Drug Class Review
on
Second Generation Antidepressants

FINAL REPORT

November 2004

The Agency for Healthcare Research and Quality has not yet seen or approved this report

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Table of Contents

Exhibits

Figures

Evidence Tables

Appendices

Many thanks to our abstractors Heather Himburg and Melissa Butler and to our supporting staff Leah Randolph, Laura Morgan, Diane Greer, and Susan Goulet.

INTRODUCTION

A. Overview

Axis I psychiatric disorders such as depressive disorder, bipolar disorder, anxiety disorder, adjustment disorder, and premenstrual disorders, are serious disabling illnesses. Combined, they affect approximately one in five Americans.[1] Major depressive disorder is the most prevalent, affecting more than 16 percent (lifetime) of US adults.[2] In 2000, the economic burden of depressive disorders was estimated to be $83.1 billion.[3] More than 30 percent of these costs were attributable to direct medical expenses.

Pharmacotherapy dominates the medical management of Axis I psychiatric disease. Before the late 1980s, pharmacologic treatment was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (with the exception of premenstrual disorder, which historically was untreated). The TCAs and MAOIs sometimes are referred to as traditional or first-generation antidepressants. Because 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; MAOIs have the potential to produce hypertensive crisis if taken along with certain foods or dietary supplements containing excessive amounts of tyramine), 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]

The mechanism of action of most second-generation antidepressants is understood poorly. 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.

With the exception of fluvoxamine, which is approved only for the treatment of obsessive-compulsive disorder, all of the other second-generation antidepressants are approved for the treatment of major depressive disorder. Table 1 summarizes the newer products that are available in the US by drug class.

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, venlafaxine, bupropion, and nefazodone. We will examine the role of these agents in treating patients with conditions in diagnostic categories classified by the Diagnostic and Statistical Manual of Mental Disorders (DSM); these include depressive disorders (major depressive disorder [MDD] and dysthymic disorder), bipolar disorder (specifically bipolar I disorder, which is the classic manic-depressive disease), generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), social anxiety disorder, and adjustment disorders (mixed anxiety, depressed mood subtype, and others). 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 version 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 major depressive disorder in pediatric outpatient populations. Tables 1 and 2 show included drugs, FDA approved uses, and recommended dosages.

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

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
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†††; 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
	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 sustained, controlled, 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.
† 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

Table 2: Usual Dosing Range and Frequency of Administration (adults)

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
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 sustained, controlled, 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, bipolar, anxiety, adjustment and premenstrual dysphoric disorders, do SSRIs, SNRIs, and other second-generation antidepressants differ in efficacy or effectiveness?
2. For outpatients with depressive, bipolar, anxiety, adjustment, and premenstrual dysphoric disorders, do SSRIs and other 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 SSRI or other 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: Outcome Measures and Study Eligibility Criteria

Outcome	Outcome Measures	Study Eligibility Criteria

Efficacy/ Effectiveness	• Response
	• Remission
	• Speed of response/remission
	• Relapse
	• Quality of life
	• Functional capacity
	• Hospitalization
		• Head-to-head randomized controlled clinical trials or meta-analyses evaluating:
		  • SSRI vs. SSRI
		  • SSRI vs. SNRI
		  • SSRI vs. other second- generation antidepressant
		• 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*
	  • *activation of mania/hypomania*
	  • *seizures*
	  • *suicide*
	  • *hepatoxicity*
	  • *weight gain*
	  • *gastrointestinal symptoms*
	  • *loss of libido*
	  • *others*
		• Head-to-head randomized controlled clinical trials or meta-analyses evaluating:
		  • SSRI vs. SSRI
		  • SSRI vs. SNRI
		  • SSRI vs. other second-generation antidepressant
		• When sufficient evidence was not available for head-to-head trials within a specific diagnostic group, we evaluated
		  • Placebo-controlled trials
		  • Observational studies

METHODS

A. Literature Search

To identify articles relevant to each key question we searched MEDLINE, Embase, The Cochrane Library, PsychLit, and the International Pharmaceutical Abstracts. We used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (major depressive disorder, bipolar disorder, dysthymia, general anxiety disorder, posttraumatic stress disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, adjustment disorder, premenstrual dysphoric disorder), drug interactions, and adverse events with a list of 10 specific SSRIs and second-generation antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, mirtazapine, venlafaxine, bupropion, and nefazodone). We limited the electronic searches to "human" and "English language." Sources were searched from 1980 to 2004 (January) 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 (ProCite5.0). Additionally, we handsearched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the FDA (Food and Drug Administration).

Furthermore the Center for Evidence-based Policy at the Oregon Health and Science University (OHSU) contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy (http://www.ohsu.edu/drugeffectiveness/pharma/Dossier_Submission_Protocol_Ver_1_2.pdf). We received dossiers from six pharmaceutical companies.

Our searches found 1,717 citations, unduplicated across databases. Additionally we detected 124 articles from manually reviewing the reference lists of pertinent review articles. No included studies stemmed from pharmaceutical dossiers. The total number of citations included in the database was 1,841.

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 SSRI, SNRI, or 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 562 articles on an abstract level and retrieved 343 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 145 eligible studies we excluded 38 on the grounds of poor methodological quality (Appendix C).

E. Data Synthesis

We did 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 based on the pooled risk difference as well as based on the empirical observed counts. All statistical analyses were conducted using StatsDirect, version 2.3.8.

RESULTS

Overview

We identified 1,841 citations from searches and reviews of reference lists. We identified 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 107 studies: 85 RCTs, 10 meta-analyses, 8 observational studies, and 4 studies of other design. Furthermore, we retrieved 44 articles for background information. One study of interest could not be retrieved after multiple attempts.[15]

Reasons for exclusions were based on eligibility criteria or methodological criteria (Figure 1, QUORUM Tree). Thirty-four 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. This problem arose because of a simple lack of pretrial power calculations or because of a specific interest of the sponsoring industry to report efficacy equivalency between two drugs.

Of 107 included studies, 70 percent were financially supported by pharmaceutical companies; 14 percent were funded by governmental agencies or independent funds. For 16 percent of included studies, we could not determine funding source.

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

Table 4: Abbreviations and Full Names of Diagnostic Scales and Other Instruments

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

KEY QUESTION 1.

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

We included 74 RCTs and 8 meta-analyses. Of the RCTs, 46 were head-to-head trials; 28 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 SSRIs, SNRIs, or other 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, venlafaxine, bupropion, and nefazodone.

One systematic review and 43 RCTs compared the effectiveness or efficacy of one SSRI, SNRI, or other second-generation antidepressant to another for treating patients with major depressive disorder (MDD) (Table 8). 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 (Diagnostic and Statistical Manual of Mental Disorders [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 or 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; forty percent reported a follow-up of 12 weeks or more. Three European trials[16, 17, 18] and one US trial [19] in primary care settings, with less stringent eligibility criteria could be viewed as effectiveness trials. Three studies had long periods of follow-up.[16,18,19] 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) was 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 18 trials (24%) 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

A fair-rated European/Canadian trial 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] The study duration was 8 weeks; loss to follow-up was 7 percent. Intention-to-treat results showed that the escitalopram group had significantly more responders ($\geq$ 50% improvement on MADRS; 63.7% vs. 52.6%; $p = 0.021$) and remitters (MADRS < 12; 52.1% vs. 42.8%; $p < 0.036$) than the citalopram group. Escitalopram was numerically better at all time points on all three efficacy scales (MADRS, CGI-I, CGI-S). The study did not assess health outcomes.

A fair-rated, fixed-dose, multicenter, placebo-controlled trial (n = 491) compared escitalopram (10mg/d and 20mg/d) to citalopram (40mg/d) over 8 weeks.[21] Outcome measures included a quality-of-life questionnaire assessed at baseline and endpoint. Loss to follow-up was 24 percent. Intention-to-treat analysis showed that all treatment groups were significantly more effective than placebo. The mean change from baseline to endpoint did not differ significantly between escitalopram 20mg and citalopram 40mg on MADRS and CGI-S. Escitalopram 10mg was as effective as citalopram on most efficacy measures. Treatments were not directly compared with respect to quality of life in the article. No significant differences in adverse events were reported.

Citalopram vs. fluoxetine

In a fair-rated trial from France, 397 outpatients with major depressive disorder attending general practices were randomly assigned to citalopram (20mg/d) or fluoxetine (20mg/d) over 8 weeks.[17] 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, there were no statistically significant differences in MADRS or HAM-D scores.

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.[16] 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

A fair-rated, recent, multicenter European, 6-week trial assessed efficacy and tolerability of fluoxetine (20mg/d) and fluvoxamine (100mg/d) in 184 outpatients.[22] Loss to follow-up was 20.9 percent. HAM-D, the primary outcome measure, was not significantly different at any time. The drugs were equally effective as assessed by secondary outcome measures (CGI, Clinical Anxiety Scale [CAS], the Irritability, depression, and anxiety scale [IDAS], Beck's Scale for Suicide Ideation [Beck's SSI], sleep evaluation) for suicidal ideation, sleep, anxiety, and severity of illness at endpoint. At week 2, fluvoxamine had significantly more responders on CGI-S (29% vs. 16%; $p < 0.05$) and a greater reduction of CGI-S scores ($p < 0.05$) but not at 4 or 6 weeks. Frequency of adverse events did not differ significantly.

Fluoxetine vs. paroxetine

Seven fair-rated studies compared fluoxetine to paroxetine.[23, 24, 25, 26, 27, 28,14] Two RCTs were conducted in a population older then 60 years.[23, 26] 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).[23] 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[24, 25, 26, 27, 28,14] lasted six to twelve weeks. Loss to follow up was between 20 and 36 percent. Two studies supported a faster onset of action of paroxetine than fluoxetine,[25,26] four trials did not.[14, 24, 27, 28] 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 anxious depression.[23,24, 27, 28,14] A Canadian RCT assessed anxiolytic activity and akathisia as secondary outcome measure and could not detect any significant differences between treatment groups.[24] 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.[24]

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.[24, 28, 25, 26, 27,14] A "response" was defined as an improvement of 50% or more on the HAM-D scale. The seventh study could not be included because the article did not provide the necessary data.[23] The statistical analysis included 795 patients. Results (Exhibit 1) 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 and L'Abbe plot did not indicate major biases.

Fluoxetine vs. sertraline

Six studies compared fluoxetine to sertraline.[29, 30, 28, 31,18,19]

The top level evidence consisted of two effectiveness trials[18,19] and one efficacy trial[30] with long periods of follow-up.

Two fair-rated, multicenter trials from France were conducted in office settings (private psychiatrists and general physicians [GPs]).[30,18] 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 analysis 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).[29, 31-34,28] Treatment durations varied from 6 to 16 weeks.One study was conducted in 236 participants older than 60 years.[31,33] 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 ($p = 0.027$).[33]

We conducted a meta-analysis of five of these studies comparing the effects of fluoxetine to sertraline on HAM-D scores at study endpoint.[29, 28, 31,18,30] All but one studies were financially supported by the manufacturer of sertraline. Results are presented in Exhibit 2. 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 number needed to treat to gain one additional responder based on the pooled risk difference as well as on empirical observed counts is 17.

A meta-analysis of responders based only on the HAM-D scale did not provide 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 and L'Abbe plot did not indicate major biases.

Paroxetine vs. sertraline

One fair-rated Swedish RCT compared paroxetine (20-40mg/d) to sertraline (50-150mg/d) in a 24-week study.[35] 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 (50-200mg/d) and fluvoxamine (50-150mg/d) in 97 depressed patients.[36] 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.[37, 38] 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

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.[39] 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).[40,41] The German study enrolled 275 patients in a 6-week trial.[40] The US trial randomized 255 participants for 8 weeks.[41] 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.[42] 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. 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.[43] 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[44,45] or generalized anxiety disorder.[46,47] 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.[44] 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).[44] Two studies reported significantly more dizziness ($p < 0.001$) and sweating ($p < 0.05$) in the venlafaxine group than in the fluoxetine group.[46,47,45]

Three additional trials also provided inconsistent evidence on the efficacy of venlafaxine compared to fluoxetine[48-50] One study reported a significantly higher response rate of venlafaxine than fluoxetine (72% vs. 60%; p = 0.023).[49] Two other trials did not support this finding[48, 50] 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.[48]

We conducted a meta-analysis of six studies comparing venlafaxine to fluoxetine.[49,44, 48,45, 46,50] All studies were financially supported by the manufacturer of venlafaxine. One study was excluded because of missing data.[43] The main outcome measure was the response to treatment on HAM-D or MADRS scales at study endpoint. Results (Exhibit 3), 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 and L'Abbe plot did not indicate major biases.

The number needed to treat based on the pooled risk difference and empirical observed counts 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) [51]. 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.[52,53] 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.[52] 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).[53] 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

One good quality Scandinavian trial compared efficacy and tolerability of venlafaxine (75-150mg/d) to sertraline (50-100mg/d) in 147 patients who were mainly moderately to markedly ill.[54] 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.

A recent, fair-rated meta-analysis compared bupropion to SSRIs in major depressive disorder of 1,332 adult outpatients.[55] 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, CGI-I and HAM-D scores could not be pooled 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.[56] 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 major depressive disorder.[57] 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 good 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.[58,59] The majority of patients were white (bupropion SR: 98%, paroxetine: 90%) and female (bupropion SR: 54%, paroxetine: 60%) and had not used antidepressants for the current episode before enrollment (bupropion SR 83%; paroxetine 88%). The overall loss to follow-up was 16 percent with no significant difference between treatment groups. Statistical LOCF analysis showed that efficacy in any outcome measure did not differ significantly between treatment groups. Response rates (≥ 50% reduction in HAM-D scores) were similar in both groups (bupropion SR 71%; paroxetine 77%). Both treatment groups improved significantly in quality of life scales (Quality-of-Life in Depression Scale [QLDS], Short Form-36 Health Survey [SF-36]) between baseline and endpoint ($p < 0.0001$), but the treatment groups did not differ significantly.

Bupropion 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.[60] 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.[61, 62] 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.[61] 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 ($p < 0.05$).[62]

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.[63, 64, 65] Data from these trials were pooled into one analysis.[65] 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).[66,67] Patients who responded to acute treatment were enrolled in an open-label continuation phase (n = 108) from w eek 8 to month 6.[67] 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.[68] 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

Forty-four 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. Studies were often small and relatively underpowered to detect significant differences in efficacy. 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, bupropion has fewer sexual side effects than fluoxetine and sertraline; mirtazapine presents a faster onset of action than paroxetine and sertraline; nefazodone improves sleep quality; 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. Generally, high rates of loss to follow-up limit the validity of many studies.

Effectiveness

One good and three fair-rated[16,17,18,19] effectiveness trials provide good to fair evidence that treatment effectiveness does not differ among compared drugs. These comparisons included citalopram to sertraline, citalopram to fluoxetine, 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.[16] However, this finding is limited to a single trial.

Efficacy

Nine 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).[35,21 30,23,22,34,26,31,18]

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.[65] All three studies were financially supported by a manufacturer of nefazodone.

Several other efficacy studies assessed quality of life and health-related functional capacity in SSRIs compared to other second generation antidepressants.[42,59,68] 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.

Thirty-nine 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.

We conducted a meta-analysis of five trials[29,28,31,18,30] 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 number needed to treat 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[24,34,25, 26, 27,28] 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,[23,25, 26] four other trials do not support this finding.[14,24,27,28] Four studies provide fair evidence that paroxetine and fluoxetine do not differ significantly in the improvement of anxiety in patients with anxious depression.[23,24,27,28]

Eight of nine additional studies comparing SSRIs to each other report good to fair evidence that efficacy does not differ among the compared drugs. Only one fair study reported that the efficacy of escitalopram is significantly greater than the efficacy of citalopram.[20] However, this result is inconsistent with another trial comparing escitalopram to citalopram.[21]

Seven good to fair studies provide mixed evidence about a higher efficacy and a greater anxiolytic effect of venlafaxine compared to fluoxetine.[49, 44, 48, 43, 45, 46,50] 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 number needed to treat 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.

Three studies yielded fair evidence that mirtazapine has a significantly faster onset of action than paroxetine and sertraline.[42,40,41] 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.[39] The overall efficacy did not differ significantly between mirtazapine and SSRIs.

Six trials[58,60,56,57,62,61] and a meta-analysis[55] 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.[61,62,60] The NNT to yield 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.[57]

Several other studies compared SSRIs to other second generation antidepressants.[17,52,54,53,67,68,37,65,38] 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 5: Study Characteristics and Effect Sizes of Trials Indicating a Faster Onset of Mirtazapine than Fluoxetine. Paroxetine, and Sertraline

Study	Sample size	Comparison	Effect size	P-value	Comments
Faster onset of mirtazapine					
Behnke et al., 2003 [42]	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 [41]	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 [39]	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 [40]	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 6: Study Characteristics and Effect Sizes of Trials Indicating Fewer Sexual Adverse Events for Bupropion than Fluoxetine, Paroxetine, and Sertraline

Study	Sample size	Comparison	Effect measure	P-value	Comments
Lower rate of sexual side effects with bupropion SR					
Coleman et al., 2001[57]	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[62]	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[61]	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 6: Study Characteristics and Effect Sizes of Trials Indicating Fewer Sexual Adverse Events for Bupropion than Fluoxetine, Paroxetine, and Sertraline, continued

Study	Sample size	Comparison	Effect measure	P-value	Comments
Kavoussi et al. 1997 [60 69]	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 [56]	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 7: Study Characteristics and Effect Sizes of Trials Indicating a Better Sleep Profile with Nefazodone than Fluoxetine

Study	Sample size	Comparison	Effect measure	P-value	Comments
Better sleep profile with nefazodone					
Rush et al. 1998 [65]	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

Table 8: Interventions, Numbers of Patients, and Quality Ratings of Studies in Adults with Major Depressive Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Ekselius et al., 1997 [16]	Citalopram vs. Sertraline	400	No differences	Good
Burke et al., 2002 [21]	Citalopram vs. Escitalopram	491	No differences	Fair
Lepola et al., 2003 [20]	Citalopram vs. Escitalopram	471	Significantly more responders and remitters in the escitalopram group	Fair
Patris et al., 1996 [17]	Citalopram vs. Fluoxetine	357	Faster onset of citalopram	Fair
Dalery J et al., 2003 [22]	Fluoxetine vs. Fluvoxamine	184	Faster onset of fluvoxamine	Fair
Cassano et al., 2002 [23]	Fluoxetine vs. Paroxetine	242	Faster onset of paroxetine	Fair
Chouinard et al., 1999 [24]	Fluoxetine vs. Paroxetine	203	No differences	Fair
DeWilde et al., 1993 [25]	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 [26]	Fluoxetine vs. Paroxetine	108	Faster onset of paroxetine	Fair
Fava et al., 1998 [27]	Fluoxetine vs. Paroxetine	128	No differences	Fair
Bennie et al., 1995 [29]	Fluoxetine vs. Sertraline	286	No differences	Fair
Boyer et al., 1998 [30]	Fluoxetine vs. Sertraline	242	No differences	Fair
Fava et al., 2002 [28]	Fluoxetine vs. Sertraline vs. Paroxetine	284	No differences	Fair
Finkel et al., 1999 [33]	Fluoxetine vs. Sertraline	75	No differences	Fair
Sechter et al., 1999 [18]	Fluoxetine vs. Sertraline	238	No differences	Fair
Newhouse et al., 2000 [31]	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 [35]	Paroxetine vs. Sertraline	353	No differences	Fair
Nemeroff et al., 1995 [36]	Sertraline vs. Fluvoxamine	97	No differences	Fair
Franchini et al., 1997 [37]	Sertraline vs. Fluvoxamine	64	No differences	Fair

Table 8: 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				
Hong et al., 2003 [39]	Mirtazapine vs. Fluoxetine	133	No differences	Fair
Schatzberg et al., 2002 [40]	Mirtazapine vs. Paroxetine	255	Faster onset of mirtazapine	Fair
Benkert et al., 2000 [41]	Mirtazapine vs. Paroxetine	275	Faster onset of mirtazapine	Fair
Behnke et al., 2003 [42]	Mirtazapine vs. Sertraline	346	Faster onset of mirtazapine	Fair
Costa e Silva et al., 1998 [43]	Venlafaxine vs. Fluoxetine	382	No differences	Good
Alves et al., 1999 [48]	Venlafaxine vs. Fluoxetine	87	Faster onset of venlafaxine	Fair
Tylee et al., 1997 [50]	Venlafaxine vs. Fluoxetine	341	No differences	Fair
Dierick et al., 1996 [49]	Venlafaxine vs. Fluoxetine	314	Significantly higher response rate for venlafaxine	Fair
De Nayer et al., 2002 [44]	Venlafaxine vs. Fluoxetine	146	Significantly greater improvement for venlafaxine	Fair
Rudolph et al., 1999 [45]	Venlafaxine XR vs. Fluoxetine	301	No differences	Fair
Silverstone et al., 1999 [46]	Venlafaxine XR vs. Fluoxetine	368	No differences	Fair
Ballus et al., 2000 [52]	Venlafaxine vs. Paroxetine	84	No differences	Fair
McPartlin et al., 1998 [53]	Venlafaxine XR vs. Paroxetine	361	No differences	Fair
Mehtonen et al., 2000 [54]	Venlafaxine vs. Sertraline	147	Significantly higher response rate for venlafaxine	Good
Other second-generation antidepressants (DopRi, 5-HT$_2$) versus SSRIs				
Nieuwstraten et al., 2001 [55]	Bupropion vs. SSRIs (SR)	1,332	No differences	Good
Feighner et al., 1991 [56]	Bupropion vs. Fluoxetine	123	No differences	Fair
Coleman et al., 2001 [57]	Bupropion vs. Fluoxetine	456	No differences	Fair
Weihs et al., 2000 [58]	Bupropion SR vs. Paroxetine	100	No differences	Good
Coleman et al., 1999 [62]	Bupropion vs. Sertraline	364	No differences	Fair
Croft et al., 1999 [61]	Bupropion vs. Sertraline	360	No differences	Fair
Kavoussi et al.,1997 [60]	Bupropion vs. Sertraline	248	No differences	Fair
Rush et al., 1998 [65]	Nefazodone vs. Fluoxetine	125	No differences	Fair
Baldwin et al., 1996,2001 [67]	Nefazodone vs. Paroxetine	206	No differences	Fair
Feiger et al., 1996 [68]	Nefazodone vs. Sertraline	160	No differences	Fair

(SR)= Systematic review

B. Dysthymia in Adults

The following drugs are currently approved by the FDA for the treatment of dysthymia in adults: citalopram, escitalopram, fluoxetine, paroxetine, sertraline mirtazapine, venlafaxine, bupropion, and nefazodone.

We did not find any head-to-head trials among patients with dysthymia. Three placebo-controlled studies (Table 9) assessed efficacy and tolerability of sertraline and paroxetine in a population with dysthymia.[70, 71, 72, 73, 74,75]

1. SSRIs compared to placebo in adults with dysthymia

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 (10-40mg/d), placebo, or behavioral therapy.[74,75] 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. [70,71,72] 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.[73] 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.[74,75]

Efficacy

Fair evidence from two studies indicates that sertraline has a significantly greater efficacy in the treatment of dysthymia than placebo.[70,71,72,73] In both trials sertraline treatment lead to a significantly greater improvement of quality of life and psychosocial functioning than placebo.

Table 9: Interventions, Numbers of Patients, and Quality Ratings in Controlled Trials of Adults with Dysthymia

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus Placebo				
Barrett et al., 2001 Williams et al., 2000 [74, 75]	Paroxetine vs. Placebo vs. Behavioral therapy	656	Significantly more responders for paroxetine in patients older than 60 years	Fair
Thase et al., 1996 [70]	Sertraline vs. Imipramine vs. Placebo	412	Significantly more responders for sertraline than placebo	Fair
Ravindran et al., 2000 [73]	Sertraline vs. Placebo	310	Significantly more responders and remitters for sertraline	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.

Recent reports not published in the peer-reviewed literature motivated an evaluation of second-generation antidepressants in children and adolescents. Specifically, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) evaluated published and unpublished data (data available at http://medicines.mhra.gov.ukT) for the second-generation antidepressants. Based on data from RCTs submitted to the MHRA, the efficacy of second-generation antidepressants in treating MDD in children and adolescents was demonstrated only for fluoxetine. Reported evidence failed to confirm efficacy for citalopram, paroxetine, sertraline, mirtazapine, and venlafaxine.

In 2003, the makers of paroxetine and venlafaxine issued public warnings regarding the potential risk for hostility and suicidality. Since this time, the FDA has issued a public health advisory urging doctors, patients, families, and other caregivers to be particularly cautious of signs of worsening depression or suicidal thoughts at the beginning of antidepressant therapy or whenever the dose is changed. The makers of citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, mirtazapine, venlafaxine, bupropion, and nefazodone were asked to add the caution to their product labeling (for both pediatric and adult populations). The FDA continues to review existing published and unpublished evidence for the risk of suicidal ideation with second-generation antidepressants, particularly in children and adolescents.

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.

The NIMH is currently conducting research to help clarify the potential value and risks of antidepressants, and to explore how medications compare with psychotherapy in adolescent depression. In particular, an NIMH-funded, multi-site controlled clinical trial, the Treatment for Adolescents with Depression Study (TADS), was launched in the late 1990s to directly compare the efficacy of fluoxetine, cognitive-behavioral therapy, and a combination of the two. Results are expected later in 2004 (http://www.nimh.nih.gov/Press/stmntantidepmeds.cfm).

We did not identify any head-to-head trials comparing one second-generation antidepressant to another for treatment of major depressive disorder in children and adolescents. We found three fair controlled trials comparing a non-FDA-approved SSRI or SNRI to placebo (Table 10).

In addition, two systematic reviews evaluated placebo-controlled evidence for the use of SSRIs and an SNRI.[76,77] One review highlighted placebo-controlled evidence already included in this discussion,[76] so we do not comment on it further here. A second review analyzed published and unpublished data for citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine.[77] 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

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.[78] 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 (≥ 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 patients and placebo ($p = 0.13$ 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 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.[79] These identically designed, concurrently conducted 10-week trials randomized 376 children and adolescents (6 to 17 years) to flexible-dose sertraline (50-200 mg/d) or placebo. Significantly more sertraline-treated patients were female ($p = 0.02$). Twenty percent of randomized participants did not complete the study. The

primary efficacy measure was mean change from baseline score on the CDRS-R. In the intention-to-treat analysis, sertraline-treated patients had a significantly greater mean change in CDRS-R score ($p < 0.01$). Significant differences were observed as early as week 3. Secondary efficacy measures included treatment response (≥ 40% decrease in CDRS-R or CGI-I score of 2 or lower), symptoms of anxiety (Multidimensional Anxiety Scale for Children [MASC]), patient's social functioning [CGAS], and quality of life [PQ-LES-Q]). Significantly more sertraline-treated patients were defined as treatment responders ($p < 0.05$). Statistically significant differences were not observed for measures of anxiety, social functioning, or quality of life. Sertraline-treated patients reported a higher incidence of insomnia, diarrhea, vomiting, anorexia, and agitation.

Of note for this study is the fact that only pooled data were published. Before pooling data from the two independent trials, neither trial 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.[80] 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 17 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.[77] 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 major depressive disorder. Recent evidence from a systematic review of published and unpublished data suggests that only fluoxetine has a favorable risk-benefit profile in pediatric populations.

Effectiveness

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

Efficacy

Three placebo-controlled trials provide fair evidence that efficacy to improve health outcomes does not differ between placebo and sertraline, paroxetine, and venlafaxine.[81, 79, 80] There is FDA-approved evidence to support the efficacy of fluoxetine in treating major depressive disorder in children and adolescents. Of note, however, published trials supporting the efficacy of fluoxetine[82,83] were excluded from our review due to 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 10: Interventions, Numbers of Patients, and Quality Ratings of Studies in Children and Adolescents with Major Depressive Disorder

Author, Year	Interventions	N	Results	Quality Rating
Systematic Review				
Whittington et al., 2004 [77]	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				
Keller et al., 2001 [78]	Paroxetine vs. Imipramine vs. Placebo	275	No differences	Fair
Wagner et al., 2003 [79]	Sertraline vs. Placebo	376	Significantly greater efficacy for sertraline	Fair
SNRIs versus placebo				
Mandoki et al., 1997 [80]	Venlafaxine vs. Placebo	40	No differences	Fair

(SR)= Systematic review

II. For adult outpatients with bipolar disorder, do SSRIs or other second-generation antidepressants differ in efficacy?

Currently, no SSRIs or other second-generation antidepressants are approved by the FDA for the treatment of bipolar depression.

No head-to-head trial comparing one second-generation antidepressant to another was included in this review. One Spanish study[84] compared an SSRI (paroxetine) to venlafaxine over a 6-week period. We excluded this trial because only raters, but neither patients nor care providers, were blinded to treatment. A second head-to-head trial compared sertraline, venlafaxine, and bupropion.[85] However, published results evaluated only switch rates into hypomania or mania before the investigators broke the blinding code. Further reports on efficacy and safety data for this trial have not (yet) been published.

Because head-to-head evidence was insufficient, we evaluated placebo-controlled studies. One 10-week RCT comparing paroxetine to placebo was included.[86]

1. SSRIs compared to placebo in adult outpatients with bipolar disorder

Paroxetine vs. placebo

One fair-rated randomized double-blind placebo-controlled trial evaluated paroxetine (20-50 mg/d) and imipramine (150-300 mg/d) over a 10-week period[86] (Table 11). This multicenter study evaluated 35 paroxetine-treated patients, 39 imipramine-treated patients, and 43 placebo controls. Inclusion was defined by a criteria-based diagnosis (DSM-III-R) of bipolar disorder with at least one manic episode in the past 5 years. Also, participants were required to have a physician-rated depression score (HAM-D) of 15 or greater with no more than a 25 percent decrease in score between screening and baseline. Patients were required to be on a mood stabilizer regimen of lithium alone or in combination with sodium valproate or carbamazepine for at least 7 weeks before screening. Mood stabilizers were continued throughout the study. Rapid cyclers or patients who experienced a manic/hypomanic episode during the 4 weeks prior to baseline evaluation were excluded.

Main outcome measures examined included response rate (e.g., defined as a score of 7 or less on the physician-rated HAM-D scale, or much or very much improved as assessed by a global assessment method). Mean change in score on a clinician-rated global assessment scales also was assessed. An LOCF intention-to-treat analysis was used. Loss to follow-up was 33 percent, with more than a 10-percentage-point differential between paroxetine- and placebo-treated groups. At 10 weeks, differences in mean response (HAM-D, CGI-S) were not statistically significant. Switches to mania were not observed among paroxetine-treated patients.

2. Summary of the evidence

There is insufficient evidence to support the use of an SSRI or other second-generation antidepressant in patients with bipolar disorder.

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

Efficacy
One placebo-controlled study provides fair evidence that paroxetine is no more efficacious than placebo for the treatment of bipolar depression. No FDA-approved evidence exists for the use of a second-generation antidepressant (monotherapy) in the treatment of bipolar depression.

Table 11: **Interventions, Numbers of Patients, and Quality Ratings of Studies in Adults with Bipolar Disorder**

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus Active Control versus Placebo				
Nemeroff CB, et al., 2001 [86]	Paroxetine vs. Imipramine vs. Placebo	117	No differences	Fair

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

A. Generalized Anxiety Disorder

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

No head-to-head trials compared one second-generation antidepressant to another for the treatment of generalized anxiety disorder (GAD). FDA-approved evidence supports the general efficacy of escitalopram, paroxetine, and venlafaxine for treating GAD. Additional placebo-controlled evidence supporting these drugs was not reviewed. No published trials compared a non-FDA-approved second-generation antidepressant to placebo. Two RCTs comparing paroxetine to placebo evaluated measures of functional capacity[87,88,89] (Table 12).

Across two 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 Hamilton Rating Scale for Anxiety (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 17 or higher on the MADRS.

Secondary outcome measures included disability and comorbid depression in two studies comparing paroxetine to placebo. Both studies used the Sheehan Disability Scale (SDS) to assess health-related disability.

Both trials used an intention-to-treat analysis. Withdrawals because of adverse effects were higher in the active treatment groups.[88,87] One study used a fixed dosing protocol[87] and the other used a flexible dosing protocol.[88] Doses were comparable across the two studies.

1. SSRIs compared to placebo in adult outpatients with GAD

Paroxetine vs. placebo

Two fair studies comparing paroxetine to placebo included health outcome measures.[87,88] 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.[87] 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.[88] 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).

2. 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

FDA-approved evidence shows the general efficacy of escitalopram, paroxetine, and venlafaxine for treating GAD. Evidence is insufficient about efficacy of citalopram, fluoxetine, fluvoxamine, sertraline, mirtazapine, bupropion, and nefazodone for treating GAD. Two trials comparing paroxetine to placebo included measures of functional impairment.[87,88] Significant improvement in Sheehan Disability Scale (SDS) total score was observed at endpoint in both studies.

Table 12: Interventions, Numbers of Patients, and Quality Ratings of Studies in Adults with Generalized Anxiety Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus Placebo				
Pollack et al. , 2001[88]	Paroxetine vs. Placebo	331	Significantly greater reduction in SDS for paroxetine	Fair
Rickels et al. , 2003[87]	Paroxetine vs. Placebo	566	Significantly greater reduction in SDS for paroxetine	Fair

B. 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). 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.[90,91,92] In addition, one review included a comparison of paroxetine to placebo.[91]

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 pre-defined 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.[93] 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.[94] 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.

3. SSRIs compared to placebo in adult outpatients with OCD

Meta-analyses

Three meta-analyses reviewed available evidence from placebo-controlled studies;[90, 91, 92] we rated these analyses as fair quality. One study pooled results from 10 trials that compared SSRIs *as a class* with placebo.[90] 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.[95, 96] 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.[91] 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[97, 98, 99, 100] showed a net improvement of -4.84 (95% CI, -7.78, -1.83). For the three fluoxetine studies,[101, 102, 103] net improvement was -1.61 (95% CI -2.18, -1.04); for four sertraline studies,[104,105,95,106] 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; [92] two fluvoxamine studies;[97, 98] two sertraline studies;[104, 105] and two fluoxetine studies.[101, 102] 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.[96] 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.

4. 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[93, 94] and three meta-analyses[90-92] 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[94, 107]. One fair placebo-controlled study showed a significantly greater improvement in disability for citalopram compared to placebo.[96]

One study provides fair evidence that sertraline has a faster onset of action than fluoxetine[93] in the treatment of OCD. Another fair-rated study reported a faster response for venlafaxine XR compared to paroxetine.[94]

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.[96]

Table 13: Interventions, Numbers of Patients, and Quality Ratings of Studies in Adults with Obsessive-Compulsive Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Bergeron et al., 2002 [93]	Fluoxetine vs. Sertraline	150	No differences	Fair
Other second-generation antidepressants versus SSRIs				
Denys et al., 2003 [94]	Venlafaxine vs. Paroxetine	150	No differences	Fair
SSRIs versus Placebo				
Piccinelli et al., 1995 [90]	SSRIs vs. Placebo (SR)	1,076	Significantly greater efficacy of SSRIs	Fair
Ackerman et al., 2002 [91]	SSRIs vs. Placebo (SR)	530	No differences among SSRIs	Fair
Stein et al., 1995 [92]	SSRIs vs. Placebo (SR)	516	No differences among SSRIs	Fair
Montgomery et al., 2001 [96]	Citalopram vs. Placebo	401	Significantly greater efficacy of citalopram	Fair

(SR) = Systematic Review

C. Panic Disorder

Only fluoxetine, paroxetine, and sertraline 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, and sertraline, 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.[108, 109 110] We excluded one study – a single-blinded RCT with a poor quality rating for internal validity [109] – from our findings, but we discuss it here briefly because of the minimal amount of published research on this topic. Furthermore, we identified three placebo-controlled trials assessing the efficacy and tolerability of fluvoxamine.[111, 112,113] One additional RCT compared sertraline to placebo and assessed quality of life as a secondary outcome measure[114] (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.[108] 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).[110] 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.[109] 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.[111, 112, 113] The first study enrolled 75 patients to fluvoxamine (50-300mg/d), placebo, or cognitive therapy.[111] 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.[112] 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.[113] 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.[114] 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 ($p = 0.006$).

3. Summary of the evidence

Only one fair head-to-head study provides evidence that there is no difference in efficacy 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 there is no significant difference in the efficacy of reducing panic attacks and improving quality of life between citalopram and escitalopram,[108] and paroxetine and sertraline[110] in outpatients with panic disorder. Fair evidence exists from four placebo-controlled trials that the improvement of health outcomes and functional capacity is

significantly greater for fluvoxamine and sertraline than for placebo.[111,112,113,114] Three placebo-controlled trials provide fair evidence of significantly greater efficacy of fluvoxamine than placebo.[111,112,113] 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: Interventions, Numbers of Patients, and Quality Ratings of Controlled Trials in Adults with Panic Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Bandelow et al., 2004 [110]	Paroxetine vs. Sertraline	225	No difference	Fair
Stahl et al., 2003 [108]	Citalopram vs. Escitalopram vs. Placebo	366	No difference	Fair
SSRIs versus Placebo				
Asnis et al., 2001 [113]	Fluvoxamine vs. Placebo	188	Significantly greater efficacy of fluvoxamine	Fair
Black et al., 1993 [115]	Fluvoxamine vs. Placebo	75	Significantly greater efficacy of fluvoxamine	Fair
Hoehn-Saric et al., 1993 [112]	Fluvoxamine vs. Placebo	50	Significantly greater efficacy of fluvoxamine	Fair
Pohl et al., 1998 [114]	Sertraline vs. Placebo	168	Significantly greater efficacy of sertraline	Fair

D. Post-Traumatic Stress Disorder

For post-traumatic stress disorder (PTSD), we did not find any head-to-head studies comparing an SSRI or other second-generation antidepressants to 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[116, 117, 118, 119,120] (Table 15). One open-label continuation study[121] and a subsequent maintenance trial[122] 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,[116,117,122,121,118,119] the third was financed by grant from the National Institute of Mental Health (NIMH).[120]

1. SSRIs compared to placebo in adult outpatients with PTSD

Fluoxetine vs. placebo

A small, fair-rated study (supported by NIMH) enrolled 54 civilians to 12 weeks of fluoxetine (10-60mg) or placebo.[120] 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.[119] The enrolled population represented a wide range of trauma. The large majority of participants were Caucasian (> 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.[116, 117] 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.[118] Patients who completed the acute phase treatment could enter an open-label continuation phase for 24 weeks ($n = 252$);[121] 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 (50-200mg/d) or placebo in a 28-week, double-blind maintenance trial [122]. 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 ($p = 0.0002$).

2. Summary of the evidence

We identified no head-to head trials. 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.

Effectiveness

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

Efficacy

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.[116, 117, 122, 121, 118, 119, 120] 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: Interventions, Numbers of Patients, and Quality Ratings of Controlled Trials in Adults with Post-Traumatic Stress Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus Placebo				
Connor et al., 1999 [120]	Fluoxetine vs. Placebo	54	Significantly greater efficacy of fluoxetine	Fair
Marshall et al., 2001 [119]	Paroxetine vs. Placebo	563	Significantly greater efficacy of paroxetine	Fair
Brady et al., 2000 [116]	Sertraline vs. Placebo	187	Significantly greater efficacy of sertraline	Fair
Davidson JR, Rothbaum BO et al., 2001 [117]	Sertraline vs. Placebo	208	Significantly greater efficacy of sertraline	Fair

E. 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.

No head-to-head trial compared one second-generation antidepressant to another for the treatment of social anxiety disorder. One meta-analysis compared fluvoxamine, sertraline, and paroxetine to placebo.[123] In addition, two placebo-controlled studies evaluated second-generation antidepressants currently not approved by the FDA for social anxiety disorder: one fluoxetine study[124] and one fluvoxamine study[125] (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,[126, 127, 128 129] and sertraline.[130, 131, 132]

Inclusion was based on a criteria-based diagnosis (DSM-IV) of social anxiety disorder. Three studies required a minimal duration of current illness of 6 months,[132] 12 months,[124] or 24 months.[131] Several studies limited eligibility using a predefined cut-off point on a validated anxiety rating scale.[131,124,132,125,126]

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.[128] In two studies, withdrawals because of adverse effects were higher in the active treatment groups.[125,130]

All included trials are characterized as efficacy studies. All studies evaluated flexible dosing regimens with comparable doses across study drugs and trials. One study incorporated 8 weeks of open-label treatment and then randomized responders to placebo or active treatment. This study evaluated the rate of relapse between paroxetine-treated patients and placebo subjects.[126]

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

Fluvoxamine, paroxetine, and sertraline vs. placebo

One fair meta-analysis evaluated published and unpublished evidence comparing SSRIs with placebo in the treatment of social anxiety disorder.[123] 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.

Fluoxetine vs. placebo

One fair study compared flexible doses of fluoxetine to placebo.[124] 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 statistical 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 statistical 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

A 12-week study randomized 92 participants with a primary diagnosis of social anxiety disorder and a score of 20 or greater on the BSPS.[125] Participants were randomized to flexible doses of fluvoxamine (50-300 mg/d) or placebo. Although loss to follow-up was not reported explicitly, 25 percent of fluvoxamine-treated patients and 9.1 percent of placebo-treated patients withdrew from the study because of adverse events. The primary outcome measure was change in CGI global improvement item between baseline and endpoint. In the LOCF intention-to-treat analysis, significantly more fluvoxamine-treated patients responded ($p < 0.05$). Secondary efficacy measures included the clinician-rated BSPS, LSAS, Sheehan Disability Scale, and the patient-rated SPI. At endpoint, fluvoxamine was better than placebo on all 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, dizziness, reduced libido, nervousness, and somnolence.

Paroxetine vs. placebo

FDA-approved evidence supports the general efficacy for paroxetine. In addition to efficacy, four placebo-controlled paroxetine studies evaluated health outcomes.[128,126,127,129] 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.[128,127] Compared to placebo, immediate release paroxetine-treated patients 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.[127] Controlled release paroxetine-treated patients showed significantly greater improvement than placebo-treated patients in SDS total score, family life, social life, and work domains.[129]

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).[126] 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.[130,131,132] Each study assessed disability using the SDS, and significant improvement in SDS total score was observed at

endpoint in all studies.[130, 131, 132] One study assessed health status with the SF-36 and reported a significant improvement in the mental health component.[132] Another study assessed quality of life using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[131] Compared to patients on placebo, sertraline-treated patients showed a significant improvement in quality of life.

2. Summary of the evidence

No head-to-head trial compared one second-generation antidepressant to another. 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 meta-analysis of placebo-controlled studies provided fair evidence of comparable efficacies of fluvoxamine, paroxetine, and sertraline for the treatment of social anxiety disorder.[123] Nine trials provide fair evidence that SSRIs significantly improve health outcomes compared to placebo.[124, 128, 127, 125, 126, 130, 131, 132, 129]

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.[124] Evidence is insufficient about the efficacy of citalopram, escitalopram, 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, one study evaluated continuation of therapy among responders.[126] At 24 weeks, paroxetine-treated patients were significantly less likely to relapse than placebo-treated patients; 14 percent of paroxetine-treated patients relapsed compared with 39 percent of placebo-treated patients ($p < 0.001$).

Table 16: Interventions, Numbers of Patients, and Quality Ratings of Studies in Adults with Social Anxiety Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus Placebo				
Van der Linden et al., 2000 [123]	Fluvoxamine vs. Placebo Paroxetine vs. Placebo Sertraline vs. Placebo (SR)	1,482	No differences between active treatments	Fair
Kobak et al., 2002 [124]	Fluoxetine vs. Placebo	60	No differences in efficacy	Fair
Stein et al., 1999 [125]	Fluvoxamine vs. Placebo	92	Significantly greater efficacy of fluvoxamine	Fair
Stein et al., 1998 [128]	Paroxetine vs. Placebo	187	Significantly greater improvement in social life and work domains for paroxetine	Fair
Baldwin et al., 1999 [127]	Paroxetine vs. Placebo	290	Significantly greater improvement in social life, family life, and work life for paroxetine	Fair
Stein et al., 2002 [126]	Paroxetine vs. Placebo	323	Significant reduction in relapse for paroxetine	Fair
Lepola et al., 2004 [129]	Paroxetine (CR) vs. Placebo	370	Significantly greater improvement in SDS for paroxetine CR	Fair
Van Ameringen et al., 2001 [130]	Sertraline vs. Placebo	204	Significantly greater improvement in SDS for sertraline	Fair
Liebowitz et al., 2003 [131]	Sertraline vs. Placebo	415	Significantly greater improvement in SDS and quality of life for sertraline	Fair
Blomhoff et al., 2001 [132]	Sertraline vs. Placebo	387	Significantly greater improvement in SDS and mental health for sertraline	Fair

(SR)= Systematic review

IV. For adult outpatients with adjustment disorder, do SSRIs or other second-generation antidepressants differ in efficacy?

We could not identify any head-to-head or other controlled trials assessing the efficacy of SSRIs or other second-generation antidepressants in patients with adjustment disorder.

V. 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)[133,133,134] and three RCTs[135,136,137] 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 three placebo-controlled trials, one trial examined continuous therapy,[135] one examined intermittent therapy during the luteal phase only,[137] and the third examined both.

Included studies were conducted in women of reproductive age (18 to 45 years) with a clinical diagnosis of premenstrual dysphoric disorder (PMDD) or late luteal phase dysphoric disorder (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 three trials used a patient-assessed daily symptom rating or report in addition to the CGI.[135, 136,137] 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.[135] Studies included in the meta-analysis used similar efficacy outcome measures. One study measured health outcomes including social adjustment and quality of life.[137]

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 dysphoric disorder or late luteal phase dysphoric disorder

SSRIs vs. placebo

Only one study reported on efficacy outcomes of non-FDA-approved SSRIs.[134, 133] 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.[134] 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).[133]

Sertraline vs. placebo

Only one RCT assessed health outcomes.[137] This fair-quality 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. This study reported 21 percent of subjects as lost to follow-up. Sertraline-treated subjects had significantly more improvement on both scales than did placebo-treated subjects.

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-quality RCT compared an SNRI, specifically a continuous daily dose of venlafaxine (50-200 mg/d), to placebo over four menstrual cycles.[135] 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 then 50% reduction in baseline symptom report score), whereas only 35 percent of placebo-treated subjects were characterized as responders.

Nefazodone vs. placebo

One fair-quality 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.[136] This trial did not, however, compare intermittent and continuous therapy to each other. Twenty-two percent of subjects were reported as lost to follow-up in this trial. For both dosing methods, no significant differences were seen between nefazodone and placebo in either patient self-rated global improvement or any of the individual symptoms assessed (irritability, depressed mood, affect lability, tension, breast tenderness, bloating and food craving).

4. Summary of the evidence

We identified no head-to-head trials. Good to fair evidence exists from 2 meta-analyses that the efficacy of SSRIs as a class is significantly greater than placebo. Three additional trials provide fair evidence that the efficacies of 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.[134] 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.[135] One RCT provides fair evidence that sertraline improves quality of life significantly more than placebo does.[137] Lastly, evidence from one fair RCT indicates that nefazodone does not have greater efficacy than placebo in the treatment of PMDD or LLPDD.[136] 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 no trial involving a head-to-head comparison of intermittent (e.g., luteal phase only) therapy against continuous therapy. A subgroup analysis in a good meta-analysis concludes that two dosing schedules do not differ significantly. However, different populations and different dosages may give this conclusion a limited validity.[134]

Table 17: Interventions, Numbers of Patients, and Quality Ratings of Studies in Adults with Premenstrual Dysphoric Disorder or Late Luteal Phase Dysphoric Disorder

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Dimmock et al., 2000 * [134]	5 SSRIs vs. Placebo (SR)	904	Significantly greater efficacy of SSRIs	Good
Wyatt et al., 2004 [133]	5 SSRIs vs. Placebo (SR)	844	Significantly greater efficacy of SSRIs	Fair
Halbreich et al., 2002 [137]	Sertraline vs. Placebo	281	Significantly greater efficacy of sertraline	Fair
SNRIs versus Placebo				
Freeman et al., 2001 (79) [135]	Venlafaxine vs. Placebo	157	Significantly greater efficacy of venlafaxine	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.
(SR) = Systematic Review

KEY QUESTION 2.

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

Most of the studies that examined the efficacy of one drug relative to another also determined differences in tolerability. Methods of adverse events assessment differed greatly. Few studies used objective scales such as the UKU-SES (Utvalg for Kliniske Undersogelser Side Effect Scale) or the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient- reported adverse events with a regular clinical examination by an investigator. Often it was hard to determine whether assessment methods were unbiased and adequate. Rarely were adverse events prespecified and defined. Short study durations and small sample sizes additionally limited the validity of adverse events assessment in many trials.

Few RCTs were designed to assess adverse events as primary outcomes. Most published studies were post hoc analyses or retrospective reviews of databases. We included observational studies if the sample size was larger than 100 and the study duration was at least 1 year (Table 18).

A. Tolerability and Discontinuation Rates

From 46 head-to-head studies reviewed for this report, 14 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. Discontinuation rates because of adverse events were generally not statistically significantly different, except in three trials. One study reported that significantly more patients on fluvoxamine than on sertraline discontinued treatment;[36] the other two trials provided conflicting evidence on the discontinuation rates of mirtazapine and paroxetine.[41,40]

Venlafaxine had a consistently higher rate of nausea and vomiting than SSRIs. In four studies, the difference reached statistical significance.[50, 49, 45, 52] In six additional trials, the higher rates of nausea or vomiting for venlafaxine were not statistically significant.[46,53,54,44,48,43] The rate of patients reporting nausea or vomiting ranged from 25 percent to 36 percent. Three trials reported a significantly higher rate of dizziness in the venlafaxine group than in the fluoxetine group.[50,45,46] Three other studies reported significantly higher rates of diarrhea in sertraline-treated patients than in comparison drugs.[42,35,28] In another trial conducted in patients 65 years and older, patients using fluoxetine had significantly more severe adverse events than patients treated with paroxetine.[23]

A British study pooled data from Prescription-Event-Monitoring (PEM) of general practitioners 6 months to 1 year after they had issued prescriptions.[138,139] 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 11. 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.

Two RCTs were powered primarily to detect differences in adverse events between fluvoxamine and citalopram[140] and fluvoxamine and paroxetine.[141] 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).[140] 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.[141] Sweating was the only significantly higher adverse event: 30 percent in paroxetine patients vs.10 percent in fluvoxamine patents ($p = 0.028$).

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).[142] 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 due to adverse events, and the discontinuation rates due to lack of of efficacy of SSRIs as a class compared to other second generation antidepressants in adult outpatients with major depressive disorder (Exhibit 4). Overall, no significant differences could be detected between SSRIs and mirtazapine, SSRIs and venlafaxine, and SSRIs and bupropion. We did not have sufficient data on nefazodone. Numerical differences in discontinuation rates due to adverse events generally favored SSRIs but never reached statistical significance. Due to

heterogeneity we did not pool data of discontinuation rates due to adverse events comparing SSRIs to mirtazapine and SSRIs to bupropion.

B. Specific Adverse Events

1. Suicidality

We identified no trial comparing the risk of suicidality (suicidal acts and ideation) of SSRIs, SNRIs, or other second-generation antidepressant to each other. One prospective observational study and one meta-analysis of published RCTs assessed the suicidal risk of fluoxetine. Similarly, another meta-analysis determined the risk of suicide in fluvoxamine-treated patients. A retrospective data review examined the risk of suicide in SSRIs compared to other antidepressants and placebo. Include studies are presented in Table 18.

A fair-rated meta-analysis assessed the association of fluoxetine and suicidality.[143,144,145,146] The study pooled data from 17 placebo-and active-controlled RCTs with a total of 3,065 patients. Suicidal acts did not differ significantly among study groups. Suicidal ideation was significantly lower in the fluoxetine group than in the placebo ($p = 0.042$) and the TCA groups ($p = 0.001$). Suicidal ideation improved significantly with fluoxetine compared to placebo ($p < 0.001$). An additional analysis of the data reported no statistical association between suicidality and the incidence of other adverse events.[146]

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.[147] 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.[148] A total of 555 cases of nonfatal suicidal behavior were matched with 2062 controls. Compared to dothiepin, the risk of suicidal behavior was similar among users of amitryptilin (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).

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.[149] Crude suicide rates and 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]

There is limited evidence to support the risk of hostility or suicidality among children and adolescents with MDD. One review published by the National Institute for Clinical Excellence (NICE) provides fair evidence that only fluoxetine has a favorable risk-benefit profile.[77] Doctors, patients, families and other caregivers are urged to be cautious of signs of worsening

depression or suicidal thoughts at the beginning of antidepressant therapy or whenever the dose is changed.

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)[150,16] 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.

Three studies assessed the incidence of sexual dysfunction in depressed outpatients treated with bupropion or sertraline.[61,62,69]

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.[61,62] 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 [61]. 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 ($p < 0.05$).[62]

The third RCT assessed the sexual side effects of bupropion SR (150-400mg/d) and sertraline (100-300mg/d) in 248 depressed outpatients.[69] 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 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[57]. 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 ($p < 0.05$).

A multicenter (1,101 primary care clinics), cross-sectional study surveyed 6,297 patients already taking antidepressants on sexual side effects.[151] Eligible patients had to be older than 18 years, sexually active, and on a monotherapy of citalopram, fluoxetine, paroxetine, sertraline, mirtazapine, venlafaxine, or bupropion. The Changes in Sexual Functioning Questionnaire (CSFQ) was used for outcome assessment. The overall prevalence of sexual dysfunction was 37 percent. Bupropion IR (22%), bupropion SR (25%) and nifenazone (28%) were associated with the lowest risks of sexual dysfunction. Paroxetine (43%) and mirtazapine (41%) had the highest rates of sexual dysfunction. The article did not report *p*-values on the differences between groups.

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[27,35,60,36,42,68,36] 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).[60]

3. Changes in weight

A 32-week acute and continuation trial assessed differences in weight changes among patients treated with fluoxetine, paroxetine, and sertraline.[152] 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.[153] Initially, fluoxetine treatment led to a modest weight loss; from week 12 to week 50, however, a significant weight gain compared to placebo was reported (+3.1kg; p < 0.001).

A double-blinded placebo-controlled 52-week acute and continuation trial assessed weight changes during bupropion treatment.[154] 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.[40, 41]

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.[155, 156] 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 antidepressant deliberate self-poisening reported that seizures were more common in patients with venlafaxine overdose than in patients with TCA or SSRI overdose.[157]

5. Cardiovascular adverse events

A post hoc analysis examined pooled data from 3,744 patients participating in venlafaxine trials.[158] 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 ($p = 0.05$).

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.[159] 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.[160] One maker of nefazodone has announced that it is withdrawing the drug due to safety concerns from the U.S. market by June 2004 (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. At the same time, however, fair to good evidence from the same head-to-head trials also shows that the general tolerability, reflected in discontinuation rates because of adverse events during the studies, does generally not differ significantly among drugs.

Suicidality

Evidence from controlled trials and observational studies is insufficient to conclude for or against a higher risk of suicidality in patients treated with SSRIs, SNRIs, and other second-generation antidepressants. Retrospective data reviews of prescription event monitoring yield conflicting results. Three studies report no increased risk,[138, 139, 149,13] a fourth study showed a significantly higher rate of suicides in fluoxetine-treated patients compared to treated-treated patients.[147]

Sexual dysfunction

Fair evidence from three RCTs indicates that the rate of sexual side effects is significantly lower for bupropion than for sertraline.[62, 57, 69] 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.[60]

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.[151] Multiple trials give fair evidence that paroxetine, sertraline, and mirtazapine tend to have higher rates of sexual side effects than other second-generation antidepressants.[28,27 35 60,42,36 68 151]

Weight changes

Multiple studies provide fair evidence that mirtazapine and paroxetine lead to a greater weight gain than do fluoxetine and sertraline.[40 41 152 153] Additionally, one fair study presents evidence that bupropion treatment leads to a moderate loss of body weight.[154]

Cardiovascular adverse events

A post hoc analysis of pooled data reports that venlafaxine significantly increases the supine DBP.[158] 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.

Other adverse events

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.[159] Similarly, reports of liver toxicity with nefazodone have not been confirmed by controlled trials and observational studies.[160] 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 18: Intervention, Numbers of Patients, and Quality Ratings of Studies Assessing Adverse Events

Author, Year	Interventions	N	Results	Quality Rating
Tolerability and Discontinuation				
Mackay et al., 1997, 1999 [138]	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
Haffmans et al, 1996 [140]	Fluvoxamine vs. Paroxetine	217	Significantly more diarrhea and nausea with fluvoxamine	Fair
Kiev et al., 1997 [141]	Fluvoxamine vs. Paroxetine	60	Significantly more sweating with paroxetine	Fair
Meijer et al., 2002 [142]	Sertraline vs. SSRIs (OS)	1251	Significantly more diarrhea with sertraline	Fair
Suicidality				
Jick et al., 2004 [148]	Case-control; database review	159,810	No differences	N/A
Jick et al., 1995 [147]	Open cohort; database review	172,598	Significantly higher risk of suicide with fluoxetine and mianserin compared to dothiepin	N/A
Khan et al., 2003 [149]	Data review	NR	No differences	N/A
Lopez-Ibor 1993 [13]	Database review	4686	No differences	N/A
Beasley et al., 1991, 1992 [143] [1]Tollefson et al. 1994 [146 146]	Fluoxetine vs. Placebo (SR)	3065	Suicidal ideation significantly lower with fluoxetine	Fair
Sexual Dysfunction				
Ekselius et al., 2001 [150]	Citalopram vs. Sertraline	308	No differences	Fair
Coleman et al., 2001 [57]	Bupropion vs. Fluoxetine	456	Significantly more sexual adverse events with fluoxetine	Fair
Coleman et al., 1999 [62]	Bupropion vs. Sertraline	364	Significantly more sexual adverse events with sertraline	Fair
Segraves et al., 2000 [69]	Bupropion vs. Sertraline	248	Significantly more sexual adverse events with sertraline	Fair
Croft et al., 1999 [61]	Bupropion vs. Sertraline	360	No differences	Fair
Clayton et al., 2002 [151]	Cross-sectional survey	6297	Highest risk for paroxetine and mirtazapine; lowest risk for bupropion	N/A
Changes in Weight				
Fava et al., 2002 [28], Michelson et al., 1999 [153 153]	Fluoxetine vs. Paroxetine vs. Sertraline	284	Highest weight gain with paroxetine	Fair
Croft et al., 2002 [154]	Bupropion vs. Placebo	360	Significant weight loss with bupropion	Fair
Benkert et al., 2000 [41]	Mirtazapine vs. Paroxetine	275	Significant weight gain with mirtazapine	Fair
Schatzberg et al., 2002 [40]	Mirtazapine vs. Paroxetine	255	Significant weight gain with mirtazapine	Fair
Cardiovascular Events				
Thase et al., 1998 [158]	Post hoc analysis	3744	Significantly higher diastolic blood pressure for venlafaxine	N/A

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

KEY QUESTION 3.

Are there subgroups of patients based on demographics (age, racial groups, sex), other medications, or co-morbidities for which one SSRI or other 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 19.

A. Demographics

1. Age

Fluoxetine vs. paroxetine

Two RCTs were conducted in a population older then 60 years.[23, 26] The first trial was an Italian study lasting one 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%, 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.[26] Loss to follow-up was not reported. An ITT 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.

Fluoxetine vs. sertraline

One fair-rated, 12-week study comparing fluoxetine to sertraline was conducted in 236 participants older than 60 years.[31, 33] 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).[33]

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]

Paroxetine vs. placebo vs. behavioral therapy

A large, fair-rated, primary-care-based study randomized 656 patients with dysthymia or minor depression to eleven weeks of paroxetine (10-40mg), placebo, or behavioral therapy.[74, 75] Participants were stratified into patients 60 years and older (n = 415) and patients younger than 60 years (n = 241) for ITT 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.[161] 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.[40] Loss to follow-up was 27%. Mirtazapine and paroxetine were equally effective in reducing HAM-D scores at the endpoint, however, mirtazapine lead to a faster response. A Kaplan-Meier analysis presented 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 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.[162] 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 good 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.[58, 59] 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% with no significant difference between treatment groups. Efficacy according to any outcome measure did not differ significantly between treatment groups. Response rates (≥ 50% reduction in HAM-D scores) were similar in both groups (bupropion SR, 71%; paroxetine, 77%). Quality of life scales (QLDS, SF-36) showed statistically significant improvements in both treatment groups from baseline to endpoint ($p < 0.0001$), but they did not differ significantly between treatment groups.

A meta-analysis combined original data from eight comparable, double-blind, active-controlled, randomized trials.[163] We gave the efficacy results of this study a poor quality rating because of the lack of a systematic literature search and the failure to maintain the units of the trials during statistical analysis. Additionally, one included study had enrolled an inpatient population. However, a second 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. There is fair evidence from a pooled analysis of two placebo-controlled trials for the efficacy of sertraline.[79] Existing evidence does not support the efficacy of other second-generation antidepressants. Additional evidence suggests that sertraline may not be as efficacious as reported in previous reports. Based on a systematic review of published and unpublished studies comparing second-generation antidepressant to placebo, only fluoxetine was shown to be safe and effective in the treatment of major depressive disorder in children and adolescents.[77] This review reported an increased risk of suicidal thoughts and behavior for citalopram, paroxetine, sertraline, and venlafaxine, but not for fluoxetine.

2. Ethnicity

Fluoxetine versus placebo

An RCT examined ethnic differences in response to antidepressant treatment among depressed HIV-positive patients.[164] A total of 118 patients were randomized to either fluoxetine (20-80mg/d) or placebo for eight weeks. Of all participants, 67% were white, 19% black, and 14% Latino; only 1.1% (n = 2) were female. The primary outcome measure was response on HAM-D scale. At baseline, no relationship between ethnicity and type or severity of depressive symptoms could be detected. 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 vs. 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 did not find any significant associations between sex and outcomes or sex and treatment.[163]

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 there is very little agreement in reporting clinical significance of drug-drug interactions.[165] 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.[166]

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.[167] 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.[168]

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.[169] 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).[170, 171, 172] 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 major depressive disorder.[173] 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.[174] 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 five weeks studied the efficacy of fluoxetine in 91 cancer patients with depression or adjustment disorder.[175] 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%. 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.[176] Study duration was three months; loss to follow-up was 15.9%. Both groups had significantly decreased scores on BDI and HADRS (z = 2.37; p = 0.01). There was no significant difference in efficacy between placebo and fluoxetine treatment. However, the sample size was small and the study is likely to be underpowered (no power calculations were reported).

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.[177] 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.[163]

Six studies provide fair to good indirect evidence that efficacy and tolerability for patients older than 60 years and those younger do not differ.[33, 58, 59, 40, 31, 23, 75, 162] 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.[26] 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.[162]

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[82, 83] and sertraline.[79] 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.[77] 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 single RCT suggests that response rates, loss to follow-up, and response to placebo treatment might differ between groups of different ethnic background.[164] This small trial was conducted in a subgroup of HIV-positive patients, and the generalizabilty of results may be limited.

Sex

A meta-analysis rated fair to poor did not find significant associations between sex and outcomes or sex and treatment.[163]

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.[177, 169] Various other trials conducted in populations with different comorbidities can provide indirect evidence.[170, 171, 172, 174, 175, 176] 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.[175, 176] 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.[174, 170, 171, 172]

Table 19: Interventions, Numbers of Patients, and Quality Ratings in Controlled Trials Assessing Efficacy and Effectiveness in Subgroups

Author, Year	Interventions	N	Results	Quality Rating
Age				
Cassano et al., 2002 [23]	Fluoxetine vs. Paroxetine	242	Faster onset of paroxetine	Fair
Schone et al., 1993 [26]	Fluoxetine vs. Paroxetine	108	Faster onset of paroxetine	Fair
Newhouse et al., 2000 [31]	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 [161]	Paroxetine vs. Placebo	323	Significantly more responders and remitters for paroxetine IR and paroxetine CR than for placebo	Fair
Williams et al., 2000 [75]	Paroxetine vs. Placebo	415	No differences	Fair
Wagner et al., 2003 [79]	Sertraline vs. Placebo	376	Significantly greater efficacy for sertraline	Fair
Schatzberg et al.., 2002 [40]	Mirtazapine vs. Paroxetine	255	Faster onset of mirtazapine	Fair
Weihs et al., 2000 [58]	Bupropion SR vs. Paroxetine	100	No differences	Good
Entsuah et al., 2001 [163]	Meta-analysis	2,045	No significant interaction between age and treatment	NA
Whittington et al., 2004 [77]	Meta-analysis	2,145	Only fluoxetine had favorable risk-benefit profile	Fair
Ethnicity				
Wagner et al., 1998 [164]	Fluoxetine vs. Placebo	118	Ethnicity was not associated with side effects; whites had a higher response rate, Latinos a higher drop-out rate	Fair
Sex				
Entsuah et al., 2001 [163]	Meta-analysis	2,045	No significant interaction between sex and treatment	NA
Comorbities				
Linden et al., 1994 [169]	Fluoxetine vs. Paroxetine	89	No difference in GI-side effects in somatizing patients	Fair
Cornelius et al., 1997, 1998, 2000 [170-172]	Fluoxetine vs. Placebo	51	Significantly greater efficacy for fluoxetine in depressed alcoholics	Fair
Rabkin et al, 1999 [174]	Fluoxetine vs. Placebo	120	No difference in depressed HIV/AIDS patients	Fair
Razavi et al, 1996 [175]	Fluoxetine vs. Placebo	91	No difference in depressed cancer patients	Fair
Petrakis et al., 1998 [176]	Fluoxetine vs. Placebo	44	No difference in depressed opioid addicts	Fair
Schmitz et al., 2001 [173]	Fluoxetine vs. Placebo	68	No difference in depressed cocaine abusers	Fair
Krishnan et al., 2001 [177]	Sertraline vs. Placebo	220	Vascular comorbidity not associated with more adverse events and premature discontinuation	Fair

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Exhibit 1: Meta-analysis of studies comparing fluoxetine to paroxetine

Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Chouinard et al., 1999[24]	203	40.9	61%	12 weeks	HAM-D
DeWilde et al.,1993[25]	78	44.0	61%	6 weeks	HAM-D
Fava et al., 1998[27]	128	41.3	51%	10-16 weeks	HAM-D
Fava et al., 2002[28]	188	42.0	65%	10-16 weeks	HAM-D
Gagiano 1993 [14]	90	38.7	80%	6 weeks	HAM-D
Schöne et al., 1993[26]	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 [23]	242	75.3	55%	52 weeks	HAM-D	Missing data

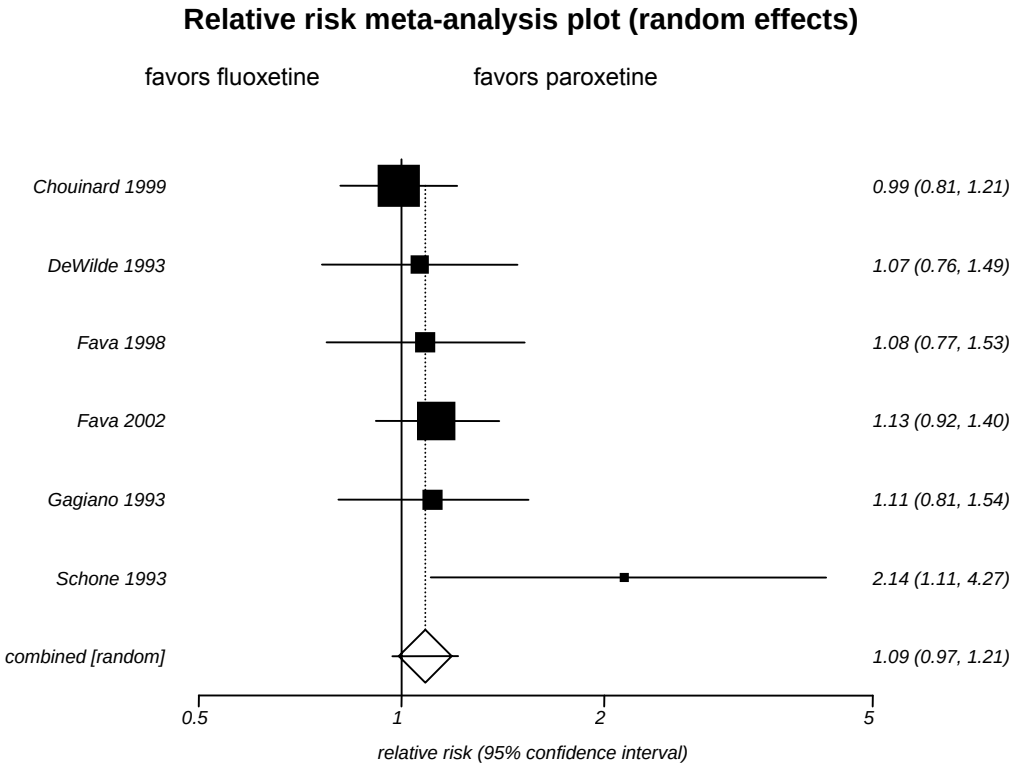

Relative risk meta-analysis plot (random effects)
favors fluoxetine
favors paroxetine
Chouinard 1999
0.99 (0.81, 1.21)
DeWilde 1993
1.07 (0.76, 1.49)
Fava 1998
1.08 (0.77, 1.53)
Fava 2002
1.13 (0.92, 1.40)
Gagiano 1993
1.11 (0.81, 1.54)
Schone 1993
2.14 (1.11, 4.27)
combined [random]
1.09 (0.97, 1.21)
0.5
1
2
5
relative risk (95% confidence interval)

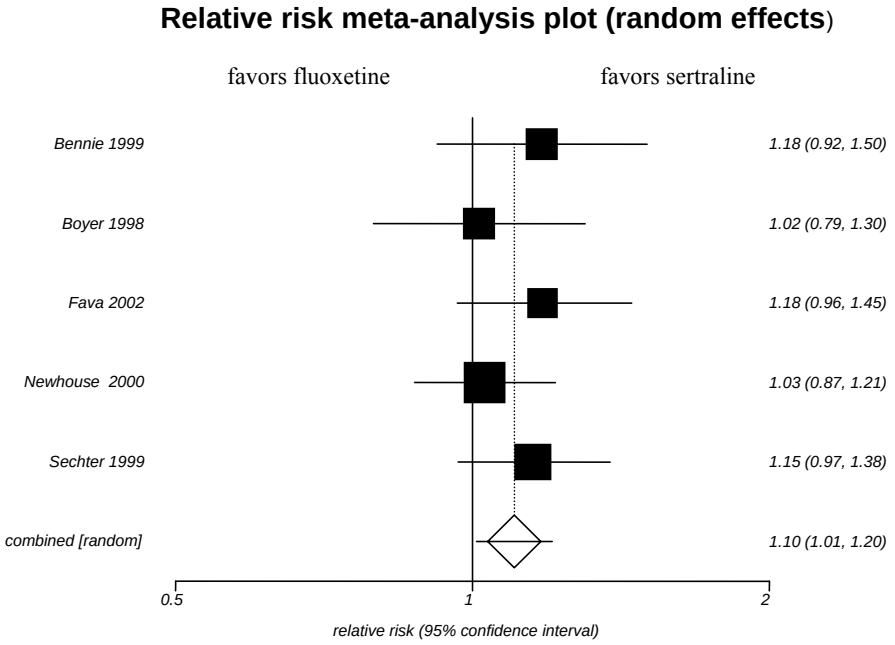
Exhibit 2: Meta-analysis of studies comparing fluoxetine to sertraline

Characteristics of included studies

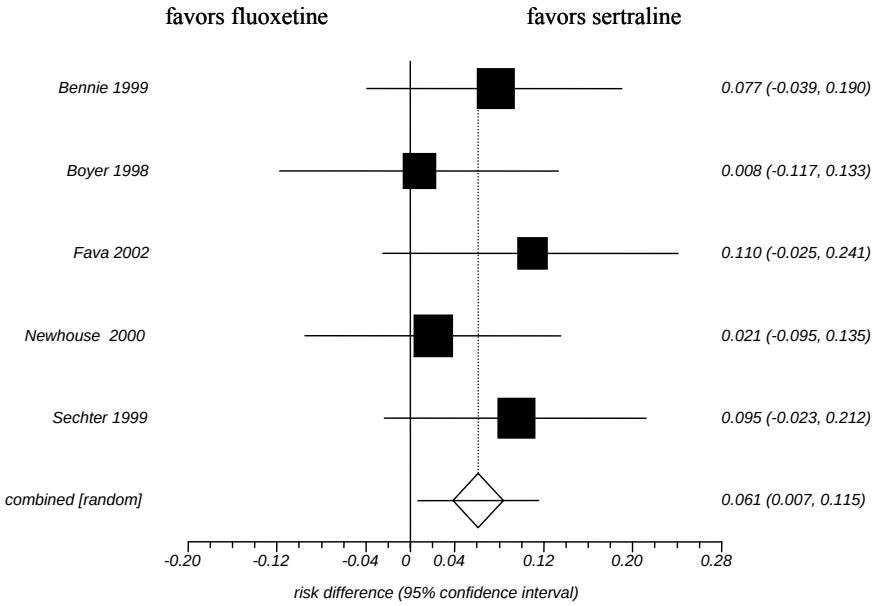
	Sample size	Mean Age	Women	Duration	Scale
Bennie et al., 1999[29]	286	49.9	61%	6 weeks	HAM-D
Boyer et al., 1998[30]	242	43.4	78%	26 weeks	MADRS
Fava et al., 2002[28]	188	42.0	65%	10-16 weeks	HAM-D
Newhouse et al., 2000[31]	236	67.5	57%	12 weeks	HAM-D
Sechter et al., 1999[18]	238	42.8	67%	24 weeks	HAM-D

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



Risk difference meta-analysis plot [random effects]



Number needed to treat (empirical results using observed counts only)
Estimates with 95% confidence intervals:

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

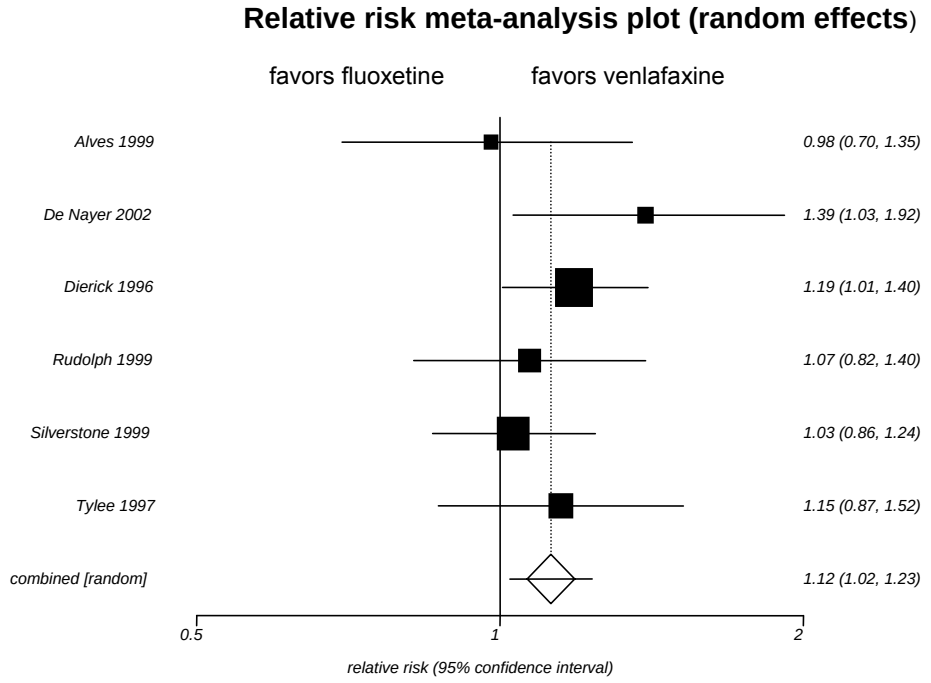
Exhibit 3: Meta-analysis of studies comparing venlafaxine to fluoxetine

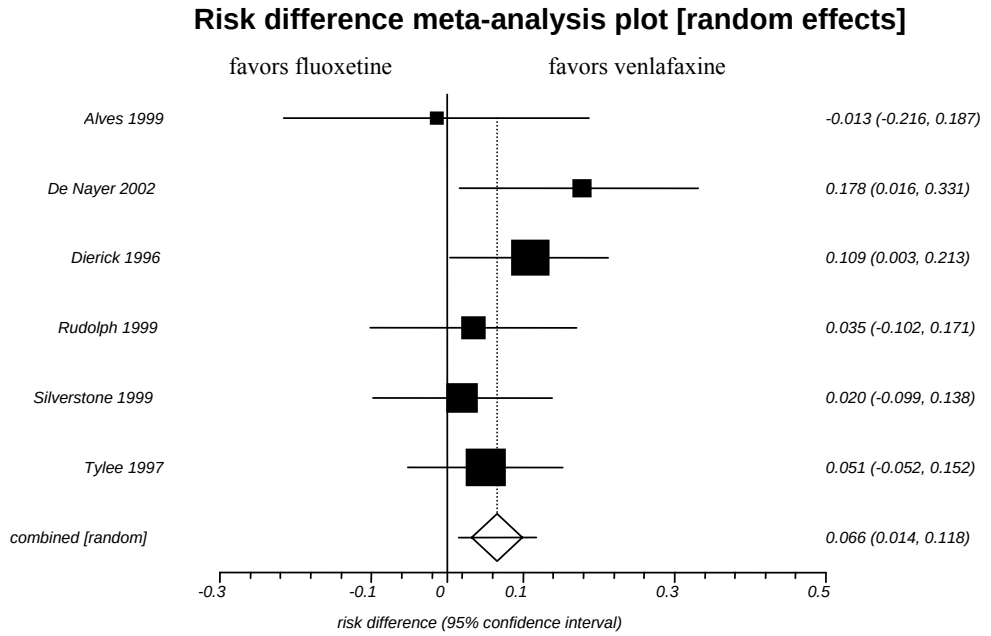
Characteristics of included studies

	Sample size	Mean Age	Women	Duration	Scale
Alves et al., 1999 [48]	87	43.8	92%	12 weeks	HAM-D
De Nayer et al., 2002[44]	146	42.7	68%	12 weeks	MADRS
Dierick et al., 1996 [49]	314	43.4	64%	8 weeks	HAM-D
Rudolph et al., 1999[45]	301	40	69%	8 weeks	HAM-D
Silverstone et al., 1999 [46]	378	41.9	60%	12 weeks	HAM-D
Tylee et al., 1997 [50]	341	44.5	71%	12 weeks	HAM-D

Characteristics of excluded studies

	Sample size	Mean Age	Women	Duration	Scale	Reason for exclusion
e Silva et al., 1998[43]	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

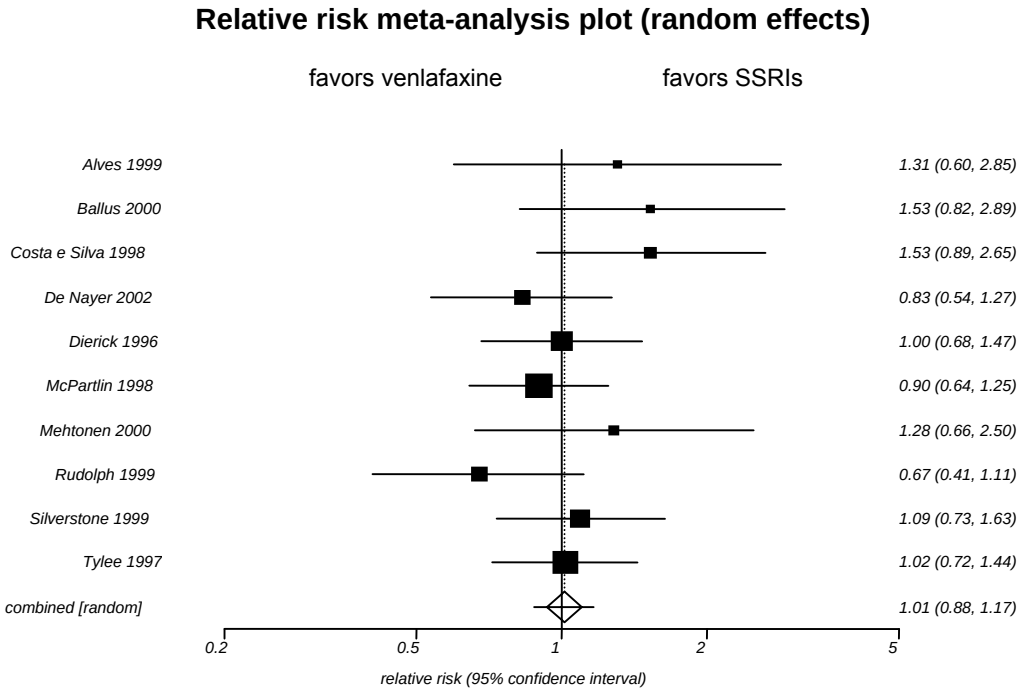
Exhibit 4: Meta-analyses of discontinuation rates

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

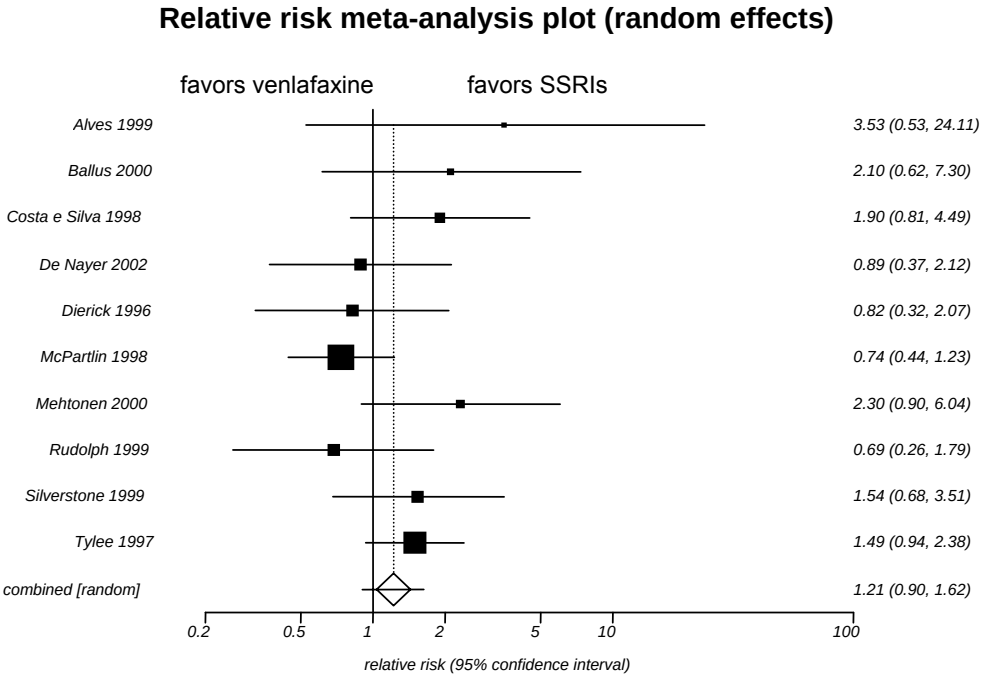
Reason (%)	Venlafaxine (n= 1160)	SSRIs (n=1154)	p*
Overall loss to follow-up	284 (24.5)	278 (24.1)	0.826
Adverse events	127 (10.9)	104 (9.0)	0.121
Lack of efficacy	42 (3.6)	61 (5.3)	0.053

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

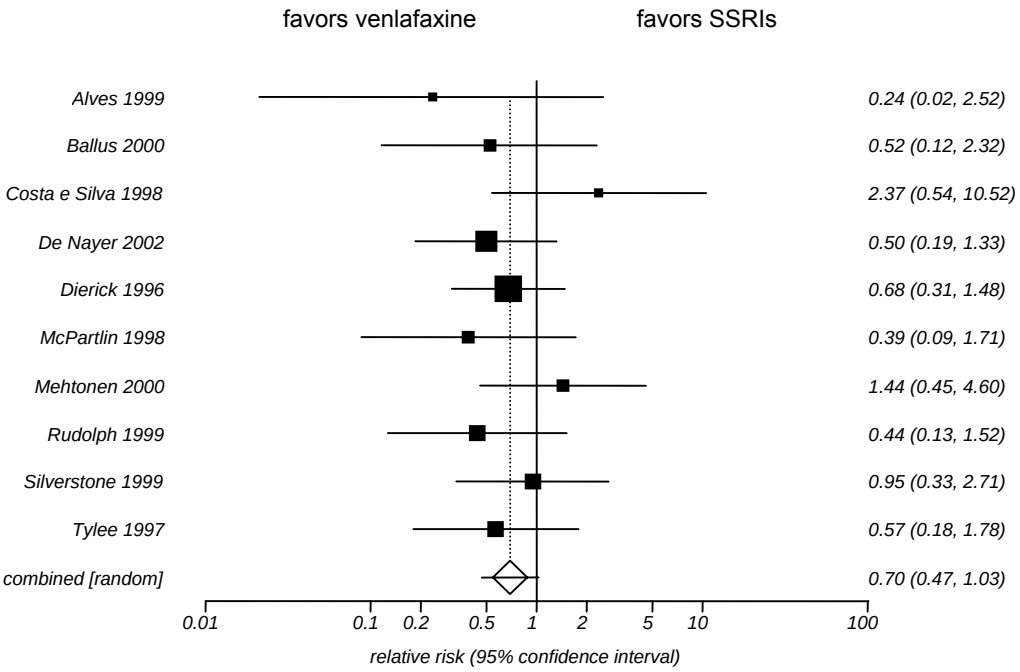
Relative risk meta-analysis of overall loss to follow-up comparing SSRIs to venlafaxine



Relative risk meta-analysis of discontinuation rates due to adverse events comparing SSRIs to venlafaxine



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

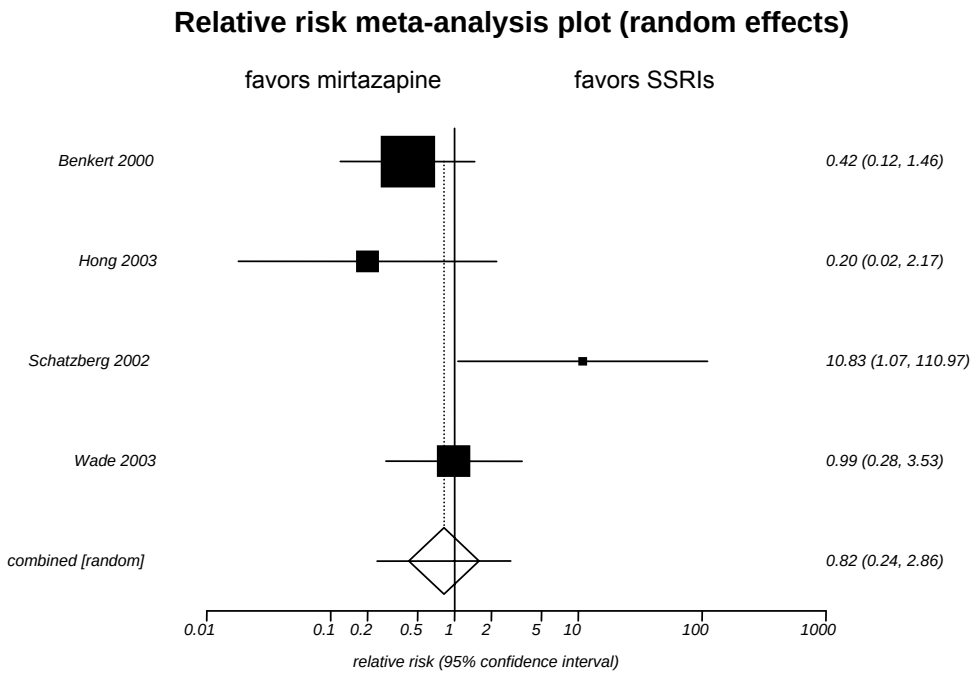


Reasons for treatment discontinuation and overall loss to follow-up of mirtazapine compared to SSRIs

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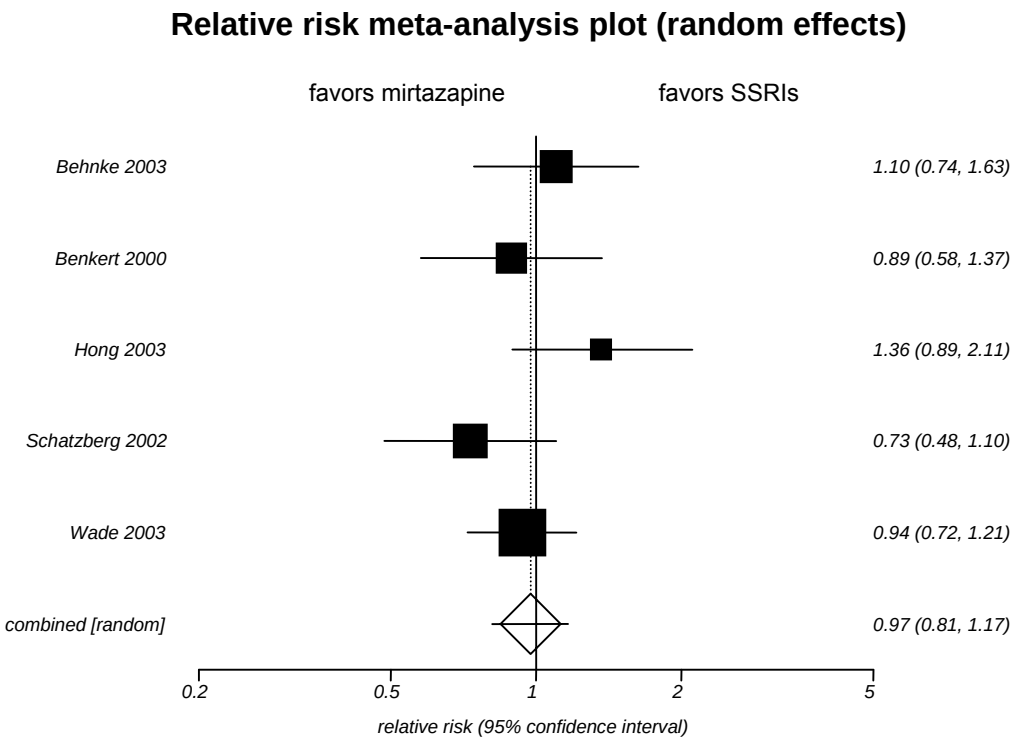
Relative risk meta-analysis of discontinuation rates due to lack of efficacy comparing SSRIs to mirtazapine

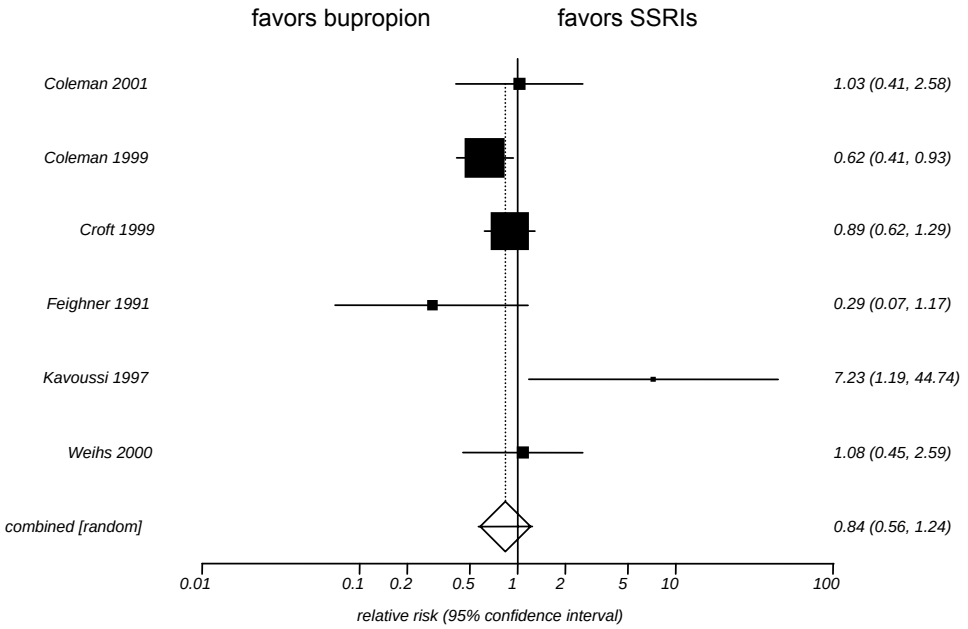


Reasons for treatment discontinuation and overall loss to follow-up of bupropion compared to SSRIs

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

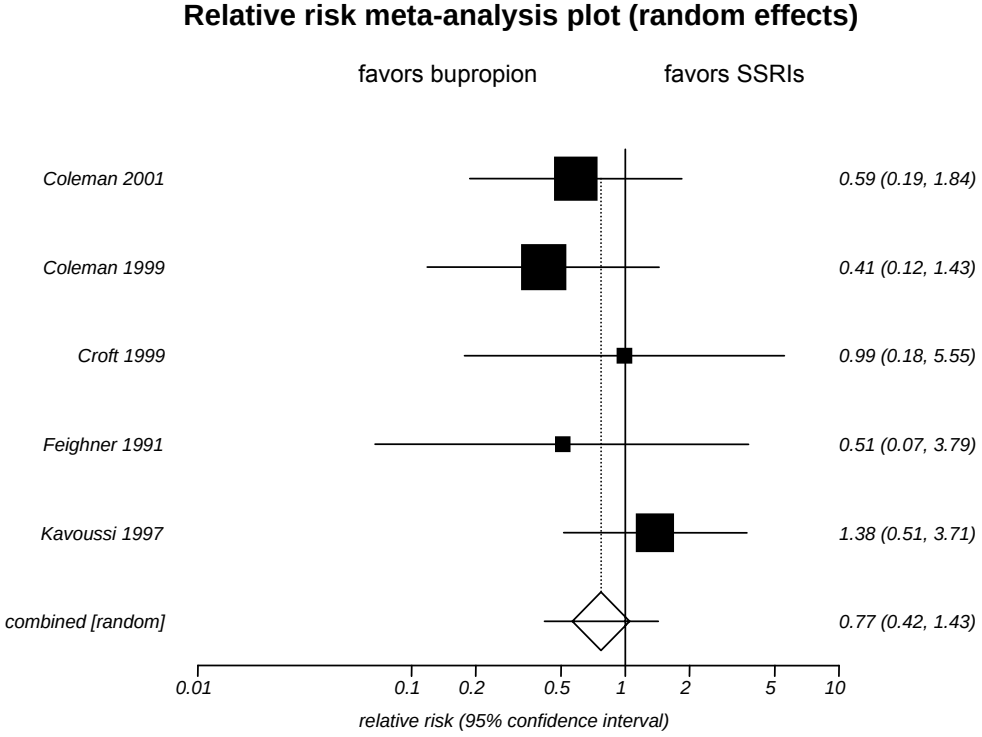
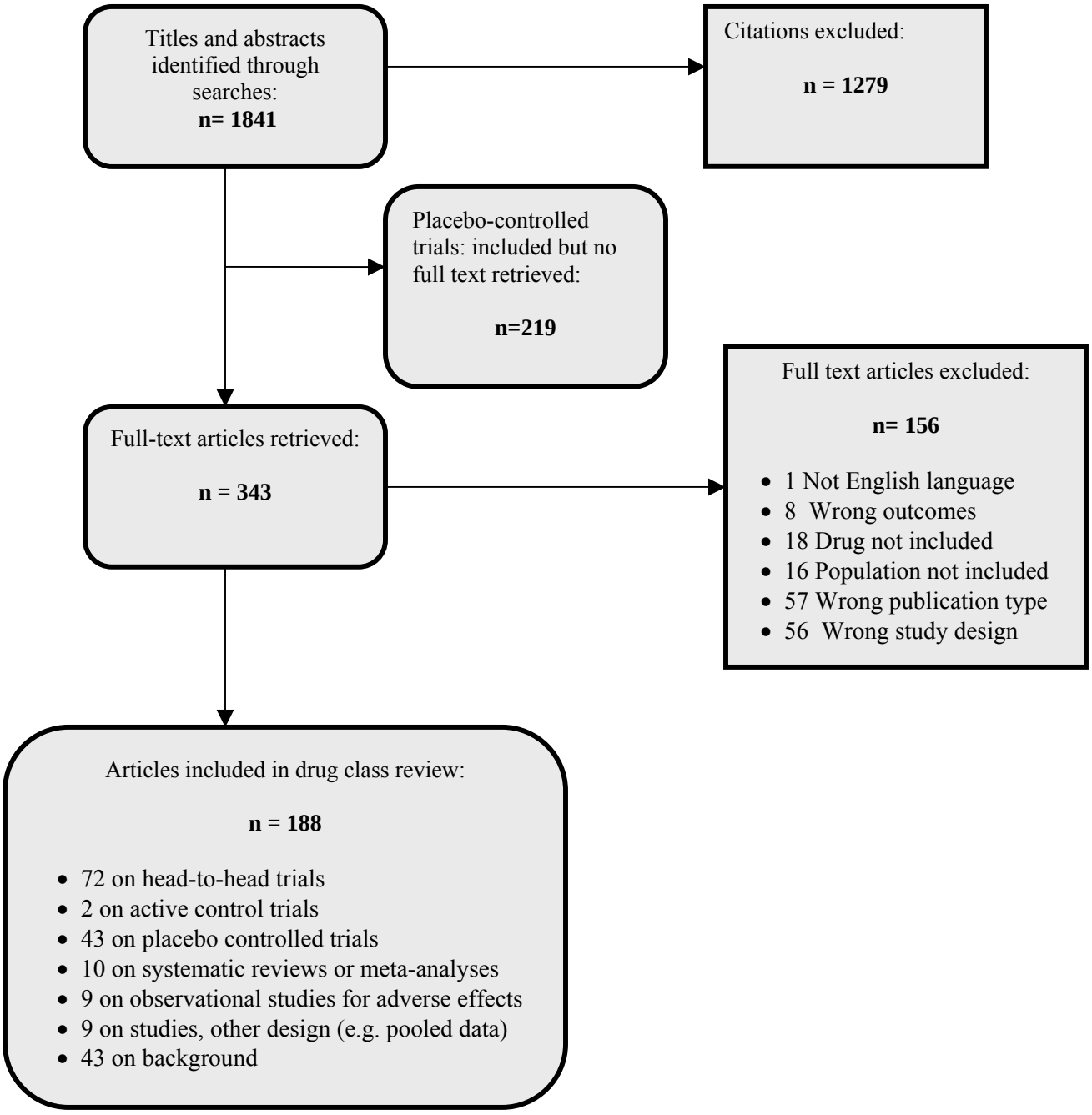


Figure 1. Results of Literature Search



EVIDENCE TABLES

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Aberg-Wistedt A, et al.** [35] ***Year:*** **2000** ***Country:*** Sweden ***Trial name:***			
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 then 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 evidences 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 years ***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 ***Trial name:***	
OUTCOME ASSESSMENT:	***Measures:*** MADRS, CGI-S, Secondary Battelle Quality of Life Measure (BQOL), SCID-II before and after treatment ***Timing of assessments:*** Primary measures done 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 Adults

STUDY:	***Authors:*** **Alves C, et al.** [48] ***Year:*** **1999** ***Country:*** Portugal ***Trial name:***			
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		From day 15 doses could be increased 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 ***Trial name:***	
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 the 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**

Authors: **Baldwin DS, et al.** ***Year:*** **1996, 2001** ***Country:*** UK, Ireland ***Trial name:***	
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 clinically and statistically significant differences between study groups regarding efficacy • Clinical improvement either maintained or improved in continuation phase
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** Unable to determine
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.**[52] ***Year:*** 2000 ***Country:*** Spain ***Trial name:***			
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 with each drug could be increased after 4 wks
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, but not specifically reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** venlafaxine: 44 (21-65), paroxetine: 45.1(18-65) ***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 ***Trial name:***	
OUTCOME ASSESSMENT:	***Measures:*** 21 item HAM-D, MADRS, CGI scale ***Timing of assessments:*** Baseline, weeks 1, 2, 4, 6, 8, 12, 16, 24
RESULTS:	• Both groups improved; no significant differences were observed 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 but possible
ATTRITION:	***Loss to follow-up:*** 32%, venlafaxine: 39%, paroxetine: 26% ***Withdrawals due to adverse events:*** 11%, venlafaxine: 15%, paroxetine: 7%* *paper reports 8%, however 3 of 43 paroxetine patients = 7% ***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.** [42] ***Year:*** **2003** ***Country:*** Multinational ***Trial name:***			
FUNDING:	Organon NV			
DESIGN:	***Study design:*** RCT ***Setting:*** Multinational, 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 ***Trial name:***	
OUTCOME ASSESSMENT:	***Measures and timing of assessment:*** HAM-D, MADRS, (Montgomery Asberg Depression Rating Scale), CGI at baseline, and days 4, 7, 10, 14, 28, 4 2, 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:*** 1 reported, may be more
ATTRITION:	***Loss to follow-up:*** 20.8%; sertraline: 18% , mirtazapine: 23% ***Withdrawals due to adverse events:*** mirtazapine: 12.5%, 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.** [41] ***Year:*** **2000** ***Country:*** Germany ***Trial name:***			
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 (21-68), paroxetine: 47.3 (21-69) ***Gender:*** (% female) mirtazapine: 63%, paroxetine: 65% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Benkert O, et al.** ***Year:*** **2000** ***Country:*** Germany ***Trial name:***	
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.** [29] ***Year:*** **1995** ***Country:*** UK ***Trial name:***			
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 ***Trial name:***	
OUTCOME ASSESSMENT:	***Measures:*** HAM-D, HAM-A, CGI-I, CGI-S, Covi Anxiety Scale, Raskin Depression Scale, Leeds Sleep Questionnaire ***Timing of assessments:*** 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:*** **Boyer P, et al.** [30] ***Year:*** **1998** ***Country:*** France ***Trial name:***			
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 ***Trial name:***	
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:*** (Overall: 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 significant 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:*** USA ***Trial name:***			
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. Caps looked the same.)	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:*** USA ***Trial name:***	
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 for ITT analysis
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 20 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.** [23] ***Year:*** **2002** ***Country:*** Italy ***Trial name:***			
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 ***Trial name:***	
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 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 ≥ 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.** [24] ***Year:*** **1999** ***Country:*** Canada ***Trial name:***			
FUNDING:	Not specifically stated, but last author is employee of SmithKline Beecham			
DESIGN:	***Study design:*** Multi-center double blind randomized controlled trial ***Setting:*** Patients recruited from newspaper ads and referrals ***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 years; paroxetine: 40.6, fluoxetine: 41.2 ***Gender:*** (% female) paroxetine: 63.7%, fluoxetine: 59.4% ***Ethnicity:*** 96.5% white, 1.5 % Asian, rest unknown ***Other population characteristics:*** Paroxetine group may have had more repeated episodes, 2 or more depressive episodes: paroxetine 76.5%, fluoxetine 59.5%			

Authors: **Chouinard G, et al.** ***Year:*** **1999** ***Country:*** Canada ***Trial name:***	
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:	• None of these results were significantly different • Responders: (Observed cases at 12 weeks) paroxetine 85.7%, fluoxetine 88.4%, (LOCF endpoint) paroxetine 67.0%, fluoxetine 68.4% • Remitters: (Observed cases at 12 weeks) paroxetine 77.8%, fluoxetine 81.2%, (LOCF endpoint) paroxetine 58.0%, fluoxetine 59.2%
ANALYSIS:	***ITT:*** Yes. LOCF ***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.** [62] ***Year:*** **1999** ***Country:*** USA ***Trial name:***			
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 anorexia or bulimia; pregnant, lactating or unwilling to take contraceptives; history of 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); prior treatment with bupropion or sertraline			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep (first 2 weeks only)			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 38.3 (19-74), buproprion SR: 38.1 (18-64), placebo: 38.5 (18-65) ***Gender:*** (% female) 59%; sertraline: 54%, buproprion SR: 56%, placebo: 59% ***Ethnicity:*** sertraline: white: 92%, black: 8%,other: < 1%; buproprion SR: 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:*** USA ***Trial name:***	
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 not 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.** [57] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
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; treatment with buproprion SR or fluoxetine in the past year; used any psychoactive drug within 1 week of study (2 weeks for MAOI or protriptyline or any investigational drug; prior treatment with bupropion or fluoxetine; non-responders to antidepressant treatment			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** fluoxetine: 37.1 (18-76), buproprion SR: 36.6 (18-67), placebo: 36.7 (19-62) ***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:*** At baseline more patients in the fluoxetine and buproprion SR groups had sexual desire disorder than the placebo group			

Authors: **Coleman CC, et al.** ***Year:*** **2001** ***Country:*** USA ***Trial name:***	
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:*** 18: 5%; fluoxetine: 4%, buproprion SR: 9%, placebo: 3% ***Withdrawals due to adverse events:*** 6% ***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 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 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Costa e Silva JC, et al.** [43] ***Year:*** **1998** ***Country:*** South America ***Trial name:***			
FUNDING:	Wyeth-Ayerst International			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 382			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Venlafaxine 75-150 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 ***Trial name:***	
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) was achieved by 80.6% in the venlafaxine group and 83.9 in the fluoxetine group • 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:	**Good**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Croft H, et al.** [61] ***Year:*** **1999** ***Country:*** USA ***Trial name:***			
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 anorexia or bulimia; pregnant, lactating or unwilling to take contraceptives; history of 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 protriptyline or 4 weeks for fluoxetine or any investigational drug); prior treatment with bupropion or sertraline			
OTHER MEDICATIONS/ INTERVENTIONS:	Not reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: 36.0 (19-61), buproprion: 35.9 (19-70), placebo: 37.4 (19-64) ***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:*** USA ***Trial name:***	
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, 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: 3%; sertraline: 3%, buproprion sr: 7%, placebo: 0% ***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.** [22] ***Year:*** **2003** ***Country:*** Europe ***Trial name:***			
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 ***Trial name:***	
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:*** **DeWilde J, et al.** [25] ***Year:*** **1993** ***Country:*** Belgium ***Trial name:***			
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:*** 44 ***Gender*** (female%) paroxetine: 57%, fluoxetine: 66% ***Ethnicity:*** Not reported ***Other population characteristics:*** 65% of paroxetine group had prior depression, 70% of fluoxetine had prior depression			

Authors: **DeWilde J, et al.** ***Year:*** **1993** ***Country:*** Belgium ***Trial name:***	
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:*** Cannot determine ***Post randomization exclusions:*** Yes
ATTRITION: ITT n = 99 (LOCF)	***Loss to follow-up:*** 22% ***Withdrawals due to adverse events:*** Not reported ***Loss to follow-up differential high:*** Cannot determine
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.** [44] ***Year:*** **2002** ***Country:*** Belgium ***Trial name:***			
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; 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 ***Trial name:***	
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.** [49] ***Year:*** **1995** ***Country:*** France ***Trial name:***			
FUNDING:	Wyeth-Ayerst			
DESIGN:	***Study design:*** RCT ***Setting:*** France ***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:*** **1995** ***Country:*** France ***Trial name:***	
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. 7 patients
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.** [178] ***Year:*** **1997** ***Country:*** Sweden ***Trial name:***			
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 50-150 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 ***Trial name:***	
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:*** 18% ***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: 34.5%, citalopram: 32% • Diarrhea: sertraline: 22%, citalopram: 15.5% • Increased sweating: sertraline: 19%, citalopram16.5% • Dry mouth: sertraline: 18.5%, citalopram: 16% • Headache: sertraline: 19.5%, citalopram: 24.5% • Sexual dysfunction was experienced in 8% in the sertraline group and 13.5% in the citalopram group
QUALITY RATING:	**Good**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Fava M, et al.** [27] ***Year:*** **1998** ***Country:*** USA ***Trial name:***			
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 ≥ 8 (and larger in value than the Covi anxiety scale) score of ≥ 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 contraceptives			
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:*** ***Trial name:***	
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:*** Cannot determine
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%) Note: The article states that these differences become non-significant when the bonferroni correction for multiple comparisons is used
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Fava M, et al.** [28 153] ***Year:*** **2002** ***Country:*** USA ***Trial name:***			
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 major depressive disorder; 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:*** USA ***Trial name:***	
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 <u>Subgroup analysis (Fava 2000): Anxious depression</u> • 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:*** Unable to determine
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 <u>Subgroup analysis (Fava 1999)</u> • 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.** [68] ***Year:*** **1996** ***Country:*** Europe ***Trial name:***			
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 was 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 ***Trial name:***	
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.** [56] ***Year:*** **1991** ***Country:*** USA ***Trial name:***			
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; or other unstable medical condition; pregnant; lactating; no acceptable contraceptive 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:*** USA ***Trial name:***	
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.** [33] ***Year:*** **1999** ***Country:*** USA ***Trial name:***			
FUNDING:	Not reported; 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 20-100 mg/day 12 weeks		
INCLUSION:	DSM III-R criteria for major depression; Hamilton Rating Scale-D: ≥ 18; age 70 or older			
EXCLUSION:	Significant medical problems; Axis I psychiatric disorders; cognitive impairment; suicidal risk; drug abuse or dependence; history of failure to respond to antidepressant treatment			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate, temazepam			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** 74 ***Gender (female%)*** 53% ***Ethnicity:*** 97% white, 3% black ***Other population characteristics:*** Not reported			

Authors: **Finkel SI, et al.** ***Year:*** **1999** ***Country:*** USA ***Trial name:***	
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%, fluoxitine: 39% ***Withdrawals due to adverse events:*** sertraline: 19%, fluoxitine: 30% ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Sertraline-treated patients reported “shaking” to a greater degree (14.3%) than did fluoxitine treated patients (0%) (p = 0.03) • Fluoxitine-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.** [179 37] ***Year:*** **1999, 1997** ***Country:*** Italy ***Trial name:***			
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:*** **1999, 1997** ***Country:*** Italy ***Trial name:***	
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 ***Trial name:***			
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 years, paroxetine: 37.8 years ***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 ***Trial name:***	
OUTCOME ASSESSMENT:	***Measures:*** Physical exam, HAM-D, MADRS, CGI, HAM-A, routine haematology 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:*** LOCF ***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:*** **Hong CJ, et al.** [39] ***Year:*** **2003** ***Country:*** Taiwan ***Trial name:***			
FUNDING:	NV Organon, Oss, the Netherlands			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 133			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Mirtazapine: 30 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 ***Trial name:***	
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. LOCF ***Post randomization exclusions:*** Yes. 1 individual excluded after randomization but before study medication was given
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.** [60] ***Year:*** **1997** ***Country:*** USA ***Trial name:***			
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:	18 years of age or older; 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 drug 1 or drug 2; 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 ***Other population characteristics:*** Prior antidepressant use for current episode: bupropion SR: 22%, sertraline: 21%			

Authors: **Kavoussi et al.** ***Year:*** **1997** ***Country:*** USA ***Trial name:***	
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:*** 3.2%; bupropion SR: 6%, sertraline: 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: 0%, sertraline: 3.1% • 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 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** ***Country:*** ***Trial name:*** ARTIST (A randomized trial investigating SSRI treatment)	
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%. (numbers reported are derived from patients who actually started treatment not from patients who got randomized) ***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 Adults

STUDY:	***Authors:*** **Lepola, et al.** [20] ***Year:*** **2003** ***Country:*** Europe, Canada ***Trial name:***			
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 years ***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 ***Trial name:***	
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:*** LOCF ***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 was the most common adverse events: citalopram 23%, escitalopram 27%
QUALITY RATING:	**Fair**

Evidence Table 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **McPartlin GM, et. al.** [53] ***Year:*** **1998** ***Country:*** UK ***Trial name:***			
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 ***Trial name:***	
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.** [54] ***Year:*** **2000** ***Country:*** Scandinavia ***Trial name:***			
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 ***Trial name:***	
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:*** **Nemeroff CB, et al.** [36] ***Year:*** **1995** ***Country:*** USA ***Trial name:***			
FUNDING:	Solvay Pharmaceuticals			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 97			
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:*** USA ***Trial name:***	
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 fluoxetine 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.** [31] ***Year:*** **2000** ***Country:*** USA ***Trial name:***			
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 (±5.3), fluoxetine: 67 (±5.9) ***Gender:*** (% female) sertraline: 63.2%, fluoxetine: 51.3% ***Ethnicity:*** Majority white ***Other population characteristics:*** Not reported			

Authors: **Newhouse PA, et al.** ***Year:*** **2000** ***Country:*** USA ***Trial name:***	
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:*** 19%, sertraline: 17.2%, fluoxetine: 21.2%, p = 0.5 (In text this was reported as: sertraline: 18.8%, fluoxetine: 24.4%) ***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 X Major Depressive Disorder Adults

STUDY:	***Authors:*** **Nieuwstraten C and Dolovich LR** [55] ***Year:*** **2001** ***Country:*** Canada ***Trial name:***
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 (reported in text), Weihs et al studied elderly patients with major depression. Mean age in this study reported as 70 years. Unless all patients were 70 years old the above statement could not be true. Proportion of females: 48.0% to 61.8%

Authors **Nieuwstraten C and Dolovich LR** ***Year:*** **2001** ***Country:*** Canada ***Trial name:***	
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 Adults

STUDY:	***Authors :*** **Patris M, et al.** [17] ***Year:*** **1996** ***Country:*** France ***Trial name:***			
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 ***Trial name:***	
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. Only analyzed those who completed at least 2 weeks of treatment
ATTRITION:	***Loss to follow-up:*** Not reported ***Withdrawals due to adverse events:*** 4.2%; citalopram: 7.2%, fluoxetine: 3.1% ***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:*** **Rudolph RL, et al.** [45] ***Year:*** **1999** ***Country:*** USA ***Trial name:***			
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 matched placebo 8 weeks	Initial dosage could be increased after 2 weeks
INCLUSION:	≥ 18 years of age; met DSM-IV criteria for major depressive disorder; 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:*** USA ***Trial name:***	
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.** [65] ***Year:*** **1998** ***Country:*** USA and Canada ***Trial name:***			
FUNDING:	Bristol Myers Squibb, Seay Center for Research (UT Southwestern), NIMH			
DESIGN:	***Study design:*** Pooled analysis from 3 RCTs: Gillin 1997 [63], Armitage 1997 [64], Rush 1998 [65] ***Setting:*** Multi-center ***Sample size:*** 125			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Nefazodone 20-40 mg/d 8 weeks	Fluoxetine 20-40 mg/d 8 weeks		
INCLUSION:	Outpatient; ages 19-55; non-psychotic moderate to severe major depressive disorder by DSM-IIIR criteria; min 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:*** 78-85% white, 7-9% black, 1-5% Asian ***Other population characteristics:*** Not reported			

Authors: **Rush AJ, et al.** ***Year:*** **1998** ***Country:*** USA and Canada ***Trial name:***	
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 group 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. Used LOCF method for missing data at endpoint ***Post randomization exclusions:*** Yes. 3 were excluded because “not evaluative for efficacy”
ATTRITION:	***Loss to follow-up:*** 17% ***Withdrawals due to adverse events:*** 8.8% ***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.** [40] ***Year:*** **2002** ***Country:*** USA ***Trial name:***			
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; 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) mirtazapine: 63%, paroxetine: 64% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Schatzberg et al.** ***Year:*** **2002** ***Country:*** USA ***Trial name:***	
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% ***Withdrawals due to adverse events:*** 20.4%; mirtazapine 14%, 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.** [26] ***Year:*** **1993** ***Country:*** Austria and Germany ***Trial name:***			
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; know 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 ***Trial name:***	
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. 2 were excluded for reasons not reported
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 ***Trial name:***			
FUNDING:	Pfizer France			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center (45 private psychiatrists) ***Sample size:*** 238			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Sertraline 50-150 mg/d 24 weeks	Fluoxetine 20-60 mg/d 24 weeks	Mean daily dose: 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 ***Trial name:***	
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:*** 29.8%; sertraline: 25.4%, fluoxetine: 34.2% ***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.** [69] **Year: 2000** ***Country:*** USA ***Trial name:***			
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 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: **Seagraves et al.** ***Year:*** **2000** ***Country:*** USA ***Trial name:***	
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 (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 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 1 Major Depressive Disorder Adults

STUDY:	***Authors:*** **Silverstone PH et al.** [46 47] ***Year:*** **1999, 2001** (subgroup analysis) ***Country:*** Canada ***Trial name:***			
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 matched placebo 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%) placebo: 57.6, venlafaxine: 64%, fluoxetine: 60% ***Ethnicity:*** Not reported ***Other population characteristics:*** Subgroup analysis: Patients with generalized anxiety disorder (n = 92)			

Authors: **Silverstone PH, et al.** ***Year:*** **1999, 2001** ***Country:*** Canada ***Trial name:***	
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 Adults

STUDY:	***Authors:*** **Tylee A, et al.** [50] ***Year:*** **1997** ***Country:*** UK ***Trial name:***			
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:*** 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 ***Trial name:***	
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:*** 27.3%; 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.** [58,59] ***Year:*** **2000, 2001** (QOL analysis presented in Doraiswamy PM, et al.) ***Country:*** USA ***Trial name:***			
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.** ***Year:*** **2000, 2001** ***Country:*** USA ***Trial name:***	
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 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:	**Good**

Evidence Table 2 Dysthymia

STUDY:	***Authors:*** **Barrett, et. al.** [74] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
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 20-40 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 ; symptoms for at least 4 weeks with at least 3 symptoms; diagnosis made by research psychiatrist using PRIME-MD			
EXCLUSION:	Not actually stated in this article. The other article published from this same trial (Williams, 2000 JAMA) stated the following exclusions: 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:*** USA ***Trial name:***	
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:*** Not reported ***Withdrawals due to adverse events:*** 2.5% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 2 Dysthymia

STUDY:	***Authors:*** **Ravindran et. al.** [73] ***Year:*** **2000** ***Country:*** Canada and Europe ***Trial name:***			
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 ***Trial name:***	
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:*** (Overall: 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: 3% • 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., Kocsis et. al., Hellerstein et. al.** [70, 71, 72] ***Year:*** **1996, 1997, 2000** ***Country:*** USA ***Trial name:***			
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 ***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:*** USA ***Trial name:***	
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:*** **Williams et. al.** [75] ***Year:*** **2000** ***Country:*** USA ***Trial name:***			
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:*** 21.8% “minority ethnic groups” ***Gender:*** (% female) paroxetine: 39%, placebo: 45% ***Other population characteristics:*** Mean of 3.4 medical conditions per patient			

Authors: **Williams et al.** ***Year:*** **2000** ***Country:*** USA ***Trial name:***	
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:*** Not reported ***Withdrawals due to adverse events:*** 4.8% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Good**

Evidence Table 3 Major Depressive Disorder Pediatrics

STUDY:	***Authors:*** **Keller, et. al.** [81] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
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:*** white: 80.5-87.4%, African American: 3.2-6.9%, Asian: 1.1-2.3%, other: 7.4-10.8% ***Other population characteristics:*** Anxiety: 19-28%, externalizing disorder: 20-26%			

Authors: **Keller et. al.** ***Year:*** **2001** ***Country:*** USA ***Trial name:***	
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 explicitly stated but it appears to be LOCF ***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 (but not for paroxetine-placebo comparison)
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 liability (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.** [80] ***Year:*** **1997** ***Country:*** USA ***Trial name:***			
FUNDING:	Not reported			
DESIGN:	***Study design:*** RCT ***Setting:*** Single center ***Sample size:*** 40			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Venlafaxine 8-12 years old: 12.5-37.5 mg/d 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, Gilles de la 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:*** none reported			

Authors: **Mandoki MW, et al.** ***Year:*** **1997** ***Country:*** USA ***Trial name:***	
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:*** **Wagner, et. al.** [79] ***Year:*** **2003** ***Country:*** Multinational ***Trial name:***			
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) with a 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, both as sleep aids			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean age:*** sertraline: age 6-11, 45.5%; age 12-17, 54.5%; placebo: age 6-11, 48.7%; age 12-17, 51.3% ***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:*** Multi-national ***Trial name:***	
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:*** **Whittington CJ, et. al.** [77] ***Year:*** **2004** ***Country:*** UK ***Trial name:***
FUNDING:	(National Institute for Clinical Excellence) NICE
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 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 ***Trial name:***	
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 • Additionally, there is an increased risk of serious adverse events • 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 Bipolar Disorder

STUDY:	***Authors:*** **Nemeroff et al.** [86] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
FUNDING:	Glaxo Smith Kline, NIMH			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 117			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20-50 mg/d 10 weeks	Imipramine 150-300 mg/d 10 weeks	Placebo n/a 10 weeks	
INCLUSION:	Age $\geq$ 18; DSM-III R criteria for bipolar disorder and minimum score of $\geq$ 15 on HAM-D_{21} with no more than a 25% decrease in score between screening and baseline; currently in a major depressive episode; at least one previous episode of mania or major depression in the past 5 yrs and maintained on a regimen of lithium alone or a combo with sodium valporate or carbamazepine for at least 7 weeks before screening with serum lithium levels between 0.5-1.2 or at least 6 wks before screening			
EXCLUSION:	Not currently depressed; therapy with both valporate and carbamazepine; primary diagnosis of an axis I disorder other than bipolar disorder within 6 months of screening; rapid cyclers or recent manic/hypo manic episode within 4 weeks of baseline or prone to spontaneous remission; any serious medical disorder or condition that would preclude use of a TCA; concomitant therapy with other psychotropic drugs: warfarin, digoxin, phenytoin, cimetidine; type Ic anti-arrhythmics, quinidine, sulfonylurea derivatives or tryptophan; substance abuse within 3 months or substance dependence within 6 months; serious suicidal or homicidal risk			
ALLOWED OTHER MEDICATIONS/ INTERVENTIONS:	Concurrent treatment with lithium was required, either carbamazapine or valporate but not both also was allowed, chloral hydrate			

Authors: **Nemeroff et. al.** ***Year:*** **2001** ***Country:*** USA ***Trial name:***	
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** 41; paroxetine: 42.5, placebo: 40.4 ***Gender:*** (female%) paroxetine: 54.3%, placebo: 53.5% ***Ethnicity:*** Caucasian: 95% ***Other population characteristics:*** Used concomitant medications: paroxetine: 82.9%, imipramine: 76.9%, placebo: 81.4%; concomitant valporate use: paroxetine: 11.4%, placebo: 9.3%
OUTCOME ASSESSMENT:	***Measures:*** HAM-D-17, (Remitters $\leq$ 7), CGI-S, CGI-I (% $\leq$ 2) ***Timing of assessments:*** Baseline, weeks 1, 2, 3, 4, 5, 6, 8, 10
RESULTS:	Mean change in HAM-D and CGI-S not significantly different than placebo. Remitters (HAM-D17 $\leq$ 7): paroxetine 45.5%, imipramine 38.9%, placebo 34.9%. No significant differences. Remitters (CGI-I): paroxetine: 54.5%, imipramine: 58.3%, placebo 45.6%. No significant differences.
ANALYSIS:	***ITT:*** Not reported ***Post randomization exclusions:*** Yes
ATTRITION:	***Loss to follow-up:*** paroxetine: 28.5%, imipramine: 41%, placebo: 37.2% ***Withdrawals due to adverse events:*** paroxetine: 2.9%, imipramine: 30.8%, placebo: 11.6% ***Loss to follow-up differential high:*** Yes (but less than 15% points difference)
ADVERSE EVENTS:	• Serious adverse events: paroxetine: 0, imipramine: 2 (5.1%), placebo 4 (9.3%) • Treatment emergent mania: paroxetine: 0, imipramine: 3 (7.7%), placebo 1 (2.3%) • No statistical comparisons made for the most frequently reported side effects • Paroxetine: tremor: 40%, insomnia: 37.1%, somnolence: 34.3% • Imipramine: dry mouth: 61.5%, tremor: 38.5%, headache: 41% • Placebo: headache: 39.5%, somnolence: 25.6%, insomnia: 23.3%
QUALITY RATING:	**Fair**

Evidence Table 5 General Anxiety Disorder

STUDY:	***Authors:*** **Pollack MH, et. al.** [88] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
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 generalized anxiety disorder; score ≥ 20 on the 14 item HAM-A; ≥ 18 years of age			
EXCLUSION:	Any other Axis-I diagnosis; MADRS ≥ 17 at baseline; substance abuse; patients 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 group and placebo group (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:*** USA ***Trial name:***	
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, libido decreased, nausea, and somnolence (> 10% and at least twice placebo rate) • All adverse effects were experienced by more paroxetine patients than placebo patients
QUALITY RATING:	**Fair**

Evidence Table 5 General Anxiety Disorder

STUDY:	***Authors:*** **Rickels K, et al.** [87] ***Year:*** **2003** ***Country:*** USA and Canada ***Trial name:***			
FUNDING:	GSK			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 566			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Paroxetine 20 mg/d 8 weeks	Paroxetine N40 mg/d 8 weeks	Placebo n/a 8 weeks	
INCLUSION:	DSM-IV criteria for GAD; HAM-A score ≥ 20; score of 2 or more on item 1 & 2 (anxious mood, tension); mean age ≥ 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:*** USA and Canada ***Trial name:***	
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 6 Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Ackerman, et al.** [91] ***Year:*** **2002** ***Country:*** USA ***Trial name:***
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 like 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** ***Country:*** ***Trial name:***	
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 6 Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Bergeron, et al.** [93] ***Year:*** **2002** ***Country:*** Canada ***Trial name:***			
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 ≥ 17 on Y-BOCS; ≥ 7 on NIMH-OC; and CGI-S ≥ 4 and HAM-D17 ≤ 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 ***Trial name:***	
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**

Evidence Table 6 Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Denys D, et al.** [94] ***Year:*** **2003** ***Country:*** USA ***Trial name:***			
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 at a 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:*** **2002** ***Country:*** Canada ***Trial name:***	
OUTCOME ASSESSMENT:	***Measures:*** Yale-Brown Obsessive Compulsive scale (Y-BOCS), Hamilton Anxiety Scale (HAS), HAM-D-17, Global Assessment of Functioning ***Timing of assessments:*** Baseline, weeks 1, 3, 5, 8, 10, 12
RESULTS:	• Paroxetine showed significantly greater improvement in HAMD 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
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 6 Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Montgomery SA, et. al.** [96] ***Year:*** **2001** ***Country:*** Europe, South Africa ***Trial name:***			
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:*** Mot 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 ***Trial name:***	
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 20mg 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:*** Unable to determine
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 moth , ejaculation failure, and diarrhea was significantly higher in one or more citalopram groups compared to placebo
QUALITY RATING:	**Fair**

Evidence Table 6 Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Piccinelli M, et. al.** [90] ***Year:*** **1995** ***Country:*** Italy ***Trial name:***
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 ***Trial name:***	
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 6 Obsessive-compulsive Disorder

STUDY:	***Authors:*** **Stein DJ, et al.** [92] ***Year:*** **1995** ***Country:*** South Africa and USA ***Trial name:***
FUNDING:	Not reported
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 516 (SSRI vs. placebo only)
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, USA ***Trial name:***	
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 7 Panic Disorder

STUDY:	***Authors:*** **Asnis G, et al.** [113] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
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 lactating women as well as women without adequate birth control			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate or lorazepam for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Authors state groups were well matched, however no statistical results were provided ***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: fluoxetine: 2.7, paroxetine: 3.3			

Authors: **Asnis G, et al.** ***Year:*** **2001** ***Country:*** USA ***Trial name:***	
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%, paroxetine: 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 7 Panic Disorder

STUDY:	***Authors:*** **Bandelow B, et al.** [110] ***Year:*** **2004** ***Country:*** Germany ***Trial name:***		
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, major depressive disorder, obsessive-compulsive disorder, 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 ($\leq$ 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 7 Panic Disorder

STUDY:	***Authors:*** **Black DW, et al.** [115] ***Year:*** **1993** ***Country:*** USA ***Trial name:***			
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 IIIR criteria for panic disorder; in good physical health			
EXCLUSION:	Pregnant; lactating; psychotic; suicidal or demented subjects excluded			
OTHER MEDICATIONS/ INTERVENTIONS:	None specifically mentioned although authors do state “we made no attempt to assess subjects for surreptitious use of anxiolytic or other medications during the washout”			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Not reported ***Mean Age:*** 36.5 ***Gender:*** 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:*** USA ***Trial name:***	
OUTCOME ASSESSMENT:	***Measures:*** **#** 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 with placebo • MADRS score was significantly more improved with fluvoxamine than with 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 attempted suicide in the fluvoxamine group
QUALITY RATING:	**Fair**

Evidence Table 7 Panic Disorder

STUDY:	***Authors:*** **Hoehn-Saric R, et al.** [112] ***Year:*** **1993** ***Country:*** USA ***Trial name:***			
FUNDING:	Not reported			
DESIGN:	***Study design:*** RCT ***Setting:*** Single center ***Sample size:*** Unclear; around 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; needed 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:*** USA ***Trial name:***	
OUTCOME ASSESSMENT:	***Measures:*** **#** 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 7 Panic Disorder

STUDY:	***Authors:*** **Pohl RB, et al.** [114] ***Year:*** **1998** ***Country:*** USA ***Trial name:***			
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 panic attacks during past 4 weeks but not more than 100; 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: 9.5yrs			

Authors: **Pohl RB, et al.** ***Year:*** **1998** ***Country:*** USA ***Trial name:***	
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 higher 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 group than in the placebo group
QUALITY RATING:	**Fair**

Evidence Table 7 Panic Disorder

STUDY:	***Authors:*** **Stahl SM, et al.** [108] ***Year:*** **2003** ***Country:*** USA ***Trial name:***			
FUNDING:	Forest Laboratories Inc. (NY)			
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; obsessive compulsive disorder 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:*** USA ***Trial name:***	
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 8 Post Traumatic Stress Disorder

STUDY:	***Authors:*** **Brady K, et al., 2000, (1 of 2 acute phase)**[116] **Londborg PD, et al., 2001 (24 week open label)**[121] **Rapaport MH, et al., 2002 (64 weeks qol)**[118] **Davidson JRT, Pearlstein T, et al., 2001 (28 week continuation)**[122] ***Country:*** USA ***Trial name:***			
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 <u>Open-label continuation treatment:</u> 24 weeks <u>Maintenance:</u> 28 weeks	Placebo n/a 12 weeks <u>Open-label continuation treatment:</u> 24 weeks <u>Maintenance:</u> 28 weeks		

Authors: **Brady K, et al. 2000,** **Londberg PD, et al., 2001** **Rapaport MH, et al., 2002** **Davidson JRT, Pearlstein T, 2001** ***Country:*** USA ***Trial name:***	
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 ≥ 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:*** USA ***Trial name:***	
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) <u>Quality of life (pooled data from Brady 2000 and Davidson 2001</u>) • 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) <u>Open-label continuation treatment</u> • 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 <u>Maintenance</u> • 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:*** USA ***Trial name:***	
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 8 Post Traumatic Stress Disorder

STUDY:	***Authors:*** **Connor K, et al.** [120] ***Year:*** **1999** ***Country:*** USA ***Trial name:***			
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 and then 12 weeks for continuation phase	Placebo n/a 12 weeks for acute treatment and then 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:*** 18-55, median 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 yrs of PTSD 6			

Authors: **Connor K, et al.** ***Year:*** **1999** ***Country:*** USA ***Trial name:***	
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 8 Post Traumatic Stress Disorder

STUDY:	***Authors:*** **Davidson JRT, et al.** [117] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
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:*** USA ***Trial name:***	
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 subjects given sertraline 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 8 Post Traumatic Stress Disorder

STUDY:	***Authors:*** **Marshall RD, et al.** [119] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
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 litigations 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:*** USA ***Trial name:***	
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 9 Social Anxiety Disorder

STUDY:	***Authors:*** **Baldwin et. al.**[127] ***Year:*** **1999** ***Country:*** Belgium, France, Germany, Ireland, South Africa, Spain, United Kingdom ***Trial name:***			
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:*** 89% white ***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 ***Trial name:***	
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 < 0.001from 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 9 Social Anxiety Disorder

STUDY:	***Authors:*** **Blomhoff S, et. al.**[132] ***Year:*** **2001** ***Country:*** Norway and Sweden ***Trial name:***			
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 or 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 ***Trial name:***	
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 9 Social Anxiety Disorder

STUDY:	***Authors:*** **Kobak KA, et. al.**[124] ***Year:*** **2002** ***Country:*** USA ***Trial name:***			
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; needed 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:*** 39.47 ***Gender:*** (%female) 58% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Kobak KA, et. al.** ***Year:*** **2002** ***Country:*** USA ***Trial name:***	
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 patients had asthenia than placebo (p = 0.02) • Significantly more placebo patients had myalgia than fluoxetine (p = 0.04)
QUALITY RATING:	**Fair**

Evidence Table 9 Social Anxiety Disorder

STUDY:	**Authors: Lepola et al.**[129] **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; women who were 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 (3 paroxetine CR and 2 placebo patients)
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 adverse 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 9 Social Anxiety Disorder

STUDY:	***Authors:*** **Liebowitz**[131] ***Year:*** **2003** ***Country:*** USA ***Trial name:***			
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 ≥ 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 obsessive compulsive disorder; primary diagnosis of GAD; HAM-D-17 ≥ 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** ***Year:*** **2003** ***Country:*** ***Trial name:***	
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:*** 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 9 Social Anxiety Disorder

STUDY:	***Authors:*** **Stein MB, et. al.**[125] ***Year:*** **1999** ***Country:*** USA ***Trial name:***			
FUNDING:	Solvay Pharmaceuticals Inc., Marietta GA and The Pharmacia and Upjohn Co., Kalamazoo MI			
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 group than in placebo group (p = 0.04) ***Ethnicity:*** Not reported ***Other population characteristics:*** No other significant population differences reported			

Authors: **Stein MB, et. al.** ***Year:*** **1999** ***Country:*** ***Trial name:***	
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:	• There was a significantly higher proportion of responders in the fluvoxamine group than the placebo (fluvoxamine: 42.9%, placebo: 22.7%; p = 0.04) • Fluvoxamine was 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 9 Social Anxiety Disorder

STUDY:	***Authors:*** **Stein MB, et. al.**[128] ***Year:*** **1998** ***Country:*** US, Canada ***Trial name:***			
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; women who were pregnant, lactating, or not using clinically acceptable method of birth control			
OTHER MEDICATIONS/ INTERVENTIONS:	Chloral hydrate for sleep			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** 36 (18-76) ***Gender:*** (% female) 53% ***Ethnicity:*** 81% white ***Other population characteristics:*** Not reported			

Authors: **Stein MB, et. al**. ***Year:*** **1998** ***Country:*** US, Canada ***Trial name:***	
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 9 Social Anxiety Disorder

STUDY:	***Authors:*** **Stein D, et. al.**[126] ***Year:*** **2002** ***Country:*** Multinational ***Trial name:***			
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 ***Trial name:***	
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 of relapse in placebo group = 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** (for maintenance phase)

Evidence Table 9 Social Anxiety Disorder

STUDY:	***Authors:*** **Van Ameringen R, et. al.**[130] ***Year:*** **2001** ***Country:*** Canada ***Trial name:***			
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:	Subjects had another 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 (19-56), placebo: 35.6 (20-54) ***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 ***Trial name:***	
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 9 Social Anxiety Disorder

STUDY:	***Authors:*** **van der Linden et. al.**[123] ***Year:*** **2000** ***Country:*** South Africa, the Netherlands ***Trial name:***
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:*** ***Trial name:***	
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 10 Premenstrual Dysphoric Disorder

STUDY:	***Authors:*** **Dimmock PW, et al.**[134] ***Year:*** **2000** ***Country:*** ***Trial name:***
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** ***Country:*** ***Trial name:***	
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:	No sufficient 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 10 Premenstrual Dysphoric Disorder

STUDY:	***Authors:*** **Freeman EW, et al.**[135] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
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:*** all female ***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:*** USA ***Trial name:***	
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 $p < 0.001$) • Fatigue (not significant) • Headache (not significant) • Dry mouth (not significant) • Decreased libido (venlafaxine vs. placebo $p < 0.001$) • Dysmenorrhea (not significant)
QUALITY RATING:	**Fair**

Evidence Table 10 Premenstrual Dysphoric Disorder

STUDY:	***Authors:*** **Halbreich U, et al.**[137] ***Year:*** **2002** ***Country:*** USA and Canada ***Trial name:***			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** RCT ***Setting:*** Multi-center ***Sample size:*** 281			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	 Sertraline 50-100 mg/d –only taken 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 contraceptive; 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:*** all female ***Ethnicity:*** 91% caucasian ***Other population characteristics:*** Comparable clinical characteristics at baseline			

Authors: **Halbreich U, et al.** ***Year:*** **2002** ***Country:*** USA and Canada ***Trial name:***	
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 on sertraline (16.9%) than placebo (7.1%); $p = 0.022$
QUALITY RATING:	**Fair**

Evidence Table 10 Premenstrual Dysphoric Disorder

STUDY:	***Authors:*** **Landen M, et al.**[136] ***Year:*** **2001** ***Country:*** Sweden ***Trial name:***			
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 the 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; major depressive disorder; 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:*** all female ***Ethnicity:*** Not reported ***Other population characteristics:*** No differences reported			

Authors: **Landen M, et al.** ***Year:*** **2001** ***Country:*** Sweden ***Trial name:***	
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); however, 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 10 Premenstrual Dysphoric Disorder

STUDY:	***Authors:*** **Wyatt KM, et al.**[133] ***Year:*** **2004** ***Country:*** UK ***Trial name:***
FUNDING:	Cochrane Collaboration
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 844
AIMS OF REVIEW:	To evaluate the effectiveness of SSRIs in reducing premenstrual syndrome 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, premenstrual dysphoric disorder, or late luteal phase disorder; diagnosis must have been established by a clinician prior to inclusion in the trial

Authors: **Wyatt KM, et al.** ***Year:*** **2004** ***Country:*** UK ***Trial name:***	
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 11 Adverse Events

STUDY:	***Authors:*** **Beasley CM, et al., 1991, 1992, Tollefson GD, et al., 1994** [143, 144, 102] ***Country:*** USA ***Trial name:***
FUNDING:	Not reported
DESIGN:	***Study design:*** Meta-analysis ***Number of patients:*** 3065
AIMS OF REVIEW:	To assess the possible association of fluoxetine and suicidality
STUDIES INCLUDED IN META-ANALYSIS	17 RCTs; placebo controlled or active controlled with tricyclic antidepressants (TCA)
TIME PERIOD COVERED:	Includes trials up to December 1989; starting date not reported
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs, placebo or active controlled with TCAs
CHARACTERISTICS OF INCLUDED POPULATIONS:	Non-psychotic with MDD; age 12-90

Authors: **Beasley CM, et al., 1991, 1992, Tollefson GD, et al., 1994** ***Country:*** USA ***Trial name:***	
CHARACTERISTICS OF INCLUDED INTERVENTIONS:	Fluoxetine, placebo, tricyclic antidepressants
MAIN RESULTS:	• Suicidal acts did not differ significantly in comparisons between fluoxetine with placebo (p = 0.494) and with TCAs (p = 0.419) • Pooled incidence of suicidal acts was: fluoxetine: 0.3%, placebo: 0.2%, tricyclics: 0.4% • Pooled incidence of suicidal ideation was significantly lower for fluoxetine compared to placebo (1.2% vs. 2.6%, p = 0.042) and to tricyclics (1.2% vs. 3.6%, p = 0.001) • Pooled incidence of worsening suicidal ideation did not differ significantly among treatment groups • Suicidal ideation improved significantly with fluoxetine compared to placebo (p < 0.001) and was similar to TCAs (p = 0.294) • The incidence of suicidality was not significantly higher when temporally associated with an adverse event than when the suicidal event was not associated with an adverse event • There was no significant difference in increased risk of suicidality associated with an adverse event between the treatment groups (fluoxetine vs. placebo, fluoxetine vs. TCAs)
ADVERSE EVENTS:	Not reported
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	No
QUALITY RATING:	**Fair**

Evidence Table 11 Adverse Events

STUDY:	***Authors:*** **Benkert O, et al.** [41] ***Year:*** **2000** ***Country:*** Germany ***Trial name:***			
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 (21-68), paroxetine: 47.3 (21-69) ***Gender:*** (% female) mirtazapine: 63%, paroxetine: 65% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Benkert O, et al.** ***Year:*** **2000** ***Country:*** Germany ***Trial name:***	
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 11 Adverse Events

STUDY:	***Authors:*** **Clayton AH, et al.** [151] ***Year:*** **2002** ***Country:*** USA ***Trial name:***			
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** ***Country:*** ***Trial name:***	
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 11 Adverse Events

STUDY:	***Authors:*** **Coleman CC, et al.** [62] ***Year:*** **1999** ***Country:*** USA ***Trial name:***			
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; 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 (19-74), buproprion: 38.1 (18-64), placebo: 38.5 (18-65) ***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:*** USA ***Trial name:***	
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 not 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 11 Adverse Events

STUDY:	***Authors:*** **Coleman CC, et al.** [57] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
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		
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 (18-76), buproprion sr: 36.6 (18-67), placebo: 36.7 (19-62) ***Gender:*** (% female) fluoxetine: 66%, buproprion: 63%, placebo: 61% ***Ethnicity:*** fluoxetine: 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 groups had sexual desire disorder than the placebo group			

Authors: **Coleman CC, et al.** ***Year:*** **2001** ***Country:*** USA ***Trial name:***	
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:*** 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:*** 18: 5%; fluoxetine: 4%, buproprion: 9%, placebo: 3% ***Withdrawals due to adverse events:*** 6% ***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 or placebo • Dry mouth, nausea, and insomnia were reported more frequently in buproprion patients than fluoxetine or placebo • 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 11 Adverse Events

STUDY:	***Authors:*** **Croft H, et al.** [61] ***Year:*** **1999** ***Country:*** USA ***Trial name:***			
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 (19-61), buproprion: 35.9 (19-70), placebo: 37.4 (19-64) ***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:*** USA ***Trial name:***	
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 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: 3%; sertraline: 3%, buproprion sr: 7%, placebo: 0% ***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 11 Adverse Events

STUDY:	***Authors:*** **Ekselius, et al.** [150] ***Year:*** **2001** ***Country:*** Sweden ***Trial name:***			
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 ***Mean age:*** sertraline: 47.3, citalopram: 48.1 ***Gender :*** (female%) sertraline: 72%, citalopram: 71% ***Ethnicity:*** Not reported ***Other population characteristics:*** No significant population differences			

Authors: **Ekselius, et al.** ***Year:*** **2001** ***Country:*** ***Trial name:***	
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% ***Withdrawals due to adverse events:*** 11% ***Loss to follow-up differential high:*** Not reported
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Fair**

Evidence Table 11 Adverse Events

STUDY:	***Authors:*** **Fava M, et al.** [28] ***Year:*** **2002** ***Country:*** USA ***Trial name:***			
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 major depressive disorder; 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:*** USA ***Trial name:***	
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 <u>Subgroup analysis (Fava 2000): Anxious depression</u> • 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:*** Unable to determine
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 <u>Subgroup analysis (Fava 1999)</u> • 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 11 Adverse Events

STUDY:	***Authors:*** **Haffmans, et al.** [140] ***Year:*** **1996** ***Country:*** The Netherlands ***Trial name:***			
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; depressed; 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:*** citalopram: 43% previous depressive disorder, fluvoxamine: 54% previous depressive disorder; previous antidepressant therapy (within 3 weeks of starting trial): citalopram: 65%, fluvoxamine: 73%			

Authors: **Haffmans, et al.** ***Year:*** **1996** ***Country:*** The Netherlands ***Trial name:***	
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%, fluvosamine: 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 either 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 drug 2: paraesthesia: 10.4%
QUALITY RATING:	**Fair**

Evidence Table 11 Adverse Events

STUDY:	***Authors:*** **Jick, et al.** ***Year:*** **2004** ***Country:*** UK ***Trial name:***
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:*** 75.3% of cases were aged 20-49 and 12.3% were 10-19 years old ***Gender:*** 65.4% female (cases only) ***Ethnicity:*** Not reported ***Other population characteristics:*** ~85% of cases had attempted suicide while 15% had suicidal ideation

Authors: **Jick, et al.** ***Year:*** **2004** ***Country:*** UK ***Trial name:***	
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 11 Averse Events

STUDY:	***Authors:*** **Jick, et al.** [147] ***Year:*** **1995** ***Country:*** UK ***Trial name:***
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 computers ***Sample size:*** 11,860
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 ***Trial name:***	
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 11 Adverse Events

STUDY:	***Authors:*** **Khan, et al.** [149] ***Year:*** **2003** ***Country:*** USA ***Trial name:***
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 on 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:*** USA ***Trial name:***	
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 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 11 Adverse Events

STUDY:	***Authors:*** **Kiev, et al.** [141] ***Year:*** **1997** ***Country:*** USA ***Trial name:***			
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** ***Country:*** ***Trial name:***	
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:*** 30% ***Withdrawals due to adverse events:*** fluvoxamine: 7%, paroxetine: 14% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Significant differences: • 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 11 Adverse Events

STUDY:	***Authors*: Lopez-Ibor JJ** [13] ***Year:* 1993** ***Country*:** Spain ***Trial name:***		
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 ***Trial name:	
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 11 Adverse Events

STUDY:	***Authors:*** **MacKay, et al.** [138 180] ***Year:*** **1997** ***Country:*** UK ***Trial name:***
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 screened/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
Trial name:

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 11 Adverse Events

STUDY:	***Authors:*** **Meijer WEE, et. al.** [142] ***Year:*** **2002** ***Country:*** The Netherlands ***Trial name:***
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:*** Median: 41 ***Gender:*** (% female) 64.1% ***Ethnicity:*** Not reported ***Other population characteristics:*** Significantly more sertraline patients had the diagnosis of depressive disorder than patients on other SSRIs ($p < 0.001$); anxiety disorder was seen 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 WEE, et al.** ***Year:*** **2002** ***Country:*** ***Trial name:***	
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 11 Adverse Events

STUDY:	***Authors:*** **Schatzberg et al.** [40] ***Year:*** 2002 ***Country:*** USA ***Trial name:***			
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:*** USA ***Trial name:***	
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%, 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 11 Adverse Events

STUDY:	***Authors:*** **Segraves, et al.** [69] **Year: 2000** ***Country:*** USA ***Trial name:***			
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 min 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; 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: **Seagraves et al.** ***Year:*** **2000** ***Country:*** USA ***Trial name:***	
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 (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 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 11 Adverse Events

STUDY:	***Authors:*** **Thase** [158] ***Year:*** **1998** ***Country:*** USA ***Trial name:***
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:	The groups were not similar at baseline. It appears the imipramine treated group had more severe depression, as more of them were inpatients. The mean age was < 40 37-47%, 40-64 48-50%, >=65 5-13%. Gender was reported as male 38-40%, female 60-62%. Ethnicity was not reported. Other population characteristics include: outpatient 74-93%, inpatient 7-26 %, baseline SBDP: placebo: 75.5, imipramine: 76.7, venlafaxine: 77.8

Authors: **Thase** ***Year:*** **1998** ***Country:*** USA ***Trial name:***	
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 12 Subgroups

STUDY:	***Authors:*** **Cassano GB, et al.** [23] ***Year:*** **2002** ***Country:*** Italy ***Trial name:***			
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 ***Trial name:***	
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 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 ≥ 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 12 Subgroups

STUDY:	***Authors:*** **Cornelius JR, et. al.** [170, 171, 172] ***Year:*** **1997**, Subgroup analysis-**1998**, Follow up study-**2000** ***Country:*** USA ***Trial name:***			
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:*** USA ***Trial name:***	
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 12 Subgroups

STUDY:	***Authors:*** **Emslie GJ, et al.** [82] ***Year:*** **1997** ***Country:*** USA ***Trial name:***			
FUNDING:	National Institute of Mental Health			
DESIGN:	***Study design:*** placebo control trial ***Setting:*** Single-center ***Sample size:*** 96			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluoxetine 20 mg/d 8 weeks			
INCLUSION:	Children and adolescents 7-17 years old; DSM-III-R criteria for Major Depression; CDRS-R score > 40; good general health			
EXCLUSION:	Bipolar disorder, sleep-wake disorder, psychotic depression, bulimia, anorexia, substance abuse; previous treatment with fluoxetine			
OTHER MEDICATIONS/ INTERVENTIONS:	None reported			
POPULATION CHARACTERISTICS:	***Groups similar at baseline:*** Yes ***Mean Age:*** fluoxetine: 12.2 (+/- 2.7), placebo: 12.5 (+/- 2.6) ***Gender:*** (% female) fluoxetine: 46%; placebo: 46% ***Ethnicity:*** fluoxetine: 72.9 % white, placebo: 85.4 % white ***Other population characteristics:*** Those assigned to fluoxetine had a greater lifetime incidence of comorbid anxiety disorders. p = 0.04.			

Authors: **Emslie GJ, et al**. ***Year:*** **1997** ***Country:*** USA ***Trial name:***	
OUTCOME ASSESSMENT:	***Measures:*** Children's Depression Rating Scale Revised (CDRS-R), CGI-I, Children's Depression Inventory (CDI) or BDI, Children's Global Assessment Scale, Brief Psychiatric Rating Scale Children ***Timing of assessments:*** Weekly
RESULTS:	• Fluoxetine patients had significantly greater improvement than placebo patients on the CGI-I at exit from the study. p = .02. • A linear regression of CDRS-R versus time for fluoxetine and placebo revealed the fluoxetine slope was significantly different from the placebo. p < 0.001
ANALYSIS:	***ITT:*** Yes ***Post randomization exclusions:*** No
ATTRITION:	***Loss to follow-up:*** 31 (32%) ***Withdrawals due to adverse events:*** 5 (5%) fluoxetine: 4 (8.3%), placebo: 1 (2%) ***Loss to follow-up differential high:*** Yes
ADVERSE EVENTS:	• Manic symptoms and rash were given as reasons for study discontinuation • Other adverse effects not reported
QUALITY RATING:	**Fair**

Evidence Table 12 Subgroups

STUDY:	***Authors:*** **Entsuah AR, et. al.** [163] ***Year:*** **2001** ***Country:*** Not reported ***Trial name:***
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 ***Trial name:***	
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:	**Poor**

Evidence Table 12 Subgroups

STUDY:	***Authors:*** **Krishnan KRR, et. al.** [177] ***Year:*** **2001** ***Country:*** USA ***Trial name:***			
FUNDING:	Pfizer			
DESIGN:	***Study design:*** Pooled data of 2 RCTs (only one meets entry criteria) ***Setting:*** USA ***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 ***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:*** HTN (hypertension); VAS (vascular disease); NOVASC (no hypertension, no vascular comorbidity)			

Authors: **Krishnan KRR, et. al.** ***Year:*** **2001** ***Country:*** USA ***Trial name:***	
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 12 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 (A randomized trial investigating SSRI treatment)	
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%. (numbers reported are derived from patients who actually started treatment not from patients who got randomized) ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	No significant differences in adverse events between treatment groups
QUALITY RATING:	**Fair**

Evidence Table 12 Subgroups

STUDY:	***Authors:*** **Linden RD, et al.** [169] ***Year:*** **1994** ***Country:*** USA ***Trial name:***			
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** ***Country:*** ***Trial name:***	
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 12 Subgroups

STUDY:	***Authors:*** **Newhouse PA, et al.** [31] ***Year:*** **2000** ***Country:*** USA ***Trial name:***			
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 (±5.3), fluoxetine: 67 (±5.9) ***Gender:*** (% female) sertraline: 63.2%, fluoxetine: 51.3% ***Ethnicity:*** Majority white ***Other population characteristics:*** Not reported			

Authors: **Newhouse PA, et al.** ***Year:*** **2000** ***Country:*** USA ***Trial name:***	
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:*** 19%, sertraline: 17.2%, fluoxetine: 21.2%, p = 0.5 (In text this was reported as: sertraline: 18.8%, fluoxetine: 24.4%) ***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 12 Subgroups

STUDY:	***Authors:*** **Petrakis I, et. al.** [176] ***Year:*** **1998** ***Country:*** USA ***Trial name:***			
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:	Opioid 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:*** USA ***Trial name:***	
OUTCOME ASSESSMENT:	***Measures:*** BDI, HAMD (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 12 Subgroups

STUDY:	***Authors:*** **Rabkin JG, et al.** [174] ***Year:*** **1999** ***Country:*** USA ***Trial name:***			
FUNDING:	NIMH, Eli Lilly			
DESIGN:	***Study design:*** RCT ***Setting:*** University-affiliated research outpatient clinic ***Sample size:*** 120			
INTERVENTION: ***Drug:*** ***Dose:*** ***Duration:***	Fluoxetine 20 mg- not reported (mean dose 37 mg/day)/d 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:*** USA ***Trial name:***	
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:*** Not specifically mentioned in methods but results are presented as "ITT population" and "study completers" ***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 12 Subgroups

STUDY:	**Authors: Rapaport MH, et al.** [161] **Year: 2003** **Country:** USA and Canada **Trial name:** NR		
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: USA	
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:** NR **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:** NR
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 12 Subgroups

STUDY:	***Authors:*** **Razavi D, et. al.** [175] ***Year:*** **1996** ***Country:*** Europe ***Trial name:***			
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:*** fluoxetine: 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:*** USA ***Trial name:***	
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:*** Unable to determine
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 12 Subgroups

STUDY:	***Authors:*** **Schatzberg et al.** [40] ***Year:*** **2002** ***Country:*** USA ***Trial name:***			
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) mirtazapine: 63%, paroxetine: 64% ***Ethnicity:*** Not reported ***Other population characteristics:*** Not reported			

Authors: **Schatzberg et al.** ***Year:*** **2002** ***Country:*** USA ***Trial name:***	
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% ***Withdrawals due to adverse events:*** 20.4%; mirtazapine 14%, 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 12 Subgroups

STUDY:	***Authors:*** **Schöne W, et al.** [26] ***Year:*** **1993** ***Country:*** Austria and Germany ***Trial name:***			
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 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; know 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 ***Trial name:***	
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. 2 were excluded for reasons not reported
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 12 Subgroups

STUDY:	***Authors:*** **Wagner GJ, et. al.** [164] ***Year:*** **1998** ***Country:*** USA ***Trial name:***			
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; care under HIV doc			
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:*** Not reported ***Gender:*** (% emale) 1.1% ***Ethnicity:*** white: 67%, black: 19%, Latino:14% ***Other population characteristics:*** All HIV +			

Authors: **Wagner GJ, et. al.** ***Year:*** **1998** ***Country:*** ***Trial name:***	
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: 28%, 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:	**Fair**

Evidence Table 12 Subgroups

STUDY:	***Authors:*** **Weihs KL, et al.** [58, 59] ***Year:*** **2000, 2001** (QOL analysis presented in Doraiswamy PM, et al.) ***Country:*** USA ***Trial name:***			
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.** ***Year:*** **2000, 2001** ***Country:*** USA ***Trial name:***	
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 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:	**Good**

Evidence Table 12 Subgroups

STUDY:	***Authors:*** **Whittington CJ, et. al.** [77] ***Year:*** **2004** ***Country:*** UK ***Trial name:***
FUNDING:	(National Institute for Clinical Excellence) NICE
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 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 ***Trial name:***	
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 • Additionally, there is an increased risk of serious adverse events • 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 12 Subgroups

STUDY:	***Authors:*** **Williams et. al.** [75] ***Year:*** **2000** ***Country:*** USA ***Trial name:***			
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:*** 21.8% “minority ethnic groups” ***Gender:*** (% female) paroxetine: 39%, placebo: 45% ***Other population characteristics:*** Mean of 3.4 medical conditions per patient			

Authors: **Williams et al.** ***Year:*** **2000** ***Country:*** USA ***Trial name:***	
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:*** Not reported ***Withdrawals due to adverse events:*** 4.8% ***Loss to follow-up differential high:*** No
ADVERSE EVENTS:	Not reported
QUALITY RATING:	**Good**

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

Quality Criteria

Assessment of Internal Validity

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

For Controlled Trials

Assessment of Internal Validity

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

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

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

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

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

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

9. Did the study maintain comparable groups?

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

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

Assessment of External Validity (Generalizability)

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

2. How many patients were recruited?

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

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

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

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

Appendix C. Characteristics of excluded studies

Study	Design	Sample size	Intervention	Reason for exclusion
Major depressive disorder				
Aguglia et al., 1993 [171]	RCT	108	Sertraline vs. fluoxetine	High loss to follow-up; High differential loss to follow-up
Davidson, 2002 [172]	Pooled analysis	1097	Venlafaxine vs. fluoxetine	No systematic literature search
Entsuah et al., 2001 [153]	Meta-analysis	2045	Venlafaxine, paroxetine, fluoxetine, placebo	No systematic literature search
Feiger, 2003 [173]	Pooled analysis	1088	Sertraline vs. fluoxetine	No systematic literature search
Gorman et al., 2002 [174]	Meta-analysis	1321	Escitalopram vs. citalopram	No systematic literature search
Oslin et al., 2003[152]	RCT	52	Venlafaxine vs. sertraline	High loss to follow-up
Stahl, 2000 [175]	RCT	323	Citalopram vs. sertraline vs. placebo	High loss to follow-up
Stahl, 2002 [176]	Pooled analysis	1622	Venlafaxine fluoxetine paroxetine placebo	No systematic literature search
Suri et al., 2000 [177]	Randomized single-blind parallel	53	Fluoxetine vs. sertraline	Single-blinded
Thase, 2001 [181]	Pooled analysis	2117	Venlafaxine vs. SSRI vs. placebo	No systematic literature search
Wade et al., 2003[182]	RCT	197	Mirtazapine vs. paroxetine	High loss to follow-up
MDD-Ped				
DeVane, 1996 [183]	Meta-analysis	61	Fluoxetine vs. placebo	No systematic literature search
Emslie et al., 1997[82]	RCT	96	Fluoxetine vs. placebo	Loss to follow-up differential > 15 percentage points
Emslie et al., 2002 [83]	RCT	219	Fluoxetine vs. placebo	Loss to follow-up differential > 15 percentage points
Bipolar				
Vieta et al., 2002 [84]	RCT	60	Venlafaxine vs. paroxetine	Single-blinded
Cohn, 1989[184]	RCT	89	Fluoxetine vs. imipramine vs. Placebo	High loss to follow-up

OCD				
Cox et al., 1993[185]	Meta-analysis	Not reported	Clomipramine vs. fluoxetine vs. behavior therapy	Lack of information on included studies
Greist et al., 1995[186]	Meta-analysis	1530	Clomipramine vs. fluoxetine vs. fluvoxamine vs. sertraline	No systematic literature search
Kobak et al., 1998 [187]	Meta-analysis	Not reported	Fluoxetine vs. fluvoxamine vs. paroxetine vs. sertraline	Included uncontrolled trials; lack of information on included studies
Mundo et al., 1997 [188]	RCT	30	Fluvoxamine vs. paroxetine vs. citalopram	Single- blinded
Panic				
Perna et al., 2001 [109]	RCT	58	Citalopram vs. paroxetine	Single-blinded
Nair 1996 [189]	RCT	148	Fluvoxamine vs. placebo	High loss to follow-up
PTSD				
Davidson et al. 1998 [190]	Open-label trial	15	Fluovoxamine	Open-label, high loss to follow-up
Davidson et al., 1998 [191]	Open-label trial	17	Nefazodone	Open-label, high loss to follow-up
De Boer et al., 1992 [192]	Open-label trial	24	Fluovoxamine	Open-label, high loss to follow-up
Martenyi et al., 2002 [193, 194]	RCT	301	Fluoxetine vs. placebo	High loss to follow-up
Smajkic et al., 2001 [195]	RCT	40	Sertraline vs. paroxetine vs. venlafaxine	Small sample size, no ITT analysis
Tucker et al., 2001 [196]	RCT	323	Paroxetine vs. placebo	High loss to follow-up
Social Anxiety Disorder				
Allgulander et al., 2001 [197]	RCT	96	Paroxetine vs. placebo	No ITT, lack of statistical comparisons
PMDD				
Diegoli et al., 1998 [198]	RCT	120	Pyridoxine, alprazolam, fluoxetine, propanolol	Important information about study methodology not reported
Carr et al.,2002[199]	Systematic review	NR	fluoxetine	No critical appraisal of study quality; no description of review process
Subgroups				
Roy-Byrne et al. 2000 [200]	RCT	64	Nefazodone vs. placebo	High loss to follow-up

Adverse Events				
Croft et al., 2002 [154]	RCT	432	Buprprion vs. placebo	High loss to follow-up
Ferguson et al., 2001 [201]	RCT	72	Nefazodone vs. sertraline	Selection bias
Letizia et al., 1996[202]	Systematic review	3,828	Fluvoxamine vs. TCA vs. placebo	Search strategy not reported; no critical appraisal of study quality
Michelson et al., 1999 [153]	RCT	395	Fluoxetine vs. placebo	Selection bias
Montejo et al. 2001 [203]	Open-label study	1022	SSRIs	Selection bias
Wernicke et al., 1997 [166]	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)	
Sumatriptan		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]
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 of second generation antidepressants (not included)

1. Ackerman DL, Greenland S, Bystritsky A, Small GW. Characteristics of fluoxetine versus placebo responders in a randomized trial of geriatric depression. 33. 1997:707-14.

2. Agosti V, McGrath PJ. Comparison of the effects of fluoxetine, imipramine and placebo on personality in atypical depression. 71. 2002:113-20.

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5. Amsterdam JD, Garcia-Espana F, Fawcett J *et al*. Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. 18. 1998:435-40.

6. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. 25. 1994:1099-104.

7. Appleby L, Warner R, Whitton A, Faragher B. A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. 314. 1997:932-6.

8. 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. 155. 1998:36-42.

9. Barak Y, Kimhi R, Weizman R. Is selectivity for serotonin uptake associated with a reduced emergence of manic episodes in depressed patients? 15. 2000:53-6.

10. Beasley CMJ, Potvin JH. Fluoxetine: activating and sedating effects. 8. 1993:271-5.

11. Beasley CMJ, Sayler ME, Weiss AM, Potvin JH. Fluoxetine: activating and sedating effects at multiple fixed doses. 12. 1992:328-33.

12. Blumenfield M, Levy NB, Spinowitz B *et al*. Fluoxetine in depressed patients on dialysis. 27. 1997:71-80.

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APPENDIX G: ACKNOWLEDGEMENTS

Acknowledgments

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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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