presentation and response in panic disorder: pooled data from sertraline treatment studies. Arch Women Ment Health 2005.

223. Abarca J, Malone DC, Armstrong EP, Grizzle AJ, Hansten PD, Van Bergen RC, et al. Concordance of severity ratings provided in four drug interaction compendia. J Am Pharm Assoc (Wash DC) 2004;44(2):136-41.

224. Wernicke JF, Sayler ME, Koke SC, Pearson DK, Tollefson GD. Fluoxetine and concomitant centrally acting medication use during clinical trials of depression: the absence of an effect related to agitation and suicidal behavior. Depress Anxiety 1997;6(1):31-9.

225. Harvey AT, Preskorn SH. Cytochrome P450 Enzymes: interpretation of their interactions with selective serotonin reuptake inhibitors. J Clin Psychopharmacol 1996;16(5):345-55.

226. Sproule BA, Naranjo CA, Bremner KE, Hassan PC. Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. Clin Pharmacokinet 1997;33(6):454-71.

227. Linden RD, Wilcox CS, Heiser JF, Cavanaugh E, Wisselink PG. Are selective serotonin reuptake inhibitors well tolerated in somatizing depressives? Psychopharmacol Bull 1994;30(2):151-6.

228. Cornelius JR, Salloum IM, Ehler JG, Jarrett PJ, Cornelius MD, Perel JM, et al. Fluoxetine in depressed alcoholics. A double-blind, placebo-controlled trial. Arch Gen Psychiatry 1997;54(8):700-5.

229. Cornelius JR, Salloum IM, Thase ME, Haskett RF, Daley DC, Jones-Barlock A, et al. Fluoxetine versus placebo in depressed alcoholic cocaine abusers. Psychopharmacol Bull 1998;34(1):117-21.

230. Cornelius JR, Salloum IM, Haskett RF, Daley DC, Cornelius MD, Thase ME, et al. Fluoxetine versus placebo in depressed alcoholics: a 1-year follow-up study. Addict Behav 2000;25(2):307-10.

231. Schmitz JM, Averill P, Stotts AL, Moeller FG, Rhoades HM, Grabowski J. Fluoxetine treatment of cocaine-dependent patients with major depressive disorder. Drug Alcohol Depend 2001;63(3):207-14.

232. Rabkin JG, Wagner GJ, Rabkin R. Fluoxetine treatment for depression in patients with HIV and AIDS: a randomized, placebo-controlled trial. Am J Psychiatry 1999;156(1):101-7.

233. Razavi D, Allilaire JF, Smith M, Salimpour A, Verra M, Desclaux B, et al. The effect of fluoxetine on anxiety and depression symptoms in cancer patients. Acta Psychiatr Scand 1996;94(3):205-10.

234. Petrakis I, Carroll KM, Nich C, Gordon L, Kosten T, Rounsaville B. Fluoxetine treatment of depressive disorders in methadone-maintained opioid addicts. Drug Alcohol Depend 1998;50(3):221-6.

235. Roscoe JA, Morrow GR, Hickok JT, Mustian KM, Griggs JJ, Matteson SE, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat 2005;89(3):243-9.

236. Krishnan KR, Doraiswamy PM, Clary CM. Clinical and treatment response characteristics of late-life depression associated with vascular disease: a pooled analysis of two multicenter trials with sertraline. Prog Neuropsychopharmacol Biol Psychiatry 2001;25(2):347-61.

237. Aguglia E, Casacchia M, Cassano GB, Faravelli C, Ferrari G, Giordano P, et al. Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. Int Clin Psychopharmacol 1993;8(3):197-202.

238. Davidson JR, Meoni P, Haudiquet V, Cantillon M, Hackett D. Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms. Depress Anxiety 2002;16(1):4-13.

239. Feiger AD, Flament MF, Boyer P, Gillespie JA. Sertraline versus fluoxetine in the treatment of major depression: a combined analysis of five double-blind comparator studies. Int Clin Psychopharmacol 2003;18(4):203-10.

240. Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. J Clin Psychopharmacol 2004;24(4):389-99.

241. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: Pooled analysis of placebo-controlled trials. 2002;7(4 Suppl 1):40-44.

242. Llorca PM, Azorin JM, Despiegel N, Verpillat P. Efficacy of escitalopram in patients with severe depression: a pooled analysis. Int J Clin Pract 2005;59(3):268-75.

243. Shelton C, Entsuah R, Padmanabhan SK, Vinall PE. Venlafaxine XR demonstrates higher rates of sustained remission compared to fluoxetine, paroxetine or placebo. Int Clin Psychopharmacol 2005;20(4):233-8.

244. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. Biol Psychiatry 2000;48(9):894-901.

245. Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. Biol Psychiatry 2002;52(12):1166-74.

246. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234-41.

247. Thase ME, Haight BR, Richard N, Rockett CB, Mitton M, Modell JG, et al. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. J Clin Psychiatry 2005;66(8):974-81.

248. Wade A, Crawford GM, Angus M, Wilson R, Hamilton L. A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. Int Clin Psychopharmacol 2003;18(3):133-41.

249. DeVane CL, Sallee FR. Serotonin selective reuptake inhibitors in child and adolescent psychopharmacology: a review of published experience. J Clin Psychiatry 1996;57(2):55-66.

250. Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Carmody T, Mayes TL. Fluoxetine in child and adolescent depression: acute and maintenance treatment. Depress Anxiety 1998;7(1):32-9.

251. Cox BJ, Swinson RP, Morrison B, Lee PS. Clomipramine, fluoxetine, and behavior therapy in the treatment of obsessive-compulsive disorder: a meta-analysis. J Behav Ther Exp Psychiatry 1993;24(2):149-53.

252. Greist JH, Jefferson JW, Kobak KA, Katzelnick DJ, Serlin RC. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. A meta-analysis. Arch Gen Psychiatry 1995;52(1):53-60.

253. Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ, Henk HJ. Behavioral versus pharmacological treatments of obsessive compulsive disorder: a meta-analysis. Psychopharmacology (Berl) 1998;136(3):205-16.

254. Nair NP, Bakish D, Saxena B, Amin M, Schwartz G, West TE. Comparison of fluvoxamine, imipramine, and placebo in the treatment of outpatients with panic disorder. Anxiety 1996;2(4):192-8.

255. Chung MY, Min KH, Jun YJ, Kim SS, Kim WC, Jun EM. Efficacy and tolerability of mirtazapine and sertraline in Korean veterans with posttraumatic stress disorder: a randomized open label trial. Hum Psychopharmacol 2004;19(7):489-94.

256. Davidson JRT, Weisler RH, Malik M, Tupler LA. Fluvoxamine in civilians with posttraumatic stress disorder. J Clin Psychopharmacol 1998;18(1):93-95.

257. Davidson JRT, Weisler RH, Malik ML, Connor KM. Treatment of posttraumatic stress disorder with nefazodone. Int Clin Psychopharmacol 1998;13(3):111-13.

258. De Boer M, Op den Velde W, Falger PJR, Hovens JE, De Groen JHM, Van Duijn H. Fluvoxamine treatment for chronic PTSD: a pilot study. Psychother Psychosom 1992;57:158-63.

259. Martenyi F, Brown EB, Zhang H, Prakash A, Koke SC. Fluoxetine versus placebo in posttraumatic stress disorder. J Clin Psychiatry 2002;63(3):199-206.

260. Martenyi F, Brown EB, Zhang H, Koke SC, Prakash A. Fluoxetine v. placebo in prevention of relapse in post-traumatic stress disorder. Br J Psychiatry 2002;181:315-20.

261. Smajkic A, Weine S, Djuric-Bijedic Z, Boskailo E, Lewis J, Pavkovic I. Sertraline, paroxetine, and venlafaxine in refugee posttraumatic stress disorder with depression symptoms. J Trauma Stress 2001;14(3):445-52.

262. Tucker P, Zaninelli R, Yehuda R, Ruggiero L, Dillingham K, Pitts CD. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001;62(11):860-8.

263. Diegoli MSC, da Fonseca AM, Diegoli CA, Pinotti JA. A double-blind trial of four medications to treat severe premenstrual syndrome. Int J Gynecol Obstet 1998;62:63-67.

264. Carr RR, Ensom MH. Fluoxetine in the treatment of premenstrual dysphoric disorder. Ann Pharmacother 2002;36(4):713-7.

265. Beasley CMJ, Dornseif BE, Bosomworth JC, Sayler ME, Rampey AHJ, Heiligenstein JH, et al. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. BMJ 1991;303(6804):685-92.

266. Beasley CM, Dornseif BE, Bosomworth JC, Sayler ME, Rampey AH, Heiligenstein JH, et al. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. Int Clinic Psychopharmacol 1992;6 Suppl 6:35-37.

267. Tollefson GD, Rampey AHJ, Beasley CMJ, Enas GG, Potvin JH. Absence of a relationship between adverse events and suicidality during pharmacotherapy for depression. J Clin Psychopharmacol 1994;14(3):163-9.

268. Gulseren L, Gulseren S, Hekimsoy Z, Mete L. Comparison of fluoxetine and paroxetine in type II diabetes mellitus patients. Arch Med Res 2005;36(2):159-65.

269. Roy-Byrne PP, Pages KP, Russo JE, Jaffe C, Blume AW, Kingsley E, et al. Nefazodone treatment of major depression in alcohol-dependent patients: a double-blind, placebo-controlled trial. J Clin Psychopharmacol 2000;20(2):129-36.

270. Demyttenaere K, Albert A, Mesters P, Dewe W, De Bruyckere K, Sangeleer M. What happens with adverse events during 6 months of treatment with selective serotonin reuptake inhibitors? J Clin Psychiatry 2005;66(7):859-63.

271. Ferguson JM. The effects of antidepressants on sexual functioning in depressed patients: a review. J Clin Psychiatry 2001;62 Suppl 3:22-34.

272. Letizia C, Kapik B, Flanders WD. Suicidal risk during controlled clinical investigations of fluvoxamine. J Clin Psychiatry 1996;57(9):415-21.