Drug Class Review
on
Second Generation Antidepressants

Final Report
September 2006

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

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TABLE OF CONTENTS

INTRODUCTION............................................................................................................................... 4
   A. Overview .................................................................................................................................... 4
   B. Scope and Key Questions ....................................................................................................... 7

METHODS........................................................................................................................................... 10
   A. Literature Search .................................................................................................................... 10
   B. Study Selection .................................................................................................................... 10
   C. Data Abstraction .................................................................................................................. 12
   D. Quality Assessment .............................................................................................................. 12
   E. Data Synthesis ..................................................................................................................... 13

RESULTS........................................................................................................................................... 14
   Overview ..................................................................................................................................... 14
   KEY QUESTION 1. Efficacy ...................................................................................................... 16
      A. Major Depressive Disorder in Adults ................................................................................. 16
      B. Dysthymia in Adults ........................................................................................................... 37
      C. Major Depressive Disorder in Children and Adolescents .................................................. 40
      D. Generalized Anxiety Disorder .......................................................................................... 45
      E. Obsessive-Compulsive Disorder ....................................................................................... 49
      F. Panic Disorder ..................................................................................................................... 52
      G. Post-Traumatic Stress Disorder ......................................................................................... 56
      H. Social Anxiety Disorder .................................................................................................... 59
   KEY QUESTION 2. Adverse Events .......................................................................................... 70
   KEY QUESTION 3. Subgroups .................................................................................................. 82

REFERENCES...................................................................................................................................... 514

IN-TEXT TABLES
   Table 1: Approved Second-Generation Antidepressants ................................................................. 6
   Table 2: Dosing Range and Frequency ......................................................................................... 7
   Table 3: Outcomes and Eligibility Criteria .................................................................................. 9
   Table 4: Abbreviations and Diagnostic Scales ............................................................................. 15
   Table 5: Characteristics of studies comparing Citalopram to Escitalopram ............................... 18
   Table 6: Included studies for Major Depressive Disorder .......................................................... 32
   Table 7: Studies Indicating a Faster Onset of Mirtazapine .......................................................... 34
   Table 8: Studies Indicating Fewer Sexual Adverse Events for Bupropion ................................. 35
   Table 9: Study Indicating a Better Sleep Profile with Nefazodone ............................................. 36
   Table 10: Included Studies for Dysthymia .................................................................................. 39
   Table 11: Included Studies for Major Depressive Disorder ....................................................... 44
   Table 12: Included Studies for Generalized Anxiety Disorder .................................................. 48
   Table 13: Included Studies for Obsessive-Compulsive Disorder ............................................... 52
   Table 14: Included Studies for Panic Disorder .......................................................................... 55
   Table 15: Included Studies for Post-Traumatic Stress Disorder ............................................... 58
   Table 16: Included Studies for Social Anxiety Disorder ............................................................ 65
   Table 17: Included Studies for Premenstrual Dysphoric Disorder ............................................ 69
   Table 18: Mean incidence of specific adverse events ............................................................... 73
   Table 19: Included Studies for Adverse Events ....................................................................... 80
   Table 20: Included Studies for Subgroups .............................................................................. 91
EXHIBITS
Exhibit 1. Meta-Analysis- Relative Risk of response rates Citalopram - Escitalopram .........................................92
Exhibit 2. Meta-analysis- Effect size on the MADRS Citalopram - Escitalopram ................................................92
Exhibit 3: Meta-analysis- Fluoxetine - Paroxetine .............................................................................................93
Exhibit 4: Meta-analysis- Fluoxetine - Sertraline ..................................................................................................94
Exhibit 5: Meta-analysis- of Venlafaxine - Fluoxetine .........................................................................................95
Exhibit 6: Meta-analysis- Discontinuation rates ....................................................................................................96

FIGURES
Figure 1: Results of Literature Search ..................................................................................................................103

EVIDENCE TABLES
Evidence Table 1: Major Depressive Disorder Adults ..........................................................................................105
Evidence Table 2: Dysthymia ..............................................................................................................................223
Evidence Table 3: Major Depressive Disorder Pediatrics .....................................................................................235
Evidence Table 4: General Anxiety Disorder ......................................................................................................247
Evidence Table 5: Obsessive-compulsive Disorder .............................................................................................263
Evidence Table 6: Panic Disorder ..........................................................................................................................279
Evidence Table 7: Post-Traumatic Stress Disorder ...............................................................................................293
Evidence Table 8: Social Anxiety Disorder ...........................................................................................................307
Evidence Table 9: Premenstrual Dysphoric Disorder ...........................................................................................341
Evidence Table 10: Adverse Events .......................................................................................................................355
Evidence Table 11: Subgroups ..............................................................................................................................428

APPENDICES
Appendix A. Search Strategy .................................................................................................................................476
Appendix B: Quality Assessment ..........................................................................................................................478
Appendix C. Excluded Studies ..............................................................................................................................482
Appendix D. Pharmacokinetic Properties and Drug Interactions .........................................................................485
Appendix E. Placebo-controlled Trials (not included) ........................................................................................490
Appendix F. Abstract-only Studies (not included) ...............................................................................................511
Appendix G: Acknowledgements ........................................................................................................................513

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INTRODUCTION

A. Overview

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

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

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

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

With the exception of fluvoxamine, which is approved only for the treatment of obsessive-compulsive disorder (OCD), all of the other second-generation antidepressants are approved for the treatment of MDD. Table 1 summarizes the newer products that are available in the US by mechanism of action.

Since their introduction, the second-generation antidepressants have established a prominent role in the US pharmaceutical market. To illustrate their importance, the top 10 drug therapy classes accounted for 35.1 percent of US prescription sales in 2003. The antidepressant class, including SSRIs and SNRIs, ranked third among this group, accounting for $10.9 billion in US prescription sales. The serotonergic class dominates this market, accounting for 57.6 percent of market share in 2002. 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. However, comparative differences in efficacy, tolerability, and safety are not well defined for the second-generation drugs. The tremendous volume and large variability in the quality of evidence to support use of these products makes it difficult for clinicians and decision makers to make evidence-based decisions.

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

Also, we examine the role of these agents in treating premenstrual dysphoric disorder (PMDD, known as late luteal phase dysphoric disorder [LLPDD] in the DSM, version III revised [III-R]) among adult outpatient populations. Technically, PMDD is not considered a discrete diagnostic entity by DSM version IV; instead, it is listed as an example of a Depressive Disorder Not Otherwise Specified. It does, however, have specific research criteria defined in DSM-IV; these are identical to LLPD in DSM III-R except for the addition of one item. Of note, as of 1999, the FDA Neuropharmacology Advisory Committee supported the concept of PMDD as a distinct clinical entity.
Finally, we examine the role of these agents in treating MDD in pediatric outpatient populations. Tables 1 and 2 show included drugs, dosage forms and recommended doses, and FDA-approved (labeled) uses.

### Table 1: Approved Second-Generation Antidepressants

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

*CR, SR, XL, and XR are registered trademarks referring to controlled, sustained, or extended-release dosage forms
**GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; PMDD, premenstrual dysphoric disorder; DPNP, diabetic peripheral neuropathic pain
† Generic available for some dosage forms.
†† Only Paxil CR® (not Paxil®) is approved for the treatment of PMDD.
††† Only Effexor XR® is approved for the treatment of GAD and Social Anxiety Disorder
‡ Lexapro was denied approval for social anxiety disorder 3/30/2005
Table 2: Dosing Range and Frequency

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

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

B. Scope and Key Questions

The purpose of this review is to compare the efficacy, effectiveness, and tolerability (adverse events) of second-generation antidepressant medications. The participating organizations of the Drug Effectiveness Review Project (DERP) are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. Initially, the Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed, revised, and approved by representatives of organizations participating in the DERP in conjunction with experts in the fields of health policy, psychiatry, pharmacotherapy, and research methods. The participating organizations approved the following key questions:

1. For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders, do second-generation antidepressants differ in efficacy or effectiveness?
2. For outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders, do second-generation antidepressants differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, and sex), other medications, or comorbidities for which one second-generation antidepressant is more effective or associated with fewer adverse events than another?
This report addresses the initial use of antidepressants. The use of these agents for patients who are not responding to initial treatment are not addressed in this report. Throughout this report, we highlight effectiveness studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most efficacy studies. 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>
<thead>
<tr>
<th>Outcome</th>
<th>Outcome Measures</th>
<th>Study Eligibility Criteria</th>
</tr>
</thead>
</table>
| Efficacy/Effectiveness | • Response  
• Remission  
• Speed of response/remission  
• Relapse  
• Quality of life  
• Functional capacity  
• Hospitalization | • Head-to-head randomized controlled clinical trials or meta-analyses evaluating:  
• One second-generation antidepressant vs. another  
• When sufficient evidence was not available for head-to-head trials within a specific diagnostic group, we evaluated:  
• Placebo-controlled trials |
| Safety/Tolerability | • Overall adverse effect reports  
• Withdrawals because of adverse effects  
• Serious adverse event reports  
• Specific adverse events or withdrawals because of specific adverse events, including:  
  • hyponatremia  
  • seizures  
  • suicide  
  • hepatotoxicity  
  • weight gain  
  • gastrointestinal symptoms  
  • loss of libido  
  • others | • Head-to-head randomized controlled clinical trials or meta-analyses evaluating:  
• One second-generation antidepressant vs. another  
• When sufficient evidence was not available for head-to-head trials within a specific diagnostic group, we evaluated  
• Placebo-controlled trials  
• Observational studies |
METHODS

A. Literature Search

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

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

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

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

B. Study Selection

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

For this review, results from well-conducted, valid head-to-head trials provide the strongest evidence to compare drugs with respect to effectiveness, efficacy, and adverse events. RCTs of at least 6 weeks’ duration and an outpatient study population with a sample size greater than 40 participants were eligible for inclusion. We defined head-to-head trials as those comparing one second-generation antidepressant with another.
We did not examine placebo-controlled trials in detail if head-to-head trials were available. We viewed FDA approval as evidence for general efficacy; therefore, we did not review placebo-controlled trials for FDA-approved indications except when outcome measures assessed quality of life or other health outcomes that are not generally required for FDA approval.

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

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

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

We included meta-analyses in our evidence report if we found them to be relevant for a key question and of good or fair methodological quality (based on the QUORUM9 statement). We did not review individual studies if they were included in a high-quality meta-analysis. We excluded meta-analyses that were not based on a comprehensive systematic literature search or did not maintain the units of the studies in their statistical analyses. We checked our database to guarantee that our literature search had detected trials included in any meta-analyses that we discarded, and we then obtained any missing articles.

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

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

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

D. Quality Assessment

We assessed the internal validity (quality) of trials based on predefined criteria (Appendix B). These criteria are based on those developed by the US Preventive Services Task Force (ratings: good-fair-poor)\(^\text{10}\) and the National Health Service Centre for Reviews and Dissemination.\(^\text{11}\) 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,\(^\text{12}\) independent of the reason and the use of intention-to-treat analysis. We adopted a cut-off point of 20 percent loss to follow-up as a limit beyond which bias was likely to be introduced because of missing endpoint assessments. Trials with more than 20 percent but less than 40 percent loss to follow-up were eligible for a quality rating of fair (but not good). Studies with more than 40 percent overall loss to follow-up or more than 15 percentage points differential loss to follow-up between study groups were rated as poor. These cut-off points took into consideration that loss to follow-up appears to be higher in psychiatric populations than in other study populations.

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

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

For each meta-analysis, we conducted a test of heterogeneity and applied both a random and a fixed effects model. We report the random effects model results because, in all three meta-analyses, the results from random and fixed effects models were very similar. If the RR was statistically significant, we then conducted a meta-analysis of the risk differences to calculate the number needed to treat (NNT) on the pooled risk difference.

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

Overview

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

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

Reasons for exclusions were based on eligibility criteria or methodological criteria (Figure 1, QUORUM Tree). Forty-seven studies that met the eligibility criteria but were later rated as poor quality for internal validity were excluded from the analysis (Appendix C). The two main reasons for a poor quality rating among RCTs were high loss to follow-up (more than 40%) and lack of double-blinding. Among meta-analyses, lack of a systematic literature search or failure to maintain the units of the trials during statistical analysis were the main reasons for exclusions. A lack of systematic literature search leads to a selected spectrum of trials and subsequently to biased results. Similarly, pooling data of trials without maintaining the units of the individual trials during statistical analysis fails to preserve randomization and introduces bias and confounding.

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

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

Studies reviewed for this report employed a notable array of diagnostic scales and health status or quality of life instruments. Most were pertinent to depressive and other disorders considered in this report, but some are considered more generic instruments to assess, e.g., health-related quality of life. Table 4 lists diagnostic scales and health status or quality-of-life instruments encountered in this literature and used in this report.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name of Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI II</td>
<td>Beck Depression Inventory II</td>
</tr>
<tr>
<td>BQOL</td>
<td>Battelle Quality of Life Measure</td>
</tr>
<tr>
<td>Beck’s SSI</td>
<td>Scale for Suicide Ideation</td>
</tr>
<tr>
<td>CAS</td>
<td>Clinical Anxiety Scale</td>
</tr>
<tr>
<td>CAPS</td>
<td>Clinician Administered PTSD Scale</td>
</tr>
<tr>
<td>CCEI</td>
<td>Crown Crisp Experiential Index</td>
</tr>
<tr>
<td>CDRS</td>
<td>Cornell Dysthymia Rating Scale</td>
</tr>
<tr>
<td>CGI</td>
<td>Clinical Global Impressions</td>
</tr>
<tr>
<td>CGI -I</td>
<td>Clinical Global Impressions Improvement Scale</td>
</tr>
<tr>
<td>CGI – S</td>
<td>Clinical Global Impressions Severity Scale</td>
</tr>
<tr>
<td>CIS</td>
<td>Clinical Interview Schedule</td>
</tr>
<tr>
<td>DSM – IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, version IV</td>
</tr>
<tr>
<td>ESRS</td>
<td>Extrapyrarmidal Symptom Rating Scale</td>
</tr>
<tr>
<td>FSQ</td>
<td>Functional Status Questionnaire</td>
</tr>
<tr>
<td>GHQ</td>
<td>General Health Questionnaire</td>
</tr>
<tr>
<td>HAD</td>
<td>Hospital Anxiety and Depression Rating Scale</td>
</tr>
<tr>
<td>HADRS</td>
<td>Hamilton Depression Rating Scale</td>
</tr>
<tr>
<td>HAM – A</td>
<td>Hamilton Rating Scale for Anxiety</td>
</tr>
<tr>
<td>HAM – D</td>
<td>Hamilton Rating Scale for Depression</td>
</tr>
<tr>
<td>IDAS</td>
<td>Irritability, depression, and anxiety scale</td>
</tr>
<tr>
<td>IDS C</td>
<td>Inventory for Depressive Symptomatology - Clinician Rated</td>
</tr>
<tr>
<td>IDS SR</td>
<td>Inventory for Depressive Symptomatology – Self Rated</td>
</tr>
<tr>
<td>MADRS</td>
<td>Montgomery Asberg Depression Rating Scale</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
</tr>
<tr>
<td>MOCI</td>
<td>Maudsley Obsessive Compulsive Inventory</td>
</tr>
<tr>
<td>PAS</td>
<td>Panic and Agoraphobia Scale</td>
</tr>
<tr>
<td>PRIME MD</td>
<td>Primary Care Evaluation of Mental Disorder</td>
</tr>
<tr>
<td>PSE</td>
<td>Present State Examination</td>
</tr>
<tr>
<td>PGIS</td>
<td>Patient Global Improvement Scale</td>
</tr>
<tr>
<td>QLDS</td>
<td>Quality of Life in Depression Scale</td>
</tr>
<tr>
<td>QLSQ</td>
<td>Quality of Life Enjoyment and Satisfaction Questionnaire</td>
</tr>
<tr>
<td>RCIS</td>
<td>Revised Clinical Interview Schedule—Shona Version</td>
</tr>
<tr>
<td>SADS</td>
<td>Schedule for Affective Disorders and Schizophrenia</td>
</tr>
<tr>
<td>SCAG</td>
<td>Sandoz Clinical Assessment Geriatric Scale</td>
</tr>
<tr>
<td>SF-36</td>
<td>Medical Outcomes Study Health Survey - Short Form 36</td>
</tr>
<tr>
<td>SIGH SAD</td>
<td>Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version</td>
</tr>
<tr>
<td>SIP</td>
<td>Sickness Impact Profile</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM III Revised</td>
</tr>
<tr>
<td>SCL 25</td>
<td>Hopkins Symptom Checklist 25 item version</td>
</tr>
<tr>
<td>SLT</td>
<td>Shopping List Task</td>
</tr>
<tr>
<td>SDS</td>
<td>Sheehan Disability Scale</td>
</tr>
<tr>
<td>SDS</td>
<td>Self rating Depression Scale</td>
</tr>
<tr>
<td>SSQ</td>
<td>Shona Symptom Questionnaire</td>
</tr>
<tr>
<td>Y-BOCS</td>
<td>Yale Brown Obsessive Compulsive Scale</td>
</tr>
</tbody>
</table>
KEY QUESTION 1. Efficacy

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

We included 105 RCTs, 9 meta-analyses, and 3 studies of other design. Of the RCTs, 64 were head-to-head trials; 40 were placebo-controlled trials.

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

A. Major Depressive Disorder in Adults

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

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

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

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

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

Quality of life and functional capacity were rarely assessed, and if they were, they were considered only as a secondary outcome. Most studies employed both physician-rated scales (e.g., HAM-D, MADRS, Clinical Global Impressions Scale [CGI]) and patient-rated scales (e.g., Hospital Anxiety and Depression Rating Scale [HAD-A], Battelle Quality of Life Scale). All studies used physician-rated scales to assess the main outcome measures.
In the majority of studies, the primary endpoints were changes from baseline or rates of response or remission on investigator-rated diagnostic depression scales such as the HAM-D or MADRS. Changes on such diagnostic depression scales are generally viewed as intermediate outcomes rather than health outcomes and are not always reliably related to changes in health outcomes. Response or remission, even when deducted from such a scale (e.g., response is defined as a 50% improvement of scores on HAM-D or MADRS), could be seen as proxies to health outcomes. Therefore, we focused on differences in response or remission rates rather than differences in changes of scores.

Most studies received a fair rating for internal validity. The generalizability of the results was hard to determine and might often be limited. Most trials (60%) were of short (6 to 8 weeks) or medium (9 to 11 weeks) duration; 40 percent reported a follow-up of 12 weeks or more. Two European trials\(^1\)\(^7\), \(^1\)\(^8\) and one US trial\(^1\)\(^9\) in primary care settings, with less stringent eligibility criteria, could be viewed as effectiveness trials. These studies also had long periods of follow-up.\(^1\)\(^8\), \(^1\)\(^9\) Drug equivalency was present in all included studies.

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

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

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

*Citalopram vs. escitalopram*

Four trials compared the efficacy of escitalopram and citalopram.\(^2\)\(^0\)-\(^2\)\(^3\) Three studies were conducted over 8 weeks, two of them as fixed dose trials\(^2\)\(^0\), \(^2\)\(^1\), \(^2\)\(^3\) (escitalopram 10mg/d and 20mg/d to citalopram 20mg/d and 40mg/d). Overall, results favored escitalopram over citalopram. Two studies reported statistically significantly higher response rates for escitalopram than for citalopram treated patients (76.1% vs. 61.3%, \(p < 0.05\) and 63.7% vs. 52.6%; \(p = 0.021\)). In both studies escitalopram also led to higher remission rates than escitalopram. One trial was a fair-rated European/Canadian flexible dose study that compared the efficacy and tolerability of citalopram (20-40mg/d) to escitalopram (10-20mg/d) and placebo in 471 depressed outpatients attending primary care centers.\(^2\)\(^0\) Loss to follow-up was 7 percent. Intention-to-treat results showed that the escitalopram group had significantly more responders (≥ 50% improvement on MADRS; 63.7% vs. 52.6%; \(p = 0.021\)) and remitters (MADRS < 12; 52.1% vs. 42.8%; \(p < \)
0.036) than the citalopram group. Escitalopram was numerically better at all time points on all three efficacy scales (MADRS, CGI-I, CGI-S). The study did not assess health outcomes.

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

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

It may be significant, however, that both citalopram and escitalopram are produced by the same manufacturer who funded all four available studies. Generic brands of citalopram are available in the US, while escitalopram is still patented.

### Table 5: Characteristics of studies comparing Citalopram to Escitalopram

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Dosage Esc. - Cit. mg/d</th>
<th>Response(%)</th>
<th>Remission(%)</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke et al., 2002²¹</td>
<td>491</td>
<td>8 weeks</td>
<td>20 vs. 40</td>
<td>51.2 vs. 45.6 p = NR (ns)</td>
<td>NR</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 vs. 40</td>
<td>50 vs. 45.6 p = NR (ns)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Colonna et al., 2005²²</td>
<td>357</td>
<td>8 weeks</td>
<td>10 vs. 20</td>
<td>63 vs. 55 p &lt; 0.05</td>
<td>NR</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 weeks</td>
<td>80 vs. 78 p = NR (ns)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Lepola et al., 2003²⁰</td>
<td>471</td>
<td>8 weeks</td>
<td>10-20 vs. 20-40</td>
<td>63.7 vs. 52.6 p = 0.021</td>
<td>52.1 vs. 42.8 p = 0.036</td>
<td>Fair</td>
</tr>
<tr>
<td>Moore et al., 2005²³</td>
<td>280</td>
<td>8 weeks</td>
<td>20 vs. 40</td>
<td>76.1 vs. 61.5 p = 0.009</td>
<td>56.1 vs. 43.6 p = 0.04</td>
<td>Fair</td>
</tr>
</tbody>
</table>

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

The second meta-analysis was an effect size meta-analysis assessing the pooled difference of points on the MADRS scale (Exhibit 2). The weighted mean difference (WMD) presented an additional treatment effect of a 1.25 point reduction (95% CI: 0.10-2.39; p = 0.01) for
escitalopram compared to citalopram. Although statistically significant, the clinical significance of the actual difference in effect sizes may be questionable. A 1.3 point change on the MADRS represents about one-fifth to one-quarter of a standard deviation. A recent methods study concluded that, in general, a change of about one-half of a standard deviation on a health-related scale reflects a minimally important difference for a patient.25

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

**Citalopram vs. fluoxetine**

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

**Citalopram vs. sertraline**

A good-quality Swedish study assessed the effectiveness of citalopram (20-60mg/d) and sertraline (50-150mg/d) in 400 patients in general practice during 24 weeks of treatment.17 The majority of patients suffered recurrent depression (sertraline, 56%; citalopram, 65%) and used other medications for medical illnesses (sertraline, 55%; citalopram, 44.5%). Loss to follow-up was 18 percent. The investigators found no significant differences between treatment groups in any measures of depression severity at any point in time (MADRS, Clinical Global Impressions Severity Scale [CGI-S]), Clinical Global Impressions Improvement Scale [CGI-I]). Also, in a subgroup analysis of patients with recurrent depression, they did not report any differences in effectiveness between drugs. Response rates were similar at week 24 (sertraline, 75.5%. citalopram, 81.0%). Treatment groups did not differ significantly in adverse events. This study was one of only a few trials that had not been funded by the pharmaceutical industry.

**Fluoxetine vs. fluvoxamine**

Two fair studies evaluated the comparative effectiveness and safety of fluoxetine and fluvoxamine in outpatients with MDD.27, 28 A 7-week flexible dose study (fluoxetine: 20-80 mg/d; fluvoxamine 100-150mg/d) did not identify any statistically significant differences in efficacy between the two treatment groups (HAM-D, HAM-A, CGI-S, Raskin-Covi Scale, Hopkins Symptoms Checklist).28 Both treatment regimens significantly improved scores on assessment scales. The second study was a 6-week fixed dose European trial (fluoxetine 20mg/d; fluvoxamine 100mg/d) in 184 outpatients with MDD.27 Results are consistent with those of the flexible-dose study; the primary outcome measure (HAM-D) was not significantly different at any time. The drugs were equally effective for secondary outcome measures (CGI, Clinical Anxiety Scale [CAS], the Irritability, Depression, and Anxiety Scale [IDAS], Beck’s Scale for Suicide Ideation [Beck’s SSI]) such as suicidal ideation, sleep, anxiety, and severity of illness at
Fluvoxamine had significantly more responders on CGI-S (29% vs. 16%; p < 0.05) and a greater reduction of CGI-S scores (p < 0.05) at week 2 but not at weeks 4 or 6.

**Fluoxetine vs. paroxetine**

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

The other six studies14, 30-34 lasted 6 to 12 weeks. Loss to follow-up was between 20 and 36 percent. Two studies supported a faster onset of action of paroxetine than fluoxetine,31, 32 four trials did not.14, 30, 33, 34 In one study paroxetine-treated patients older than 60 years had a significantly greater response rate on HAM-D and MADRS scales (37.5% vs. 17.5%; p = 0.04) than fluoxetine-treated patients. Patients on paroxetine had significantly better Mini Mental State Examination (MMSE) and Sandoz Clinical Assessment Geriatric Scale (SCAG) scores assessing cognitive function at week 3 than did those on fluoxetine. Five studies did not find differences in the improvement of anxiety in patients with depression.14, 29, 30, 33, 34 A Canadian RCT assessed anxiolytic activity and akathisia as secondary outcome measures and could not detect any significant differences between treatment groups.30 However, study groups in this trial were not similar at baseline with respect to recurrent depression (paroxetine 76.5% vs. fluoxetine 59.5%), the validity of results might be limited.30

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

**Fluoxetine vs. sertraline**

Six studies compared fluoxetine to sertraline.18, 19, 34-37 The top-level evidence consisted of two effectiveness trials18, 19 and one efficacy trial38 with long periods of follow-up.
Two fair-rated, multicenter trials from France were conducted in office settings (private psychiatrists and general physicians [GPs]). 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. Treatments were randomly allocated. This study enrolled 601 patients at 76 primary care sites. Initial diagnosis for enrollment was not based on diagnostic criteria but rather on the judgment of the treating physician. Criteria-based evaluation classified 74 percent of patients as having MDD, 18 percent dysthymia, and 8 percent minor depression. Patients’ treatments could be switched among study drugs or to other antidepressive medications as needed. Intention-to-treat analysis maintained the original randomization. Outcome measures assessing changes in depression and health-related quality of life measures (work, social and physical functioning, concentration and memory, sexual functioning) were administered over the telephone by a blinded third party. Range of dosage and loss to follow-up were incompletely reported. Results did not reveal any significant differences among drugs in any outcome measures at either 3 or 9 months. All treatment groups significantly improved during the study compared to baseline. Subgroup analyses did not show different effectiveness for patients with MDD or for those older than 60 years.

Three additional fair-rated trials did not find any significant differences in primary outcome measures (HAM-D, MADRS, CGI-S). Treatment durations varied from 6 to 16 weeks. One study was conducted in 236 participants older than 60 years. 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).

We conducted a meta-analysis of five of these studies comparing the effects of fluoxetine to sertraline on HAM-D scores at study endpoint. All studies except one were financially supported by the manufacturer of sertraline. Results are presented in Exhibit 4. We excluded one study because a different diagnostic scale measured the outcome. Our outcome measure was the relative risk of being a responder on HAM-D or MADRS scales at study endpoint. A “response” was defined as an improvement of 50% or more on the HAM-D scale. Pooled results included 1,190 patients and yielded a modest additional treatment effect for sertraline just reaching statistical significance. The relative risk of being a responder at study endpoint was 1.10 (95% CI 1.01-1.22) for sertraline relative to fluoxetine. Both random effects and fixed
effects models presented similar, statistically significant results. The NNT to gain one additional responder based on the pooled risk difference is 17.

A meta-analysis of responders based only on the HAM-D scale did not yield different results. However, all included studies were of fair quality, with some having a loss to follow-up of more than 30 percent. Tests for heterogeneity were not significant. Funnel plot, Kendell’s test and L’Abbe plot did not indicate major biases. However, given the small number of component studies results of these tests must be viewed cautiously.

**Paroxetine vs. fluvoxamine**

One fair 7-week RCT compared the efficacy and safety of paroxetine (20-50mg/d) and fluvoxamine (50-150mg/d) in 60 outpatients with MDD. Loss to follow-up was 30 percent. Results presented no statistically significant differences on HAM-D, Ham-A, CGI, and SCL-56. Significantly more paroxetine than fluvoxamine patients suffered from sweating (33% vs. 10%; p = 0.028)

**Paroxetine vs. sertraline**

One fair-rated Swedish RCT compared paroxetine (20-40mg/d) to sertraline (50-150mg/d) in a 24-week study. A total of 353 patients participated. Outcome measures included MADRS, CGI, and Battelle Quality of Life Measure (BQOL). Loss to follow-up was 35.4 percent. LOCF analysis yielded no significant differences in primary outcome measures (MADRS, CGI) at any point in time. Clinically significant improvement occurred over baseline among all quality-of-life factors. Treatment groups did not differ significantly on BQOL factors. Diarrhea was more frequent in the sertraline group (35.2% vs. 15.2%; p < 0.01). Patients in the paroxetine group had higher rates of fatigue (45.8% vs. 21.0%; p < 0.01), decreased libido in females (8.8% vs. 1.8%; p < 0.05), micturition problems (6.2% vs. 0.6%; p < 0.05), and constipation (16.4% vs. 5.7%; p < 0.01).

**Sertraline vs. fluvoxamine**

A fair-rated, 7-week study compared the depression scores and tolerability of sertraline (50-200 mg/d) and fluvoxamine (50-150 mg/d) in 97 depressed patients. 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. Patients who remained without recurrence (n = 47) prolonged their treatment for another 24 months in an open-label manner. Primary outcome measures were monthly HAM-D assessments. There was no loss to follow-up. Recurrence during the first 2 years of prophylactic treatment did not differ
significantly between treatment groups (single recurrence: 21.9% of sertraline-treated patients vs. 18.7% of fluvoxamine patients; z = 0.14, p = 0.88). At the 4-year follow-up, no significant differences in recurrences were apparent (sertraline, 13.6%; fluvoxamine, 20%). Adverse events did not differ significantly during the first 24 months of prophylactic treatment.

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

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

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

Mirtazapine vs. fluoxetine
A Taiwanese study compared mirtazapine (30-45mg/d) to fluoxetine (20-40mg/d) over 6 weeks in 133 moderately depressed Chinese patients. 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). The German study enrolled 275 patients in a 6-week trial. The US trial randomized 255 participants for 8 weeks. In both trials, mirtazapine and paroxetine were equally effective in reducing HAM-D scores at the endpoint. Mirtazapine led to a faster response in both trials. In the German study, 23.2 percent of mirtazapine-treated patients and 8.9 percent of paroxetine-treated patients responded to the treatment at week 1 (p < 0.002). A Kaplan-Meier analysis in the US trial showed a significantly
faster time to response for mirtazapine than for paroxetine (mean 26 days versus mean 40 days; \( p = 0.016 \)). No significant difference in response rates on the CGI scale was noted. Both trials reported weight gain in significantly more mirtazapine-treated patients than in paroxetine-treated patients (\( p < 0.05 \)). Paroxetine-treated patients in the US study reported significantly higher rates of nausea, tremor, and flatulence (\( p < 0.05 \)). The NNT to yield one additional responder at weeks 1 or 2 is 7.

**Mirtazapine vs. sertraline**

One fair-rated, recent multinational European study examined the onset of efficacy of mirtazapine (30-45mg/d) compared to that of sertraline (50-150mg/d) in 346 outpatients.\(^{50}\) Loss to follow-up was 20.8 percent. Onset of action was faster for the mirtazapine group. The mean change of HAM-D scores was significantly greater during the first 2 weeks for mirtazapine than for sertraline (\( p < 0.05 \)); after 2 weeks the difference remained greater but lacked statistical significance. CGI scores did not show significant differences, but MADRS score were significantly greater at week 1 in the mirtazapine group. The Changes in Sexual Functioning Questionnaire did not show significant differences although for mirtazapine the trend was positive. A significantly higher number of patients withdrew because of adverse events in the mirtazapine group (12.5% vs. 3%; \( p = NR \)).

**Venlafaxine vs. citalopram**

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

**Venlafaxine vs. escitalopram**

Two fair 8-week studies assessed the comparative effectiveness of venlafaxine XR and escitalopram.\(^{52,53}\) A fair European, multinational study assigned 293 patients to escitalopram (10-20mg/d) or venlafaxine XR (75-150mg/d).\(^{52}\) Results presented no statistically significant differences in response (Venlafaxine XR: 79.6%; escitalopram: 77.4%) and remission (Venlafaxine XR: 69.7%; escitalopram: 69.9%). Survival analysis of the intention-to-treat population indicated that escitalopram-treated patients achieved sustained remission 6.6 days earlier than patients on venlafaxine XR (\( p < 0.01 \)). Significantly more patients on venlafaxine XR than on escitalopram reported nausea (26% vs. 17%; \( p < 0.05 \)), sweating (12.5% vs. 6%; \( p < 0.05 \)), and constipation (6% vs. 2%; \( p < 0.05 \)).

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

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

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

We conducted a meta-analysis of six studies comparing venlafaxine to fluoxetine. All studies were financially supported by the manufacturer of venlafaxine. One study was excluded because of missing data. The main outcome measure was the response to treatment on HAM-D or MADRS scales at study endpoint. Results (Exhibit 5), based on 1,567 patients, show a modest additional treatment effect for venlafaxine just reaching statistical significance (RR 1.13; 95% CI 1.03-1.24) for the random effects model; the fixed effects model yielded similar significant results. Tests for heterogeneity were not significant. Funnel plot, Kendell’s test, and L’Abbe plot did not indicate major biases. However, given the small number of component studies results of these tests must be viewed cautiously.

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

These findings are similar to results of a meta-analysis recently reported by Smith et al. (2002). Venlafaxine showed a modest but statistically significantly greater standardized effect size (-0.14; 95% CI -0.22 to -0.06) and a significantly greater odds ratio (OR) for remission (OR 1.42;
95% CI 1.17 to 1.73) compared to fluoxetine. The OR for response was numerically greater for venlafaxine but did not reach statistical significance (OR: 1.17; 95% CI 0.99 to 1.38). This study included inpatients and therefore did not meet the eligibility criteria for this report.

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

A 12-week, British fixed-dose trial randomized 361 mainly moderately ill patients (based on CGI severity score) treated in 43 general practices to either venlafaxine XR (75mg/d) or paroxetine (20mg/d).64 Loss to follow-up was 27.4 percent. Results revealed no significant differences in efficacy measures, quality of life scores, or adverse events between study groups.

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

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

A fair, 6-week study compared the efficacy of bupropion (225-450mg/d) and fluoxetine (20-80 mg/d) in 123 patients with moderate to severe depression.\(^{68}\) Loss to follow-up was 27.6 percent but similar in the two treatment groups. Results presented no significant differences in efficacy measures (changes of HAM-D, HAM-A, CGI-S, CGI-I scores). Response rates were similar for both drugs (bupropion, 62.7%; fluoxetine, 58.3%). Adverse events did not differ significantly between treatment groups.

Another fair, 8-week RCT compared efficacy and sexual side effects of bupropion SR (150-400mg/d), fluoxetine (20-60mg/d), and placebo in 456 outpatients with MDD.\(^{69}\) Loss to follow-up was 36 percent. Results showed no statistically significant differences in efficacy. At endpoint, bupropion SR had more remitters than fluoxetine (47% vs. 40%). Bupropion SR also showed significantly fewer sexual side effects than fluoxetine throughout the study. Beginning at week 1 until endpoint, significantly more fluoxetine-treated patients than bupropion SR-treated patients (\(p < 0.05\)) were dissatisfied with their overall sexual function.

**Bupropion vs. paroxetine**

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

**Bupropion vs. sertraline**

A fair, 16-week trial assessed efficacy and tolerability of bupropion SR (100-300mg/d) and sertraline (50-200mg/d) in outpatients (\(n = 248\)) with moderate to severe depression.\(^72\) Intention-to-treat analysis with a LOCF method was used to assess main outcome measures. Loss to follow-up was 31.5 but similar in the two treatment groups. Efficacy measures (changes of scores on HAM-D, HAM-A, CGI-S, CGI-I) did not differ significantly by treatment group. The article did not report on response or remission rates. Some adverse events (nausea, diarrhea, somnolence, sweating) were significantly higher among sertraline-treated patients (\(p < 0.05\)). Discontinuation rates because of sexual adverse events were also significantly higher in the sertraline group (13.5% vs. 3.3%, \(p = 0.004\)).

Two fair-rated RCTs compared the incidence of sexual dysfunction in 360 and 364 patients with MDD during 8 weeks of treatment with bupropion SR (150-400mg/d), sertraline (50-200mg/d), or placebo.\(^{73, 74}\) Outcome measures were efficacy (HAM-D, CGI) and sexual dysfunction as assessed by investigators using DSM-IV definitions for sexual dysfunction disorders. Intention-
to-treat analyses reported no significant differences in any efficacy measures between bupropion SR and sertraline at endpoints.

During the studies, sertraline showed more sexual adverse events than bupropion at various time points. However, in one trial overall satisfaction with sexual function did not differ significantly between the bupropion and the sertraline group at endpoint. 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).

**Nefazodone vs. fluoxetine**

Three studies with identical protocols examined the effects of antidepressive treatment with either nefazodone or fluoxetine on sleep in outpatients with MDD. Data from these trials were pooled into one analysis. 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). Patients who responded to acute treatment were enrolled in an open-label continuation phase (n = 108) from week 8 to month 6. 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. One hundred-sixty outpatients with moderate to severe depression were enrolled in this 6-week trial. Loss to follow-up was 24.4 percent. Intention-to-treat results did not show significant differences in efficacy between treatment groups. Response rates were similar (nefazodone 59%, sertraline 57%). Additional outcome measures assessed by questionnaire were sexual function and satisfaction under antidepressant treatment. Overall satisfaction with sexual function was significantly higher in the nefazodone group (p < 0.01). Among men, 67 percent in the sertraline group and 19 percent in the nefazodone group reported
difficulty with ejaculation (p < 0.01). Other adverse events did not differ significantly between the two groups.

3. Summary of the evidence

Fifty-five head-to-head trials compared the effectiveness and efficacy of one SSRI or other second-generation antidepressant to another. All studies addressed initial use of antidepressants.

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

For all the other comparisons, discontinuation rates and response and remission rates assessed on multiple diagnostic scales did not differ substantially when taking all the evidence into consideration. We did not find any evidence that one group has a greater benefit from an individual drug than another. Differences among medications exist in adverse events, speed of response, and some aspects of health-related quality of life. For example, mirtazapine presents a faster onset of action than paroxetine and sertraline (table 7); bupropion has fewer sexual side effects than fluoxetine and sertraline (table 8); nefazodone improves sleep quality (Table 9); venlafaxine has a slightly higher response rate than sertraline and fluoxetine but a higher incidence of nausea and vomiting and a risk of seizures in overdose.

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

Effectiveness

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

Ten studies comparing one SSRI to another provide good to fair evidence that no significant differences exist among SSRIs in improving health-related quality of life or measures of functional capacity (e.g., sleep quality, cognitive function).\(^{18, 21, 27, 32, 38, 40, 41, 82}\)

A pooled analysis of data from three fair-rated trials with identical study protocols comparing nefazodone to fluoxetine reports that improvement of sleep quality is significantly greater in nefazodone-treated patients than in fluoxetine-treated patients.\(^{77}\) All three studies were financially supported by a manufacturer of nefazodone. Similarly, pooled data indicates greater benefits of escitalopram than citalopram in reducing sleep disturbance.\(^{24}\)

Several other efficacy studies assessed quality of life and health-related functional capacity in SSRIs compared to other second-generation antidepressants.\(^{50, 71, 80}\) The body of evidence for these comparisons is either inconsistent or based on a single trial. No firm conclusions can be drawn from their results.

Forty-five efficacy studies assessed intermediate outcomes such as changes on HAM-D or MADRS scales. Overall, efficacy was similar and the majority of trials did not identify substantial differences among drugs. Statistically significant differences of pooled response rates of some metaanalyses are likely not clinically significant.

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

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

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

Seven good to fair studies provide mixed evidence about a higher efficacy and a greater anxiolytic effect of venlafaxine compared to fluoxetine.\(^{54-57, 59-61}\) We conducted a meta-analysis of data from six of these studies. Results provide fair evidence that venlafaxine has a modest but statistically significant additional treatment effect compared to fluoxetine as measured by the number of responders on the HAM-D and MADRS scales at endpoint (RR 1.12; 95% CI 1.02-
1.23). The NNT to yield one additional responder is 34. However, this meta-analysis is limited to response on only two diagnostic scales and the included studies are of fair quality.

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

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

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

Several other studies compared SSRIs to other second-generation antidepressants.\textsuperscript{26, 28, 40, 43, 44, 51, 63, 64, 66, 77, 79, 80} The body of evidence for these comparisons is either inconsistent or based on a single trial. No firm conclusions can be drawn from their results.
Table 6: Included studies for Major Depressive Disorder

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke et al., 2002&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Citalopram vs. Escitalopram</td>
<td>491</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Colonna et al. 2005&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Citalopram vs. Escitalopram</td>
<td>357</td>
<td>Significantly more responders and remitters in the escitalopram group at 8 weeks but not at 24 weeks</td>
<td>Fair</td>
</tr>
<tr>
<td>Lader et al. 2005&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Citalopram vs. Escitalopram (pooled data)</td>
<td>1321</td>
<td>Greater efficacy of escitalopram in reducing sleep disturbance</td>
<td>Fair</td>
</tr>
<tr>
<td>Lepola et al., 2003, 2004&lt;sup&gt;20, 83&lt;/sup&gt;</td>
<td>Citalopram vs. Escitalopram</td>
<td>471</td>
<td>Significantly more responders and remitters in the escitalopram group</td>
<td>Fair</td>
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<tr>
<td>Moore et al. 2005&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Citalopram vs. Escitalopram</td>
<td>280</td>
<td>Significantly more responders and remitters in the escitalopram group</td>
<td>Fair</td>
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<tr>
<td>Patris et al., 1996&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Citalopram vs. Fluoxetine</td>
<td>357</td>
<td>Faster onset of citalopram</td>
<td>Fair</td>
</tr>
<tr>
<td>Ekselius et al., 1997&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Citalopram vs. Sertraline</td>
<td>400</td>
<td>No differences</td>
<td>Good</td>
</tr>
<tr>
<td>Dalery et al., 2003&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Fluoxetine vs. Fluvoxamine</td>
<td>184</td>
<td>Faster onset of fluvoxamine</td>
<td>Fair</td>
</tr>
<tr>
<td>Rapaport et al., 1996&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Fluoxetine vs. Fluvoxamine</td>
<td>100</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Cassano et al., 2002&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Fluoxetine vs. Paroxetine</td>
<td>242</td>
<td>Faster onset of paroxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Chouinard et al., 1999&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Fluoxetine vs. Paroxetine</td>
<td>203</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>De Wilde et al., 1993&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Fluoxetine vs. Paroxetine</td>
<td>100</td>
<td>Faster onset of paroxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Gagiano et al., 1993&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Fluoxetine vs. Paroxetine</td>
<td>90</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Schone et al., 1993&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Fluoxetine vs. Paroxetine</td>
<td>108</td>
<td>Faster onset of paroxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Fava et al., 1998&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Fluoxetine vs. Paroxetine</td>
<td>128</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Bennie et al., 1995&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Fluoxetine vs. Sertraline</td>
<td>286</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Boyer et al., 1998&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Fluoxetine vs. Sertraline</td>
<td>242</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Fava et al., 2002&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Fluoxetine vs. Sertraline vs. Paroxetine</td>
<td>284</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Finkel et al., 1999&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Fluoxetine vs. Sertraline</td>
<td>75</td>
<td>Faster onset of sertraline</td>
<td>Fair</td>
</tr>
<tr>
<td>Sechter et al., 1999&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Fluoxetine vs. Sertraline</td>
<td>238</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Newhouse et al., 2000&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Fluoxetine vs. Sertraline</td>
<td>236</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Kroenke et al., 2001&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Fluoxetine vs. Sertraline vs. Paroxetine</td>
<td>601</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Aberg-Wistedt et al., 2000&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Paroxetine vs. Sertraline</td>
<td>353</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Kiev et al., 1997&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Paroxetine vs. Fluvoxamine</td>
<td>60</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Nemeroff et al., 1996&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Sertraline vs. Fluvoxamine</td>
<td>97</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Franchini et al., 1997, 2000&lt;sup&gt;43, 44&lt;/sup&gt;</td>
<td>Sertraline vs. Fluvoxamine</td>
<td>64</td>
<td>No differences</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Table 6: Interventions, Numbers of Patients, and Quality Ratings of Studies in Adults with Major Depressive Disorder, (continued)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRIs versus SSRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detke et al., 2004&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Duloxetine vs. paroxetine</td>
<td>367</td>
<td>No difference</td>
<td>Fair</td>
</tr>
<tr>
<td>Goldstein et al., 2002&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Duloxetine vs. paroxetine</td>
<td>173</td>
<td>No difference</td>
<td>Fair</td>
</tr>
<tr>
<td>Hong et al., 2003&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Mirtazapine vs. Fluoxetine</td>
<td>133</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Schatzberg et al., 2002&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Mirtazapine vs. Paroxetine</td>
<td>255</td>
<td>Faster onset of mirtazapine</td>
<td>Fair</td>
</tr>
<tr>
<td>Benkert et al., 2000&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Mirtazapine vs. Paroxetine</td>
<td>275</td>
<td>Faster onset of mirtazapine</td>
<td>Fair</td>
</tr>
<tr>
<td>Behnke et al., 2003&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Mirtazapine vs. Sertraline</td>
<td>346</td>
<td>Faster onset of mirtazapine</td>
<td>Fair</td>
</tr>
<tr>
<td>Bielski et al., 2004&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Venlafaxine vs. escitalopram</td>
<td>198</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Montgomery et al., 2004&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Venlafaxine vs. escitalopram</td>
<td>293</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Allard et al. 2004&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Venlafaxine vs. citalopram</td>
<td>151</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Costa e Silva et al., 1998&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Venlafaxine vs. Fluoxetine</td>
<td>382</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Alves et al., 1999&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Venlafaxine vs. Fluoxetine</td>
<td>87</td>
<td>Faster onset of venlafaxine</td>
<td>Fair</td>
</tr>
<tr>
<td>Tylee et al., 1997&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Venlafaxine vs. Fluoxetine</td>
<td>341</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Dierick et al., 1996&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Venlafaxine vs. Fluoxetine</td>
<td>314</td>
<td>Significantly higher response rate for venlafaxine</td>
<td>Fair</td>
</tr>
<tr>
<td>De Nayer et al., 2002&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Venlafaxine vs. Fluoxetine</td>
<td>146</td>
<td>Significantly greater improvement for venlafaxine</td>
<td>Fair</td>
</tr>
<tr>
<td>Rudolph et al., 1999&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Venlafaxine XR vs. Fluoxetine</td>
<td>301</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Silverstone et al., 1999&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Venlafaxine XR vs. Fluoxetine</td>
<td>368</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Ballus et al., 2000&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Venlafaxine vs. Paroxetine</td>
<td>84</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>McPartlin et al., 1998&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Venlafaxine XR vs. Paroxetine</td>
<td>361</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Mehtonen et al., 2000&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Venlafaxine vs. Sertraline</td>
<td>147</td>
<td>Significantly higher response rate for venlafaxine</td>
<td>Good</td>
</tr>
<tr>
<td>Sir et al. 2005&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Venlafaxine XR vs. Sertraline</td>
<td>163</td>
<td>No differences</td>
<td>Good</td>
</tr>
<tr>
<td>Other second-generation antidepressants (DopR1, 5-HT&lt;sub&gt;2&lt;/sub&gt;) versus SSRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nieuwstraten et al., 2001&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Bupropion vs. SSRIs (SR)</td>
<td>1332</td>
<td>No differences in patients with comorbid anxiety</td>
<td>Good</td>
</tr>
<tr>
<td>Panzer et al. 2005&lt;sup&gt;68&lt;/sup&gt;</td>
<td>SSRIs vs. other 2nd generation antidepressants (SR)</td>
<td>NR</td>
<td>No differences in patients with comorbid anxiety</td>
<td>Fair</td>
</tr>
<tr>
<td>Feighner et al., 1994&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Bupropion vs. Fluoxetine</td>
<td>123</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Coleman et al., 2001&lt;sup&gt;70&lt;/sup&gt;</td>
<td>Bupropion vs. Fluoxetine</td>
<td>456</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Weihls et al., 2000&lt;sup&gt;71&lt;/sup&gt;</td>
<td>Bupropion SR vs. Paroxetine</td>
<td>100</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Coleman et al., 1999&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Bupropion vs. Sertraline</td>
<td>364</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Croft et al., 1999&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Bupropion vs. Sertraline</td>
<td>360</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Kavoussi et al., 1997&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Bupropion vs. Sertraline</td>
<td>248</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Rush et al., 1998&lt;sup&gt;75&lt;/sup&gt;</td>
<td>Nefazodone vs. Fluoxetine</td>
<td>125</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Baldwin et al., 1996, 2001&lt;sup&gt;76, 77&lt;/sup&gt;</td>
<td>Nefazodone vs. Paroxetine</td>
<td>206</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Feiger et al., 1996&lt;sup&gt;78&lt;/sup&gt;</td>
<td>Nefazodone vs. Sertraline</td>
<td>160</td>
<td>No differences</td>
<td>Fair</td>
</tr>
</tbody>
</table>

(SR)= Systematic review
Table 7: Studies Indicating a Faster Onset of Mirtazapine

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Comparison</th>
<th>Effect size</th>
<th>p-value</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Behnke et al., 2003<sup>50</sup> | 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<sup>49</sup> | 275 | paroxetine | More responders (23.2% vs. 8.9%) and remitters (8.8% vs. 2.4%) at day 7 with mirtazapine.  
response: RRR: 0.15  
RD: 0.14  
NNT: 8  
remission: RRR: 0.07  
RD: 0.07  
NNT: 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<sup>47</sup> | 133 | fluoxetine | At day 28 significantly more responders with mirtazapine (53.3% vs. 39.0%)  
R: 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<sup>48</sup> | 255 | paroxetine | Significantly more responders at day 14 with mirtazapine (27.8% vs. 13.3%);  
R: RRR: 0.17  
RD: 0.14  
NNT: 7  
significantly greater decrease of HAM-D scores from day 7 to day 21 with mirtazapine;  
median time to response: Mirtazapine: 26 days  
Paroxetine: 40 days | p = 0.005  
p < 0.01 (day 7, 14)  
p = 0.024 (day 21)  
Kaplan-Mayer: p = 0.016 | No statistically significant differences in overall response rate at week 8; more responders in the mirtazapine group (58% vs. 51%) at endpoint. |

RRR : Relative Risk Reduction ; RD : Risk Difference ; NNT : Number Needed to Treat
Table 8: Studies Indicating Fewer Sexual Adverse Events for Bupropion

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Comparison</th>
<th>Effect measure</th>
<th>p-value</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Coleman et al., 2001   | 456         | fluoxetine, placebo | Significantly more bupropion SR patients were satisfied with overall sexual functioning (analysis only for patients satisfied at baseline; no rates reported) | p < 0.05 | DSM-IV criteria for sexual dysfunction disorders  
No statistically significant differences in efficacy outcome measures at endpoint (week 8) |
| Coleman et al., 1999   | 364         | sertraline  | Beginning at day 21 significantly more patients on bupropion SR were satisfied with their sexual functioning (endpoint: 85% vs. 62%) | 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     | 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%) | p < 0.05 | Assessment of sexual function in an investigator-conducted structured interview  
No statistically significant differences in efficacy outcome measures at endpoint (week 8) |
### Table 8: Studies Indicating Fewer Sexual Adverse Events for Bupropion (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Comparison</th>
<th>Effect measure</th>
<th>p-value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kavoussi et al. 199772, 85</td>
<td>248</td>
<td>sertraline,</td>
<td>Significantly more patients on sertraline experienced orgasm delays and/or failure</td>
<td>p &lt; 0.01</td>
<td>Assessment of sexual function in an investigator-conducted structured interview ; No statistically significant differences in efficacy outcome measures at endpoint (week 16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Women : 41% vs. 7% RRR : 0.85 RD : 0.38 NNT : 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Men : 61% vs. 10% RRR : 0.84 RD : 0.51 NNT : 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Higher overall satisfaction with sexual functioning with bupropion SR at endpoint (79% vs. 58%)</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RRR : 0.50 RD : 0.21 NNT : 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feighner et al. 199148</td>
<td>61</td>
<td>fluoxetine</td>
<td>NR</td>
<td>NR</td>
<td>bupropion IR ; study does not report on differences in sexual adverse events</td>
</tr>
</tbody>
</table>

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

### Table 9: Study Indicating a Better Sleep Profile with Nefazodone

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Comparison</th>
<th>Effect measure</th>
<th>p-value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rush et al. 199877</td>
<td>125</td>
<td>fluoxetine</td>
<td>Significantly greater improvements from baseline for nefazodone on HDRS Sleep Disturbance Factors ,IDS-C, and IDSR Total Sleep factors</td>
<td>p &lt; 0.05</td>
<td>Pooled analysis of 3 identical studies assessing sleep quality ;</td>
</tr>
</tbody>
</table>

RRR : Relative Risk Reduction ; RD : Risk Difference ; NNT : Number Needed to Treat
B. Dysthymia in Adults

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

We did not find any head-to-head trials among patients with dysthymia. Five placebo-controlled studies (Table 10) assessed efficacy and tolerability of fluoxetine, paroxetine, and sertraline in a population with dysthymia.86-93

1. SSRIs compared to placebo in adults with dysthymia

Fluoxetine vs. placebo

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

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

Paroxetine vs. placebo vs. behavioral therapy

A large, fair-rated, primary-care-based study randomized 656 patients with dysthymia or minor depression to 11 weeks of paroxetine (10-40 mg/d), placebo, or behavioral therapy.90, 91 Participants were stratified into patients 60 years and older (n = 415) and patients younger than 60 years (n = 241) for intention-to-treat analysis. Loss to follow-up was not reported for either subgroup.

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

One RCT compared sertraline (50-200mg/d) to imipramine (50-300mg/d) and placebo in 416 patients who had had the diagnosis of dysthymia for more than 5 years.\(^86-88\) Study duration was 12 weeks; loss to follow-up was 24.3 percent. Outcomes included quality of life and other measures of functional capacity. Both imipramine (64.0%) and sertraline (59.0%) had significantly more responders (CGI 1 or 2) than placebo (44.3%), but the two therapeutic groups did not differ significantly. Quality of life and overall psychosocial functioning improved significantly in both active treatment groups compared to the placebo group. The number of patients who discontinued therapy because of adverse events was significantly higher for imipramine than for sertraline (18.4% vs. 6.0%; \(p = 0.001\)).

**Sertraline vs. placebo**

A multinational study enrolled 310 dysthymic patients for 12 weeks to compare sertraline (50-200mg/d) to placebo.\(^89\) Loss to follow-up was 24.2 percent. Patients in the sertraline group had significantly greater reductions in most efficacy measures (MADRS, CGI, HAD-A, HAD-D, Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version [SIGH-SAD]), than did those in the placebo group. The rates of responders and remitters were also significantly higher in the sertraline group (Hamilton Rating Scale for Anxiety (HAM-A): \(p = 0.001\); CGI-I: \(p < 0.001\)). The quality of life scale (BQLS) showed significantly greater improvements in eight of nine domains in the sertraline group.

### 2. Summary of the evidence

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

**Effectiveness**

One fair study, based in a primary care setting, provides mixed evidence on the effectiveness of paroxetine compared to placebo. A subgroup of patients older than 60 years showed a significantly greater improvement than those on placebo; a subgroup of patients younger than 60 years did not show any difference in effectiveness between paroxetine and placebo.\(^89,91\)

**Efficacy**

Evidence from one good study indicates that fluoxetine has only limited efficacy in elderly patients with dysthymia.\(^92\) Fair evidence from two studies indicates that sertraline has a significantly greater efficacy in the treatment of dysthymia than placebo.\(^86-89\) In both trials, sertraline treatment led to a significantly greater improvement of quality of life and psychosocial functioning than placebo.
Table 10: Included Studies for Dysthymia

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett et al., 2001</td>
<td>Paroxetine vs. Placebo</td>
<td>656</td>
<td>Significantly more responders for paroxetine in patients older than 60 years</td>
<td>Fair</td>
</tr>
<tr>
<td>Williams et al., 2000</td>
<td>Behavioral therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Devanand et al., 2005</td>
<td>Fluoxetine vs. Placebo</td>
<td>90</td>
<td>No differences in response rates and quality of life</td>
<td>Good</td>
</tr>
<tr>
<td>Thase et al., 1996</td>
<td>Sertraline vs. Imipramine vs.</td>
<td>412</td>
<td>Significantly more responders for sertraline than placebo</td>
<td>Fair</td>
</tr>
<tr>
<td>Ravindran et al., 2000</td>
<td>Sertraline vs. Placebo</td>
<td>310</td>
<td>Significantly more responders and remitters for sertraline</td>
<td>Fair</td>
</tr>
<tr>
<td>Vanelle et al. 1997</td>
<td>Fluoxetine vs. Placebo</td>
<td>111</td>
<td>Significantly more responders for fluoxetine</td>
<td>Fair</td>
</tr>
</tbody>
</table>
C. Major Depressive Disorder in Children and Adolescents

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

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

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

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

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

In addition, two systematic reviews evaluated placebo-controlled evidence for the use of SSRIs and an SNRI. One review highlighted placebo-controlled evidence already included in this discussion, so we do not comment on it further here. A second review analyzed published and
unpublished data for citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine. We cite the evidence reported in this article because of its contrast with other published evidence.

Of the primary studies evaluated, patient populations generally were between the ages of 6 and 18 years. In general, inclusion was determined by a combination of several factors, often including a criteria-based diagnosis for MDD (DSM-III, DSM-IV) in addition to a predefined severity of disease (HAM-D ≥ 12; CDRS-R > 40; Children’s Global Assessment Scale < 60). Several studies used different inclusion cut-off points when defining severity of disease. All studies lasted between 6 and 10 weeks. Patients were excluded if they were suicidal, had a current or past failure on a study drug, had a seizure disorder, or had a current or past history of bipolar disorder, panic disorder, schizoaffective disorder, OCD, or other significant mental illness.

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

1. SSRIs compared to placebo in pediatric outpatients with major depressive disorder

Citalopram vs. placebo

One 8-week study randomized 174 children (7 to 11 years) and adolescents (12 to 17 years) with MDD to citalopram (20-40 mg/d) or placebo. Diagnosis was established with the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL). Overall loss to follow-up was 22 percent. The primary outcome was the mean change from baseline to endpoint in the CDRS-R. Secondary outcome measures included the CGI-I and CGI-S. At 8 weeks, intention-to-treat analysis confirmed significantly greater reduction in the CDRS-R for citalopram-treated patients then for placebo-treated patients (p < 0.05). Significant differences were not reported for secondary outcome measures. More than 10 percent of citalopram-treated patients experienced rhinitis, nausea, and abdominal pain (p = NR for comparison with placebo).

Fluoxetine vs. placebo

Although we did not review placebo-controlled evidence for fluoxetine because the FDA has already established its general efficacy and tolerability, we did review the Treatment for Adolescents with Depression Study (TADS) because it specifically compared fluoxetine, fluoxetine plus CBT, CBT alone, and placebo. In this good, 12-week, US-based multicenter...
study of 439 adolescents (12 to 17 years), placebo and flexible-dose fluoxetine (10-40 mg/d) were administered double-blind; CBT alone and CBT with fluoxetine were administered unblinded. Primary outcome measures included the CDRS-R and CGI-I. Overall loss to follow-up was 18 percent. Compared to fluoxetine alone (p = 0.02) and CBT alone (p = 0.01), treatment with fluoxetine plus CBT was superior on the CDRS-R. Both fluoxetine alone (p < 0.001) and fluoxetine plus CBT (p < 0.001) demonstrated significantly greater improvement on the CGI-I compared to placebo. Differences in harm-related adverse events were not significant across treatment groups (p = 0.15).

Paroxetine vs. placebo
An 8-week study randomized 275 adolescents (12 to 18 years) to double-blind flexible-dose treatment with paroxetine (20-40 mg/d), imipramine (200-300 mg/d), or placebo. 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 and placebo-treated patients (p = 0.13 and p = 0.11, respectively). Paroxetine was not statistically different from placebo on secondary measures of functioning, health status, and behavior (Autonomous Function Checklist, Self-Perception Profile, and Sickness Impact Profile). Compared to those on placebo, significantly more paroxetine-treated patients experienced somnolence or insomnia.

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

Of note for this study is the fact that only pooled data from the two independent trials were published. Before this pooling, neither trial had demonstrated a consistent advantage for sertraline over placebo (data available at http://medicines.mhra.gov.uk). One trial reported significantly more sertraline-treated CDRS-R responders (p = 0.033 compared to placebo).
2. SNRIs compared to placebo in pediatric outpatients with major depressive disorder

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

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

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

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

4. Summary of the evidence

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

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

Efficacy
Two placebo-controlled trials provide fair evidence that efficacy to improve health outcomes does not differ between placebo and sertraline, paroxetine, and venlafaxine.99, 101 Two placebo-controlled trials support greater efficacy for citalopram and sertraline compared to placebo.97, 100 Some FDA-approved evidence supports the efficacy of fluoxetine in treating MDD in children and adolescents; one trial supports greater efficacy of fluoxetine when combined with CBT.98 Of note, however, published trials supporting the efficacy of fluoxetine102, 103 were excluded from our review because of a differential loss to follow-up of more than 15 percentage points between active treatment and placebo control. Evidence is inconclusive about the efficacy of citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, mirtazapine, venlafaxine, bupropion, and nefazodone.

Table 11: Included Studies for Major Depressive Disorder

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whittington et al., 200496</td>
<td>Citalopram vs. Placebo (SR)</td>
<td>2,145</td>
<td>Only fluoxetine had favorable risk-benefit profile</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine vs. Placebo</td>
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<td></td>
<td>Sertraline vs. Placebo</td>
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<tr>
<td></td>
<td>Venlafaxine vs. Placebo</td>
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<tr>
<td>Systematic Review</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Wagner et al., 200497</td>
<td>Citalopram vs. Placebo</td>
<td>174</td>
<td>Significantly greater efficacy for citalopram</td>
<td>Fair</td>
</tr>
<tr>
<td>March et al., 200498</td>
<td>Fluoxetine plus CBT vs. Fluoxetine vs. CBT vs. placebo</td>
<td>439</td>
<td>Greater improvement on the CDRS-R for fluoxetine plus CBT compared to fluoxetine alone, CBT alone, or placebo</td>
<td>Good</td>
</tr>
<tr>
<td>Keller et al., 200199</td>
<td>Paroxetine vs. Imipramine vs. Placebo</td>
<td>275</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Wagner et al., 2003100</td>
<td>Sertraline vs. Placebo</td>
<td>376</td>
<td>Significantly greater efficacy for sertraline</td>
<td>Fair</td>
</tr>
<tr>
<td>SNRIs versus placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandoki et al., 1997101</td>
<td>Venlafaxine vs. Placebo</td>
<td>40</td>
<td>No differences</td>
<td>Fair</td>
</tr>
</tbody>
</table>

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

D. Generalized Anxiety Disorder

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

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

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

1. SSRIs compared to SSRIs in adult outpatients with GAD

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

A second RCT compared escitalopram (10-20mg/d) to paroxetine (20-50mg/d) in 121 patients with GAD. Although we excluded this study because of high loss to follow-up, results were consistent with the only other comparative trial; no statistically significant differences in efficacy
were reported. The mean change in HAM-A scores were -15.3 and -13.3 for escitalopram and paroxetine, respectively (p = 0.13). The frequency of treatment-emergent adverse events was greater among paroxetine-treated patients than among escitalopram-treated patients (88.7% vs. 77.0%, respectively; p = NR).

2. SSRIs compared to placebo in adult outpatients with GAD

**Escitalopram vs. Placebo**

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

**Paroxetine vs. placebo**

Two fair studies comparing paroxetine to placebo included health outcome measures. 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. 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. This study randomized 331 patients, ages 18 or older, with DSM-IV criteria for GAD. Of randomized participants, 21 percent did not complete 8 weeks of follow-up. The primary efficacy measure was the mean change from baseline in the total score of the HAM-A. The change from baseline in illness-related impairment was assessed using the SDS. Beginning at week 6 and continuing through endpoint, the paroxetine group had a significantly greater reduction in the total HAM-A score, the anxious mood item, and the tension item (p < 0.05). At week 8, the paroxetine group had a significantly greater reduction than the placebo group in the total score of the SDS (p < 0.001). All adverse events were experienced by more paroxetine patients than placebo patients. Asthenia, constipation, abnormal ejaculation (men only), decreased libido, nausea, and
somnolence were reported in at least twice as many patients in the paroxetine group compared to placebo. More paroxetine-treated patients withdrew from the study because of adverse events (10.5% vs. 3.7% for placebo).

**Sertraline vs. placebo**

Currently, sertraline is not FDA-approved for the treatment of GAD. We identified one placebo-controlled trial that assessed the efficacy and tolerability of sertraline in GAD. This 12-week, multicenter, multicountry trial randomized 378 outpatients with a primary diagnosis of DSM-IV-defined anxiety disorder to sertraline 50-150 mg/d or placebo. Patients with a history of other psychiatric disorders, including MAD, were excluded. The primary efficacy measure was the HAM-A; secondary assessments included the CGI-I, CGI-S, MADRS, HADS, Q-LES-Q, the Endicott Work Productivity Scale, and the HAM-A psychic and somatic anxiety factors. At endpoint, the mean reduction in HAM-A total score was -11.7 for the sertraline group and -8.0 for the placebo (p < 0.0001). Additionally, sertraline was significantly better than placebo on all secondary assessments, including the quality-of-life and work productivity measures.

**Venlafaxine vs. placebo**

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

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

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

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

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

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

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

Table 12: Included Studies for Generalized Anxiety Disorder

<table>
<thead>
<tr>
<th>Author, Year</th>
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<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
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<td>SSRIs versus Placebo</td>
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<tr>
<td>Ball et al. 2005104</td>
<td>Paroxetine vs. Sertraline</td>
<td>55</td>
<td>No difference</td>
<td>Fair</td>
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<td>Davidson et al., 2004</td>
<td>Escitalopram vs. Placebo</td>
<td>315</td>
<td>Significantly greater improvement in QoL for escitalopram</td>
<td>Fair</td>
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<tr>
<td>Pollack et al., 2004</td>
<td>Paroxetine vs. Placebo</td>
<td>331</td>
<td>Significantly greater reduction in SDS for paroxetine</td>
<td>Fair</td>
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<tr>
<td>Rickels et al., 2003</td>
<td>Paroxetine vs. Placebo</td>
<td>566</td>
<td>Significantly greater reduction in SDS for paroxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Allgulander et al., 2004114</td>
<td>Sertraline vs. Placebo</td>
<td>378</td>
<td>Significantly greater improvement in HAM-A total score; HAM-A psychic and somatic factors, QoL, and work productivity</td>
<td>Fair</td>
</tr>
<tr>
<td>Dahl et al., 2005115</td>
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<tr>
<td>Meoni et al., 2004112, 113</td>
<td>Venlafaxine XR vs. Placebo</td>
<td>1,839</td>
<td>Significantly greater reduction in psychic and somatic factor scores for venlafaxine</td>
<td>Fair</td>
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</table>

QoL = quality of life
E. Obsessive-Compulsive Disorder

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

Two head-to-head trials addressing the use of SSRIs or other second-generation antidepressants met our inclusion criteria for the review of OCD (Table 13). One of these head-to-head trials had a 12-week extension phase in which nonresponders were switched to the alternative treatment.\textsuperscript{120} One additional trial compared citalapram plus mirtazapine to citalopram alone.\textsuperscript{121} Three meta-analyses pooled data from studies comparing SSRIs to placebo. Additionally, one placebo-controlled trial was included because it evaluated an SSRI not covered in the reviews or approved by the FDA (Table 13). All systematic reviews included comparisons of fluoxetine, fluvoxamine, and sertraline to placebo.\textsuperscript{122-124} In addition, one review included a comparison of paroxetine to placebo.\textsuperscript{123}

Generally, inclusion was based on a criteria-based diagnosis (DSM-III, DSM-IV) of OCD and a predefined cut-off point on an accepted obsessive-compulsive scale (e.g., Y-BOCS, NIMH-OC). The majority of patients could be labeled as having moderate or severe disease with mild or no comorbid depression. Multiple studies limited inclusion by duration of current illness of 1 year or more.

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

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

1. SSRIs compared to SSRIs in adult outpatients with OCD

Sertraline vs. fluoxetine
A multicenter Canadian study evaluated the use of sertraline (50-200 mg/d) and fluoxetine (20-80 mg/d) in 150 patients over a 24-week period.\textsuperscript{125} More than 79 percent of patients had a duration of illness of 10 years or more. Loss to follow-up was 29 percent, with no differential between fluoxetine- and sertraline-treated groups. At 24 weeks, mean response (Y-BOCS) did not differ significantly between the groups, although sertraline-treated patients had shown statistically greater improvement in mean change from baseline (Y-BOCS) at weeks 4, 8, and 12. Remission rates were greater for sertraline-treated patients at week 12 but not at week 24. Both sertraline and fluoxetine showed equivalent efficacy in improving secondary symptoms of
depression (HAM-D) and generalized anxiety (CAS). No significant differences in the incidence of side effects between groups were reported.

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

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

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

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

4. SSRIs compared to placebo in adult outpatients with OCD

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

As a 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. Specifically, this study used meta-regression to identify sources of heterogeneity in these trials (and clomipramine trials). They identified 12 trials published before 2000 that compared SSRIs to placebo. Only studies that assessed efficacy with Y-BOCS were incorporated in the meta-regression. Effect sizes were estimated as the difference in improvement (decrease in Y-BOCS) between active drug and placebo.

Four fluvoxamine studies showed a net improvement of -4.84 (95% CI, -7.78, -1.83). For the three fluoxetine studies, net improvement was -1.61 (95% CI -2.18, -1.04); for four sertraline studies, the pooled difference in Y-BOCS was calculated to be -2.47 (95% CI, -6.13, 1.20). Only one paroxetine study was included; the difference in improvement was estimated as -3.00 (95% CI, -4.91, -1.09).

A third meta-analysis assessed medication effect sizes in six published placebo-controlled trials; two fluvoxamine studies; two sertraline studies; and two fluoxetine studies. 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. Loss to follow-up was 16 percent, with small differences between groups. All three doses of citalopram produced significantly more responders (≥ 25% improvement in Y-BOCS) than placebo (p < 0.01). The high-dose citalopram (60mg) response reached statistical significance at week 3, whereas the lower doses (20mg and 40mg) reached statistical significance at week 7. On the patient-rated Sheehan Disability Scale, the citalopram-treated patients showed significant improvements for most items. Adverse events were reported in 71 percent of subjects in the active treatment groups. The number of adverse events reported by persons on different citalopram doses did not differ significantly. Ejaculation failure was significantly different from placebo only in the 40mg citalopram group.

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

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

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

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

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

Table 13: Included Studies for Obsessive-Compulsive Disorder

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

(SR) = Systematic Review

F. Panic Disorder

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

For panic disorder, we identified only three head-to-head trials comparing one SSRI, or other second-generation antidepressant to another.\textsuperscript{141-143} We excluded one study – a single-blinded
RCT with a poor quality rating for internal validity from our findings, but we discuss it here briefly because of the minimal amount of published research on this topic. Furthermore, we identified five placebo-controlled trials assessing the efficacy and tolerability of fluvoxamine, sertraline, and venlafaxine ER. One additional RCT compared sertraline to placebo and assessed quality of life as a secondary outcome measure (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. 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). 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.\textsuperscript{142} Patients and care providers were not blinded to treatment allocation; therefore, this study received a poor quality rating for internal validity. Loss to follow-up was 10 percent. Results reported no statistically significant differences between citalopram and paroxetine in any efficacy measures. However, results may be biased because of lack of double blinding.

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

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

The second study randomized 50 patients to fluvoxamine (50-300mg/d) or placebo.\textsuperscript{145} Loss to follow-up was 28 percent, and no intention-to-treat analysis was done. The fluvoxamine group reported significantly fewer major panic attacks starting at week 4 until the endpoint (p < 0.05); they also had significantly lower scores on CAS and MADRS (p < 0.05). By contrast, active drug and placebo groups did not differ significantly in terms of minor panic attacks and Sheehan disability scores.

The third trial enrolled 188 participants.\textsuperscript{146} Loss to follow-up was about 35 percent. Results were consistent with the other studies. Fluvoxamine showed a significantly greater efficacy in most primary (Daily Panic Attack Inventory) and secondary (MADRS, CGI-I, CGI-S, CAS, Sheehan Disability Scale) outcome measures compared to placebo.

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

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

3. Summary of the evidence

One fair head-to-head study provides evidence that efficacy does not differ between citalopram and escitalopram. In other trials, significant differences in study design and outcome selection make this evidence insufficient to identify differences between treatments.

Effectiveness

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

Efficacy

Two fair RCTs provide evidence that the efficacy of reducing panic attacks and improving quality of life does not differ significantly between citalopram and escitalopram\textsuperscript{141} or between paroxetine and sertraline\textsuperscript{143} in outpatients with panic disorder. Fair evidence exists from five placebo-controlled trials that the improvement of health outcomes and functional capacity is significantly greater for fluvoxamine, sertraline, and venlafaxine ER than for placebo.\textsuperscript{144-148} Three placebo-controlled trials provide fair evidence of significantly greater efficacy of fluvoxamine than placebo.\textsuperscript{144-146} FDA-approved evidence supports the general efficacy of fluoxetine, paroxetine, and sertraline for the treatment of panic disorder. Evidence is insufficient about the efficacy mirtazapine, venlafaxine, bupropion, and nefazodone for treating panic disorder.

Table 14: Included Studies for Panic Disorder

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs versus SSRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bandelow et al., 2004\textsuperscript{143}</td>
<td>Paroxetine vs. Sertraline</td>
<td>225</td>
<td>No difference</td>
<td>Fair</td>
</tr>
<tr>
<td>Stahl et al., 2003\textsuperscript{141}</td>
<td>Citalopram vs. Escitalopram vs. Placebo</td>
<td>366</td>
<td>No difference</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>SSRIs versus Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asnis et al., 2001\textsuperscript{146}</td>
<td>Fluvoxamine vs. Placebo</td>
<td>188</td>
<td>Significantly greater efficacy of fluvoxamine</td>
<td>Fair</td>
</tr>
<tr>
<td>Black et al., 1993\textsuperscript{149}</td>
<td>Fluvoxamine vs. Placebo</td>
<td>75</td>
<td>Significantly greater efficacy of fluvoxamine</td>
<td>Fair</td>
</tr>
<tr>
<td>Hoehn-Saric et al., 1993\textsuperscript{145}</td>
<td>Fluvoxamine vs. Placebo</td>
<td>50</td>
<td>Significantly greater efficacy of fluvoxamine</td>
<td>Fair</td>
</tr>
<tr>
<td>Pohl et al., 1998\textsuperscript{147}</td>
<td>Sertraline vs. Placebo</td>
<td>168</td>
<td>Significantly greater efficacy of sertraline</td>
<td>Fair</td>
</tr>
<tr>
<td>Bradwejn et al., 2005\textsuperscript{148}</td>
<td>Venlafaxine ER vs. placebo</td>
<td>361</td>
<td>Significantly greater efficacy of sertraline except in percentage of patients free from panic attacks</td>
<td>Fair</td>
</tr>
</tbody>
</table>
G. Post-Traumatic Stress Disorder

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

We included four placebo-controlled trials assessing the efficacy of paroxetine, fluoxetine, and sertraline compared to placebo (Table 15). One open-label continuation study and a subsequent maintenance trial 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, the third was financed by grant from the National Institute of Mental Health (NIMH).

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

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

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

2. SSRIs compared to placebo in adult outpatients with PTSD

Fluoxetine vs. placebo
A small fair-rated study enrolled 54 patients to 12 weeks of fluoxetine (10-60mg) or placebo. 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. The enrolled population represented a wide range of trauma. The large majority of participants were white ($> 90\%$) and female ($67\%$). Loss to follow-up was 37 percent. Intention-to-treat results showed a significantly greater change in CAPS Part 2 scores for paroxetine 20mg/d ($p < 0.001$) and paroxetine 40mg/d ($p < 0.001$) compared to placebo at endpoint. Improvements on the CGI-I were also significantly greater for both paroxetine groups ($p < 0.001$). Functional improvement was significantly greater for paroxetine-treated patients (SDS) in all three domains (work, social life, family life). Treatment response did not vary by trauma type, time since trauma, or severity of baseline PTSD scores.

**Sertraline vs. placebo**

Two fair studies with an identical design randomized patients ($n = 187$; $n = 208$) with moderate to severe PTSD to 12 weeks of sertraline (50-200mg) or placebo. 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. Patients who completed the acute phase treatment could enter an open-label continuation phase for 24 weeks ($n = 252$); 92 percent of sertraline-treated patients maintained response during this open-label treatment. Ninety-six patients who completed the continuation phase were randomized to sertraline (50-200 mg/d) or placebo in a 28-week, double-blind maintenance trial. Treatment with sertraline yielded a significantly lower relapse rate than placebo ($5\%$ vs. $26\%$; $p < 0.02$). Kaplan-Meier analysis showed highly significant relapse prevention for sertraline ($p = 0.0002$).

**3. Summary of the evidence**

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

**Effectiveness**

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

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

**Table 15: Included Studies for Post-Traumatic Stress Disorder**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
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<tbody>
<tr>
<td>Tucker et al., 2005(^{150})</td>
<td>Citalopram vs. Sertraline</td>
<td>59</td>
<td>No difference in efficacy</td>
<td>Fair</td>
</tr>
<tr>
<td>McRae et al., 2004(^{151})</td>
<td>Sertraline vs. Nefazodone</td>
<td>37</td>
<td>No difference in efficacy</td>
<td>Fair</td>
</tr>
<tr>
<td>Connor et al., 1999(^{156})</td>
<td>Fluoxetine vs. Placebo</td>
<td>54</td>
<td>Significantly greater efficacy of fluoxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Marshall et al., 2001(^{155})</td>
<td>Paroxetine vs. Placebo</td>
<td>563</td>
<td>Significantly greater efficacy of paroxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Brady et al., 2000(^{152, 154, 157, 158})</td>
<td>Sertraline vs. Placebo</td>
<td>187</td>
<td>Significantly greater efficacy of sertraline</td>
<td>Fair</td>
</tr>
<tr>
<td>Davidson et al., 2001(^{153})</td>
<td>Sertraline vs. Placebo</td>
<td>208</td>
<td>Significantly greater efficacy of sertraline</td>
<td>Fair</td>
</tr>
</tbody>
</table>
H. Social Anxiety Disorder

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

Three placebo-controlled head-to-head trials compared one second-generation antidepressant to another for the treatment of social anxiety disorder.\textsuperscript{159-161} Two 12-week trials compared paroxetine to venlafaxine ER;\textsuperscript{159, 161} a 24-week trial compared escitalopram to paroxetine.\textsuperscript{160} All three trials included measures of functional capacity in addition to efficacy and tolerability.

We reviewed additional evidence from placebo-controlled trials if they assessed a second-generation antidepressant not currently FDA-approved for social anxiety disorder or if they included health outcome measures not commonly assessed in efficacy trials. One meta-analysis compared fluvoxamine, sertraline, and paroxetine to placebo.\textsuperscript{162} In addition, four placebo-controlled studies evaluated second-generation antidepressants currently not approved by the FDA for social anxiety disorder: two escitalopram studies;\textsuperscript{163, 164} one fluoxetine study;\textsuperscript{165} two fluvoxamine studies;\textsuperscript{166, 167} and one mirtazapine study.\textsuperscript{168} (Table 16). Evidence on specific health outcomes are included for seven additional placebo-controlled studies evaluating two SSRIs with FDA-supported efficacy (Table 16): paroxetine,\textsuperscript{169-172} and sertraline.\textsuperscript{173-175}

In general, inclusion was based on a criteria-based diagnosis (DSM-IV) of social anxiety disorder. Several studies required a minimal duration of current illness of 6 months or greater.\textsuperscript{159, 161, 165, 174, 175} Additionally, several studies limited eligibility using a predefined cut-off point on a validated anxiety rating scale.\textsuperscript{159-161, 164-166, 169, 174, 175}

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

Trial reporting was often incomplete. All trials used an intention-to-treat analysis. Among the included studies, loss to follow-up was between 20 percent and 35 percent. One study had a loss-to-follow-up differential between treatment groups greater than 10 percentage points.\textsuperscript{171} In two studies, withdrawals because of adverse effects were higher in the active treatment groups.\textsuperscript{166, 173}

All included trials are characterized as efficacy studies. Two studies assessed relapse prevention; one randomized escitalopram responders (CGI-I score of 1 or 2) to 24 weeks of escitalopram or placebo,\textsuperscript{163} and one study randomized open-label paroxetine responders to placebo or active treatment.\textsuperscript{169} Both studies evaluated the rate of relapse between active treatment and placebo.
1. SSRIs compared to SSRIs in adult outpatients with social anxiety disorder

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

**Escitalopram vs. paroxetine**

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

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

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

**Venlafaxine vs. paroxetine**

Two 12-week multicenter trials compared venlafaxine ER to paroxetine and placebo. A European trial randomized 436 patients with social anxiety disorder and an American trial randomized 440 patients with social anxiety disorder to venlafaxine ER (75-225 mg/d), paroxetine (20-50 mg/d), or placebo. Eligible patients were 18 years or older who met DSM-IV criteria for social anxiety disorder at least 6 months before enrollment. In the European trial, significantly more females were randomized to placebo than to venlafaxine or paroxetine. The primary outcome measure was the LSAS; secondary outcome measures included the CGI-I, CGI-S, SPI, and SDI. The European trial also included a measure of work productivity WPAI. At 12 weeks, no significant differences in any outcome measure were observed between venlafaxine ER and paroxetine in either trial. Both venlafaxine ER and paroxetine were significantly better than placebo for all primary and secondary outcome measures (p < 0.05), including the measures of functional capacity (SDI) and work productivity (WPAI).
3. SSRIs compared to placebo in adult outpatients with social anxiety disorder

One meta-analysis and nine placebo-controlled trials provide additional evidence.

**Fluvoxamine, paroxetine, and sertraline vs. placebo**

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

**Escitalopram vs. placebo**

One fair 12-week study compared flexible doses of escitalopram to placebo. This trial randomized 358 participants meeting DSM-IV criteria for social anxiety disorder with a score of at least 70 on the LSAS to escitalopram (10-20 mg/d) or placebo. Overall loss to follow-up was 19 percent (18% for placebo and 20% for escitalopram). The primary efficacy measure was the LSAS total score; secondary outcome measures included the LSAS subscales, CGI-S, CGI-I, SDS, and MADRS. At endpoint, escitalopram was significantly better than placebo as assessed by the LSAS total score (p < 0.01), LSAS subscales (p < 0.05), CGI-S (p < 0.01), CGI-I (p < 0.01), and the work and social domains of the SDS (p < 0.05). Results were similar to the placebo comparison reported by Lader et al. The most common adverse event reported for escitalopram or placebo was headache (25% in both groups); compared to placebo, more patients randomized to escitalopram reported nausea (12% vs 22%; p = NR).

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

**Fluoxetine vs. placebo**

One fair study compared flexible doses of fluoxetine to placebo. This trial randomized 60 participants meeting DSM-IV criteria for social anxiety disorder for at least 6 months to 14 weeks of fluoxetine (20-60 mg/d) or placebo. Loss to follow-up was 20 percent with a higher rate in the placebo control group than the active fluoxetine group (23% vs. 16%, respectively). The primary efficacy measure was the LSAS. Significant improvements in LSAS scores were
reported for fluoxetine and placebo, with no statistically significant differences between groups (p = 0.901). Secondary efficacy measures included the BSPS, FQ, HAM-A, HAM-D, Global Assessment of Functioning (GAF), and SF-36. Overall, no statistically significant differences were reported on secondary efficacy measures. Compared to placebo, fluoxetine-treated patients had a significant increase in the bodily pain subscale of the SF-36 (p = 0.05). Significantly more fluoxetine-treated patients had asthenia than placebo-treated patients (p < 0.05).

**Fluvoxamine vs. placebo**

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

**Mirtazapine vs. placebo**

One fair 10-week trial compared mirtazapine to placebo in 114 women with social phobia.168 The primary outcome measure was the change in SPIN score; LSAS and SF-36 scores also were assessed. After 10 weeks, mirtazapine-treated patients were significantly more improved than placebo-treated patients on the SPIN (difference in change = -8.1; p < 0.001), LSAS (difference in change -20.2; p < 0.001), and the SF-36 domains of general health perception, vitality, social functioning, role-emotional, and mental health (p < 0.001 for all). Statistically significant differences were not noted in physical functioning (p = 0.91), role-physical (p = 0.77), and bodily pain (p = 0.53).

**Paroxetine vs. placebo**

FDA-approved evidence supports the general efficacy for paroxetine. In addition to efficacy, four placebo-controlled paroxetine studies evaluated health outcomes.169-172 Two 12-week trials comparing paroxetine (20-50 mg/d) to placebo and one 12-week trial comparing controlled-release paroxetine (12.5-37.5 mg/d) to placebo measured disability.170,171 Compared to patients on placebo, those on immediate-release paroxetine showed significantly greater improvement in
both studies on the social life and work domains of the SDS; family life was statistically better in paroxetine-treated patients in one of the two immediate-release paroxetine trials.\textsuperscript{170} Patients treated with controlled-release paroxetine showed significantly greater improvement than placebo-treated patients in SDS total score, family life, social life, and work domains.\textsuperscript{172}

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

\textit{Sertraline vs. placebo}

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

2. Summary of the evidence

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

\textit{Effectiveness}

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

\textit{Efficacy}

One comparative trial provides fair evidence of comparable efficacy between escitalopram and paroxetine for the treatment of social anxiety disorder.\textsuperscript{160} Two comparative trials provide fair evidence of comparable efficacy between venlafaxine ER and paroxetine.\textsuperscript{159, 161} One meta-analysis of placebo-controlled studies provided fair evidence of comparable efficacies of fluvoxamine, paroxetine, and sertraline for the treatment of social anxiety disorder.\textsuperscript{162} Fourteen
trials provide fair evidence that SSRIs significantly improve health outcomes compared to placebo.\textsuperscript{159-161, 164-167, 169-175}

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

Although no identified study addressed the use of second-generation antidepressants as a prophylactic treatment for social anxiety disorder, two studies evaluated continuation of therapy among responders.\textsuperscript{163, 169} At 24 weeks, escitalopram-treated\textsuperscript{163} and paroxetine-treated patients\textsuperscript{169} were significantly less likely to relapse than placebo-treated patients; 22 percent of escitalopram-treated patients relapsed compared with 50 percent of placebo-treated patients (p < 0.001); 14 percent of paroxetine-treated patients relapsed compared with 39 percent of placebo-treated patients (p < 0.001).
<table>
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<th>Author, Year</th>
<th>Interventions</th>
<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
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<td></td>
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<td></td>
<td></td>
</tr>
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</tr>
<tr>
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<td>Fluvoxamine (CR) vs. Placebo</td>
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<td>Significantly greater efficacy of mirtazapine</td>
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</tr>
<tr>
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<td>187</td>
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<td>Baldwin et al., 1999</td>
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<td>Stein et al., 2002</td>
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</table>

(SR) = Systematic review
III. For adult outpatients with premenstrual dysphoric disorder or late luteal phase dysphoric disorder, do SSRIs or second generation antidepressants differ in efficacy?

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

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

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

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

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

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

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

SSRIs vs. placebo

Only one study reported on efficacy outcomes of non-FDA-approved SSRIs.\(^{176,177}\) This good-quality meta-analysis pooled data from 15 trials comparing various SSRIs to placebo; seven used fluoxetine, five used sertraline, one used citalopram, one used paroxetine, and one used fluvoxamine. The investigators converted data from each trial to standardized mean differences (SMDs) for the proportion of patients who showed improvement in overall premenstrual symptoms; they used a random effects model to estimate pooled efficacy. The pooled SMD favoring SSRI over placebo was -1.066 (95% CI, -1.381, -0.750) equivalent to an odds ratio of 6.91 (95% CI, 3.90, 12.2). However, this meta-analysis also included cross-over studies.\(^{177}\) In the more conservative analysis, which excluded...
five studies with a cross-over design, the authors estimated a smaller SMD of -0.75 (95% CI, -0.98, -0.51).\textsuperscript{176}

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

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

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

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

**Nefazodone vs. placebo**
One fair RCT compared a second-generation antidepressant, specifically both a continuous and intermittent daily dose of nefazodone (100-400 mg/d), to placebo over two menstrual cycles.\textsuperscript{179} This trial did not, however, compare intermittent and continuous therapy to each other. Twenty-two percent of subjects were reported as lost to follow-up in this trial. For both dosing methods, no significant differences were seen between nefazodone and placebo in either patient self-rated global
improvement or any of the individual symptoms assessed (irritability, depressed mood, affect lability, tension, breast tenderness, bloating, and food craving).

4. Summary of the evidence

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

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

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

Continuous Therapy as compared to Intermittent Therapy
We identified one trial examining the efficacy of intermittent (e.g., luteal phase only) sertraline therapy against continuous sertraline therapy.181 Both sertraline groups improved significantly compared to placebo. Premenstrual dosing did not differ in efficacy from continuous dosing. A subgroup analysis in a good meta-analysis reported similar results.177
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
</tr>
</thead>
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<tr>
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</table>

(SR) = Systematic review

* This meta-analysis, from the same authors as the Dimmock et al. meta-analysis, represents a more conservative analysis of the same studies; it excluded 5 of the 15 studies from the main effects calculation because of their use of a cross-over design.
KEY QUESTION 2. Adverse Events

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

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

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

A. Tolerability and Discontinuation Rates

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

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

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

Venlafaxine had a consistently higher rate of nausea and vomiting than SSRIs. In six studies, the difference reached statistical significance. In six additional trials, the higher rates of nausea or vomiting for venlafaxine were not statistically significant. The rate of patients reporting nausea or vomiting ranged from 25 percent to 36 percent. A pooled analysis of published and unpublished trials of duloxetine did not find significant differences in nausea between duloxetine (40-120mg/d) and paroxetine (20mg/d) or between duloxetine (120mg/d) and fluoxetine (20mg/d). Three trials reported a significantly higher rate of dizziness in the venlafaxine group than in the fluoxetine group. Three other studies reported significantly higher rates of diarrhea in sertraline-treated patients than in comparison drugs. In another trial conducted in patients 65
years and older, patients using fluoxetine had significantly more severe adverse events than patients treated with paroxetine.\textsuperscript{29}

A British study pooled data from Prescription-Event-Monitoring (PEM) of general practitioners 6 months to 1 year after they had issued prescriptions.\textsuperscript{184, 185} Included drugs were fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, and nefazodone. The final cohort exceeded 10,000 patients for each drug. Demographics and indications were comparable among study groups. Nausea and vomiting were the two most frequent clinical reasons for withdrawal in the first month of treatment for all drugs. Venlafaxine had the highest rate of nausea and vomiting per 1000 patient months. Like patients using paroxetine, venlafaxine patients also most frequently reported male sexual dysfunction. However, sweating, impotence, and ejaculation failure were significantly higher in the paroxetine group than in the other groups (p = 0.004; p < 0.001). In addition, patients using paroxetine and those using nefazodone most frequently reported drowsiness and sedation. Rate ratios are provided in Evidence Table 10. Sertraline and fluoxetine had significantly lower rate ratios of agitation and anxiety. However, there were more reports of mania during 90 days with fluoxetine than with any other drug. The death and suicide rates did not differ significantly among study groups. Among SSRIs only, drowsiness and sedation were significantly higher in the fluvoxamine and paroxetine group than in the fluoxetine and sertraline group. Overall, the mean incidence density per 1000 patient months for SSRIs was highest for fluvoxamine (fluvoxamine 17.6; fluoxetine 7.0; paroxetine 7.6; sertraline 6.2). Suicide rates did not differ significantly among study groups. Adverse events were reported by physicians rather than patients; the nonresponse rate was 40 percent. Therefore, measurement bias, selection bias, and potential confounding may compromise these results.

Three RCTs were powered primarily to detect differences in adverse events between fluvoxamine and citalopram\textsuperscript{186} and fluvoxamine and paroxetine,\textsuperscript{40} and fluvoxamine and fluoxetine.\textsuperscript{28} A Dutch multicenter trial was designed to assess between-group comparisons of gastrointestinal side effects between citalopram (20-40mg/d) and fluvoxamine (100-200mg/d).\textsuperscript{186} A total of 217 patients were enrolled for 6 weeks. Overall, 57 percent of patients reported adverse events. Significantly more patients in the fluvoxamine group had an excess incidence of diarrhea (+13%; p = 0.026) or nausea (+16%; p = 0.017). However, the authors did not provide a baseline comparison of gastrointestinal illnesses between groups. Differences at baseline could bias results.

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

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

A meta-analysis of 15 RCTs did not find any statistically significant differences in discontinuation rates because of adverse events between fluoxetine and other SSRIs as a class.\textsuperscript{187}

A fair-rated, Dutch prospective observational study followed 1,251 patients for up to 12 months to assess adverse events of sertraline (n = 659) compared to other SSRIs (fluoxetine, fluvoxamine, paroxetine).\textsuperscript{188} No exclusion criteria were applied. Psychiatrists recorded adverse events at each patient visit. The WHO adverse reaction terminology was used for outcome assessment. Significantly
more sertraline patients had the diagnosis of depressive disorder at baseline ($p < 0.001$). Overall, 74.1 percent of patients reported at least one adverse event. Diarrhea occurred more frequently in the sertraline group than in the other SSRI groups ($p < 0.05$). However, abdominal pain was reported more frequently by other SSRI users than sertraline users ($p < 0.05$). No other adverse event differed significantly across groups.

We conducted meta-analyses to assess differences in the overall loss to follow-up, the discontinuation rates because of adverse events, and the discontinuation rates because of lack of efficacy of SSRIs as a class compared to some other second-generation antidepressants (bupropion, mirtazapine, and venlafaxine) in adult outpatients with MDD (Exhibit 6). Available data were insufficient to determine results for duloxetine and nefazodone. The only statistically significant difference in pooled estimates was a higher discontinuation rate because of adverse events for venlafaxine-treated patients than for patients on SSRIs (RR: 1.36; 95% CI 1.04-1.77). Overall, this finding was balanced by lower discontinuation rates because of lack of efficacy for venlafaxine (RR: 0.69; 95% CI 0.47-0.99). Overall discontinuation rates did not differ significantly between venlafaxine and SSRIs (RR: 1.06; 95% CI 0.93-1.22). No significant differences could be detected between SSRIs and mirtazapine or between SSRIs and bupropion. Numerical differences in discontinuation rates attributed to adverse events generally favored SSRIs over mirtazapine and bupropion but did not reach statistical significance. Because of heterogeneity we did not pool data of discontinuation rates related to adverse events when comparing SSRIs to mirtazapine and SSRIs to bupropion.
Table 18: Mean incidence of specific adverse events

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

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

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

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

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

A meta-analysis limited the CSM data to placebo-controlled trials of SSRIs in adults. Results did not yield any evidence that SSRIs increase or protect against the risk of suicide (OR 0.85; 95% CI 0.20 to 3.40).\(^{189}\) However, weak evidence of an increased risk of self-harm was detected (OR 1.57; 95% CI 0.99 to 2.55).

In addition, the Expert Group commissioned an observational study (a nested case-control study) using the General Practice Research Database (GPRD) to investigate the association between antidepressants and self-harm based on data on more than 146,000 patients with a first prescription of an antidepressant for depression.\(^{190}\) This study did not find any evidence that the risk of suicide (OR 0.57; 95% CI 0.26 to 1.25) or self-harm (OR 0.99; 95% CI 0.86 to 1.14) is greater in patients on second-generation antidepressants than in patients on TCAs. In patients younger than 18 years, however, the risk of self-harm was significantly greater in patients on SSRIs than on TCAs (OR 1.59; 95% CI 1.01 to 2.50). Although no statistically significant differences among SSRIs were detected, the greatest risk of self-harm was among paroxetine users.

Findings of other studies are mixed. A recent, good meta-analysis of published data on more than 87,000 patients in SSRI trials for various conditions reported a significantly higher risk of suicide attempts for SSRI patients than for placebo-treated patients (2.25; 95% CI 1.14 to 4.55).\(^{191}\) Furthermore, an increase in the odds ratio of suicide attempts was observed for SSRIs compared to interventions other than TCAs (OR 1.94; 95% CI 1.06 to 3.57). No significant difference existed in the pooled analysis of SSRIs compared to TCAs (OR 0.88; 95% CI 0.54 to 1.42).
Findings of the CSM Expert Group on suicidality in children are consistent with results from an earlier NICE (National Institute for Clinical Excellence) report. Results of other studies on suicidality in adults are mixed. Included studies are presented in Table 19 and described below.

A fair-rated open cohort study using UK data observed 172,598 people to compare the suicide rates of 10 commonly used antidepressants (fluoxetine, dothiepin, amitriptyline, clomipramine, imipramine, flupenthixol, lofepramine, mianserin, doxepin, and trazodone) for 5 years. 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. A total of 555 cases of nonfatal suicidal behavior were matched with 2,062 controls. Compared to dothiepin, the risk of suicidal behavior was similar among users of amitryptilin (RR: 0.83; 95% CI 0.61 to 1.13), fluoxetine (RR 1.16; 95% CI 0.90 to 1.50), and paroxetine (RR: 1.29; 95% CI 0.97 to 1.70).

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

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) in 308 study completers with MDD. Outcome assessment was conducted at baseline and at week 24. Citalopram and sertraline did not differ significantly in the magnitude and frequency of sexual side effects. Only one patient was lost to follow-up attributable to sexual side effects in this study. Similarly, citalopram did not differ from paroxetine in sexual side effects in a nonrandomized trial.

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

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

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

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

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

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

Sexual side effects were also commonly reported adverse event for SSRIs and SNRIs in efficacy trials. Most of these studies did not report the use of targeted questions for sexual side effects. Therefore, patient-reported numbers might not reflect the true incidence. Paroxetine- and sertraline-treated patients frequently reported significantly higher rates of sexual side effects than did...
patients in the active control groups. In one trial, significantly more patients on sertraline withdrew because of sexual side effects than did patients on bupropion (3.3% vs. 13.5%; p = 0.004).72

3. Changes in weight
A 32-week acute and continuation trial assessed differences in weight changes among patients treated with fluoxetine, paroxetine, and sertraline.82 Paroxetine patients showed a significantly greater mean weight change (+3.6%) than did those taking fluoxetine (-0.2%; p = 0.015) and sertraline (+1.0%; p < 0.001). Significantly more patients in the paroxetine group (25.5%) had a weight gain of more than 7 percent than in the fluoxetine (6.8%; p = 0.016) and sertraline groups (4.2%; p = 0.003). A 1-year, placebo-controlled continuation trial of fluoxetine reported similar findings.34 Initially, fluoxetine treatment led to a modest weight loss; from week 12 to week 50, however, a significant weight gain compared to placebo was reported (+3.1kg; p < 0.001). An open-label, nonrandomized, 2.5-year study on OCD patients also reported the lowest increase in weight gain for fluoxetine (+0.5 kg). Other SSRIs lead to greater weight gains (sertraline +1.0 kg; citalopram +1.5 kg; paroxetine +1.7 kg; fluvoxamine +1.7 kg), however, differences are neither statistically nor clinically significant.201

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

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

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

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

A post-hoc analysis of six RCTs (published and unpublished) comparing duloxetine to fluoxetine and paroxetine did not find any statistically significant differences in supine systolic or diastolic blood
Duloxetine treated patients had a greater mean change in heart rates than fluoxetine- (+2.8beats/min. vs. -1.0 beat/min.) and paroxetine-treated patients (+1.0 beats/min. vs. -1.4 beats/min.)

6. Hyponatremia
Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of hyponatremia in patients treated with SSRIs. However, the methods of our report did not include case reports and case series. The published literature includes numerous case reports of hyponatremia and inappropriate secretion of antidiuretic hormone as rare side effects.208 Even if this evidence is considered weak, it could be important in the absence of studies with the methodological strength to account for rare adverse events.

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

C. Summary of the evidence
Fair to good evidence from multiple randomized controlled head-to-head trials and retrospective data analyses of prescription event monitoring documents that side-effects profiles differ significantly among reviewed drugs. Venlafaxine had a significantly higher rate of nausea and vomiting in multiple trials; paroxetine frequently led to higher sexual side effects; mirtazapine to higher weight gains; and sertraline to a higher rate of diarrhea than comparable second-generation antidepressants. A retrospective review of prescription event monitoring data provides fair evidence that, among SSRIs, fluvoxamine has the highest mean incidence of adverse events.184 Pooled estimates from efficacy trials suggest that venlafaxine has a statistically significantly higher rate of discontinuation because of adverse events than do SSRIs as a class (RR 1.34; 95% CI 1.00 to 1.80). However, overall discontinuation rates do not differ significantly between venlafaxine and SSRIs.

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

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

A cross-sectional survey supports this evidence by reporting the lowest rates of sexual side effects for bupropion and nefazodone in patients treated with SSRIs or other second-generation antidepressants.200 Multiple trials give fair evidence that paroxetine, sertraline, and mirtazapine tend
to have higher rates of sexual side effects than other second-generation antidepressants.\textsuperscript{33, 34, 41, 42, 50, 72, 80, 200}

\textit{Weight changes}

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

\textit{Cardiovascular adverse events}

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

\textit{Other adverse events}

A database analysis in the UK on fatal toxicity of second generation antidepressants found vanlafaxine to have the highest fatal toxicity rate (13.2/1,000,000 prescription) among second generation antidepressants.\textsuperscript{210}

A case-control study did not find an association between SSRIs and breast cancer.\textsuperscript{164} Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the risk of rare but potentially fatal adverse events such as hyponatremia or liver toxicity. However, multiple case reports have indicated that many of the SSRIs are associated with hyponatremia, especially in older patients.\textsuperscript{208} Similarly, reports of liver toxicity with nefazodone have not been confirmed by controlled trials and observational studies.\textsuperscript{209} Owing to a lack of studies with the methodological strength to assess these rare events, conclusions should be made on other grounds such as comorbidities, taking case reports into consideration.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brambilla et al., 2005^{187}</td>
<td>Fluoxetine vs. SSRIs (SR)</td>
<td>NR</td>
<td>No difference in discontinuation rates because of adverse events</td>
<td>Good</td>
</tr>
<tr>
<td>Greist et al. 2004^{193}</td>
<td>Pooled analysis: Duloxetine vs. Paroxetine vs. Fluoxetine</td>
<td>2345</td>
<td>No differences in nausea between duloxetine and paroxetine, and duloxetine and fluoxetine</td>
<td>N/A</td>
</tr>
<tr>
<td>Haffmans et al, 1996^{186}</td>
<td>Fluvoxamine vs. Paroxetine</td>
<td>217</td>
<td>Significantly more diarrhea and nausea with fluvoxamine</td>
<td>Fair</td>
</tr>
<tr>
<td>Kiev et al., 1997^{40}</td>
<td>Fluvoxamine vs. Paroxetine</td>
<td>60</td>
<td>Significantly more sweating with paroxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Mackay et al., 1997, 1999^{184, 185}</td>
<td>Prescription Event Monitoring</td>
<td>≥ 60,000</td>
<td>Venlafaxine had highest rate of nausea and vomiting; paroxetine highest rate of sexual side effects; among SSRIs, most overall adverse events with fluvoxamine</td>
<td>N/A</td>
</tr>
<tr>
<td>Meijer et al., 2002^{188}</td>
<td>Sertraline vs. SSRIs (OS)</td>
<td>1251</td>
<td>Significantly more diarrhea with sertraline</td>
<td>Fair</td>
</tr>
<tr>
<td>Rapaport et al., 1996^{28}</td>
<td>Fluvoxamine vs. Fluoxetine</td>
<td>100</td>
<td>Significantly more nausea with fluoxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Didham et al. 2005^{195}</td>
<td>SSRIs</td>
<td>57,000</td>
<td>No difference in suicides or self-harm among citalopram, fluoxetine, and paroxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Fergusson et al., 2005^{191}</td>
<td>SSRIs vs. placebo (SR)</td>
<td>87,650</td>
<td>Higher risk of suicide attempts for SSRI-treated patients</td>
<td>Good</td>
</tr>
<tr>
<td>Gunnell et al., 2005^{189}</td>
<td>2nd gen. AD vs. placebo (SR)</td>
<td>40,000</td>
<td>No differences in adults</td>
<td>Good</td>
</tr>
<tr>
<td>Jick et al., 2004^{211}</td>
<td>Case-control; database review</td>
<td>159,810</td>
<td>No differences</td>
<td>N/A</td>
</tr>
<tr>
<td>Jick et al., 1995^{192}</td>
<td>Open cohort; database review</td>
<td>172,598</td>
<td>Significantly higher risk of suicide with fluoxetine and mianserin compared to dothiepin</td>
<td>N/A</td>
</tr>
<tr>
<td>Khan et al., 2003^{184}</td>
<td>Data review</td>
<td>NR</td>
<td>No differences</td>
<td>N/A</td>
</tr>
<tr>
<td>Lopez-Ibor 1993^{13}</td>
<td>Database review</td>
<td>4686</td>
<td>No differences</td>
<td>N/A</td>
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<tr>
<td>Martinez et al., 2005^{190}</td>
<td>Database review</td>
<td>146,095</td>
<td>No differences</td>
<td>N/A</td>
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<tr>
<td>Pederson et al., 2005^{212}</td>
<td>Retrospective cohort study</td>
<td>4091</td>
<td>Higher rate of self-harm in escitalopram than in placebo</td>
<td>Fair</td>
</tr>
<tr>
<td>Nieuwstraten et al, 2001^{67}</td>
<td>Bupropion vs. SSRIs (SR)</td>
<td>1332</td>
<td>Significantly higher rate of sexual satisfaction in bupropion group</td>
<td>Good</td>
</tr>
<tr>
<td>Clayton et al., 2002^{200}</td>
<td>Cross-sectional survey</td>
<td>6297</td>
<td>Highest risk for paroxetine and mirtazapine; lowest risk for bupropion</td>
<td>N/A</td>
</tr>
<tr>
<td>Coleman et al., 2001^{69}</td>
<td>Bupropion vs. Fluoxetine</td>
<td>456</td>
<td>Significantly more sexual adverse events with fluoxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Coleman et al., 1999^{74}</td>
<td>Bupropion vs. Sertraline</td>
<td>364</td>
<td>Significantly more sexual adverse events with sertraline</td>
<td>Fair</td>
</tr>
<tr>
<td>Croft et al., 1999^{72}</td>
<td>Bupropion vs. Sertraline</td>
<td>360</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Ekselius et al., 2001^{157}</td>
<td>Citalopram vs. Sertraline</td>
<td>308</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Landen et al. 2005^{188}</td>
<td>Citalopram vs. Paroxetine</td>
<td>119</td>
<td>No differences</td>
<td>Good</td>
</tr>
<tr>
<td>Segraves et al., 2000^{85}</td>
<td>Bupropion vs. Sertraline</td>
<td>248</td>
<td>Significantly more sexual adverse events with sertraline</td>
<td>Fair</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>Event</td>
<td>Rating</td>
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<tr>
<td>Montejo et al., 2001&lt;sup&gt;196&lt;/sup&gt;</td>
<td>Prospective cohort study</td>
<td>1022</td>
<td>Highest incidence of sexual dysfunction for citalopram, paroxetine and venlafaxine; lowest for mirtazapine and nefazodone</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Changes in Weight</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Maina et al. 2004&lt;sup&gt;401&lt;/sup&gt;</td>
<td>Open-label SSRIs</td>
<td>149</td>
<td>Highest weight gain with paroxetine, fluvoxamine, and citalopram</td>
<td>Fair</td>
</tr>
<tr>
<td>Fava et al., 2000&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Fluoxetine vs. Paroxetine vs. Sertraline</td>
<td>284</td>
<td>Highest weight gain with paroxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Benkert et al., 2000&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Mirtazapine vs. Paroxetine</td>
<td>275</td>
<td>Significant weight gain with mirtazapine</td>
<td>Fair</td>
</tr>
<tr>
<td>Schatzberg et al., 2002&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Mirtazapine vs. Paroxetine</td>
<td>255</td>
<td>Significant weight gain with mirtazapine</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Cardiovascular Events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thase et al., 1998&lt;sup&gt;206&lt;/sup&gt;</td>
<td>Post hoc analysis</td>
<td>3744</td>
<td>Significantly higher diastolic blood pressure for venlafaxine</td>
<td>N/A</td>
</tr>
<tr>
<td>Thase et al. 2005&lt;sup&gt;207&lt;/sup&gt;</td>
<td>Post hoc analysis</td>
<td>1873</td>
<td>Greater change in heart rate for duloxetine than for fluoxetine and paroxetine</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Other Adverse Events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buckley et al., 2005&lt;sup&gt;210&lt;/sup&gt;</td>
<td>Database analysis</td>
<td>47,329</td>
<td>Highest rate of fatal toxicity for venlafaxine</td>
<td>N/A</td>
</tr>
<tr>
<td>Coogan et al., 2005&lt;sup&gt;213&lt;/sup&gt;</td>
<td>Case-control</td>
<td>4996</td>
<td>No association between breast cancer and SSRIs</td>
<td>Fair</td>
</tr>
<tr>
<td>Dunner et al., 1998&lt;sup&gt;204&lt;/sup&gt;</td>
<td>Prospective observational</td>
<td>3100</td>
<td>Rate of seizures for bupropion within range of other antidepressants</td>
<td>Fair</td>
</tr>
<tr>
<td>Johnston et al., 1991&lt;sup&gt;203&lt;/sup&gt;</td>
<td>Prospective observational</td>
<td>3341</td>
<td>Rate of seizures for bupropion within range of other antidepressants</td>
<td>N/A</td>
</tr>
<tr>
<td>Whyte et al., 2003&lt;sup&gt;205&lt;/sup&gt;</td>
<td>Prospective observational</td>
<td>538</td>
<td>Seizures more common in venlafaxine overdose than TCA or SSRI overdose</td>
<td>Good</td>
</tr>
</tbody>
</table>

(SR)= Systematic review
(OS)= Observational study
KEY QUESTION 3. Subgroups

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

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

A. Demographics

1. Age

SSRIs as a class
A pooled data data-analysis of trials comparing venlafaxine to SSRIs reported that older women responded poorer to SSRI-treatment than younger women. This difference could not be observed in men.\(^{214}\)

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

The second trial conducted in an elderly population enrolled 108 patients with major depression in Austria and Germany for 6 weeks using the same dosage as the Italian study.\(^{32}\) Loss to follow-up was not reported. An intention-to-treat analysis revealed no differences between the treatment groups in changes of scores on MADRS and HAM-D; the paroxetine group had significantly more responders at 6 weeks on MADRS and HAM-D scales (37.5% vs. 17.5%; \(p = 0.04\)). Patients on paroxetine also had significantly better MMSE and SCAG scores assessing cognitive function at Week 3 than did those on fluoxetine. No statistically significant differences in adverse events were reported.

A post hoc analysis of two placebo controlled trials of duloxetine reported that no differences in efficacy could be detected in women across different age groups.\(^{215}\)
**Fluoxetine vs. sertraline**

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

A subgroup analysis of a long-term effectiveness trial comparing fluoxetine, paroxetine, and sertraline reports similar response and remission rates for patients older than 65 years and the general study population.\(^{19}\)

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

**Paroxetine vs. placebo vs. behavioral therapy**

A large, fair, primary-care-based study randomized 656 patients with dysthymia or minor depression to eleven weeks of paroxetine (10-40mg), placebo, or behavioral therapy.\(^{90,91}\) Participants were stratified into patients 60 years and older (n = 415) and patients younger than 60 years (n = 241) for intention-to-treat analysis. Loss to follow-up was not reported for either subgroup. In the older subgroup, paroxetine-treated patients showed a greater change in HSCL-D 20 (Hopkins Symptom Checklist) scores than placebo-treated patients (p = 0.004) but not more than patients on behavioral therapy (p = 0.17). For older dysthymia patients with high or intermediate baseline functioning scores, paroxetine improved mental health functioning significantly compared to placebo. Overall, however, improvements for paroxetine-treated dysthymia patients were not statistically significant different from those on placebo. The younger subgroup did not show statistically significant differences between treatment groups on the HSCL-D scale. For dysthymia only, the remission rate was significantly higher in the paroxetine group than in the placebo group (80% vs. 40%; p = 0.008).

Another fair trial randomized 323 patients older than 60 years with MDD to paroxetine IR, paroxetine CR, or placebo.\(^{217}\) Study duration was 12 weeks. Both active agents presented significantly higher rates of response and remission than placebo. However, no significant differences between paroxetine IR and paroxetine CR were apparent for any primary outcomes measures (HAM-D, CGI-I) or adverse events.
**Mirtazapine vs. paroxetine**
A fair trial randomized 255 elderly participants for eight weeks. Loss to follow-up was 27 percent. Mirtazapine and paroxetine were equally effective in reducing HAM-D scores at the endpoint, but mirtazapine lead to a faster response. A Kaplan-Meier analysis showed a significantly faster time to response for mirtazapine (mean 26 days versus mean 40 days for paroxetine; p = 0.016). No significant difference in response rates on the CGI scale was noted. Significantly more mirtazapine-treated patients reported weight gain (p < 0.05). Paroxetine-treated patients reported a significantly higher rate of nausea, tremor, and flatulence (p < 0.05).

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

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

**Bupropion vs. paroxetine**
One fair RCT examined the efficacy of bupropion SR (100-300 mg/d) and paroxetine (10-40mg/d) in 100 outpatients ages 60 years or older (range 60-88 years) over 6 weeks. The majority of patients were white (bupropion SR, 98%; paroxetine, 90%), female (bupropion SR, 54%; paroxetine, 60%), and did not use antidepressants for the current episode before enrollment (bupropion SR, 83%; paroxetine, 88%). Statistical analysis used a LOCF method. The overall loss to follow-up was 16 percent with no significant difference between treatment groups. Efficacy according to any outcome measure did not differ significantly between treatment groups. Response rates (≥ 50% reduction in HAM-D scores) were similar in both groups (bupropion SR, 71%; paroxetine, 77%). Quality-of-life scales (QLDS, SF-36) showed statistically significant improvements in both treatment groups from baseline to endpoint (p < 0.0001), but they did not differ significantly between treatment groups.

A meta-analysis combined original data from eight comparable, double-blind, active-controlled, randomized trials. A primary objective of this meta-analysis was to determine differences in response and remission based on sex and age. Analysis of the pooled data showed that neither age nor sex influenced the efficacy measures (p > 0.05); no significant interaction terms emerged for age by treatment, sex by treatment, or age by sex by treatment (all p values > 0.1).
We did not identify any head-to-head trials that compare one second-generation antidepressant to another in children and adolescents. There is FDA-approved evidence for the efficacy of fluoxetine and fair evidence from a pooled analysis of two placebo-controlled trials for the efficacy of sertraline. Existing evidence does not support the efficacy of other second-generation antidepressants. Additional evidence suggests that sertraline may not be as efficacious as reported in previous reports. Based on a systematic review of published and unpublished studies comparing second-generation antidepressant to placebo, only fluoxetine was shown to be safe and effective in the treatment of MDD in children and adolescents. This review reported an increased risk of suicidal thoughts and behavior for citalopram, paroxetine, sertraline, and venlafaxine, but not for fluoxetine.

2. Ethnicity

**Paroxetine versus placebo**

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

**Fluoxetine versus placebo**

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

3. Sex

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

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

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

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

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

Clinical relevance of drug-drug interactions can be classified in three ways. The most severe type of drug interaction is usually referred to as a contraindication. A *contraindicated* medication should not be given unless required by extreme circumstances. Many drug interactions may be clinically relevant but not preclude combined use of the two medications. Instead, clinicians should acknowledge the interaction, adjust doses appropriately, and *monitor* for toxic or subtherapeutic effects. A third type of interaction is one that, although it may occur, is *not clinically significant.*
Because only limited evidence supports drug interactions among the second-generation antidepressants, our review focuses on the potential for drug interactions. In addition to published literature cited previously, we reviewed dossiers submitted by pharmaceutical companies, FDA approved labeling, and interactions reported by major reference sources. Information compiled in this search does not follow a systematic process but is provided as a summary of the evidence for drug interactions. Appendix D summarizes second-generation antidepressant pharmacokinetic properties known to be related to drug interactions. Tables in Appendix D report evidence provided in the product labeling (package insert). Some interactions are inferred based on reports of enzyme induction or inhibition. Clinical significance of the interactions are referenced as contraindicated, requires monitoring, or no significant interaction.

C. Comorbidities

Fluoxetine versus paroxetine

A retrospective evaluation of 89 patients from two trials comparing fluoxetine (20-80mg/d) to paroxetine (20-50mg/d) determined whether depressed, somatizing patients with a gastrointestinal (GI) component have a higher degree of GI side effects than nonsomatizing depressed participants. 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). Outcome measures included changes on HAM-D and BDI and in alcohol consumption. Results of the acute phase trial showed significantly greater improvements of depressive symptoms for fluoxetine-treated patients (p < 0.05) on HAM-D but not on BDI. During the 1-year open-label follow-up, HAM-D scores remained significantly lower for the fluoxetine group than for the placebo group. However, no additional improvement during the follow-up treatment was reported. A subgroup analysis showed that depressed alcoholics who were cocaine abusers (n = 17) had a significantly worse outcome than depressed alcoholics who were not (n = 34). Cocaine abusers showed significantly worse outcomes on both the HAM-D (p = 0.17) and the BDI (p = 0.001).

Another fair placebo-controlled study investigated the efficacy of fluoxetine (40mg/d) in 68 cocaine-dependent patients with MDD. 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. The majority of patients were male (97.3%) and white (65%). Loss to follow-up was 27.5 percent. The main outcome measures were response to treatment defined as a 50 percent improvement on the HAM-D scale, a score lower than 8, and a CGI score of 1 or 2. According to these criteria, the rate of response
did not differ significantly between treatment groups (fluoxetine 57%, placebo 41%). Using the HAM-D scale alone as a criterion, the investigators reported a significantly greater response rate for fluoxetine-treated patients (79% vs. 57%; \( p = 0.03 \)). The treatment groups did not differ significantly in adverse events.

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

A fair, small RCT assessed the efficacy and tolerability of fluoxetine treatment (20-60mg/d) compared to placebo in 44 methadone-maintained opioid addicts.\(^{234}\) Study duration was 3 months; loss to follow-up was 15.9 percent. Both groups had significantly decreased scores on BDI and HADRS (\( z = 2.37; p = 0.01 \)). Efficacy did not differ significantly between placebo and fluoxetine treatment. However, the sample size was small and the study is likely to be underpowered (no power calculations were reported).

**Paroxetine versus placebo**

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

**Sertraline vs. Placebo**

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

**D. Summary of the Evidence**
Age

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

Eight studies provide fair to good indirect evidence that efficacy and tolerability for patients older than 60 years and those younger do not differ.\textsuperscript{29, 37, 39, 48, 51, 70, 71, 91, 215, 218} Results of these studies, all conducted in patients with MDD or dysthymia, are generally consistent with results of trials conducted in younger populations. Only one small study reported a higher efficacy of paroxetine than fluoxetine in patients older than 60 years.\textsuperscript{32} However, this trial was small and the results are inconsistent with better evidence. Another small study, rated poor for efficacy outcomes, reported a significantly higher loss to follow-up because of adverse events in venlafaxine-treated, frail elderly patients than in sertraline-treated participants.\textsuperscript{218}

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

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

Ethnicity

Fair evidence from a pooled data study on paroxetine\textsuperscript{220} and a single RCT on fluoxetine\textsuperscript{221} suggest that response rates, loss to follow-up, and response to placebo treatment might differ between groups of different ethnic background. Hispanics tend to have lower response rates than Blacks and Whites.

Sex

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

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

**Comorbidities**

No prospective study directly compared the efficacy and tolerability of SSRIs, SNRIs, and other second-generation antidepressants in a population with a specific comorbid condition to a population without that same condition. Two retrospective data analyses provide fair evidence that efficacy does not differ between patients with vascular disease and somatizing depressions and patients without these co-morbidities.\(^{227,236}\) Various other trials conducted in populations with different comorbidities can provide indirect evidence.\(^{228-230,232-235}\) Two placebo-controlled trials provided fair evidence that treatment effects do not differ between placebo and fluoxetine in methadone-maintained opioid addicts or depressed cancer patients.\(^{233,234}\) Two different trials reported fair evidence that response rates for fluoxetine-treated alcoholics and depressed HIV patients are significantly higher than for placebo-treated subjects.\(^{228-230,232}\) A placebo controlled RCT in depressed breast cancer patients reported greater efficacy of paroxetine than placebo in reducing depression but no differences with respect to fatigue.\(^{235}\)
Table 20: Included Studies for Subgroups

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>N</th>
<th>Results</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burt et al. 2005</td>
<td>Duloxetine vs. placebo</td>
<td>117</td>
<td>No difference</td>
<td>N/A</td>
</tr>
<tr>
<td>Cassano et al., 2002</td>
<td>Fluoxetine vs. Paroxetine</td>
<td>242</td>
<td>Faster onset of paroxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Cassano et al., 2004</td>
<td>Fluoxetine</td>
<td>384</td>
<td>No differences in age groups</td>
<td>Fair</td>
</tr>
<tr>
<td>Schone et al., 1993</td>
<td>Fluoxetine vs. Paroxetine</td>
<td>108</td>
<td>Faster onset of paroxetine</td>
<td>Fair</td>
</tr>
<tr>
<td>Newhouse et al., 2000</td>
<td>Fluoxetine vs. Sertraline</td>
<td>236</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Kroenke et al., 2001</td>
<td>Fluoxetine vs. Sertraline vs. Paroxetine</td>
<td>601</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Rapaport et al., 2003</td>
<td>Paroxetine vs. Placebo</td>
<td>323</td>
<td>Significantly more responders and remitters for paroxetine IR and paroxetine CR than for placebo</td>
<td>Fair</td>
</tr>
<tr>
<td>Williams et al., 2000</td>
<td>Paroxetine vs. Placebo</td>
<td>415</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Wagner et al., 2003</td>
<td>Sertraline vs. Placebo</td>
<td>376</td>
<td>Significantly greater efficacy for sertraline</td>
<td>Fair</td>
</tr>
<tr>
<td>Schatzberg et al., 2002</td>
<td>Mirtazapine vs. Paroxetine</td>
<td>255</td>
<td>Faster onset of mirtazapine</td>
<td>Fair</td>
</tr>
<tr>
<td>Allard et al. 2004</td>
<td>Venlafaxine vs. citalopram</td>
<td>151</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Thase et al. 2005</td>
<td>Pooled data analysis of venlafaxine and SSRIs</td>
<td>2045</td>
<td>Among women, poorer response to SSRIs in the older age group</td>
<td>Fair</td>
</tr>
<tr>
<td>Weihs et al., 2000</td>
<td>Bupropion SR vs. Paroxetine</td>
<td>100</td>
<td>No differences</td>
<td>Fair</td>
</tr>
<tr>
<td>Doraiswamy et al., 2004</td>
<td>Meta-analysis</td>
<td>2,045</td>
<td>No significant interaction between age and treatment</td>
<td>Fair</td>
</tr>
<tr>
<td>Entsuah et al., 2001</td>
<td>Meta-analysis</td>
<td>2,145</td>
<td>Only fluoxetine had favorable risk-benefit profile</td>
<td>Fair</td>
</tr>
<tr>
<td>Whittington et al., 2004</td>
<td>Meta-analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roy-Byrne et al., 2005</td>
<td>Pooled analysis of paroxetine vs. placebo</td>
<td>14,875</td>
<td>Slightly lower response rates for Hispanics and Asians than for Blacks and Whites</td>
<td>Fair</td>
</tr>
<tr>
<td>Wagner et al., 1998</td>
<td>Fluoxetine vs. Placebo</td>
<td>118</td>
<td>Ethnicity was not associated with side effects; whites had a higher response rate, Latinos a higher drop-out rate</td>
<td>Poor</td>
</tr>
<tr>
<td>Clayton et al., 2005</td>
<td>Pooled data analysis of sertraline vs. placebo</td>
<td>673</td>
<td>Better response of female patients on some outcome measures</td>
<td>Fair</td>
</tr>
<tr>
<td>Entsuah et al., 2001</td>
<td>Meta-analysis</td>
<td>2,045</td>
<td>No significant interaction between sex and treatment</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Table 20 (continued)

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Sample</th>
<th>Mean Age</th>
<th>Women</th>
<th>Duration</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linden et al., 1994[227] Fluoxetine vs. Paroxetine</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>No difference in GI-side effects in somatizing patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significantly greater efficacy for fluoxetine in depressed alcoholics patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabkin et al, 1999[232] Fluoxetine vs. Placebo</td>
<td>120</td>
<td></td>
<td></td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>No difference in depressed HIV/AIDS patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No difference in depressed cancer patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roscoe et al. 2005[234] Paroxetine vs. Placebo</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td>Greater efficacy for paroxetine in depressed patients with breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petrakis et al., 1996[235] Fluoxetine vs. Placebo</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>No difference in depressed opioid addicts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krishnan et al., 2001[236] Sertraline vs. Placebo</td>
<td>220</td>
<td></td>
<td></td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>Vascular comorbidity not associated with more adverse events and premature discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Characteristics of included studies

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean Age</th>
<th>Women</th>
<th>Duration</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke et al., 2002[21]</td>
<td>491</td>
<td>40.1</td>
<td>65%</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Colonna et al., 2005[22]</td>
<td>357</td>
<td>46</td>
<td>75%</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Lepola et al., 2003[20]</td>
<td>471</td>
<td>43</td>
<td>72.1%</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Moore et al., 2005[21]</td>
<td>280</td>
<td>45.2</td>
<td>76.9%</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

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

Characteristics of included studies

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean Age</th>
<th>Women</th>
<th>Duration</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke et al., 2002[21]</td>
<td>491</td>
<td>40.1</td>
<td>65%</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Colonna et al., 2005[22]</td>
<td>357</td>
<td>46</td>
<td>75%</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Lepola et al., 2003[20]</td>
<td>471</td>
<td>43</td>
<td>72.1%</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Moore et al., 2005[21]</td>
<td>280</td>
<td>45.2</td>
<td>76.9%</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>
Exhibit 3: Meta-analysis - Fluoxetine -Paroxetine

### Characteristics of included studies

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean Age</th>
<th>Women</th>
<th>Duration</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chouinard et al., 1999&lt;sup&gt;30&lt;/sup&gt;</td>
<td>203</td>
<td>40.9</td>
<td>61%</td>
<td>12 weeks</td>
</tr>
<tr>
<td>De Wilde et al., 1993&lt;sup&gt;31&lt;/sup&gt;</td>
<td>78</td>
<td>44.0</td>
<td>61%</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Fava et al., 1998&lt;sup&gt;33&lt;/sup&gt;</td>
<td>128</td>
<td>41.3</td>
<td>51%</td>
<td>10-16 weeks</td>
</tr>
<tr>
<td>Fava et al., 2002&lt;sup&gt;34&lt;/sup&gt;</td>
<td>188</td>
<td>42.0</td>
<td>65%</td>
<td>10-16 weeks</td>
</tr>
<tr>
<td>Gagiano 1993&lt;sup&gt;34&lt;/sup&gt;</td>
<td>90</td>
<td>38.7</td>
<td>80%</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Schöne et al., 1993&lt;sup&gt;32&lt;/sup&gt;</td>
<td>108</td>
<td>74.0</td>
<td>87%</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

### Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean Age</th>
<th>Women</th>
<th>Duration</th>
<th>Scale</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cassano et al. 2002&lt;sup&gt;29&lt;/sup&gt;</td>
<td>242</td>
<td>75.3</td>
<td>55%</td>
<td>52 weeks</td>
<td>HAM-D</td>
</tr>
</tbody>
</table>

---

Second Generation Antidepressants
Final Report Update 3
Drug Effectiveness Review Project
Page 93 of 534
Exhibit 4: Meta-analysis- Fluoxetine - Sertraline

Characteristics of included studies

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean Age</th>
<th>Women</th>
<th>Duration</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennie et al., 1999</td>
<td>286</td>
<td>49.9</td>
<td>61%</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Boyer et al., 1998</td>
<td>242</td>
<td>43.4</td>
<td>78%</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Fava et al., 2002</td>
<td>188</td>
<td>42.0</td>
<td>65%</td>
<td>10-16 weeks</td>
</tr>
<tr>
<td>Newhouse et al., 2000</td>
<td>236</td>
<td>67.5</td>
<td>57%</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Sechter et al., 1999</td>
<td>238</td>
<td>42.8</td>
<td>67%</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean Age</th>
<th>Women</th>
<th>Duration</th>
<th>Scale</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kroenke et al., 2001</td>
<td>601</td>
<td>46.1</td>
<td>74%</td>
<td>9 months</td>
<td>SF-36</td>
</tr>
</tbody>
</table>

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

Estimates with 95% confidence intervals:

- Odds ratio of event in treated cf. controls = 1.288143 (1.013664 to 1.637123)
- Relative risk reduction (controls-treated) = -0.105572 (-0.213335 to -0.008186)
- Risk difference (controls-treated) = -0.060504 (-0.115759 to -0.004894)
- NNT [risk difference] (rounded up) = 17
Exhibit 5: Meta-analysis- of Venlafaxine - Fluoxetine

Characteristics of included studies

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean Age</th>
<th>Women</th>
<th>Duration</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alves et al., 1999</td>
<td>87</td>
<td>43.8</td>
<td>92%</td>
<td>12 weeks</td>
</tr>
<tr>
<td>De Nayer et al., 2002</td>
<td>146</td>
<td>42.7</td>
<td>68%</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Dierick et al., 1996</td>
<td>314</td>
<td>43.4</td>
<td>64%</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Rudolph et al., 1999</td>
<td>301</td>
<td>40</td>
<td>69%</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Silverstone et al., 1999</td>
<td>378</td>
<td>41.9</td>
<td>60%</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Tylee et al., 1997</td>
<td>341</td>
<td>44.5</td>
<td>71%</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Mean Age</th>
<th>Women</th>
<th>Duration</th>
<th>Scale</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costa e Silva et al., 1998</td>
<td>382</td>
<td>40.1</td>
<td>53%</td>
<td>8 weeks</td>
<td>HAM-D</td>
</tr>
</tbody>
</table>

Number needed to treat (empirical results using observed counts only)
Estimates with 95% confidence intervals:
Odds ratio of event in treated cf. controls = 1.129828 (0.901642 to 1.415737)
Relative risk reduction (controls-treated) = -0.055055 (-0.162471 to 0.041808)
Risk difference (controls-treated) = -0.030054 (-0.083946 to 0.023975)
NNT [risk difference] (rounded up) = 34
Exhibit 6: Meta-analysis - Discontinuation rates

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

<table>
<thead>
<tr>
<th>Reason (%)</th>
<th>Venlafaxine (n= 1489)</th>
<th>SSRIs (n=1479)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall loss to follow-up</td>
<td>362 (24.3)</td>
<td>337 (22.8)</td>
<td>0.599</td>
</tr>
<tr>
<td>Adverse events</td>
<td>171 (11.4)</td>
<td>125 (8.5)</td>
<td>0.011</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>45 (3.5)¹</td>
<td>73 (5.6)²</td>
<td>0.011</td>
</tr>
</tbody>
</table>

¹ Fisher’s exact test; two-sided mid p-value
² based on available data (45/1305)

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

- favors venlafaxine
- favors SSRIs

---

**Relative Risk**

- **1.31 (0.60, 2.85)**
- **1.53 (0.82, 2.89)**
- **1.28 (0.84, 1.97)**
- **1.53 (0.89, 2.65)**
- **0.83 (0.54, 1.27)**
- **1.00 (0.68, 1.47)**
- **0.90 (0.64, 1.25)**
- **1.28 (0.66, 2.50)**
- **0.92 (0.52, 1.63)**
- **0.67 (0.41, 1.11)**
- **1.09 (0.73, 1.63)**
- **1.81 (1.01, 3.28)**
- **1.02 (0.72, 1.44)**
- **1.06 (0.93, 1.22)**
Relative risk meta-analysis of discontinuation rates due to adverse events comparing SSRIs to venlafaxine (random effects)

- Alves 1999: $3.53 (0.53, 24.11)$
- Ballus 2000: $2.10 (0.62, 7.30)$
- Bielski 2004: $3.92 (1.44, 10.91)$
- Costa e Silva 1998: $1.90 (0.81, 4.49)$
- De Nayer 2002: $0.89 (0.37, 2.12)$
- Dierick 1996: $0.82 (0.32, 2.07)$
- McPartlin 1998: $0.74 (0.44, 1.23)$
- Mehtonen 2000: $2.30 (0.90, 6.04)$
- Montgomery 2004: $1.48 (0.73, 3.05)$
- Rudolph 1999: $0.69 (0.26, 1.79)$
- Silverstone 1999: $1.54 (0.68, 3.51)$
- Sir 2005: $1.57 (0.43, 5.80)$
- Tylee 1997: $1.49 (0.94, 2.38)$

Combined (random): $1.36 (1.04, 1.77)$
Relative risk meta-analysis of discontinuation rates due to lack of efficacy comparing SSRIs to venlafaxine (random effects)

- **Alves 1999**: 0.059 (0.001, 2.406)
- **Ballus 2000**: 0.524 (0.116, 2.320)
- **Bielski 2004**: 0.980 (0.012, 77.165)
- **Costa e Silva 1998**: 2.372 (0.538, 10.516)
- **De Nayer 2002**: 0.500 (0.186, 1.326)
- **Dierick 1996**: 0.676 (0.307, 1.482)
- **McPartlin 1998**: 0.389 (0.088, 1.714)
- **Mehtonen 2000**: 1.440 (0.454, 4.602)
- **Montgomery 20044**: 0.514 (0.143, 1.838)
- **Rudolph 1999**: 0.441 (0.127, 1.519)
- **Silverstone 1999**: 0.945 (0.329, 2.715)
- **Tylee 1997**: 0.568 (0.180, 1.783)
- **combined [random]**: 0.686 (0.469, 1.003)

**Relative risk (95% confidence interval)**

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

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

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

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

Relative risk meta-analysis plot (random effects)

`favors mirtazapine                      favors SSRIs

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benkert 2000</td>
<td>0.42 (0.12, 1.46)</td>
</tr>
<tr>
<td>Hong 2003</td>
<td>0.20 (0.02, 2.17)</td>
</tr>
<tr>
<td>Schatzberg 2002</td>
<td>10.83 (1.07, 110.97)</td>
</tr>
<tr>
<td>Wade 2003</td>
<td>0.99 (0.28, 3.53)</td>
</tr>
<tr>
<td>combined [random]</td>
<td>0.82 (0.24, 2.86)</td>
</tr>
</tbody>
</table>
Relative risk meta-analysis of discontinuation rates due to lack of efficacy comparing SSRIs to mirtazapine

Relative risk meta-analysis plot (random effects)

- **Behnke 2003**: 1.10 (0.74, 1.63)
- **Benkert 2000**: 0.89 (0.58, 1.37)
- **Hong 2003**: 1.36 (0.89, 2.11)
- **Schatzberg 2002**: 0.73 (0.48, 1.10)
- **Wade 2003**: 0.94 (0.72, 1.21)
- **combined [random]**: 0.97 (0.81, 1.17)
Reasons for treatment discontinuation and overall loss to follow-up of bupropion compared to SSRIs

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

* 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 plot (random effects)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleman 2001</td>
<td>1.03 (0.41, 2.58)</td>
</tr>
<tr>
<td>Coleman 1999</td>
<td>0.62 (0.41, 0.93)</td>
</tr>
<tr>
<td>Croft 1999</td>
<td>0.89 (0.62, 1.29)</td>
</tr>
<tr>
<td>Feighner 1991</td>
<td>0.29 (0.07, 1.17)</td>
</tr>
<tr>
<td>Kavoussi 1997</td>
<td>7.23 (1.19, 44.74)</td>
</tr>
<tr>
<td>Weihs 2000</td>
<td>1.08 (0.45, 2.59)</td>
</tr>
<tr>
<td>Combined [random]</td>
<td>0.84 (0.56, 1.24)</td>
</tr>
</tbody>
</table>
Relative risk meta-analysis of discontinuation due to lack of efficacy comparing SSRIs to bupropion

Relative risk meta-analysis plot (random effects)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleman 2001</td>
<td>0.59 (0.19, 1.84)</td>
</tr>
<tr>
<td>Coleman 1999</td>
<td>0.41 (0.12, 1.43)</td>
</tr>
<tr>
<td>Croft 1999</td>
<td>0.99 (0.18, 5.55)</td>
</tr>
<tr>
<td>Feighner 1991</td>
<td>0.51 (0.07, 3.79)</td>
</tr>
<tr>
<td>Kavoussi 1997</td>
<td>1.38 (0.51, 3.71)</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>0.77 (0.42, 1.43)</td>
</tr>
</tbody>
</table>
Figure 1: Results of Literature Search

Titles and abstracts identified through searches:

*n = 2,449*

Abstract-only

*n = 14*

Placebo-controlled trials: full text not included:

*n = 252*

Full-text articles retrieved:

*n = 537*

Citations excluded:

*n = 1,646*

Full text articles excluded:

*n = 236*

- 2 Not English language
- 19 Wrong outcomes
- 18 Drug not included
- 21 Population not included
- 65 Wrong publication type
- 109 Wrong study design
- 2 Unable to retrieve

Articles included in drug class review:

*n = 301*

- 78 on head-to-head trials
- 2 on active control trials
- 57 on placebo controlled trials
- 15 on systematic reviews or meta-analyses
- 18 on observational studies for adverse effects
- 12 on studies of other design (e.g., pooled data)
- 72 on background
- 47 determined to be of poor quality
### Evidence Table 1: Major Depressive Disorder Adults

| STUDY: | Authors: Aberg-Wistedt A, et al.*  
Year: 2000  
Country: Sweden |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer, Inc.</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 353 |
| INTERVENTION: |  
**Drug:** Sertraline  
**Dose:** 50-150 mg/d  
**Duration:** 24 weeks |
|  |  
**Drug:** Paroxetine  
**Dose:** 20-40 mg/d  
**Duration:** 24 weeks |
| INCLUSION: | Age 18 and over; met DSM-III-R criteria for MDD; MADRS score of ≥ 21 at baseline with less than 25% improvement during washout |
| EXCLUSION: | Negative pregnancy test and stable use of oral contraceptive for 3 months; current or past history of mania; hypomania; alcoholism; substance abuse; dementia; epilepsy; presence of psychotic depression or organic affective illness; history of suicide attempts or high risk; current use of psychotropic meds; treatment with lithium or MAOI in the month prior to screening; history of intolerance or allergic reaction to either study drug; clinically evidence of hepatic or renal disease or other acute or unstable medical condition; use of any meds that would interfere with safe conduct of the study |
| OTHER MEDICATIONS/INTERVENTIONS: | Nitrazepam, oxazepam, flunitrazepam |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
**Mean age:** 43  
**Gender (% Female):** 67.4%  
**Ethnicity:** Not reported  
**Other population characteristics:** 8% over 65 years, 53% less than 45 years, 33% married or live with significant other |
| Authors: Aberg-Wistedt A, et al. | **Measures:** MADRS, CGI-S, Secondary Battelle Quality of Life Measure (BQOL), SCID-II before and after treatment |
| Year: 2000                          | **Timing of assessments:** Primary measures at baseline and weeks 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24 |
| Country: Sweden                     |                                                          |

**OUTCOME ASSESSMENT:**

**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
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Allard P, et al.\textsuperscript{21}  
Year: 2004  
Country: Sweden and Denmark |
| **FUNDING:**     | Wyeth |
| **DESIGN:**      | Study design: RCT  
Setting: 12 centers  
Sample size: 151 |
| **INTERVENTION:**|   |
| Drug:            | Venlafaxine ER  
Dose: 37.5-150 mg/day  
Duration: 6 months  
Sample size: 73  |
| Citalopram:      | 10-30 mg/day  
Duration: 6 months  
Sample size: 75 |
| **INCLUSION:**   | Male or female outpatients 65 years or older; DSM-IV for major depression; MADRS greater than 20 with less than a 20% decrease from pre-study to baseline visits (one week) |
| **EXCLUSION:**   | Cognitive impairment; alcohol or drug abuse; psychotic disorder not associated with depression; psychiatric inpatient treatment within the last year; acute suicidal tendencies; anti-psychotic drug, ECT or sumatriptan within last 30 days; bipolar, clinically evident or diagnosed dementia; mental disorders due to medical conditions; history of seizure, significant CVD, cerebrovascular disorder or uncontrolled hypertension |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Zopiclone 7.5 mg/day or less; zolpidem 5 mg/day or less for sleep; medications for the treatment of somatic disorders provided they were not expected to associated with significant toxicity |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline:  
Mean age: venlafaxine: 73.6, citalopram: 72.5  
Gender (% female): venlafaxine: 73.6%, citalopram 72.7%  
Ethnicity: NR  
Other population characteristics: Baseline MDRS: venlafaxine: 27.6, citalopram: 27.0 |
<table>
<thead>
<tr>
<th>Authors: Allard P, et al.</th>
<th>Primary Outcome Measures: MADRS at 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2004</td>
<td>Secondary Outcome Measures: MADRS responders and remitters, time to sustained response using MADRS and CGI-I; CGI-S and GDS-20 scores at weeks 8 and 22</td>
</tr>
<tr>
<td>Country: Sweden and Denmark</td>
<td>Timing of assessments: Pre-study, baseline and weeks 2,4,6,8,16,22,24</td>
</tr>
<tr>
<td>OUTCOME ASSESSMENT:</td>
<td>RESULTS:</td>
</tr>
<tr>
<td></td>
<td>• No statistical differences between groups in MADRS, CGI-S, CGI-I, and GDS-20 were observed</td>
</tr>
<tr>
<td></td>
<td>• At week 22 both groups had a 93% response rate</td>
</tr>
<tr>
<td></td>
<td>• MADRS remission rate was 19% for venlafaxine and 23% for citalopram</td>
</tr>
<tr>
<td></td>
<td>ANALYSIS:</td>
</tr>
<tr>
<td></td>
<td>ITT: Yes</td>
</tr>
<tr>
<td></td>
<td>Post randomization exclusions: Yes (3)</td>
</tr>
<tr>
<td></td>
<td>ATTRITION:</td>
</tr>
<tr>
<td></td>
<td>Loss to follow-up: Overall 22.2%</td>
</tr>
<tr>
<td></td>
<td>6% Venlafaxine (6) 8%</td>
</tr>
<tr>
<td></td>
<td>Withdrawals due to adverse events: Citalopram (3) 4%</td>
</tr>
<tr>
<td></td>
<td>Withdrawals due to lack of efficacy:</td>
</tr>
<tr>
<td></td>
<td>Loss to follow-up differential high:</td>
</tr>
<tr>
<td></td>
<td>ADVERSE EVENTS:</td>
</tr>
<tr>
<td></td>
<td>• Spontaneously reported adverse events venlafaxine: 62%, citalopram: 43%</td>
</tr>
<tr>
<td></td>
<td>• Tremor more common during citalopram; nausea/vomiting during venlafaxine treatment</td>
</tr>
<tr>
<td></td>
<td>QUALITY RATING: Fair</td>
</tr>
</tbody>
</table>
### Evidence Table 1  
**Major Depressive Disorder Adults**

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

### OUTCOME ASSESSMENT:

- **Measures:** HAM-D, MADRS, CGI  
- **Timing of assessments:** Baseline, days 7, 14, 21, 28, 42, 56, 70, 84

### RESULTS:

- There were no significant differences between study groups in any outcome measures at endpoint  
- Venlafaxine showed a faster onset with significant differences in various outcome measures during weeks 1 to 4: mean decreases of HAM-D and MADRS scores were significantly greater with venlafaxine ($p < 0.05$) during weeks 1-4  
- Suicide ideation scores at week 6 were significantly lower for venlafaxine on MADRS and HAM-D scales  
- Remission (HAM-D < 8) at week 3 was found in 30% of venlafaxine treated patients and 11% of fluoxetine treated patients ($p = 0.03$)

### ANALYSIS:

- **ITT:** Yes  
- **Post randomization exclusions:** Yes

### ATTRITION:

- **Loss to follow-up:** 21.8% ; venlafaxine: 25%, fluoxetine: 19%  
- **Withdrawals due to adverse events:** venlafaxine: 7%, fluoxetine: 2%  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- There were no significant differences between study groups in the frequency of adverse events  
- At least one adverse event was recorded in 56% of the venlafaxine group and 51% of the fluoxetine group  
- Nausea was the most common adverse event: venlafaxine: 33.3%, fluoxetine: 27.7%  
- No clinically significant changes in laboratory parameters, body weight, heart rate, or blood pressure were recorded in either treatment group

### QUALITY RATING:

- **Fair**
### Evidence Table 1  
**Major Depressive Disorder Adults**

**STUDY:**  
*Authors:* Baldwin DS, et al.  
*Year:* 1996, 2001 (continuation phase)  
*Country:* UK, Ireland

**FUNDING:**  
Bristol Myers Squibb

**DESIGN:**  
*Study design:* RCT  
*Setting:* Multi-center, 20 psychiatric outpatient clinics  
*Sample size:* 206

**INTERVENTION:**  
**Drug:**  
- Nefazodone  
  - 200-600 mg/d  
  - Mean dose: 472.0 mg  
  - 8 weeks, twice a day  
- Paroxetine  
  - 20-40 mg/d  
  - Mean dose: 32.7 mg  
  - 8 weeks, twice a day

**Duration:**  
Continuation Phase: from week 8 to month 6, dose was gradually reduced wherever possible

**INCLUSION:**  
- 18 years or older; non-psychotic depression; HAM-D score of $\geq 18$; moderately ill on CGI-S scale  
- Continuation Phase: patients who responded to treatment during the 8 weeks acute treatment phase

**EXCLUSION:**  
- Pregnancy, lactation, or lack of adequate contraception; history of psychotic disorders; alcohol or substance abuse; existing suicidal risk; electroconvulsive therapy within last 6 months; previously failed to respond to at least 2 antidepressant therapies; clinically relevant progressive disease; hypersensitivity to study medication

**OTHER MEDICATIONS/INTERVENTIONS:**  
Benzodiazepines, antipyretics, analgesics, supportive psychological treatment

**POPULATION CHARACTERISTICS:**  
*Groups similar at baseline:* Yes  
*Mean age:* 38; Continuation phase mean age: 38.8  
*Gender:* (female %) nefazodone: 60%, paroxetine: 50%.  
Continuation phase: nefazodone: 51%, paroxetine: 55%  
*Ethnicity:* Not reported  
*Other population characteristics:* Not reported
**Authors:** Baldwin DS, et al.  
**Year:** 1996, 2001  
**Country:** UK, Ireland

| OUTCOME ASSESSMENT: | Measures and timing of assessments: HAM-D, CGI-S, CGI-I, Patient’s Global Assessment: Baseline, weeks 1, 2, 3, 4, 6, 8, HAM-A: weeks 2 and 8, MADRS: weeks 4 and 8  
Continuation Phase: weeks 12, 16, 20, and 24 |
|---------------------|------------------------------------------------------------------------------------------------|

### RESULTS:
- Both groups showed significant improvements from baseline HAM-D, HAM-A, and MADRS scores  
- There were no significant differences between the treatment groups  
- The proportion of CGI responders was also similar between treatment groups  
  - **Continuation Phase:**  
  - No statistically significant differences between study groups regarding efficacy  
  - Clinical improvement either maintained or improved in continuation phase

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Not reported

### ATTRITION:
- **Loss to follow-up:** 27.2%; nefazodone: 26.7%, paroxetine: 27.7%.  
  - **Continuation Phase:** 32.4%; nefazodone: 33%, paroxetine: 32.7%  
- **Withdrawals due to adverse events:** 13.5%; nefazodone: 14%, paroxetine: 13%.  
  - **Continuation Phase:** nefazodone: 7%, paroxetine: 8%  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- 84% of nefazodone treated patients and 78% of paroxetine treated patients reported side effects  
- Frequencies among adverse events were similar except a higher frequency of somnolence in the paroxetine group (24% vs. 16%) and higher frequencies of headache (35% vs. 25%) and dizziness (17% vs. 9%) in the nefazodone group  
  - **Continuation Phase:** 75% of nefazodone treated patients and 81% of paroxetine treated patients reported side effects  
  - Most common adverse events in paroxetine group were nausea (34% vs. 16% in nefazodone group) and somnolence (27% vs. 20%)  
  - Most common adverse event in nefazodone group was headache (31% vs. 28% in paroxetine group)

### QUALITY RATING:
- **Fair**
Evidence Table 1  Major Depressive Disorder Adults

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

### OUTCOME ASSESSMENT:
- **Measures:** 21 item HAM-D, MADRS, CGI scale  
- **Timing of assessments:** Baseline, weeks 1, 2, 4, 6, 8, 12, 16, 24

### RESULTS:
- No significant differences between groups on the HAM-D, MADRS, or CGI scales at 24 weeks or endpoint  
- At week 12 the percent of patients with a HAM-D score $\leq 8$ was significantly greater in the venlafaxine group than the paroxetine group (57% vs. 33%; $p = .011$)  
- More patients exhibited a drug response ($\geq 50\%$ decrease in HAM-D) on venlafaxine than paroxetine at week 6 ($p = 0.03$)

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Not reported

### ATTRITION:
- **Loss to follow-up:** 32%, venlafaxine: 39%, paroxetine: 26%  
- **Withdrawals due to adverse events:** 11%, venlafaxine: 15%, paroxetine: 8%  
- **Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:
- Venlafaxine: nausea: 28%, headache: 18%, dry mouth: 15%  
- Paroxetine: headache: 40%, constipation: 16%

### QUALITY RATING:
- Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:**       | *Authors:* Behnke K, et al. 50  
|                  | *Year:* 2003  
|                  | *Country:* Multinational |
| **FUNDING:**     | Organon NV |
| **DESIGN:**      | *Study design:* RCT  
|                  | *Setting:* Multi-center  
|                  | *Sample size:* 346 |
| **INTERVENTION:**| Sertraline  
| **Drug:**        | 50-150 mg/day  
| **Dose:**        | 8 weeks  
| **Duration:**    | Mirtazapine  
|                  | 30-45 mg/day  
|                  | 8 weeks |
| **INCLUSION:**   | DSM IV criteria for major depression; HAM-D score \( \geq 18 \); 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 \( \geq 12 \) months or \( 2 \leq \) weeks; lack of response to at least 2 prior antidepressant therapies; previous hypersensitivity; use of sildenafil |
| **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  
<p>|                  | <em>Other population characteristics:</em> Previous episodes of major depression: sertraline: 69.8%, mirtazapine: 73.3% |</p>
<table>
<thead>
<tr>
<th>Authors: Behnke K, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2003</td>
</tr>
<tr>
<td>Country: Multinational</td>
</tr>
</tbody>
</table>

| OUTCOME ASSESSMENT: | Measures and timing of assessment: HAM-D, MADRS, CGI at baseline, and days 4, 7, 10, 14, 28, 42, 56 or on premature withdrawal, changes in sexual function questionnaire at baseline and biweekly thereafter |
|---------------------|

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Onset of action was faster in the mirtazapine group</td>
</tr>
<tr>
<td>• 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 &lt; 0.05)</td>
</tr>
<tr>
<td>• After week 2 the difference remained greater with mirtazapine but lacked statistical significance</td>
</tr>
<tr>
<td>• Reduction in sleep disturbance was significantly greater in the mirtazapine group at all assessments (p ≤ 0.01)</td>
</tr>
<tr>
<td>• CGI scores did not show significant differences throughout the study</td>
</tr>
<tr>
<td>• Changes in sexual function scores did not show significant differences although the mirtazapine group showed greater improvements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT: Yes</td>
</tr>
<tr>
<td>Post randomization exclusions: Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTRITION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up: 20.8%; sertraline: 18%, mirtazapine: 23%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events: mirtazapine: 11.9%, sertraline: 3%</td>
</tr>
<tr>
<td>Loss to follow-up differential high: Loss to follow up: 20.8%, sertraline: 23%, mirtazapine: 18%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Percentage of patients reporting at least one adverse event was similar in both groups (mirtazapine: 64%, sertraline: 68%)</td>
</tr>
<tr>
<td>• A significantly higher number of patients withdrew from the mirtazapine group (21 vs. 5 in sertraline group; p = NR)</td>
</tr>
<tr>
<td>• Significantly more patients reported nausea (38 vs. 13; p &lt; 0.01), libido decrease (10 vs. 2; p &lt; 0.01) and diarrhea (16 vs. 7; p &lt; 0.01) in the sertraline-treated group</td>
</tr>
<tr>
<td>• Somnolence was significantly higher in the mirtazapine group (35 vs. 13; p &lt; 0.01)</td>
</tr>
<tr>
<td>• Weight increase higher in the mirtazapine group (16 vs. 3; p = 0.01)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
</tr>
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<tbody>
<tr>
<td>Fair</td>
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</tbody>
</table>
**Evidence Table 1**

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

| OUTCOME ASSESSMENT: | Measures: HAM-D-17, HAM-A, CGI-S, CGI-I, BDI-II, Welzel-Kohnen Colored Scales, Short Form 36 |
| Timing of assessments: Screening, baseline, weeks 1, 2, 3, 4, 6 |

### RESULTS:
- Mirtazapine and paroxetine were equally effective in reducing mean HAM-D-17 score (58.3% vs. 53.7%)
- Significantly more mirtazapine patients responded at weeks 1 & 4 on the HAM-D-17 than paroxetine patients; week 1 response: mirtazapine: 23.2%, paroxetine: 8.9% (p < 0.002).

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 23%; mirtazapine: 21.6%, paroxetine: 24.2%
- **Withdrawals due to adverse events:** 8%; mirtazapine: 8.6%, paroxetine: 7.4%
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Significantly more mirtazapine patients experienced weight increase (p < 0.05)
- At least one adverse event reported: mirtazapine: 68.1%, paroxetine: 63.4%
- Dry mouth: mirtazapine: 14.1%, paroxetine: 8.2%
- Headache: mirtazapine: 9.6%, paroxetine: 10.4%
- Nausea: mirtazapine: 4.4%, paroxetine: 11.2%
- Flu like symptoms: mirtazapine: 9.6%, paroxetine: 3.7%
- Differences all p < 0.1

### QUALITY RATING: Fair
# Evidence Table 1

## Major Depressive Disorder Adults

| STUDY: | Authors: Bennie EH, et al.  
Year: 1995  
Country: UK |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>
| DESIGN: | 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%, fluoxetine: 53.5%; duration of current episode: sertraline: 5.4 mo., fluoxetine: 5.2 mo. |
| Authors: Bennie, et al. | Measures: HAM-D, HAM-A, CGI-I, CGI-S, Covi Anxiety Scale, Raskin Depression Scale, Leeds Sleep Questionnaire  
Timing of assessments: Baseline, weeks 1, 2, 4, 6 |
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<tbody>
<tr>
<td>Year: 1995</td>
<td>OUTCOME ASSESSMENT:</td>
</tr>
<tr>
<td>Country: UK</td>
<td>RESULTS:</td>
</tr>
</tbody>
</table>
| | • 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

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

| OUTCOME ASSESSMENT: | **Primary Outcome Measures:** MADRS  
Secondary Outcome Measures: HAM-D-24; HAM-D somatic subscale; HAM-A; CGI-S; CES-D; Q-LES-Q; CGI-I  
**Timing of assessments:** Evaluations were conducted at baseline and weeks 1, 2, 4, 6, and 8 for the MADRS, HAM-D-24, CGI-I, and CGI-S. Anxiety symptoms were measured at baseline and weeks 2 and 8 |
|---|---|

### RESULTS:
- No significant differences between treatment groups observed in the LOCF analysis for any of the outcome measures
- Response rates favored escitalopram (MADRS: 58.8% vs. 48.0%; Ham-D: 61% vs. 48%); no statistical significance was reached
- No significant differences in remission rates between escitalopram and venlafaxine XR

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 30% (60); escitalopram: 27% (26); venlafaxine XR: 34% (34)
- **Withdrawals due to adverse events:** 10% (20); escitalopram: 4% (4); venlafaxine XR: 16% (16)
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Significantly more patients in the venlafaxine XR than in the escitalopram group (16% vs. 4%; p < 0.01) group withdrew due to adverse events
- Significantly more patients in the venlafaxine XR group than in the escitalopram group (24% vs. 6.1%; p < 0.05) reported nausea
- Significantly more patients had ejaculation disorders in the venlafaxine XR than in the escitalopram group (22.6% vs. 6.7%; p < 0.05)

### QUALITY RATING:
- Fair
### Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | **Authors:** Boyer P, et al.  
**Year:** 1998  
**Country:** France |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>At least 1 author is affiliated with Pfizer</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design:** RCT  
**Setting:** Multi-center, primary care settings (57 general practitioners)  
**Sample size:** 242 |
| INTERVENTION:  
**Drug:**  
**Dose:** 50-150 mg/d  
180 days  
Sertraline  
20-60 mg/d  
180 days  
| Mean daily dose:  
Fluoxetine -26 mg/d, Sertraline -55 mg/d |
| INCLUSION: | 18-65 yrs; DSM-IV criteria for major depression; ≥ 20 on MADRS |
| EXCLUSION: | Pregnancy, lactation, or lack of adequate contraception; concurrent major psychiatric disorders; alcohol or substance abuse; existing suicidal risk; previous course of antidepressant treatment ≤ 3 weeks; clinically severe medical illness; history of allergy to related drugs |
| OTHER MEDICATIONS/INTERVENTIONS: | Allowed medications for medical diseases |
| POPULATION CHARACTERISTICS:  
**Groups similar at baseline:** Yes  
**Mean age:** fluoxetine: 43.7, sertraline: 43.0  
**Gender** (% female): fluoxetine: 79.1%, sertraline: 77.6%  
**Ethnicity:** Not reported  
**Other population characteristics:** Previous depression: fluoxetine: 38.3 %, sertraline: 34.5%; concomitant medical conditions: fluoxetine: 72%, sertraline: 78% |
| **Authors:** Boyer P, et al.  
**Year:** 1998  
**Country:** UK |
| **OUTCOME ASSESSMENT:** | **Measures:** MADRS, CGI, FSQ (Functional Status Questionnaire)  
**Timing of assessments:** Baseline, 120, 180 days |
| **RESULTS:** | • No significant differences in changes in MADRS, FSQ, CGI-I, and CGI-S scores between treatment groups  
• No significant differences in response rates (improvement of MADRS ≥ 50%) between the treatment groups  
• Day 120: fluoxetine: 54.3%, sertraline: 49%  
• Day 180: fluoxetine: 42.6%, sertraline: 47.4% |
| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:** | **Loss to follow-up:** 4.5%; fluoxetine: 4.2%, sertraline: 4.9%  
**Withdrawals due to adverse events:** fluoxetine: 8.6%, sertraline: 7.7%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** | No significance between group differences in the numbers of patients who experienced adverse events, fluoxetine: 51.3%, sertraline: 57.8% |
| **QUALITY RATING:** | Fair |
### Evidence Table 1

**Major Depressive Disorder Adults**

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

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

| Study: Authors: Cassano GB, et al.  
Year: 2002  
Country: Italy |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Funding: SmithKline Beecham, Ravizza Farmaceutici</td>
<td></td>
</tr>
</tbody>
</table>
| Design: Study design: RCT  
Setting: Multi-center (38)  
Sample size: 242 |
| Intervention:  
**Drug:**  
**Dose:**  
**Duration:**  
Paroxetine  
20-40 mg/day  
1 year  
Fluoxetine  
20-60 mg/day  
1 year |
| Inclusion:  
65 yrs or older; ICD-10 criteria for depression; ≥ 18 on HAM-D-17; mini mental state ≥ 22; Raskin score higher than Covi Anxiety score |
| Exclusion: History of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; clinically relevant progressive disease; depot neuroleptics within 6 months |
| Other Medications/Interventions: Treatments for concomitant systemic diseases; short or intermediate half-life benzodiazepines; temazepam for insomnia |
| Population Characteristics: **Groups similar at baseline:** Yes  
**Mean age:** paroxetine: 75.6, fluoxetine: 74.9  
**Gender (% female):** paroxetine: 61%, fluoxetine: 50%  
**Ethnicity:** Not reported  
**Other population characteristics:** Duration of present episode was less than 6 months for 60% of patients and more than 1 year for 25%, 40% had already been treated for present episode |
| Authors: | Cassano GB, et al. |
| Year: | 2002 |
| Country: | Italy |
| **OUTCOME ASSESSMENT:** | **Measures and timing of assessments:** HAM-D, CGI, Clinical Anxiety Scale at baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52 |
| | Cognitive tests: Buschke Selective Reminding Test; Blessed Information and Memory Test; Clifton Assessment Schedule; Cancellation Task Test; Wechsler Paired Word Test; MMSE at baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52 |
| **RESULTS:** | Cognitive function:  
| | • Both treatment groups showed significant improvements in cognitive performance on all test scales  
| | • There were no significant differences between treatment groups and cognitive performance except for the Buschke test at week 3 and 6 where paroxetine showed a significantly greater improvement on a number of tests |
| | Depressive symptoms:  
| | • Both treatment groups significantly improved the HAM-D total scores  
| | • Paroxetine showed a greater improvement of HAM-D scores during the first 6 weeks (week 3: p < 0.05; week 6: p < 0.002), otherwise there were no differences between the treatment groups  
| | • A Kaplan Meier analysis evaluating the percentage of responders (HAM-D ≤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.  
Year: 1999  
Country: Canada |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>One author is employee of SmithKline Beecham</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT, double blind  
Setting: Multicenter  
Sample size: 203 |
| INTERVENTION: | | |
| **Drug:** | 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 ≥ 20 and score of “2” on the first item |
| **EXCLUSION:** | Significant coexisting illness including renal, hepatic, GI, neurological, non-stabilized diabetes; other current Axis I disorders; organic brain syndrome; past or present abuse of alcohol or other illicit drugs; significant suicide risk; pregnant or lactating; ECT or continuous lithium therapy in the prior 2 months; MAOI or oral neuroleptics use in prior 21 days; any antidepressant or sedative hypnotic in prior 7 days; fluoxetine in prior 35 days or current therapy with an anticoagulant or type 1C anti-arrhythmic; subjects with clinically significant abnormalities on physical examination, ECG, or lab |
| OTHER MEDICATIONS/ INTERVENTIONS: | Chloral hydrate for hypnotic |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 40.9; paroxetine: 40.6, fluoxetine: 41.2  
Gender (% female): paroxetine: 63.7%, fluoxetine: 59.4%  
Ethnicity: 96.5% white, 1.5 % Asian  
Other population characteristics:  
2 or more depressive episodes: paroxetine 76.5%, fluoxetine 59.5% |
| **Authors:** Chouinard G, et al.  
**Year:** 1999  
**Country:** Canada |
|---|
| **OUTCOME ASSESSMENT:** Measures: HAM-D21 measured at baseline, weeks 1-6, 8, 10 and 12. Response > 50% reduction from baseline, remission score < 10 (HAMD)  
**Timing of assessments:** Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12 |
| **RESULTS:** |
| • No statistically significant differences in response rates: (Observed cases at 12 weeks) paroxetine 85.7%, fluoxetine 88.4%; (LOCF endpoint) paroxetine 67.0%, fluoxetine 68.4%  
• No statistically significant differences in remission rates: (Observed cases at 12 weeks) paroxetine 77.8%, fluoxetine 81.2%, (LOCF endpoint) paroxetine 58.0%, fluoxetine 59.2% |
| **ANALYSIS:** |
| *ITT:* Yes  
*Post randomization exclusions:* Yes (5) |
| **ATTRITION:** |
| *Loss to follow-up:* 36%; paroxetine: 39.2%, fluoxetine: 32.67%  
*Withdrawals due to adverse events:* Not reported  
*Loss to follow-up differential high:* No |
| **ADVERSE EVENTS:** |
| No significant differences between groups |
| **QUALITY RATING:** |
| Fair |
## Evidence Table 1: Major Depressive Disorder Adults

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

### OUTCOME ASSESSMENT:

**Measures:** 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual functioning by investigator questions: sexual desire disorder, sexual arousal disorder, orgasm dysfunction, premature ejaculation, patient rated overall sexual function  
**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, and 8

### RESULTS:

- Mean HAM-D scores in the bupropion SR but not the sertraline group were statistically better than placebo (by day 28 p < 0.05)  
- There was no significant difference between the bupropion SR and sertraline groups  
- CGI-I and CGI-S for bupropion SR significantly better than placebo but not better than sertraline  
- Sertraline not statistically better than placebo  
- No differences in HAM-A; significantly fewer bupropion 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 bupropion SR patients (p < 0.05)  
- Diagnosed with at least one sexual dysfunction: sertraline: 39%, bupropion SR: 13%, placebo: 17%

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 30%; sertraline: 36%, bupropion SR: 22%, placebo: 32%  
**Withdrawals due to adverse events:** 5%; sertraline: 8%, bupropion 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 bupropion SR or placebo  
- Insomnia and agitation were reported more frequently in bupropion SR patients than sertraline or placebo

### QUALITY RATING:

Fair
## Evidence Table 1

### Major Depressive Disorder Adults

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

### OUTCOME ASSESSMENT:

- **Measures:** 21 item HAM-D, sexual function assessment, substance-induced arousal disorder and orgasm dysfunction. Assessed: orgasm dysfunction, sexual desire disorder, sexual arousal disorder, overall patient sexual functioning (1-6 scale)
- **Timing of assessments:** Assessments made at baseline and weeks 1, 2, 3, 4, 5, 6, 7, and 8

### RESULTS:

- Mean HAM-D scores were not statistically different between the three groups (in ITT analysis)
- No difference in responders (≥ 50 decrease in HAM-D), remitters (HAMD < 8)
- More buproprion SR remitters (47%) compared to placebo (32%).
- Orgasm dysfunction occurred significantly more in fluoxetine patients compared with placebo or buproprion SR patients (p < 0.001)
- At endpoint, more fluoxetine treated patients had sexual desire disorder than buproprion SR treated patients (p < 0.05).
- More fluoxetine-treated patients dissatisfied with sexual function beginning at week 1 (p < 0.05)

### ANALYSIS:

- **ITT:** Yes
- **Post randomization exclusions:** Yes

### ATTRITION:

- **Loss to follow-up:** 34%; fluoxetine: 37%, buproprion SR: 37%, placebo: 33%
- **Withdrawals due to adverse events:** 6%; fluoxetine: 4%, buproprion SR: 9%, placebo: 3%
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- Headache was the most commonly reported event in all treatment groups
- Headache, diarrhea, and somnolence occurred more frequently in fluoxetine patients than buproprion SR or placebo
- Dry mouth, nausea, and insomnia were reported more frequently in buproprion SR patients than fluoxetine or placebo
- Buproprion SR group had mean increases in DBP (1.7 mm Hg) and fluoxetine group (0.3 mm Hg) and heart rate (3.8 beats/min), authors state these were not clinically significant
- Buproprion SR group had mean increases in heart rate (3.8 beats/min) and fluoxetine group had a mean decrease in heart rate (-2.8 beats/min), authors state these were not clinically significant

### QUALITY RATING:

- Fair
## Evidence Table 1: Major Depressive Disorder

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

OUTCOME ASSESSMENT:
Primary Outcome Measures: MADRS total score
Secondary Outcome Measures: CGI-S, Responders (50% reduction in MADRS) and remitters (MADRS total score 12 or less)
Timing of assessments: Screening, baseline weeks 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24. Final safety assessment 30 days after last assessment

RESULTS:
All results are escitalopram vs. citalopram at 24 weeks
- No significant differences in changes of MADRS scores from baseline to endpoint 8.3 vs. 9.3 p = NR
- CGI-S mean 1.75 vs. 2.00 p < 0.05
  - Moderately depressed 1.57 vs. 1.95 p < 0.05
  - Severely depressed 2.02 vs. 2.13
- Responders: 80% vs. 78% p = NR
- Remitters: 76% vs. 71% p = NR
- Overall, statistically significantly fewer withdrawals in the escitalopram than in the citalopram group 13% vs. 22% p < 0.05
- Total withdrawals in the moderately depressed was 10 (11.8%) vs. 26 (30.6%) p < 0.01
- Total withdrawals in the severely depressed was 11 (13.8%) vs. 13 (14.6%) p = NR

ANALYSIS:
ITT: Yes
Post randomization exclusions: Yes (18)

ATTRITION (%):
Loss to follow-up: Overall 17.7 Escitalopram 12.7 Citalopram 22.4
Withdrawals due to adverse events: 8.3 6.1 10.3
Withdrawals due to lack of efficacy: 1.5 1.2 1.7
Loss to follow-up differential high: No

ADVERSE EVENTS:
- All results are escitalopram versus citalopram n(%)
- Patients with AEs: 110 (62.9) vs. 131 (72.0)
  - Nausea: 28 (16.0) vs. 18 (9.9), Rhinitis: 17 (9.7) vs. 12 (6.6), Headache: 12 (6.9) vs. 16 (8.8), Back pain: 11 (6.3) vs. 15 (8.2), Accidental injury: 10 (5.7) vs. 8 (4.4), Bronchitis: 10 (5.7) vs. 7 (3.8), Weight increase: 2 (1.1) vs. 12 (6.6)

QUALITY RATING: Fair
### Evidence Table 1

**Major Depressive Disorder Adults**

<table>
<thead>
<tr>
<th>STUDY:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Costa e Silva JC, et al.³⁴</td>
</tr>
<tr>
<td><strong>Year:</strong> 1998</td>
</tr>
<tr>
<td><strong>Country:</strong> South America</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>FUNDING:</th>
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<tbody>
<tr>
<td>Wyeth-Ayerst International</td>
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<table>
<thead>
<tr>
<th>DESIGN:</th>
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<tbody>
<tr>
<td><strong>Study design:</strong> RCT</td>
</tr>
<tr>
<td><strong>Setting:</strong> Multi-center</td>
</tr>
<tr>
<td><strong>Sample size:</strong> 382</td>
</tr>
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<table>
<thead>
<tr>
<th>INTERVENTION:</th>
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<tbody>
<tr>
<td><strong>Drug:</strong></td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
</tr>
<tr>
<td>Venlafaxine 75-225 mg/d</td>
</tr>
<tr>
<td>8 weeks</td>
</tr>
<tr>
<td>Fluoxetine 20-40 mg/d</td>
</tr>
<tr>
<td>8 weeks</td>
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<table>
<thead>
<tr>
<th>INCLUSION:</th>
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<tbody>
<tr>
<td>18-60 yrs; DSM-III-R criteria for major depression; ≥ 20 on HAM-D-21; symptoms for at least 1 month</td>
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<thead>
<tr>
<th>EXCLUSION:</th>
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<tbody>
<tr>
<td>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</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER MEDICATIONS/INTERVENTIONS:</th>
</tr>
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<tbody>
<tr>
<td>Zopiclone 7.5 mg</td>
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<table>
<thead>
<tr>
<th>POPULATION CHARACTERISTICS:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groups similar at baseline:</strong> Yes</td>
</tr>
<tr>
<td><strong>Mean age:</strong> venlafaxine: 40.5, fluoxetine: 39.8</td>
</tr>
<tr>
<td><strong>Gender</strong> (% female): venlafaxine: 80.1%, fluoxetine: 77.4%</td>
</tr>
<tr>
<td><strong>Ethnicity:</strong> Not reported</td>
</tr>
<tr>
<td><strong>Other population characteristics:</strong> 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%</td>
</tr>
</tbody>
</table>
**Authors:** Costa e Silva JC, et al.  
**Year:** 1998  
**Country:** South America

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>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</th>
</tr>
</thead>
</table>

| RESULTS: | • HAM-D and MADRS scores decreased significantly in both treatment groups (p < 0.05)  
• There were no significant differences between treatment groups in any primary efficacy measures (HAM-D, MADRS, CGI)  
• Global response (≥ 50% decrease in HAM-D or MADRS and CGI score of 1 or 2) was achieved by 86.8% in the venlafaxine group and 82% in the fluoxetine group (p = 0.074)  
• Remission was observed in 60.2% of patients in each group  
• In patients who increased their dose to venlafaxine 150 mg and fluoxetine 40 mg after 3 weeks significantly more achieved a CGI score of 1 in the venlafaxine group (p < 0.05)  
• There was no significant difference in remission rates between treatment groups |

| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** No |

| ATTRITION: | **Loss to follow-up:** 12.3%; venlafaxine: 14.8%, fluoxetine:9.7%  
**Withdrawals due to adverse events:** venlafaxine: 7.2%, fluoxetine: 3.8%  
**Loss to follow-up differential high:** No |

| ADVERSE EVENTS: | • There were no significant differences between groups for specific adverse events  
• At least one adverse event: venlafaxine: 69.4%, fluoxetine: 65%  
• There were no clinically significant changes in laboratory parameters, ECG, or blood pressure in either group  
• Nausea: venlafaxine: 28.9%, fluoxetine: 18.9%  
• Headache: venlafaxine: 11.3%, fluoxetine: 7% |

| QUALITY RATING: | Fair |
**Evidence Table 1**  

**Major Depressive Disorder Adults**

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

| OUTCOME ASSESSMENT: | Measures: | 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual function assessment by investigator interview-sexual desire disorder, sexual arousal disorder, orgasmic dysfunction, premature ejaculation, overall patient satisfaction with sexual functioning, vital signs  
| | Timing of assessments: | Baseline, weeks 1, 2, 3, 4, 6, and 8 |

| RESULTS: |  
| • Mean HAM-D scores in both the buproprion and sertraline group were statistically better than placebo (p < 0.05)  
| • No significant difference in HAM-D scores between the buproprion and sertraline groups  
| • CGI-S and CGI-I improvement compared to placebo but no differences between drugs at any week  
| • No difference in changes of HAM-A scores for any group  
| • By day 42 significantly fewer buproprion sr treated patients had sexual desire disorder than sertraline or placebo-treated patients (p < 0.05)  
| • At day 56, both buproprion and sertraline had higher sexual arousal disorder (p < 0.05) than placebo  
| • Orgasmic dysfunction occurred significantly more in sertraline patients compared with placebo or buproprion patients (p < 0.001)  
| • At day 56 no difference in overall satisfaction with sexual function between treatment groups |

| ANALYSIS: |  
| *ITT:* Yes  
| *Post randomization exclusions:* Yes |

| ATTRITION: |  
| *Loss to follow-up:* 32%  
| *Withdrawals due to adverse events:* (12); sertraline: 3%, buproprion sr: 3%, placebo: 7%  
| *Loss to follow-up differential high:* Yes |

| ADVERSE EVENTS: |  
| • Headache was the most commonly reported event in all treatment groups  
| • Somnolence and insomnia occurred more frequently in sertraline patients than buproprion patients  
| • Nausea and diarrhea occurred more frequently with sertraline than buproprion or placebo |

| QUALITY RATING: | Fair |
### Evidence Table 1  
**Major Depressive Disorder Adults**

| STUDY: | Authors: Dalery J, et al.  
Year: 2003  
Country: Europe |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Solvay Pharmaceuticals</td>
</tr>
</tbody>
</table>
| 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

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT</th>
<th>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</th>
</tr>
</thead>
</table>
| 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 ≤ 0.05), as was the improvement of CGI-I scores (p ≤ 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 ≤ 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  
<p>|                   | • Most common adverse events: nausea: fluvoxamine, 24%; fluoxetine, 20%; headache: fluvoxamine-13%, fluoxetine-14% |
| QUALITY RATING:   | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Detke MJ, et al.™</td>
</tr>
<tr>
<td></td>
<td>Year: 2004</td>
</tr>
<tr>
<td></td>
<td>Country: US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Eli Lilly</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Multi-center (number of centers NR)</td>
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<tr>
<td></td>
<td>Sample size: 367</td>
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<tr>
<td><strong>INTERVENTION:</strong></td>
<td>Drug:</td>
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<tr>
<td></td>
<td>Dose:</td>
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<tr>
<td></td>
<td>Duration:</td>
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<tr>
<td></td>
<td>Acute phase:</td>
</tr>
<tr>
<td></td>
<td>Continuation:</td>
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<tr>
<td></td>
<td>Sample size:</td>
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<tr>
<td>Duloxetine (low dose)</td>
<td>80 mg/d</td>
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<tr>
<td>8 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td>95</td>
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<tr>
<td>Duloxetine (high dose)</td>
<td>120 mg/d</td>
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<tr>
<td>8 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td>93</td>
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<tr>
<td>Paroxetine</td>
<td>20 mg/d</td>
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<tr>
<td>8 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>N/A</td>
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<tr>
<td>8 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td>93</td>
<td></td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>Patients ≥ 18 yrs old; met DSM-IV and MINI criteria for MDD; CGI-S rating ≥ 4; HAM-D-17 score ≥ 15 at entry</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Pregnant, Current primary DSM-IV diagnosis other than MDD; any anxiety disorder as a primary diagnosis; previous diagnosis of bipolar disorder, psychosis, or schizoaffective disorder; history of substance abuse; failed to respond to two courses of antidepressant therapy; serious suicidal risk; serious medical illness</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>Nonprescription analgesic medications allowed; no prescription analgesics</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: Duloxetine 80: 43.1, Duloxetine 120: 44.7, Paroxetine 20: 42, placebo: 42</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): Duloxetine 80: 70%, Duloxetine 120: 70%, Paroxetine 20: 58%, placebo: 58%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity (% white): Duloxetine 80: 95%, Duloxetine 120: 92%, Paroxetine 20: 86%, placebo: 86%</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Mean baseline HAM-D: Duloxetine 80: 19.9, Duloxetine 120: 20.2, Paroxetine: 20.3, placebo: 19.9; Mean baseline HAM-A: Duloxetine 80: 17.8, Duloxetine 120: 18, Paroxetine 20: 18.5, placebo: 17.9</td>
</tr>
</tbody>
</table>
Authors: Detke MJ, et al.  
Year: 2004  
Country: US

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

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

| OUTCOME ASSESSMENT: | Measures: HAM-D21, MADRS, HSCL58, CGI  
Timing of assessments: Baseline, weeks 1, 3, 4 & 6 |
|---------------------|--------------------------------------------------|

RESULTS: Responders at week 6 (i.e., reduction > 50% from baseline HAM-D21): paroxetine: ~ 67%, fluoxetine: ~ 62%, not significantly different

ANALYSIS: 
ITT: Not reported  
Post randomization exclusions: Yes

ATTRITION: 
Loss to follow-up: 21.2%  
Withdrawals due to adverse events: paroxetine: 4%, fluoxetine: 8%  
Loss to follow-up differential high: Not reported

ADVERSE EVENTS: 
- No significant differences  
- No vital sign or laboratory changes reported  
- Paroxetine: n = 3 had weight gain > 7%, fluoxetine: n = 2 had weight gain > 7%

QUALITY RATING: Fair
### Evidence Table 1: Major Depressive Disorder Adults

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

### OUTCOME ASSESSMENT:

**Measures:** HAM-D, MADRS, Covi Anxiety Scale, CGI  
**Timing of assessments:** Baseline, weeks 1, 2, 4, 8, 12 (inferred from table)

### RESULTS:

- The venlafaxine group showed significantly higher response rates in MADRS scores (75.0 vs. 49.3%, \( p = 0.001 \)) and HAM-D scores (71.9% vs. 49.3%; \( p = 0.008 \)) compared to the fluoxetine group.
- Venlafaxine treated patients also showed significantly greater improvements in the Covi Anxiety scores (\( p = 0.0004 \)) and the CGI scores (\( p = 0.016 \))
- MADRS and HAM-D scores at week 2 improved significantly more in the venlafaxine group.
- (HAM-D, \( p = 0.0058 \))
- At the final visit 59.4% of venlafaxine patients were in remission vs. 40.3 % of fluoxetine patients (\( p = 0.028 \))
- Fewer venlafaxine patients required a dose increase (37.1% vs. 52.9%)

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 36.3%; venlafaxine: 32.9%, fluoxetine: 39.7%  
**Withdrawals due to adverse events:** venlafaxine: 11%, fluoxetine: 12.3%  
**Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:

- No significant differences
- Overall most common adverse event: nausea (28.6% in venlafaxine group vs. 21.4% in fluoxetine group)
- 55.7% in the venlafaxine group and 67.1% in the fluoxetine group experienced at least one adverse event
- Most common adverse events that lead to withdrawal: venlafaxine: headache, diarrhea, nausea; fluoxetine: insomnia, dyspepsia, nausea, anxiety, nervousness

### QUALITY RATING:

Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Dierick M, et al. 60</td>
</tr>
<tr>
<td></td>
<td>Year: 1996</td>
</tr>
<tr>
<td></td>
<td>Country: France</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Wyeth-Ayerst</td>
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<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting:</td>
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<tr>
<td></td>
<td>Sample size: 314</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Drug:</strong></td>
<td>Venlafaxine</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>75-150 mg/d 8 weeks</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>Fluoxetine</td>
</tr>
<tr>
<td></td>
<td>20 mg/d 8 weeks</td>
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<tr>
<td></td>
<td>Mean daily dose for venlafaxine:</td>
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<td>109-122 mg/d from day 15 forward</td>
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<tr>
<td><strong>INCLUSION:</strong></td>
<td>18 yrs or older; DSM-III-R criteria for major depression; ≥ 20 on HAM-D-21</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTerventions:</strong></td>
<td>Oxazepam, chloral hydrate</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: venlafaxine: 43.7, fluoxetine: 43.2</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): venlafaxine: 65%, fluoxetine: 64%</td>
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<tr>
<td></td>
<td>Ethnicity: Not reported</td>
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<tr>
<td></td>
<td>Other population characteristics: Not reported</td>
</tr>
<tr>
<td>Authors: Dierick M, et al.</td>
<td>Year: 1996</td>
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</tbody>
</table>

**OUTCOME ASSESSMENT:**

- *Measures:* HAM-D, MADRS, CGI
- *Timing of assessments:* Baseline, days 7, 14, 21, 28, 56

**RESULTS:**

- Both treatment groups improved significantly in efficacy outcomes from baseline
- Response rate on HAM-D scale was significantly higher in the venlafaxine group at week 6: venlafaxine: 72%, fluoxetine: 60% (p = 0.023)
- No differences between groups on MADRS
- In a low dose comparison there were no significant differences between groups

**ANALYSIS:**

- *ITT:* Yes
- *Post randomisation exclusions:* Yes

**ATTRITION:**

- *Loss to follow-up:* 24.8%; venlafaxine: 25%, fluoxetine: 25%
- *Withdrawals due to adverse events:* venlafaxine: 9%, fluoxetine: 4%
- *Loss to follow-up differential high:* No

**ADVERSE EVENTS:**

- Significantly more patients reported nausea in the venlafaxine group: 28% vs. 14% (p = 0.003)
- Anticholinergic side effects greater in venlafaxine group: 15% vs. 7 %
- No clinically significant changes in vital signs, ECG or lab parameters
- 1 patient on fluoxetine committed suicide after 1 week treatment

**QUALITY RATING:**

- Fair
## Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Ekselius L, et al.  
Year: 1997  
Country: Sweden |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Swedish Medical Research Council, Pfizer</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (general physicians)  
Sample size: 400 |
| INTERVENTION: | **Drug:**  
Sertraline  
Citalopram  
**Dose:**  
50-100 mg/d  
20-60 mg/d  
24 weeks  
24 weeks  
**Duration:**  
(patients > 65) sertraline:50-100 mg/d  
citalopram: 20-40 mg/d |
| 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. | Measures: CGI-S, MADRS  
| Year: 1997 | Timing of assessments: Weeks 2, 4, 8, 12, 16, 20, 24  
| Country: Sweden |  
| OUTCOME ASSESSMENT: |  
| RESULTS: | Both treatment groups showed significant decreases in MADRS and CGI scores from baseline at all weeks starting at week 2  
| | There were no significant differences between treatment groups in any primary outcome variables at any time  
| | Response rates week 12: sertraline: 69.5%; citalopram: 68.0%; week 24: sertraline: 75.5%; citalopram: 81.0%  
| | Subgroup analysis: There were no significant differences between treatment groups in any primary outcome variables in patients with recurrent depression  
| ANALYSIS: | ITT: Yes. LOCF  
| | Post randomization exclusions: Yes  
| ATTRITION: | Loss to follow-up: 22%  
| | Withdrawals due to adverse events: sertraline: 12.5%, citalopram: 9.0%  
| | Loss to follow-up differential high: No  
| ADVERSE EVENTS: | No significant differences between treatment groups  
| | At least one adverse event: sertraline: 90%, citalopram: 85.5%  
| | Nausea: sertraline: 6%, citalopram: 2.5%  
| | Diarrhea: sertraline: 8.5%, citalopram: 5.5%  
| | Increased sweating: sertraline: 13%, citalopram 17%  
| | Dry mouth: sertraline: 18.5%, citalopram: 16%  
| | Headache: sertraline: 9%, citalopram: 6.5%  
| | Sexual dysfunction was experienced in 8% of the sertraline group and 13.5% of the citalopram group  
| QUALITY RATING: | Good  


### Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Fava M, et al.  
Year: 1998  
Country: US |
| FUNDING: | SmithKline Beecham Pharmaceuticals |
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 128 |
| INTERVENTION: | **Drug:**  
**Dose:** 20-50 mg/d (Initial dosage of 20 mg/d could be increased weekly by 10 mg/d up to 50 mg/d)  
**Duration:** 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)  
**Duration:** 12 weeks  
**Placebo:** N/A  
**Duration:** 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 contraception |
| OTHER MEDICATIONS/ INTERVENTIONS: | Chloral hydrate for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 41.3  
Gender (% female): 50%  
Ethnicity: Not reported  
Other population characteristics: Not reported |
| **Author:** Fava M, et al.  
**Year:** 1998  
**Country:** US |
|---|
| **OUTCOME ASSESSMENT:**  
*Measures:* 21 item HAM-D, Covi Anxiety Scale, vital signs at weeks 1, 2, 3, 4, 6, 9, 12  
*Timing of assessments:* Laboratory evaluations at weeks 3, 6, 9, 12 |
| **RESULTS:**  
No significant differences among the three treatment groups in the degree of depression and anxiety improvement |
| **ANALYSIS:**  
*ITT:* Yes  
*Post randomization exclusions:* Not reported |
| **ATTRITION:**  
*Loss to follow-up:* 28%; paroxetine: 29%, fluoxetine: 31%, placebo: 21%  
*Withdrawals due to adverse events:* 12%  
*Loss to follow-up differential high:* No |
| **ADVERSE EVENTS:**  
- Gastrointestinal effects were reported in 47% of paroxetine patients, 48% fluoxetine patients  
- 25% of paroxetine patients reported sexual dysfunction; this was significantly more than the fluoxetine (7%) or placebo groups (0%) |
| **QUALITY RATING:**  
Fair |
# Evidence Table 1

## Major Depressive Disorder Adults

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

#### OUTCOME ASSESSMENT:
- **Measures:** HAM-D-17, CGI-S, HAM-D sleep disturbance  
- **Timing of assessments:** Not reported

#### RESULTS:
- No statistical differences between fluoxetine, sertraline and paroxetine in all outcome measures  
- Response rate: 64.8%, 72.9%, and 68.8% respectively  
- Remission rates: 54.4%, 59.4%, and 57.0% respectively  
- No statistical differences in sleep disturbance factor scores. No significant differences of treatment groups in patients with high or low insomnia  

**Subgroup analysis (Fava 2000):** Anxious depression
- No significant differences between treatment groups and changes over time  
- Response: fluoxetine: 73%, sertraline: 86%, paroxetine: 77%, overall p = 0.405  
- Remission: fluoxetine: 53%, sertraline: 62%, paroxetine: 50%, overall p = 0.588  
- Fluoxetine and sertraline had a significantly greater improvement than paroxetine in week 1 on the HAM-D anxiety score

#### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Not reported

#### ATTRITION:
- **Loss to follow-up:** 27.1%; fluoxetine: 26.1%, sertraline: 27.1%, paroxetine: 28.1%  
- **Withdrawals due to adverse events:** fluoxetine: 8.7%, sertraline: 6.3%, paroxetine: 11.5%  
- **Loss to follow-up differential high:** No

#### ADVERSE EVENTS:
- Pairwise comparisons indicated that the paroxetine-treated patients reported more constipation than the fluoxetine-treated patients, and the fluoxetine-treated patients reported more twitching and cough increase than the sertraline-treated patients  
- Most common adverse events: Fluoxetine: headache (25%); sertraline: headache (28.1%), diarrhea (26.0%), insomnia (26%), nausea (20.8%); paroxetine: nausea (25.0%), headache (21.9%), insomnia (20.8%), abnormal ejaculation (20.8%)  
- There was a significant increase in weight for the paroxetine group, fluoxetine treated patients showed a significant decrease in weight and the sertraline group a non-significant decrease in weight from baseline to endpoint  

**Subgroup analysis (Fava 1999):**  
- Adverse events were similar among treatments; only “flu syndrome” was significantly higher in the sertraline treated group overall (p = 0.021)

#### QUALITY RATING:  
Fair
**Evidence Table 1**  
**Major Depressive Disorder Adults**

| STUDY:  | Authors: Feiger A, et al.  
Year: 1996  
Country: Europe |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Bristol-Myers Squibb</td>
</tr>
</tbody>
</table>
| DESIGN:  | Study design: RCT  
Setting: Multi-center  
Sample size: 160 |
| INTERVENTION:  |  
**Drug:**  
Nefazodone  
100-600 mg/d  
6 weeks  
Sertraline  
50-200 mg/d  
6 weeks |
| INCLUSION:  | 18 yrs or older; DSM-III-R criteria for major depression; ≥ 20 on HAM-D-17 after washout period |
| EXCLUSION:  | Pregnancy, lactation, or lack of adequate contraception; Axis I diagnosis; history of seizures; alcohol or substance abuse; existing suicidal risk; previous nefazodone trial; sertraline treatment within 1 year; clinically relevant progressive disease; known hypersensitivity to study drugs; psychotropic medication within 6 months; participation in other trial within 3 months; use of any other antidepressant within 3 weeks |
| OTHER MEDICATIONS/INTERVENTIONS:  | Concomitant medications |
| POPULATION CHARACTERISTICS:  | Groups similar at baseline: sertraline group had a significantly higher rate of recurring illness than the nefazodone group (73% vs. 57%; p = 0.01)  
Mean age: 43.7; sertraline: 43, nefazodone: 44.5  
Gender (% female): 51%; sertraline: 48%, nefazodone: 55%  
Ethnicity: white: 84%, black: 11%, Hispanic: 7%, Asian: 1%, other: 1%; sertraline: white: 79%, nefazodone: 90% white  
Other population characteristics: Concomitant medication taken by 85% in the nefazodone group and 78% in the sertraline group; recurrent illness: sertraline: 57%, nefazodone: 73% |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>OUTCOME ASSESSMENT:</td>
<td>Measures: HAM-D-17, CGI, sexual function questions</td>
</tr>
<tr>
<td></td>
<td>Timing of assessments: Weekly</td>
</tr>
<tr>
<td>RESULTS:</td>
<td>There were no statistically significant differences between treatment groups; response rates: nefazodone: 59%, sertraline: 57%</td>
</tr>
<tr>
<td>ANALYSIS:</td>
<td>ITT: Yes</td>
</tr>
<tr>
<td></td>
<td>Post randomization exclusions: Yes</td>
</tr>
<tr>
<td>ATTRITION:</td>
<td>Loss to follow-up: 24.4%; nefazodone: 24.4%, sertraline: 24.4%</td>
</tr>
<tr>
<td></td>
<td>Withdrawals due to adverse events: nefazodone: 19.2%, sertraline: 12.2%</td>
</tr>
<tr>
<td></td>
<td>Loss to follow-up differential high: No</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>Reported at least one adverse event: sertraline: 95%, nefazodone: 96%</td>
</tr>
<tr>
<td></td>
<td>Overall satisfaction with sexual function was significantly higher in the nefazodone group (p &lt; 0.1)</td>
</tr>
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<td></td>
<td>67% of men in the sertraline group reported difficulty with ejaculation vs. 19% in the nefazodone group (p &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td>No significant differences in other adverse events</td>
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<tr>
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<td>No clinically significant effects on the cardiovascular system in either group; no differences in withdrawals due to adverse events.</td>
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<td></td>
<td>Headache: sertraline: 55%, nefazodone: 55%</td>
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<tr>
<td></td>
<td>Nausea: sertraline: 27%, nefazodone: 32%</td>
</tr>
<tr>
<td></td>
<td>Dizziness: sertraline: 7%, nefazodone: 32%</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
</tbody>
</table>
**Evidence Table 1**

**Major Depressive Disorder Adults**

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

<p>| <strong>Authors:</strong> Feighner JP, et al. |
| <strong>Year:</strong> 1991 |
| <strong>Country:</strong> US |
| <strong>OUTCOME ASSESSMENT:</strong> Measures: HAM-D (21), CGI-S, CGI-I, HAM-A |
| <strong>Timing of assessments:</strong> Weekly |
| <strong>RESULTS:</strong> |
| • 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 |
| <strong>ANALYSIS:</strong> |
| <strong>ITT:</strong> Yes |
| <strong>Post randomisation exclusions:</strong> Yes. 3 patients |
| <strong>ATTRITION:</strong> |
| <strong>Loss to follow-up:</strong> 7.3%; bupropion: 3.3%, fluoxetine: 11.3% |
| <strong>Withdrawals due to adverse events:</strong> Bupropion: 10%, fluoxetine: 7% |
| <strong>Loss to follow-up differential high:</strong> No |
| <strong>ADVERSE EVENTS:</strong> |
| No significant differences of adverse events between treatment groups |
| <strong>QUALITY RATING:</strong> Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Finkel SI, et al.\(^{39}\)  
|                  | Year: 1999  
|                  | Country: US |
| **FUNDING:**     | Two authors are affiliated with Pfizer, Inc. |
| **DESIGN:**      | Study design: RCT, subgroup analysis  
|                  | Setting: Multi-center  
|                  | Sample size: 75 |
| **INTERVENTION:**| Drug:  
|                  | Sertraline  
|                  | 50-100 mg/day  
|                  | 12 weeks  
|                  | Fluoxetine  
|                  | 20-40 mg/day  
|                  | 12 weeks |
| **INCLUSION:**   | DSM III-R criteria for major depression; HAM-D: ≥ 18; age 70 or older |
| **EXCLUSION:**   | Significant medical problems; Axis I psychiatric disorders; cognitive impairment; suicidal risk; drug abuse or dependence; failure to respond to antidepressant treatment |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Chloral hydrate, temazepam |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: No-Fluoxetine group had higher rate of prior episodes of depression.  
|                  | Mean age: sertraline: 74, fluoxetine 75  
|                  | Gender: (female%): sertraline: 57%, fluoxetine 49%  
|                  | Ethnicity: 97% white, 3% black; sertraline 95%, fluoxetine: 100%  
<p>|                  | Other population characteristics: Prior depressive episodes: sertraline: 45%, fluoxetine 61% |</p>
<table>
<thead>
<tr>
<th>Authors: Finkel SI, et al.</th>
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<tbody>
<tr>
<td>Year: 1999</td>
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<tr>
<td>Country: US</td>
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</table>

### OUTCOME ASSESSMENT:
- **Measures and timing of assessments**: HAM-D, Baseline (pre & post washout), weeks 2, 4, 6, 8, 10, 12, 3
  - POMS (baseline, weeks 2, 4, 8, 12), 2. Q-Les-Q (baseline, week 12), cognitive tests: 1. DSST from the WAIS-R, 2. shopping list task, both given, Mini-Mental SE (baseline and week 12)

### RESULTS:
- Overall no significant differences between treatment groups on endpoint scores
- Significantly more patients in the sertaline group achieved a clinical response on HAM-D (reduction from baseline of 50% or greater) between weeks 6 to 12
- Changes in the Vigor Subscale of POMS, and 2 subscales of the Q-LES-Q (physical health, psychological health) showed significant differences favoring sertraline ($p = 0.04; p = 0.03; p = 0.03$)

### ANALYSIS:
- **ITT**: Yes
- **Post randomization exclusions**: Yes. 1 person excluded from ITT because lack of measures

### ATTRITION:
- **Loss to follow-up**: 37.3%; sertraline: 36%, fluoxetine: 39%
- **Withdrawals due to adverse events**: sertraline: 9%, fluoxetine: 30%
- **Loss to follow-up differential high**: Yes

### ADVERSE EVENTS:
- Sertraline-treated patients reported “shaking” to a greater degree (14.3%) than did fluoxetine treated patients (0%) ($p = 0.03$)
- Fluoxetine-treated patients lost more weight than sertraline-treated patients (week 12: 2.8 vs. 0.6 pounds; $p = 0.05$)

### QUALITY RATING:
- Fair
## Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Franchini L, et al.  
Year: 1997, 2000  
Country: Italy |
| FUNDING: | Not reported |
| DESIGN: | Study design: RCT  
Setting: Single center  
Sample size: 64 (4-year follow-up: enrolled 47) |
| INTERVENTION: |  
Drug:  
Sertraline  
100-200 mg/d  
24/48 months  
Fluvoxamine  
200-300 mg/d  
24/48 months  |
| INCLUSION: | Asymptomatic patients; unipolar patients with prior episodes; depressive episode within past 18 months; at least 4 months of remission confirmed by absence of symptoms according to DSM-IV; absence of other Axis I diagnosis  
4-year follow-up: patients who remained without recurrence after 2 years of prophylactic treatment (HAMD >15) |
| EXCLUSION: | Other Axis I diagnosis; low compliance with past treatments; mania or hypomania; prior long-term maintenance treatment; recurrence cycle not longer than 18 months |
| OTHER MEDICATIONS/ INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: sertraline: 47.3, fluvoxamine: 49.0  
Gender (% female): sertraline: 78%, fluvoxamine: 75%  
Ethnicity: Not reported  
Other population characteristics: Not reported |
| **Authors:** Franchini L, et al.  
**Year:** 1997, 2000  
**Country:** Italy |
|---|
| **OUTCOME ASSESSMENT:** | **Measures:** HAM-D  
**Timing of assessments:** Monthly |
| **RESULTS:** | • 21.9% of sertraline-treated patients and 18.7% of fluvoxamine-treated patients had a single recurrence ($z = 0.14; p = 0.88$)  
4-year follow-up:  
• No significant difference in recurrences between the treatment groups; sertraline: 13.6%, fluvoxamine: 20% |
| **ANALYSIS:** | **ITT:** No but not necessary since 100% completed trial with outcome assessments  
**Post randomization exclusions:** No |
| **ATTRITION:** | **Loss to follow-up:** 0  
**Withdrawals due to adverse events:** 0  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** | • No significant differences in adverse events.  
• Most common adverse events:  
  Sertraline: nausea (6.2%), abnormal ejaculation (12.5%)  
  Fluvoxamine: nausea: (9.4%), anorexia (9.4%)  
4-year follow-up: Not reported |
| **QUALITY RATING:** | Fair |
Evidence Table 1  **Major Depressive Disorder Adults**

| STUDY: | Authors: Gagiano CA  
Year: 1993  
Country: South Africa |
<table>
<thead>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
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</table>
| DESIGN: | Study design: RCT  
Setting: Single center (University hospital)  
Sample size: 90 |
| INTERVENTION: |  
**Drug:**  
Fluoxetine  
Dose: 20-60 mg/d  
Duration: 6 weeks  
Paroxetine  
Dose: 20-40 mg/d  
Duration: 6 weeks |
| INCLUSION: | Age 18-65 years; met DSM-III-R criteria for MDD; HAM-D (21-item scale) score of ≥ 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: fluoroxetine: 39.6, paroxetine: 37.8  
Gender (% female): fluoroxetine: 80%, paroxetine: 80%  
Ethnicity: Not reported  
Other population characteristics: Previous depression fluoroxetine: 60%, paroxetine: 53% |
| Authors: Gagiano CA  
Year: 1993  
Country: South Africa |
| OUTCOME ASSESSMENT: Measures: Physical exam, HAM-D, MADRS, CGI, HAM-A, routine hematology and biochemistry on blood samples at baseline and end of week 6  
Timing of assessments: Baseline and weekly intervals except week 5 |
| RESULTS: |
| - No significant differences between treatment groups in HAM-D subfactor scores at any time point  
- No significant differences in mean total scores for HAM-D, HAM-A, and MADRS at endpoint or at any other study point measures  
- No significant difference in CGI severity change score or improvement score  
- No significant difference in patients responding (at least 50% improvement of HAM-D) between treatment groups (paroxetine: 70%, fluoxetine: 63%; no p value reported)  
- No significant differences in groups on HAMD (item 3) measure for suicidal ideation, both groups showed reduction over six-week period |
| ANALYSIS: |
| ITT: Yes  
Post randomization exclusions: No |
| ATTRITION: |
| Loss to follow-up: 21%; fluoxetine 22%, paroxetine 14%  
Withdrawals due to adverse events: 6.7%  
Loss to follow-up differential high: No |
| ADVERSE EVENTS: |
| - Fluoxetine-treated patients experienced a statistically significant weight loss from baseline to endpoint (-1.46 kg; p = 0.001)  
- Headache: fluoxetine 47.0%, paroxetine 53.0%  
- Nausea: fluoxetine 33.0%, paroxetine 36.0%  
- Diarrhea: fluoxetine 13.0%, paroxetine 13.0%  
- Insomnia: fluoxetine 20.0%, paroxetine 11.0%  
- Vomiting was noted for only four (8.9%) patients in each group |
| QUALITY RATING: Fair |
### Evidence Table 1: Major Depressive Disorder Adults

| STUDY: Authors: Goldstein DJ, et al.  
Year: 2002  
Country: US |
<table>
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<tr>
<td>FUNDING: Eli Lilly</td>
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</table>
| DESIGN: Study design: RCT  
Setting: Multi-center (8 sites)  
Sample size: 173 |
| INTERVENTION:  
Drug: Duloxetine  
Dose: 40-120 mg/d  
8 weeks  
Sample size: 70  
Fluoxetine  
Dose: 20 mg/d  
8 weeks  
Sample size: 33  
Placebo  
Dose: N/A  
Duration: 8 weeks  
Sample size: 70 |
| INCLUSION: Male and female outpatients 18-65 years; met DSM-IV and MINI criteria for MDD; CGI-S score of at least 4 at visit 1; HAM-D-17 score of at least 15 at visits 1 and 2 |
| EXCLUSION: Any primary DSM-IV Axis I disorder diagnosis other than MDD; anxiety disorder as primary diagnosis within the past year; history of substance abuse or dependence; failed two or more courses of antidepressant therapy |
| OTHER MEDICATIONS/INTERVENTIONS: Not reported |
| POPULATION CHARACTERISTICS: Groups similar at baseline: Yes  
Mean age: Duloxetine: 42.3, Fluoxetine: 39.7, placebo: 41.4  
Gender (% female): Duloxetine: 62.9%, Fluoxetine: 57.6%, Placebo: 68.6%  
Ethnicity: White: 83%; African-American: 8.1%; Other: 9.2%; Percent white by drug: Duloxetine: 88.6%, Fluoxetine: 72.7%, Placebo: 81.4%  
Other population characteristics: Mean baseline HAM-D-17: Duloxetine: 18.4, Fluoxetine 17.9, Placebo 19.2 |
| Authors: Goldstein DJ, et al.  
Year: 2002  
Country: US | **Primary Outcome Measures**: HAM-D-17  
**Secondary Outcome Measures**: MADRS; CGI; HAM-A; PGI  
**Timing of assessments**: HAM-D-17 measured at baseline and weekly |
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<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
<td><strong>RESULTS:</strong></td>
</tr>
</tbody>
</table>
| | • No statistically significant differences between duloxetine and fluoxetine in response (49% vs. 45%) and remission (43% vs. 30%) rates  
• Duloxetine showed a significantly greater mean change from baseline in HAM-D-17 than placebo at week 8 ($p = 0.009$)  
• Duloxetine showed a greater change from baseline in HAM-D-17 than placebo at week 8 but the difference was not statistically different  
• Duloxetine patients showed significantly greater improvement on the MADRS ($p = 0.047$), CGI-I ($p = 0.005$), and PGI ($p = 0.006$) than placebo |
| **ANALYSIS:** | **ITT**: Yes  
**Post randomization exclusions**: Yes |
| **ATTRITION:** | **Loss to follow-up**: 35% (60); duloxetine: 34.3% (24); fluoxetine: 36.4% (12); placebo: 34.3% (24)  
**Withdrawals due to adverse events**: 6.4% (11); duloxetine: 10% (7); fluoxetine: 3% (1); placebo 4.3% (3)  
**Loss to follow-up differential high**: No |
| **ADVERSE EVENTS:** | • Significantly more duloxetine patients experienced asthenia (17.1% vs. 4.3%; $p = 0.026$), and insomnia (20.0% vs. 7.1%; $p = 0.046$) than placebo  
• Most common adverse events (duloxetine vs. fluoxetine): dry mouth: 30.0% vs. 21.2%; headache: 20% vs. 33.3%; insomnia: 20% vs. 9.1%; nausea: 12.9% vs. 18.2%; diarrhea: 14.3% vs. 30.3% |
| **QUALITY RATING:** | **Fair** |
Evidence Table 1  Major Depressive Disorder Adults

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

### Authors
Hong CJ, et al.

### Year
2003

### Country
Taiwan

#### OUTCOME ASSESSMENT:
- **Measures:** HAM-D, CGI
- **Timing of assessments:** Days 7, 14, 28, 42

#### RESULTS:
- No significant differences in HAM-D scores reduction between treatment groups
- No significant differences in HAM-D responders (mirtazapine: 58% vs. fluoxetine: 51%)
- Mirtazapine had more remitters and responders at all time points, however no statistical significance in differences was reached

#### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes

#### ATTRITION:
- **Loss to follow-up:** 39.4%; mirtazapine: 45.5%, fluoxetine: 33.3%
- **Withdrawals due to adverse events:** Mirtazapine: 19.7%, fluoxetine: 12.1%
- **Loss to follow-up differential high:** No

#### ADVERSE EVENTS:
- No statistically significant differences between treatment groups
- 71.2% of mirtazapine and 57.6% of fluoxetine treated subjects reported adverse events
- Mirtazapine: dizziness 19.7%, constipation 15.2%, weight increase 13.6%, somnolence 12.1%
- Fluoxetine: dizziness 13.6%, influenza-like symptoms 13.6%, constipation 9.1%

#### QUALITY RATING:
Fair
### Evidence Table 1  Major Depressive Disorder Adults

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

**OUTCOME ASSESSMENT:**  
*Measures:* HAM-D<sub>21</sub>, HAM-A, CGI  
*Timing of assessments:* Baseline, weeks 1, 2, 3, 4, 6, 8, 12, 16

**RESULTS:**
- HAM-D<sub>21</sub>: similar changes in scores over study, no differences at any point in study  
- CGI, CGI-S, HAMA: no differences between groups

**ANALYSIS:**  
*ITT:* Yes  
*Post randomization exclusions:* Yes

**ATTRITION:**  
*Loss to follow-up:* 31.5%; bupropion SR: 28.7%, sertraline: 34.1%  
*Withdrawals due to adverse events:* bupropion SR: 3%, sertraline: 13% (p = 0.004)  
*Loss to follow-up differential high:* Yes

**ADVERSE EVENTS:**
- Significant differences (p < 0.05):  
  - Nausea: bupropion SR: 10%, sertraline: 30%  
  - Diarrhea: bupropion SR: 3%, sertraline: 22%  
  - Somnolence: bupropion SR: 2%, sertraline: 13%  
- Sexual dysfunction: bupropion SR: 10%, sertraline: 61%  
- Orgasm failure or delay: men – bupropion SR: 10%, sertraline: 61% (p < 0.001); women – bupropion SR: 7%, sertraline: 41% (p < 0.001)

**QUALITY RATING:** Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder</th>
</tr>
</thead>
</table>
| **STUDY:** | **Authors:** Kiev A, et. al.  
**Year:** 1997  
**Country:** US |
| **FUNDING:** | Solvay Pharma, Upjohn |
| **DESIGN:** | **Study design:** RCT  
**Setting:** Multi-center (2 centers)  
**Sample size:** 60 |
| **INTERVENTION:** | **Drug:**  
**Dose:** fluvoxamine 50-150 mg/d  
7 weeks  
**Duration:** paroxetine 20-50 mg/d  
7 weeks |
| **INCLUSION:** | Age 18-65; DMS-IIIR criteria for single or recurrent MDD; minimum score of 20 on HAM-D21 (incl min score of 2 on depressed mood item) |
| **EXCLUSION:** | Not fluent in written or oral English; history of medication non-compliance; demonstration of placebo response during run-in; history of substance abuse; severe suicide risk or auto-aggressive behavior; used a drug within 30 days with anticipated major organ toxicity; pregnancy or lactation; hypersensitivity to SSRIs; participation in previous fluvoxamine studies; other significant organic disease; clinically significant lab abnormalities; other primary psychiatric diagnoses; transportation difficulties |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Antacids, laxatives, acetaminophen, aspirin, ibuprofen, chloral hydrate |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Yes  
**Mean age:** fluvoxamine: 42.7; paroxetine: 39.9  
**Gender (% female):** fluvoxamine: 53%; paroxetine: 53%  
**Ethnicity:** fluvoxamine: white 87%, non-white 13%; paroxetine: white: 93%, non-white: 7%  
**Other population characteristics:** (mean weight) fluvoxamine: 180.1 lbs; paroxetine: 175.8 lbs (mean height) fluvoxamine: 67.2 in; paroxetine: 65.8 in |
<table>
<thead>
<tr>
<th>Authors: Kiev A, et. al.</th>
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<tbody>
<tr>
<td>Year: 1997</td>
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<tr>
<td>Country: US</td>
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</table>

### OUTCOME ASSESSMENT:
- **Measures**: HAM-D-21
- **Timing of assessments**: Baseline and weeks 1,2,3,5,7

### RESULTS:
- There was a mean change in HAM-D score for fluvoxamine: -13.45 and for paroxetine: -12.86, p = 0.763

### ANALYSIS:
- **ITT**: Yes
- **Post randomization exclusions**: Yes

### ATTRITION:
- **Loss to follow-up**: 31%; fluvoxamine: 34.5%; paroxetine: 27.6%
- **Withdrawals due to adverse events**: fluvoxamine: 6.8%; paroxetine: 13.8%
- **Loss to follow-up differential high**: No

### ADVERSE EVENTS:
- Significant differences in sweating was reported: fluvoxamine 10% and paroxetine 33% (p = 0.028)
- Treatment-emergent adverse events were reported by 97% of fluvoxamine patients and 100% of paroxetine patients
- One trend that was reported although not statistically significant: fluvoxamine patients reported more sleep-related side effects and paroxetine patients reported more GI side effects

### QUALITY RATING:
- Fair
## Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Kroenke K, et al.  
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: | Paroxetine  
Dose: 20 mg/day  
Duration: 9 months  
Fluoxetine  
Dose: 20 mg/day  
Duration: 9 months  
Sertraline  
Dose: 50 mg/day  
Duration: 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% |

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Second Generation Antidepressants  
Page 175 of 534
### Authors: Kroenke K, et al.
### Year: 2001

### OUTCOME ASSESSMENT:
- **Measures:** Computer assisted telephone interview: SF-36, MSC (mental component summary), SCL-20 (symptoms checklist), PRIME-MD (primary care Evaluation of mental disorders), subscales of: medical outcomes study questionnaire (MOS); patient health questionnaire, health and daily living form, quality of social interaction scale, quality of close relationship scale, work limitations questionnaire.
- **Timing of assessments:** Months 1, 3, 6, 9

### RESULTS:
- All 3 treatment groups showed significant improvements in depression and other health related quality of life domains (social function, work function, physical function).
- There were no significant differences between treatment groups in any of the 3 and 9 months outcome measures.
- Subgroup analysis showed that there were no differences in treatment effects for patients with MDD and for patients older than 60 years.
- Switch rate to other medication: paroxetine: 22%, fluoxetine: 14%, sertraline: 17%.

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 24.3% (numbers provided are conflicting); paroxetine: 24.8%, fluoxetine: 22.5%, sertraline: 25.7%.
- **Withdrawals due to adverse events:** paroxetine: 30%, fluoxetine: 23%, sertraline: 24%.
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- No significant differences in adverse events between treatment groups

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

### Year:
2005

### Country:
UK and Denmark

### CHARACTERISTICS OF INTERVENTIONS:
Patients randomized to escitalopram, citalopram, or placebo; no concomitant psychotropic medication allowed except zolpidem or benzodiazepines for insomnia

### MAIN RESULTS:
- Mean change from baseline in total MADRS score was -11.2 for placebo, -13.1 citalopram, and -13.8 for escitalopram; not a significant difference between the active drug groups in the LOCF analysis
- Escitalopram patients with sleep problems shows statistically greater improvement (p < 0.05) in item 4 of the MADRS (sleep disturbance) than citalopram patients at weeks 1, 4, 6, 8, and endpoint (LOCF analysis)

### ADVERSE EVENTS:

<table>
<thead>
<tr>
<th></th>
<th>Citalopram</th>
<th>Escitalopram</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>8.6%</td>
<td>9.2%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4.7%</td>
<td>6.9%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

### COMPREHENSIVE LITERATURE SEARCH STRATEGY:
NR

### STANDARD METHOD OF APPRAISAL OF STUDIES:
Yes

### QUALITY RATING:
Fair
Evidence Table 1  Major Depressive Disorder Adults

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

**Measures:** MADRS, CGI-S, CGI-I

**Timing of assessments:** (Primary measures) baseline, weeks 1, 2, 3, 4, 6, 8

### RESULTS:

- Significantly more escitalopram patients responded to treatment at study endpoint on the MADRS scale than citalopram patients (63.7% vs. 52.6%; *p* =0.009)
- Significantly more escitalopram than citalopram-treated patients were in remission at endpoint (52.1% vs. 42.8%; *p* < 0.036)
- Escitalopram was numerically better than citalopram at all time points on all 3 efficacy scales
- Analysis of time to response showed that escitalopram–treated patients were responders 8.1 days faster than citalopram-treated patients

### ANALYSIS:

**ITT:** Yes

**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 7%; citalopram 5%, escitalopram 6%, placebo 10%

**Withdrawals due to adverse events:** citalopram 3.8%, escitalopram 2.6%, placebo 2.6%

**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- No significant differences between study groups
- Nausea the most common adverse event: citalopram 14.4%, escitalopram 17.4%

### QUALITY RATING:

Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Lepola UA, et al.\(^{83}\)  
                  | Year: 2004  
                  | Country: Multi-national (Canada, Europe, US) |
| **FUNDING:**     | Not reported |
| **DESIGN:**      | Study design: Pooled analysis  
<pre><code>              | Number of patients: 977 |
</code></pre>
<p>| <strong>AIMS OF REVIEW:</strong> | Compare efficacy of escitalopram (10-20 mg/d) versus citalopram (20-40 mg/d) by pooling the data from two published clinical trials |
| <strong>STUDIES INCLUDED IN META-ANALYSIS</strong> | Burke et al. (2002) and Lepola et al. (2003) |
| <strong>TIME PERIOD COVERED:</strong> | 8 weeks |
| <strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong> | RCTs of escitalopram versus citalopram |
| <strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong> | Outpatients male or female 18-65 years old who met DSM-IV criteria for major depressive episode; MADRS score of 22 or higher; Burke study et al., 2002 HAMD-17 score of 2 on item 1 was an additional requirement in the fixed dose study |</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Lepola UA, et al.</td>
<td></td>
</tr>
<tr>
<td><strong>Year:</strong> 2004</td>
<td></td>
</tr>
<tr>
<td><strong>Characteristics of Interventions:</strong></td>
<td>Escitalopram 10-20 mg/d for 8 weeks; citalopram 20-40 mg/d for 8 weeks</td>
</tr>
<tr>
<td><strong>Main Results:</strong></td>
<td>• Statistically significantly greater proportion of patients responded to escitalopram than to citalopram (56.8% vs. 48.9%; p = 0.033)</td>
</tr>
<tr>
<td></td>
<td>• Remission rates favored escitalopram but did not reach statistical significance (46.4% vs. 40.8%; p = 0.123).</td>
</tr>
<tr>
<td></td>
<td>• Escitalopram-treated patients had a significant reduction in HAMD-17 total score compared to citalopram-treated patients (estimated difference 1.62; p = 0.034, LOCF)</td>
</tr>
<tr>
<td><strong>Adverse Events:</strong></td>
<td>Headache (placebo 20%, escitalopram 16%, citalopram 19%); nausea (placebo 8%, escitalopram 16% (p &lt; 0.05 vs placebo); citalopram 18% (p &lt; 0.05 vs placebo) were reported by ≥10% of the patients in any treatment group in the pooled analysis</td>
</tr>
<tr>
<td><strong>Comprehensive Literature Search Strategy:</strong></td>
<td>Analysis includes the only 2 published studies. Authors state that data of a third, unpublished trial were not included</td>
</tr>
<tr>
<td><strong>Standard Method of Appraisal of Studies:</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Quality Rating:</strong></td>
<td>Fair</td>
</tr>
</tbody>
</table>
### Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: McPartlin GM, et. al.  
Year: 1998  
Country: UK |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth-Ayerst</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (43 general practice sites)  
Sample size: 361 |
| INTERVENTION: |  
Drug:  
Dose:  
Duration: |
| Venlafaxine XR | Paroxetine | Fixed dose trial |
| 75 mg/day | 20 mg/day | 12 weeks | 12 weeks |
| 12 weeks |  |
| 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% |
<table>
<thead>
<tr>
<th>Authors: McPartlin GM, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 1998</td>
</tr>
<tr>
<td>Country: UK</td>
</tr>
</tbody>
</table>

**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.  
Year: 2000  
Country: Scandinavia |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth-Ayerst International</td>
</tr>
</tbody>
</table>
| 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 |

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
</tr>
</thead>
</table>
| 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 |

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
</table>
| 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 (HAMD ≤ 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) |

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
</tr>
</thead>
</table>
| ITT: Yes  
| Post randomization exclusions: Not reported |

<table>
<thead>
<tr>
<th>ATTRITION:</th>
</tr>
</thead>
</table>
| 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 |

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
</table>
| 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 |

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
</tr>
</tbody>
</table>
### Evidence Table 1

**Major Depressive Disorder Adults**

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

| OUTCOME ASSESSMENT: | **Primary Outcome Measures:** MADRS total score  
Secondary Outcome Measures: HAM-D-17; response and remission rates  
Timing of assessments: Baseline, weeks 1,2,3,4,6, and 8. |
|---|---|

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
</table>
| • No statistically significant differences between escitalopram and venlafaxine XR in response (77.4 % vs. 79.6%) and remission (69.9% vs. 69.7%)  
• In the LOCF analysis there was no difference between groups in total MADRS or HAM-D-17 scores  
• Survival analysis of the ITT group showed that escitalopram patients achieved sustained remission 6.6 days faster than the venlafaxine XR patients (p < 0.01) |

| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** Yes |
|---|---|

| ATTRITION: | **Loss to follow-up:** 13.7%; escitalopram: 14%; venlafaxine XR: 13%  
**Withdrawals due to adverse events:** Escitalopram: 7.5%; venlafaxine XR: 11.2% |
|---|---|

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
</table>
| • Nausea: venlafaxine XR: 26%; escitalopram: 17% (p < 0.05).  
• Increased sweating: venlafaxine XR: 12.5%; escitalopram: 6% (p < 0.05).  
• Constipation: venlafaxine XR: 6%; escitalopram: 2% (p < 0.05) |

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

### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** MADRS; CGI-S
- **Secondary Outcome Measures:** MADRS-S
- **Timing of assessments:** Baseline, weeks 1, 4 and 8

### RESULTS:
- MADRS adjusted for baseline MADRS and investigator specialty: Esc -22.4 Cit -20.3 (p < 0.05), between groups mean difference 2.1 (95% CI 0.01-4.21; p < 0.05)
- Responders: (50% decrease in MADRS) Esc 76.1% Cit 61.3% (p = 0.008)
- Remitters: Esc 56.1% Cit 43.6% (p = 0.04); NNT for remission: 9
- MADRS-S Esc -9.9 Cit -8.6 (p < 0.05)
- CGI-S Esc -2.3 Cit -2.12 (p = 0.65)
- Overall discontinuation was significantly higher in the Cit (10.6%) than in the Esc (4.3%) group (p = 0.005)

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes, 14 (11 protocol violations and 3 GCP violations)

### ATTRITION:

<table>
<thead>
<tr>
<th>Escitalopram</th>
<th>Citalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (4.3%)</td>
<td>15 (10.6%)</td>
</tr>
<tr>
<td>4 (2.9%)</td>
<td>9 (6.3%)</td>
</tr>
<tr>
<td>1 (0.7%)</td>
<td>4 (2.8%)</td>
</tr>
</tbody>
</table>

### ADVERSE EVENTS:
- 46 patients had adverse events escitalopram: 21 (14.8%), citalopram: 25 (16.4%) (p = 0.70)
- No significant difference was reported between treatment groups

### QUALITY RATING:
Fair
**Evidence Table 1**

**Major Depressive Disorder Adults**

| STUDY: | Authors: Nemeroff CB, et al. 
Year: 1995 
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Solvay Pharmaceuticals</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT 
Setting: Multi-center 
Sample size: 95 |
| INTERVENTION: | **Drug:** 
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; sertraline 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%) |
<table>
<thead>
<tr>
<th>Authors: Nemeroff CB, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 1995</td>
</tr>
<tr>
<td>Country: US</td>
</tr>
</tbody>
</table>

### 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, MSSSI and clinical laboratory evaluation at week 7 only.

### RESULTS:
- Both treatment groups resulted in significant improvements of depression scores compared to baseline.
- Mean decrease in HAMD: sertraline: -10.98, fluvoxamine: -10.61.
- There was no significant difference in efficacy between the treatment groups.

### ANALYSIS:
*ITT:* Yes
*Post randomization exclusions:* Yes

### ATTRITION:
*Loss to follow-up:* 30.9%; fluvoxamine: 42.9%, sertraline: 18.5%.
*Withdrawals due to adverse events:* fluvoxamine: 18.4%, sertraline: 2.2% (p-value not reported).
*Loss to follow-up differential high:* Yes

### ADVERSE EVENTS:
- Significantly more patients withdrew due to adverse events in the fluvoxamine group (n = 9) than in the sertraline group (n = 1) (p = 0.016).
- Significantly greater sexual dysfunction was reported in the sertraline group (28%) than in the fluvoxamine group (10%); p = 0.047.
- Most common adverse events: sertraline: insomnia (34.8%), headache (32.6%), diarrhea (23.9%), ejaculatory abnormality (22.2%); fluvoxamine: nausea (30.6%), headache (26.5%), insomnia (26.5%), somnolence (24.5%).

### QUALITY RATING:
Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Newhouse PA, et al.\(^3\)  
                    Year: 2000  
                    Country: US |
| **FUNDING:**     | Pfizer, Inc.                     |
| **DESIGN:**      | Study design: RCT  
                    Setting: Multi-center  
                    Sample size: 236 |
| **INTERVENTION:**| Sertraline  
                    Dose: 50-100 mg/d  
                    Duration: 12 weeks  
                    (Doses could be doubled after 4 weeks)  
                    Fluoxetine  
                    Dose: 20-40 mg/d  
                    Duration: 12 weeks |
| **INCLUSION:**   | > 60 years of age; DSM-III-R criteria for major depression; > 18 on 24 item HAM-D |
| **EXCLUSION:**   | Other psychiatric disorder; significant physical illness; non-responders to antidepressants or ECT therapy |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Chloral hydrate, temazepam for sleep |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
                    Mean age: sertraline: 68, fluoxetine: 67  
                    Gender (% female): sertraline: 63.2%, fluoxetine: 51.3%  
                    Ethnicity: sertraline: 95.7% white, 3.4% black, other 0.9%, fluoxetine: 100% white  
                    Other population characteristics: Not reported |
**Authors:** Newhouse PA, et al.  
**Year:** 2000  
**Country:** US  

| OUTCOME ASSESSMENT: | Measures: 24 item HAM-D, HAM-A, CGI-S, CGI-I, BDI, MADRS, POMS, Q-LES-Q, digit symbol substitution test, SLT  
**Timing of assessments:** Baseline, week 1, 2, 3, 4, 6, 8, 10, 12 |

| RESULTS: |  
• Sertraline and fluoxetine were effective in the relief of depressive symptoms  
• There were no significant differences between sertraline and fluoxetine on the primary efficacy measures (HAM-D and CGI)  
  HAMD Responders: sertraline: 73%, fluoxetine: 71%  
  HAMD remitters: sertraline: 45%, fluoxetine: 46%  
• Overall there was no significant differences between sertraline and fluoxetine on cognitive measures (SLT and digit symbol substitution test) |

| ANALYSIS: |  
**ITT:** Yes  
**Post randomization exclusions:** Yes |

| ATTRITION: |  
**Loss to follow-up:** 32.2%; sertraline: 31.6%, fluoxetine: 32.8%  
**Withdrawals due to adverse events:** sertraline: 18.8%, fluoxetine: 24.4% (p = 0.5)  
**Loss to follow-up differential high:** No |

| AdVERSE EVENTS: |  
• Weight reduction: sertraline: -1.7lb, fluoxetine: -3.2lb (p = 0.018)  
• Otherwise no statistically significant differences between groups  
• Headache: sertraline: 33.6%, fluoxetine: 31.4%  
• Dizziness: sertraline: 7.8%, fluoxetine: 10.2%  
• Dry mouth: sertraline: 15.5%, fluoxetine: 7.6%  
• Nausea: sertraline: 14.7%, fluoxetine: 18.6%  
• Diarrhea: sertraline: 22.4%, fluoxetine: 16.1% |

| QUALITY RATING: | Fair |
## Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Nieuwstraten C, et al.  
Year: 2001  
Country: Canada |
| FUNDING: | Not reported |
| DESIGN: | Study design: Meta-analysis  
Number of patients: 1332 |
<p>| AIMS OF REVIEW: | To assess the benefits and risks of bupropion vs. SSRIs in major depression |
| TIME PERIOD COVERED: | 1966-1999 |
| CHARACTERISTICS OF INCLUDED STUDIES: | RCTs, study durations: 6-16 weeks, median 7 weeks |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Age: 36 to 70 yrs; proportion of females: 48.0% to 61.8% |
| <strong>Authors</strong> | Nieuwstraten C, et al. |
| <strong>Year</strong> | 2001 |
| <strong>Country</strong> | Canada |
| <strong>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</strong> | Bupropion vs. sertraline (3 trials), bupropion vs. paroxetine (1 trial), bupropion vs. fluoxetine (1 trial) |
| <strong>MAIN RESULTS:</strong> | 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 |
| <strong>ADVERSE EVENTS:</strong> | 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) |
| <strong>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</strong> | Yes |
| <strong>STANDARD METHOD OF APPRAISAL OF STUDIES:</strong> | Yes |
| <strong>QUALITY RATING:</strong> | Good |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Panzer MJ\textsuperscript{1}  
Y = 2005  
Country: Multinational |
| **FUNDING:**     | GSK                      |
| **DESIGN:**      | Study design: Systematic review  
Number of patients: 7299 |
| **AIMS OF REVIEW:** | To assess medication response of SSRIs to other ADs in patients suffering from MDD with secondary anxious feature |
| **STUDIES INCLUDED IN REVIEW:** | 28 studies |
| **TIME PERIOD COVERED:** | Not reported |
| **CHARACTERISTICS OF INCLUDED STUDIES:** | Double blinded, comparative trials of SSRIs to other types of ADs |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** | Adult in- and outpatients with MDD as the primary diagnosis with anxious tendencies but not anxiety as a comorbidity |
| Authors: Panzer MJ |  
| Year: 2005 |  

| CHARACTERISTICS OF INTERVENTIONS: | SSRIs vs. bupropion (7 studies); mirtazapine vs. SSRIs or amitriptyline (5 studies including 1 meta-analysis); TCAs vs. SSRIs (3 studies); SSRIs vs. SSRIs (2 studies); bupropion vs. TCAs (3 studies); nefazadone vs. TCAs or SSRIs (4 studies); venlafaxine vs. trazadone or SSRIs (4 studies) |

| MAIN RESULTS: |  
|  
| • SSRIs have not been shown to be more effective than TCAs in the treatment of anxious depression  
| • Limited evidence that mirtazapine, bupropion and nefazadone may be superior to SSRIs |

| ADVERSE EVENTS: | Not reported |

| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Yes- MedLine and PsychInfo |

| STANDARD METHOD OF APPRAISAL OF STUDIES: | Not reported |

| QUALITY RATING: | Fair |
### Evidence Table 1  
**Major Depressive Disorder Adults**

| **STUDY:** | **Authors:** Patris M, et al.  
**Year:** 1996  
**Country:** France |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Not specifically stated, one author is an employee of Lundbeck</td>
</tr>
</tbody>
</table>
| **DESIGN:** | **Study design:** RCT  
**Setting:** Multi-center (general practices)  
**Sample size:** 357 |
| **INTERVENTION:** | **Drug:** Citalopram  
**Dose:** 20 mg/d  
**Duration:** 8 weeks  
**Fluoxetine:** 20 mg/d  
**Duration:** 8 weeks |
| **INCLUSION:** | Ages 21-73; met DSM III R criteria for unipolar depression with a score on MADRS of 22 or more |
| **EXCLUSION:** | Dysthymia; cyclothymia; decrease in MADRS > 20% from baseline during the run-in period; pregnancy; lactation; failure to use contraception; alcohol or drug abuse within the past year; MAOI use within 2 weeks; severe somatic disease; organic brain syndrome; schizophrenia; epilepsy; other neurological diseases; suicide risk; known hypersensitivity |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Benzos allowed; no other psychotropics allowed; "Drug treatment for concurrent somatic illness was limited as much as possible"; high percentages of patients in both groups (83% and 81%) received concomitant medications; the use of non-psychotropic medication was similar in the 2 groups |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Yes  
**Mean age:** 43.5 years; citalopram: 44, fluoxetine: 43  
**Gender (female%):** citalopram: 79%, fluoxetine: 76%  
**Ethnicity:** Not reported  
**Other population characteristics:** Major depression single episode: citalopram: 42%, fluoxetine: 46%; recurrent episodes: citalopram: 58%, fluoxetine: 54% |
| **Authors:** Patris M, et al.  
**Year:** 1996  
**Country:** France |
|---|
| **OUTCOME ASSESSMENT:** | **Measures:** Primary outcome: MADRS, secondary outcomes: HAM-D₁₇, CGI  
**Timing of assessments:** Baseline, 1, 2, 4, 6, 8 weeks |
| **RESULTS:** | No difference in mean MADRS score at endpoint or in mean change from baseline; mean change: citalopram: -20.7, fluoxetine: -19.4; responders (reduction in score from baseline > 50%) at endpoint: citalopram: 78 %, fluoxetine: 76 %; no statistical difference |
| **ANALYSIS:** | **ITT:** No  
**Post randomization exclusions:** Yes |
| **ATTRITION:** | **Loss to follow-up:** 12.6; citalopram: 13.9%, fluoxetine: 11.4%  
**Withdrawals due to adverse events:** citalopram: 5.7%, fluoxetine: 2.2%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** | • No significant differences  
• Reported at least one adverse event: citalopram: 50%, fluoxetine: 52%  
• No difference in the global evaluation of the interference of adverse events with the patient’s daily functioning: citalopram: 34%, fluoxetine: 33% |
| **QUALITY RATING:** | Fair |
### Evidence Table 1  
**Major Depressive Disorder Adults**

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

**Authors:** Rapaport ME, et al.  
**Year:** 1996  
**Country:** US

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Measures: HAM-D-21, HAM-A, CGI-S, Raskin–Covi Scale, Hopkins Symptom Checklist, TESS (Specific treatment-emergent signs and symptoms) Barnes Akathisia Scale, Modified Scale for Suicidal Ideation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments:</td>
<td>Primary outcome measures weekly; secondary outcome measures at baseline and endpoint</td>
</tr>
</tbody>
</table>

| RESULTS: | • No statistically significant differences between fluvoxamine and fluoxetine in all outcome measures  
• Both drugs significantly improved scores on HAM-D (<10 for both groups at endpoint) |

| ANALYSIS: | ITT: Yes  
Post randomization exclusions: Yes (7) |

| ATTRITION: | Loss to follow-up: 16%  
Withdrawals due to adverse events: 4%  
Loss to follow-up differential high: No |

| ADVERSE EVENTS: | • Overall, no difference in the rate of adverse events were reported between fluvoxamine and fluoxetine and there were no differences in the average event severity (1.12 vs. 1.13; p = NR)  
• Significantly more patients on fluoxetine than on fluvoxamine reported nausea (42.5% vs. NR; p = 0.03)  
• Other frequent adverse events:  
  headache: fluoxetine 53%, fluvoxamine 50% (p not significant)  
  vomiting: fluoxetine 13%, fluvoxamine 4% (p not significant)  
  daytime agitation: fluoxetine 47%, fluvoxamine 32% (p not significant) |

<p>| QUALITY RATING: | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Rudolph RL, et al.  
Year: 1999  
Country: US |
| FUNDING:         | Wyeth-Ayerst Research            |
| **DESIGN:**      | Study design: RCT  
Setting: Multi-center  
Sample size: 301 |
| **INTERVENTION:**| Drug: Venlafaxine XR  
Dose: 75-225 mg/d  
Duration: 8 weeks  
Fluoxetine  
Dose: 20-60 mg/d  
Duration: 8 weeks  
Placebo  
Dose: N/A  
Duration: 8 weeks  
Initial dosage could be increased after 2 weeks |
| **INCLUSION:**   | ≥ 18 years of age; met DSM-IV criteria for MDD; symptoms of depression for one month or more before study; pre-study and baseline score of ≥ 20 on the 21 item HAM-D |
| **EXCLUSION:**   | Known hypersensitivity to either drug; specified medical conditions; bipolar disorder; psychotic disorder not associated with depression; drug or alcohol abuse; pregnant or lactating |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Chloral hydrate for sleep |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: 40  
Gender (female%): venlafaxine: 73%, fluoxetine: 69%, placebo: 64%  
Ethnicity: Not reported  
Other population characteristics: No statistically significant differences between groups in baseline mean 21-HAMD scores, mean MADRS scores, or duration of the current episode of depression; 24% used fluoxetine in past and 2% used venlafaxine in past |
**Authors:** Rudolph RL, et al.  
**Year:** 1999  
**Country:** US

| OUTCOME ASSESSMENT: | Measures: HAMD-21, MADRS, CGI, HAM-A)  
Timing of assessments: Weeks 1, 2, 3, 4, 6, 8 |
|---------------------|-------------------------------------------------|

**RESULTS:**
- No significant difference between venlafaxine and fluoxetine treatment on the 21-HAMD or MADRS at endpoint in the LOCF analysis  
- At endpoint in the LOCF analysis, venlafaxine patients showed a significant difference from placebo in the MADRS, CGI, and HAM-D depressed mood item  
- Fluoxetine patients only showed a significant difference in the HAM-D depressed mood item

**ANALYSIS:**
- **ITT:** Yes  
- **Post randomization exclusions:** Yes

**ATTRITION:**
- **Loss to follow-up:** 23%; venlafaxine: 19%, fluoxetine: 28%, placebo: 21%  
- **Withdrawals due to adverse events:** venlafaxine: 6%, fluoxetine: 9%  
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**
- Venlafaxine patients experienced significantly more dizziness and nausea than fluoxetine or placebo patients (p < 0.05)  
- Venlafaxine and fluoxetine patients experienced significantly more asthenia and tremor than placebo patients

**QUALITY RATING:** Fair
# Evidence Table 1

**Major Depressive Disorder Adults**

<table>
<thead>
<tr>
<th>STUDY:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Rush AJ, et al.</td>
</tr>
<tr>
<td><strong>Year:</strong> 1998</td>
</tr>
<tr>
<td><strong>Country:</strong> US and Canada</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FUNDING:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bristol Myers Squibb, Seay Center for Research (UT Southwestern), NIMH</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>DESIGN:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design:</strong> Pooled analysis from 3 RCTs: Gillin 1997,65 Armitage 1997,66 Rush 199877</td>
</tr>
<tr>
<td><strong>Setting:</strong> Multi-center</td>
</tr>
<tr>
<td><strong>Sample size:</strong> 125</td>
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</tbody>
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<table>
<thead>
<tr>
<th>INTERVENTION:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug:</strong></td>
</tr>
<tr>
<td><strong>Nefazodone</strong></td>
</tr>
<tr>
<td><strong>Dose:</strong> 200-500 mg/d</td>
</tr>
<tr>
<td><strong>Duration:</strong> 8 weeks</td>
</tr>
<tr>
<td><strong>Fluoxetine</strong></td>
</tr>
<tr>
<td><strong>Dose:</strong> 20-40 mg/d</td>
</tr>
<tr>
<td><strong>Duration:</strong> 8 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INCLUSION:</th>
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</thead>
<tbody>
<tr>
<td>Outpatient; ages 19-55; non-psychotic moderate to severe MDD by DSM-III-R criteria; minimum score of 18 on HAM-D17; 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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXCLUSION:</th>
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</thead>
<tbody>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER MEDICATIONS/INTERVENTIONS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>POPULATION CHARACTERISTICS:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groups similar at baseline:</strong> No; more people in their second or more depressive episode in fluoxetine group</td>
</tr>
<tr>
<td><strong>Age:</strong> 36.5; nefazodone: 36, fluoxetine: 37</td>
</tr>
<tr>
<td><strong>Gender</strong> (% female) nefazodone: 59%, fluoxetine: 70%</td>
</tr>
<tr>
<td><strong>Ethnicity:</strong> nefazodone: 78% white, 9% black, 0% Asian, fluoxetine: 85% white, 7% black, 5% Asian</td>
</tr>
<tr>
<td><strong>Other population characteristics:</strong> Not reported</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td><strong>Country:</strong> US and Canada</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th><strong>Measures:</strong> HAM-D17, 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</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of assessments:</strong> Baseline, weeks 1, 2, 3, 4, 6, 8</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS:</th>
<th>• No difference in efficacy between groups as measured by change in HAM-D17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Response (&lt; 10 on HAMD17): nefazodone: 47%, fluoxetine: 45%</td>
</tr>
<tr>
<td></td>
<td>• On EEG: increased sleep efficiency, decreased awakenings and decreased % AMT (awake and moving time) for nefazodone as compared to fluoxetine</td>
</tr>
<tr>
<td></td>
<td>• Also significant differences on sleep disturbance factors of the HAM-D and IDS-C and IDS-SR favoring nefazodone over fluoxetine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
<th><strong>ITT:</strong> Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Post randomization exclusions:</strong> Yes</td>
</tr>
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<table>
<thead>
<tr>
<th>ATTRITION:</th>
<th><strong>Loss to follow-up:</strong> 17%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Withdrawals due to adverse events:</strong> nefazodone 9%, fluoxetine 8%</td>
</tr>
<tr>
<td></td>
<td><strong>Loss to follow-up differential high:</strong> Not reported</td>
</tr>
</tbody>
</table>

| ADVERSE EVENTS: | No statistical comparisons reported |

| QUALITY RATING: | Fair |
## Evidence Table 1  Major Depressive Disorder Adults

<table>
<thead>
<tr>
<th>STUDY:</th>
</tr>
</thead>
</table>
| **Authors:** Schatzberg et al.  
**Year:** 2002  
**Country:** US |
| FUNDING: |
| Organon Pharma |
| DESIGN: |
| **Study design:** RCT  
**Setting:** Multi-center  
**Sample size:** 255 |
| INTERVENTION: |
| **Drug:**  
**Dose:**  
**Duration:** |
| Mirtazapine  
15-45 mg/d  
8 weeks |
| Paroxetine  
20-40 mg/d  
8 weeks |
| (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-D17 |
| EXCLUSION: |
| HAMD decrease > 20% between screening and baseline; untreated or unstable clinically significant medical condition or lab/physical exam abnormality; history of seizures; recent drug or alcohol abuse or any principal psychiatric condition other than MDD; presence of psychotic features; suicide attempt in current episode; use of MAOI within 2 weeks, or other psychotropics or herbal treatments within 1 week; use of paroxetine or mirtazapine for the current episode; ECT therapy within 6 months; use of treatment for memory deficits; prior intolerance or lack of efficacy to mirtazapine or paroxetine in the past; patients who failed more than one adequate trial of an antidepressant for the current episode |
| OTHER MEDICATIONS/INTERVENTIONS: |
| Chloral hydrate or zolpidem for sleep induction; therapy for conditions like DM, hypothyroidism, high blood pressure, chronic respiratory conditions was allowed if they had been receiving for at least 1 month prior to screening visit |
| POPULATION CHARACTERISTICS: |
| Groups similar at baseline: Yes  
**Mean age:** 72  
**Gender** (% female): mirtazapine: 50%, paroxetine: 53%  
**Ethnicity:** Not reported  
Other population characteristics: Not reported |
| **OUTCOME ASSESSMENT:** | **Measures:** HAM-D 17, CGI-S, CGI-I  
**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8 |
|------------------------|---------------------------------------------------------------|
| **RESULTS:**           | • Mean Ham-D17 scores significantly lower with mirtazapine at weeks 1, 2, 3, 6 but no difference at 8 week endpoint  
• Trend towards higher response and remission rates with mirtazapine but only significant difference at 2 weeks (response) and 6 weeks (remission)  
• Time to response: mirtazapine mean 26 days, paroxetine 40 days, p = -.016 for Kaplan-Meier plot comparing the two  
• No difference in CGI Improvement response |
| **ANALYSIS:**          | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:**         | **Loss to follow-up:** 26.8%  
**Withdrawals due to adverse events:** 20.4%; mirtazapine 14.8%, paroxetine 26.2% (p < 0.05)  
**Loss to follow-up differential high:** Moderate |
| **ADVERSE EVENTS:**    | • Frequency of treatment related adverse events: mirtazapine: 79.7%, paroxetine: 82.5%  
• Significant differences: dry mouth: mirtazapine 26.6%, paroxetine 10.3%; weight gain: mirtazapine 10.9%, paroxetine 0%; nausea: mirtazapine 6.3%, paroxetine 19.0% |
| **QUALITY RATING:**    | Fair |
**Evidence Table 1  Major Depressive Disorder Adults**

| STUDY: Authors: Schöne W, et al.  
Year: 1993  
Country: Austria and Germany |
| FUNDING: SmithKline, Beecham |
| DESIGN: Study design: RCT  
Setting: Geriatric outpatients at 6 centers in Austria and Germany  
Sample size: 108 |
| INTERVENTION:  
Drug:  
Dose:  
Duration:  
Paroxetine  
20-40 mg/d  
6 weeks  
Fluoxetine  
20-60 mg/d  
6 weeks |
| INCLUSION: Age 65 or greater; met DSM-IIR for MDD; HAM-D21 score > 18 at baseline |
| EXCLUSION: Severe physical illness (not specified further); senile dementia; schizophrenia or organic brain syndrome; known abusers of alcohol; receipt of ECT within prior 3 mos.; MAOI or oral neuroleptics within 14 days; depot neuroleptics with 4 wks.; patients whose baseline HAM-D improved by > 20% or whose score was < 18 after placebo run-in were also excluded |
| OTHER MEDICATIONS/INTERVENTIONS: Prohibited psychotropic meds except temazapam for sleep. Other allowed nonpsychotropic medications not specifically reported. |
| POPULATION CHARACTERISTICS: Groups similar at baseline: Yes  
Mean age: 74; paroxetine: 74.3, fluoxetine: 73.7  
Gender (% female): 87%, paroxetine: 83%, fluoxetine: 90%  
Ethnicity: Not reported  
Other population characteristics: History of prior depression: paroxetine: 94%, fluoxetine: 88%; duration of present episode > 12 months: paroxetine: 24%, fluoxetine: 27% |
| **Authors:** Schöne W, et al.  
**Year:** 1993  
**Country:** Germany |
|---|

**OUTCOME ASSESSMENT:**  
*Measures:* HAM-D 21, MADRS, CGI  
*Timing of assessments:* Days 7, 21, 42

**RESULTS:**  
- No significant difference in mean changes on HAM-D score  
- HAM-D responders at week 6 (i.e. reduction > 50% from baseline HAM-D 21): paroxetine: 37.5%, fluoxetine: 16% (p = 0.03)  
- MADRS: no significant difference in mean change scores between groups  
- MADRS responders at week 6 (i.e. reduction > 50% from baseline MADRS): paroxetine 37.5%, fluoxetine 17.5%, (p = 0.04)

**ANALYSIS:**  
*ITT:* Yes  
*Post randomization exclusions:* Yes

**ATTRITION:**  
*Loss to follow-up:* Not reported  
*Withdrawals due to adverse events:* 12%; paroxetine: 11.1%, fluoxetine: 13.5%  
*Loss to follow-up differential high:* No

**ADVERSE EVENTS:**  
No significant differences between paroxetine and fluoxetine on overall incidence of adverse events or of any specific adverse event

**QUALITY RATING:**  
Fair
### Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Sechter D, et al. \(^8\)  
Year: 1999  
Country: France |
| FUNDING: | Pfizer France |
| DESIGN: | Study design: RCT  
Setting: Multi-center (45 private psychiatrists)  
Sample size: 234 |
| INTERVENTION: |  
**Drug:**  
Sertraline  
Fluoxetine  
**Dose:**  
50-150 mg/d  
20-60 mg/d  
24 weeks  
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 methylidopa; drug sensitivity or lactose intolerance; previous failure on three or more antidepressants |
| OTHER MEDICATIONS/ INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: sertraline: 43.4, fluoxetine: 42.5  
Gender (% female): sertraline: 66.7%, fluoxetine: 68.1%  
Ethnicity: Not reported  
Other population characteristics: Patients with first depressive episode: sertraline: 27.4%, fluoxetine: 21.0% |
**Authors:** Sechter D, et al.  
**Year:** 1999  
**Country:** France

| OUTCOME ASSESSMENT: | Measures: HAM-D, CGI-I, CGI-S, Covi, Sickness Impact Profile, HAD scores, Leeds Sleep Evaluation  
Timing of assessments: Baseline, weeks 2, 4, 8, 12, 18, 24 |
|-------------------|-------------------------------------------------|

| RESULTS: |  
At study endpoint both treatment groups had significant improvements over baseline on all efficacy variables (p < 0.001)  
There were no significant differences between study groups in outcome measures (HAM-D, CGI, Covi) at any point in time; the magnitude of changes was higher for sertraline.  
Response was observed in 74% in sertraline patients versus 64% in fluoxetine patients on HAM-D  
The Leeds Sleep Evaluation Scale showed a trend favoring sertraline but no significant difference compared to fluoxetine  
Both treatments showed significant improvements in SIP  
SIP sub scores showed significant greater improvements for sertraline relating to sleep and rest (p = 0.04), emotional behavior (p = 0.04), and ambulation (p = 0.05) |
|-----------|-------------------------------------------------|

| ANALYSIS: |  
**ITT:** Yes  
**Post randomization exclusions:** Yes |
|-----------|-------------------------------------------------|

| ATTRITION: |  
**Loss to follow-up:** 29.2%; sertraline: 24.7%, fluoxetine: 33.6%  
**Withdrawals due to adverse events:** sertraline: 6%, fluoxetine: 10%  
**Loss to follow-up differential high:** No |
|-----------|-------------------------------------------------|

| ADVERSE EVENTS: |  
There were no significant differences in the incidence of adverse events between treatment groups  
Most common adverse event: nausea: sertraline: 23%, fluoxetine: 17% |
|----------------|-------------------------------------------------|

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
<th>Fair</th>
</tr>
</thead>
</table>
### Evidence Table 1  Major Depressive Disorder Adults

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

**POPULATION CHARACTERISTICS:**
- **Groups similar at baseline:** Yes
- **Mean age:** sertraline: 40 bupropion: 39
- **Gender (% female):** sertraline: 48%, bupropion SR: 48%
- **Ethnicity: (% white)** sertraline: 94%, bupropion SR: 93%
- **Other population characteristics:** No significant differences in diagnosis

**OUTCOME ASSESSMENT:**
- **Measures:** Sexual function assessment, Sexual desire disorder, Sexual arousal disorder, Orgasm dysfunction, Premature ejaculation (men only), patient rated overall sexual satisfaction on 6 point Likert scale
- **Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8, 12, 16

**RESULTS:**
- Significantly more sertraline patients developed one of the following sexual dysfunctions compared to bupropion SR patients: sexual arousal disorder, orgasm dysfunction, or premature ejaculation (men only); (men: 63% and 15%, respectively, p < 0.001; women: 41% and 7%, respectively, p < 0.001)
- Beginning on day 21 and continuing throughout the study, significantly more bupropion SR-treated patients were satisfied with their overall sexual functioning compared with sertraline-treated patients

**ANALYSIS:**
- **ITT:** Yes
- **Post randomization exclusions:** Yes

**ATTRITION:**
- **Loss to follow-up:** 31.5%; bupropion SR: 29%, sertraline: 34%
- **Withdrawals due to adverse events:** 1.6%; bupropion SR: 0%, sertraline: 1.6%
- **Loss to follow-up differential high:** Yes

**ADVERSE EVENTS:**
- Not reported

**QUALITY RATING:**
- Fair
<table>
<thead>
<tr>
<th>Evidence Table 1</th>
<th>Major Depressive Disorder Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: Silverstone PH et al.</td>
</tr>
<tr>
<td></td>
<td>Year: 1999, 2001 (subgroup analysis)</td>
</tr>
<tr>
<td></td>
<td>Country: Canada</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Wyeth-Ayerst Research</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Multi-center</td>
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<tr>
<td></td>
<td>Sample size: 368</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td>Drug:  Venlafaxine XR</td>
</tr>
<tr>
<td></td>
<td>Dose:  75-225 mg/d (Could be increased to 150 mg/d on day 14 and 225 mg/d on day 28)</td>
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<tr>
<td></td>
<td>Duration: 12 weeks</td>
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<tr>
<td></td>
<td>Fluoxetine 20-60 mg/d (Could be increased to 40 mg/d on day 14 and 60 mg/d on day 28)</td>
</tr>
<tr>
<td></td>
<td>Duration: 12 weeks</td>
</tr>
<tr>
<td></td>
<td>Placebo N/A 12 weeks</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>Chloral hydrate or zopiclone for sleep; cisapride for nausea.</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: placebo: 41.6, venlafaxine: 41.1, fluoxetine: 43.2</td>
</tr>
<tr>
<td></td>
<td>Gender (female%): venlafaxine: 64%, fluoxetine: 60%; placebo: 57.6</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Not reported</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Subgroup analysis: Patients with GAD (n = 92)</td>
</tr>
<tr>
<td><strong>Authors:</strong> Silverstone PH, et al.</td>
<td><strong>Measures:</strong> 21 item HAM-D, HAM-A, the Covi Scale, Hospital Anxiety and Depression scale, CGI scale</td>
</tr>
<tr>
<td><strong>Year:</strong> 1999, 2001</td>
<td><strong>Timing of assessments:</strong> Baseline, days 7, 14, 21, 28, 42, 56, 84</td>
</tr>
<tr>
<td><strong>Country:</strong> Canada</td>
<td><strong>RESULTS:</strong></td>
</tr>
<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
<td>No statistical comparisons between fluoxetine and venlafaxine (just placebo)</td>
</tr>
<tr>
<td>Response: 50% decrease in HAMD or HAMA score of 1 or 2 on CGII</td>
<td>• HAM-D scores in the venlafaxine and fluoxetine groups dropped significantly when compared with placebo</td>
</tr>
<tr>
<td>Remission Score &lt; 8 on HAMD</td>
<td>• Venlafaxine had significantly more HAM-A responders at week 12 than fluoxetine</td>
</tr>
<tr>
<td><strong>RESULTS:</strong></td>
<td>• The HAM-D remission rate in the venlafaxine group was significant compared to placebo at weeks 3, 4, 6, 8, 12 &amp; final</td>
</tr>
<tr>
<td><strong>RESULTS:</strong></td>
<td>• The HAM-D remission rate in the fluoxetine group was significant compared to placebo at weeks 8, 12, &amp; final</td>
</tr>
<tr>
<td><strong>RESULTS:</strong></td>
<td><strong>Subgroup analysis:</strong></td>
</tr>
<tr>
<td><strong>RESULTS:</strong></td>
<td>• There were no significant differences in outcome measures between the active treatment groups (compared to placebo)</td>
</tr>
<tr>
<td><strong>RESULTS:</strong></td>
<td>• 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 &lt; 0.05)</td>
</tr>
<tr>
<td><strong>RESULTS:</strong></td>
<td>• Onset of action seemed to be slower in patients with GAD compared to patients without</td>
</tr>
<tr>
<td><strong>ANALYSIS:</strong></td>
<td><strong>ITT:</strong> Yes</td>
</tr>
<tr>
<td><strong>ANALYSIS:</strong></td>
<td><strong>Post randomization exclusions:</strong> Yes</td>
</tr>
<tr>
<td><strong>ATTRITION:</strong></td>
<td><strong>Loss to follow-up:</strong> 32%; venlafaxine xr: 29%, fluoxetine: 26%, placebo: 40%</td>
</tr>
<tr>
<td><strong>ATTRITION:</strong></td>
<td><strong>Withdrawals due to adverse events:</strong> venlafaxine xr: 10%, fluoxetine: 7%</td>
</tr>
<tr>
<td><strong>ATTRITION:</strong></td>
<td><strong>Loss to follow-up differential high:</strong> No</td>
</tr>
<tr>
<td><strong>ADVERSE EVENTS:</strong></td>
<td>Significantly more dizziness (p &lt; 0.001) and sweating (p &lt; 0.05) occurred with venlafaxine than with fluoxetine</td>
</tr>
<tr>
<td><strong>QUALITY RATING:</strong></td>
<td>Fair</td>
</tr>
</tbody>
</table>
### Evidence Table 1  Major Depressive Disorder

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

*Note: From here on venlafaxine refers to venlafaxine XR*
### Authors: Sir A, et al.
Year: 2005

#### OUTCOME ASSESSMENT:
- **Primary Outcome Measures:** Q-LES-Q
- **Secondary Outcome Measures:**
  - HAM-D, HAM-A, CGI-S, CGI-I, VAS for pain and depression, Endicott Work Productivity Scale (EWPS), Antidepressant Discontinuation Scale (ADDS)
  - Discontinuation emergence: any symptom present in week 9 or 10 not present in first 8 weeks or that increased in severity during weeks 9 or 10.
- **Timing of assessments:** Baseline and every week thereafter.

#### RESULTS:
**Efficacy**
- Change in Q-LES-Q: Ser 16.8 ± 1.77 Ven 17.5 ± 14.5 p = 0.74
- Change in HAM-D: Ser -15.9 ± 0.95 Ven -14.3 ± 0.94 p = 0.17
- Change in HAM-A: Ser -14.1 ± 0.99 Ven -12.9 ± 0.99 p = 0.32
- Mean CGI-S: Ser 2.0 ± 1.22 Ven 2.2 ± 1.25 p = 0.45
- No significant difference exists in terms of efficacy between venlafaxine and sertraline.

**Discontinuation**
- Number of discontinuation-emergent symptoms with frequency of >10% vs. other drug: venlafaxine 4, sertraline 0
- Number of discontinuation-emergent symptoms of at least moderate intensity that were more than twice as common as for the other drug: venlafaxine 8, sertraline 1
- Discontinuation of sertraline associated with fewer discontinuation-emergent symptoms than for discontinuation of venlafaxine. (Although not all differences achieved statistical significance, there is a clear trend.)

#### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** No

<table>
<thead>
<tr>
<th>ATTRITION:</th>
<th>Overall</th>
<th>Sertraline</th>
<th>Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>23%</td>
<td>16.5%</td>
<td>29.8%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>6%</td>
<td>3.8%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### ADVERSE EVENTS:
- AE rates (n(%) ) include those that were evident in taper-off period (2 additional weeks following initial 8 weeks) which results in higher rates than normally found.
- Asthenia: Ser 21(26.6) Ven 21(25.6)
- Headache: Ser 35(44.3) Ven 27(32.1)
- Dry mouth: Ser 32(40.5) Ven 20(23.8)
- Nausea: Ser 41(51.9) Ven 40(47.6)
- Dizziness: Ser 26(32.9) Ven 22(26.2)
- Insomnia: Ser 28(35.4) Ven 23(27.4)
- Somnolence: Ser 17(21.5) Ven 22(26.2)
- Yawning: Ser 24(30.4) Ven 24(28.6)
- Sweating: Ser 25(31.6) Ven 18(21.4)

#### QUALITY RATING: Good
## Evidence Table 1

### Major Depressive Disorder Adults

| STUDY: | Authors: Tylee A, et al.  
Year: 1997  
Country: UK |
| FUNDING: | Wyeth |
| DESIGN: | Study design: RCT  
Setting: Multi-center (34 UK general practices)  
Sample size: 341 |
| INTERVENTION: | Drug: Venlafaxine  
Dose: 75 mg/day, fixed dose  
Duration: 12 weeks + 7 day post follow-up  
Fluoxetine  
Dose: 20 mg/day, fixed dose  
Duration: 12 weeks + 7 day post follow-up |
| INCLUSION: | ≥18 yrs; DSM-IV criteria for major depression; MADRS ≥ 19; depressive symptoms for more than 2 weeks |
| EXCLUSION: | Use of study drugs within 1 month; history of psychosis; organic mental disorder; bipolar disorder; suicidal; psychoactive drugs  
ECT therapy within 1 month; drug/alcohol dependence; pregnancy/lactation; clinically significant medical diseases/abnormalities |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: venlafaxine: 43.5, fluoxetine: 45.5  
Gender (% female): venlafaxine: 67.8%, fluoxetine: 74.7%  
Ethnicity: Not reported  
Other population characteristics: CGI severity:  
Mildly ill: venlafaxine: 8%, fluoxetine: 6%.  
Moderately ill: venlafaxine: 66%, fluoxetine: 62%.  
Markedly ill: venlafaxine: 21%, fluoxetine: 28%.  
Severely ill: venlafaxine: 4%, fluoxetine: 4% |
| Authors: Tylee A, et al.  
Year: 1997  
Country: UK |
| OUTCOME ASSESSMENT: | Measures and timing of assessments: MADRS, baseline, weeks 1, 3, 6, 8, 12, HAM-D, CGI: weeks 3, 6, 8, 12, Hospital Anxiety and Depression (HAD): weeks 3, 6, 12, patient sleep diary: first 3 weeks |
| RESULTS: | • MADRS, HAM-D, and CGI scores decreased significantly for both treatment groups  
• There were no significant differences between treatment groups  
• Remission rate: (MADRS ≤ 6) venlafaxine: 35.4 %, fluoxetine: 34.1%  
• Response rates: venlafaxine: 55.1%, fluoxetine: 62.8%  
• No significant differences in effects on sleep |
| ANALYSIS: | ITT: Yes  
Post randomization exclusions: Yes |
| ATTRITION: | Loss to follow-up: 27%; venlafaxine: 27%, fluoxetine: 27%  
Withdrawals due to adverse events: venlafaxine: 21%, fluoxetine: 14%  
Loss to follow-up differential high: Yes |
| ADVERSE EVENTS: | • No significant differences between study groups  
• At least 1 adverse event: venlafaxine: 80.7%, fluoxetine: 71.8%  
• Nausea: venlafaxine: 34.5%, fluoxetine: 18.2%  
• Vomiting: venlafaxine: 12.9%, fluoxetine: 5.3%  
• Headache: venlafaxine: 11.1%, fluoxetine: 17.1%  
• Dizziness: venlafaxine: 11.1%, fluoxetine: 6.5% |
| QUALITY RATING: | Fair |
### Evidence Table 1  Major Depressive Disorder Adults

| STUDY: | Authors: Weihs KL, et al., Doraiswamy PM, et al.  
Year: 2000, 2001  
Country: US |
| FUNDING: | Glaxo Wellcome |
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 100 |
| INTERVENTION: | **Drug:** Bupropion SR  
Dose: 100-300 mg/d  
Mean daily dose: 197 mg/d  
Duration: 6 weeks  
Paroxetine  
Dose: 10-40 mg/d  
Mean daily dose: 22 mg/d  
Duration: 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 bupropion 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: bupropion sr: 17%, paroxetine: 12% |
<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>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</th>
</tr>
</thead>
</table>
| 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, CGI, and HAMA were all similar at each week of the study  
• No significant differences in the Quality of Life scales (QLDS, SF-36) between treatment groups at the endpoint  
• Overall significant improvement in QLDS and QOL at day 42 (p < 0.0001) |
| ANALYSIS:          | ITT: Yes  
Post randomization exclusions: Yes |
| ATTRITION:         | Loss to follow-up: 16%; bupropion sr: 16.6%, paroxetine: 15.4%  
Withdrawals due to adverse events: bupropion sr: 8.3%, paroxetine: 5.8%  
Loss to follow-up differential high: No |
| ADVERSE EVENTS:    | • Significantly more patients treated with paroxetine reported somnolence (27% vs. 6%; p < 0.05), diarrhea (21% vs. 6%; p < 0.05), and constipation (15% vs. 4%; p < 0.05)  
• More than 10% in both groups reported headache, insomnia, dry mouth, nausea, dizziness, and agitation  
• Neither group showed clinically significant changes in weight or clinically significant cardiovascular effects |
| QUALITY RATING:    | Fair |
Evidence Table 2: Dysthymia

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

### OUTCOME ASSESSMENT:

**Measures and timing of assessments:** Primary Outcome was 13 items from the Hopkins Symptom Check list Depression Scale (HSCL-D-20) plus 7 additional items. Timing: baseline and each treatment visit (1, 2, 4, 6, 8, 11), also measured: Ham-D-17 and SF36, mental health component and physical health component timing: baseline, 6 and 11 weeks

### RESULTS:

- ITT analysis: mean decrease in HSCL-D-20; paroxetine: 0.88 (0.08), placebo: 0.85 (0.09); behavior therapy: 0.79 (0.09), no significant differences between arms;
- remission by HAM-D-17 score ≤ 6: paroxetine: 80%, placebo: 44.4%; behavior therapy: 56.8% (p = 0.008 for difference among all three arms)
- minor depression: paroxetine 60.7%, placebo 65.6%; behavior therapy 65.5% (p = 0.906 for difference among all three arms)
- SF 36 results were not compared head to head, they seem to only be compared within groups over time

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** No

### ATTRITION:

**Loss to follow-up:** 20.7  
**Withdrawals due to adverse events:** PAR: 7.5

### ADVERSE EVENTS:

Not reported

### QUALITY RATING:

Fair
**Evidence Table 2**

| STUDY: | **Authors:** Devanand DP, et al.  
**Year:** 2005  
**Country:** US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>NIMH and capsules provided by Eli Lilly</td>
</tr>
<tr>
<td>OBJECTIVE:</td>
<td>To determine efficacy and side effects of fluoxetine in elderly patients with dysthymia</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design:** RCT  
**Setting:** Depression clinic  
**Sample size:** 90 |
| INTERVENTION: | Drug:  
Fluoxetine  
10-60 mg/day  
12 weeks  
Sample size: 44  
Placebo  
N/A  
12 weeks  
Sample size: 46 |
| INCLUSION: | Outpatients with a primary diagnosis dysthymia following DSM-IV criteria; at least 60 years of age; HAM-D score 8-25; and, CGI-S severity score of 3 or more |
| EXCLUSION: | MDD; allergy to fluoxetine; previous lack of response to SSRI; suicide ideation or plan; Mini-Mental State exam less than 23 out of 30; alcohol or substance abuse in last 6 months; bipolar disorder, schizophrenia or other psychotic disorder; stroke, dementia or other major neurological disorder or insult |
| OTHER MEDICATIONS/ INTERVENTIONS: | Zolpidem (up to 10 mg/day) for insomnia and lorazepam (up to 2 mg/day) for anxiety |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Uncertain; fluoxetine group more likely to be unmarried males with comorbid anxiety disorder and have a family history of affective disorder.  
**Mean age:** fluoxetine: 69.0, placebo: 70.8  
**Gender (% female):** fluoxetine: 32.5%, placebo: 40.9%  
**Ethnicity (% white):** fluoxetine: 86.4%, placebo 89.1%  
**Other population characteristics:**  
**Married:** fluoxetine: 29.6%, placebo: 37%  
**Family history of affective disorder:** fluoxetine: 38.6%, placebo 21.7%  
**Comorbid anxiety disorder:** fluoxetine: 11.4%, placebo 6.5%  
**HAM-D:** fluoxetine: 15.3 (+/- 5.1), placebo: 14.4 (+/- 3.0)  
**CGI-S:** fluoxetine: 3.4 (+/- 0.5), placebo 3.2 (+/- 0.5)  
**CDRS:** fluoxetine: 28.0 (+/- 8.8), placebo 25.2 (+/- 11.5) |
<table>
<thead>
<tr>
<th>Authors: Devanand DP, et al.</th>
<th>Year: 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUTCOME ASSESSMENT:</td>
<td>Primary Outcome Measures:</td>
</tr>
<tr>
<td></td>
<td>• HAM-D and CDRS</td>
</tr>
<tr>
<td></td>
<td>• Responders classified as having a ≥ 50% decrease in Ham-D scores at final assessment relative to baseline and have a CGI improvement score of 1 or 2</td>
</tr>
</tbody>
</table>

Timing of assessments:

RESULTS:

• Response rates: fluoxetine: 27.3%, placebo: 19.6% (p < 0.4)
• No differences between treatment groups in quality of life
• Only the CDRS scores demonstrated a significant effect for treatment group in regression analysis: fluoxetine 26.2%, placebo 4.6% (p < 0.04)

ANALYSIS:

<table>
<thead>
<tr>
<th>ATTRITION:</th>
<th>ITT: Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post randomization exclusions: No</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Fluoxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up</td>
<td>21</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADVERSE EVENTS:

• The only side effect that differed significantly between the 2 groups was yawning: fluoxetine baseline 2.5%, endpoint 20% vs. placebo baseline 6.3%, endpoint 7.5% (% change p < 0.03)

QUALITY RATING: Good
**Evidence Table 2  Dysthymia**

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

**OUTCOME ASSESSMENT:**

<table>
<thead>
<tr>
<th>Measures</th>
<th>Timing of assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
<td>Weeks 1, 2, 4, 6, 8, 12</td>
</tr>
</tbody>
</table>

**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:**

<table>
<thead>
<tr>
<th>ITT</th>
<th>Post randomization exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**ATTRITION:**

<table>
<thead>
<tr>
<th>Loss to follow-up</th>
<th>sertraline: 23.4%, placebo: 25.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals due to adverse events</td>
<td>sertraline: 13.3%, placebo: 7.9%</td>
</tr>
<tr>
<td>Loss to follow-up differential high</td>
<td>No</td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**

- More patients in the sertraline group experienced adverse events: 75.3% vs. 64.5% (p = 0.047)
- Increased sweating: sertraline: 13.9%, placebo: 2%
- Tremor: sertraline: 13.9%, placebo: 0.7%
- Nausea: sertraline: 20.9%, placebo: 17.8%
- Ejaculation disorder: sertraline: 9.3%, placebo: 0

**QUALITY RATING:**

Fair
## Evidence Table 2  
**Dysthymia**

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

## OUTCOME ASSESSMENT:

**Measures and timing of assessment:** CGI weekly, HAM-D, MADRS biweekly, DSM-IV, Hopkins Symptom Checklist, Inventory for Depression Symptomatology, Social Adjustment Scale, Quality of Life Enjoyment and Satisfaction Questionnaire weeks 8 and 12

## RESULTS:

- Sertraline group showed significantly more responders than placebo (59.0% vs. 44.3%; \( p < 0.02 \))
- No significant differences in responders between sertraline and imipramine-treated patients
- A significantly greater proportion of patients in the sertraline group increased in psychosocial functioning compared to placebo (61% vs. 45%; \( p = 0.01 \)) as measured by the Global Assessment of Functioning Score of 71 or more
- Significant improvements in family relationships, marital relationships, and parental role functioning
- The harm avoidance scores (from the Tri-dimensional Personality Questionnaire) were significantly decreased in all treatment groups
- Significantly more sertraline patients than placebo patients were classified as harm avoidance responders (\( p = 0.001 \))

## ANALYSIS:

**ITT:** Yes

**Post randomization exclusions:** Yes

## ATTRITION:

**Loss to follow-up:** 24.3%; sertraline: 15.7%; imipramine: 33.1%; placebo: 24.3%

**Withdrawals due to adverse events:** sertraline: 6.0%; imipramine: 18.4%; placebo: 3.6%

**Loss to follow-up differential high:** Yes

## ADVERSE EVENTS:

Not reported

## QUALITY RATING:

Fair
<table>
<thead>
<tr>
<th>Evidence Table 2</th>
<th>Dysthymia</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Vanelle et al.\textsuperscript{95}  
Year: 1997  
Country: France |
| **FUNDING:** | NR |
| **DESIGN:** | Study design: RCT  
Setting: Psychiatric centers  
Sample size: 140 |
| **INTERVENTION:** |  
Drug:  
Dose:  
Duration:  
| fluoxetine  
20-40 mg  
phase I: 3 months  
phase II: 6 months | placebo  
N/A  
phase I: 3 months  
phase II: 6 months |
| **INCLUSION:** | Adults > 18; minimum HAM-D score of 16; dysthymia not secondary to any other axis I disorder |
| **EXCLUSION:** | Additional mental illnesses or organic mental disorder; MDD or other type of depression; secondary-type dysthymia; uncontrolled serious somatic disease; fluoxetine for a depressive disorder which had not been effective; received a psychotropic drug during the previous week (except for authorized benzodiazepines); requiring one of the following during the study: neuroleptic, lithium, or other mood regulator |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: NR  
Gender (% female): fluoxetine: 76.9%, placebo: 73.5%  
Ethnicity: NR  
Other population characteristics: Early onset of dysthymia: 22.9%, late onset: 77.1% |
**Authors:** Vanelle et al.  
**Year:** 1997  
**Country:** France

### OUTCOME ASSESSMENT:  
**Primary Outcome Measures:** HDRS, CGI  
**Secondary Outcome Measures:** HDRS, HARS, CGI, GAF-S, Paykel Life Event Questionnaire, HSCL-58, AMDP-5

### Timing of assessments:

### RESULTS:

- **# of responders at month 3 (>50% decrease in HAM-D associated with a score of 1 (very much improved) or 2 (much improved) on the CGI-I):** fluoxetine = 42, placebo = 14 (p = 0.03)
- **Remission n at month 3 (HAM-D < 7):** fluoxetine = 32, placebo = 10 (p = 0.07)  
  - **# of responders at month 6:** fluoxetine =33, placebo = 9 (p = 0.48)  
  - **Remission n at month 6:** fluoxetine = 29, placebo = 4 (p = 0.01)
- **Increase in GAF scores by month 3 significantly greater in fluoxetine (p = 0.02); mean score indicated return to functioning level compatible with normal social & relational life (mean GAF score = 70)**
- **No significant change in GAF scores from month 3 to 6 for either treatment group**

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** NR

### ATTRITION:

**Loss to follow-up:** Phase I: fluoxetine: 13.2%; placebo: 26.5%  
**Phase II:** fluoxetine: 7%; placebo: 31%  
**Withdrawals due to adverse events:** NR  
**Loss to follow-up differential high:** Yes (16.2%)

### ADVERSE EVENTS:

- **Phase I:** reported at least one adverse event: 38.5% (fluoxetine) vs. 44.9% (placebo)
- **Phase II (responders who continued from month 3 to 6):** reported at least one adverse event: 18.6% (fluoxetine) vs. 28.6% (placebo)

### QUALITY RATING:

**Fair**
### Evidence Table 2  
**Dysthymia**

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

**OUTCOME ASSESSMENT:**  
**Measures:** Hopkins Symptom Checklist Depression Scale (HSCL-D-20), HDRS, and functional status, by the Medical Outcomes Study Short-Form 36 (SF-36) physical and mental components  
**Timing of assessments:**

**RESULTS:**
- Mean (SE) decrease in HSCL-D-20:  
  - Paroxetine: 0.61 (p =0.05)  
  - Placebo: 0.40 (p = 0.05)  
  - Behavior Therapy 0.52 (p = 0.05)  
  - p = 0.004 for paroxetine vs. placebo  
- Paroxetine only statistically and clinically significantly better than placebo for subjects with dysthymia and high baseline mental health function.  
- HAM-D results not reported for the ITT population

**ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** Yes

**ATTRITION:**  
**Loss to follow-up:** 25.1% (for all 3 arms, including behavioral tx)  
**Withdrawals due to adverse events:** Paroxetine: 8.8%, Placebo: 5.7%  
**Loss to follow-up differential high:** No

**ADVERSE EVENTS:**  
Not reported

**QUALITY RATING:**  
Fair
## Evidence Table 3: Major Depressive Disorder Pediatrics

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

**OUTCOME ASSESSMENT:**

**Measures:** Remission (HAM-D ≤ 8), Response (HAM-D ≥ 50% reduction from baseline), mean HAM-D change from baseline, CGI, K-SADS-L, individual HAM-D factors, SIP self-perception profile

**Timing of assessments:** at baseline and weekly intervals weeks 1-8

**RESULTS:**

- **Mean HAM-D change:** paroxetine: 10.74 (p = 0.13 vs. placebo), imipramine: 8.91 (p = 0.81 vs. placebo), placebo: 9.09;
- **HAM-D remission:** paroxetine: 63.3% (p = 0.02 vs. placebo), imipramine: 50% (p = 0.57 vs. placebo), placebo: 46%;
- **HAM-D response:** paroxetine: 66.7% (p = 0.11 vs. placebo), imipramine: 58.5% (p = 0.61 vs. placebo), placebo: 55.2%;
- **Mean CGI:** paroxetine: 2.37 (p = 0.09 vs. placebo), imipramine 2.70 (p = 0.90 vs. placebo), placebo: 2.73
- **CGI score of 1 or 2:** paroxetine: 65.6% (p = 0.02 vs. placebo), imipramine: 52.1% (p = 0.64 vs. placebo), placebo: 48.3%

**ANALYSIS:**

**ITT:** Not reported

**Post randomization exclusions:** Yes

**ATTRITION:**

**Loss to follow-up:** 31%

**Withdrawals due to adverse events:** paroxetine: 9.7% (p = 0.5 vs. placebo) imipramine: 31.5% (p < 0.01 vs. placebo) placebo: 6.9%

**Loss to follow-up differential high:** Yes

**ADVERSE EVENTS:**

No p-values given for comparison

- Side effects with > 5% difference from placebo: paroxetine: dry mouth (20.4% vs. 13.8% in placebo); nausea (23.7% vs. 19.5% in placebo); dizziness (23.7% vs. 18.4% in placebo); emotional lability (6.5% vs. 1.1% in placebo), hostility (7.5% vs. 0 in placebo); insomnia (15.1% vs. 4.6% in placebo); somnolence (17.2% vs. 3.4% in placebo); tremor (10.8% vs. 2.3% in placebo); back pain (4.3% vs. 11.5% in placebo)
- Serious adverse effects: paroxetine: 11 (only 1 deemed to be related to medication), imipramine: 5 (2 deemed related to medication), placebo: 2 (related to medication)

**QUALITY RATING:** Fair
Evidence Table 3  
**Major Depressive Disorder Pediatrics**

<table>
<thead>
<tr>
<th>STUDY:</th>
<th>Authors: Mandoki MW, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year: 1997</td>
</tr>
<tr>
<td></td>
<td>Country: US</td>
</tr>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
</tr>
<tr>
<td>DESIGN:</td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Single center</td>
</tr>
<tr>
<td></td>
<td>Sample size: 40</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Drug:</td>
<td>Placebo</td>
</tr>
<tr>
<td>Dose:</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration:</td>
<td>6 weeks</td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>Children and adolescents 8-18 years old; DSM-IV criteria for Major Depression</td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>Female patients of childbearing age had to use oral contraceptives or depo-provera injection; Tourette’s syndrome; mental retardation; seizures; schizophrenia; suicidal; medical illness</td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS:</td>
<td>Not reported</td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: Not reported</td>
</tr>
<tr>
<td></td>
<td>Mean Age: 12.8</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): 24%</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Not reported</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Not reported</td>
</tr>
</tbody>
</table>
| Authors: Mandoki MW, et al.  
| Year: 1997  
| Country: US |
| **OUTCOME ASSESSMENT:** | **Measures:** Children’s Depression Inventory (CDI), Child Behavior Checklist (CBCL), 17 item HAM-D, Children’s Depression Rating Scale (CDRS)  
| **Timing of assessments:** Weekly |
| **RESULTS:** | • Both venlafaxine and placebo patients showed significant improvement.  
|  | • There was no difference between venlafaxine and placebo. |
| **ANALYSIS:** | **ITT:** No  
|  | **Post randomization exclusions:** Yes |
| **ATTRITION:** | **Loss to follow-up:** 7 (17.5%)  
|  | **Withdrawals due to adverse events:** 1 (2.5%) venlafaxine: 1 (5%), placebo: 0 (0%)  
|  | **Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** | • A higher percentage of patients in the venlafaxine group experienced side effects than in the placebo group at almost every week.  
|  | • At week 2 more statistically more venlafaxine patients reported nausea.  
<p>|  | • At week 6 statistically more venlafaxine patients reported increased appetite. |
| <strong>QUALITY RATING:</strong> | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 3</th>
<th>Major Depressive Disorder Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
<td>Authors: March JS&lt;sup&gt;39s&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Year: 2004</td>
</tr>
<tr>
<td></td>
<td>Country: US</td>
</tr>
<tr>
<td></td>
<td><strong>Trial name:</strong> TADS</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>NIMH</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td>Study design: RCT</td>
</tr>
<tr>
<td></td>
<td>Setting: Multi-center (13 sites-academic and community clinics)</td>
</tr>
<tr>
<td></td>
<td>Sample size: 439</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Drug:</strong></td>
<td>[blinded]</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>Sample Size:</strong></td>
<td>112</td>
</tr>
<tr>
<td></td>
<td>[blinded]</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>Fluoxetine</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>10-40 mg/d</td>
</tr>
<tr>
<td><strong>Sample Size:</strong></td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>[unblinded]</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>Fluoxetine and CBT</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>10-40 mg/d</td>
</tr>
<tr>
<td><strong>Sample Size:</strong></td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>[unblinded]</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>CBT alone</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Sample Size:</strong></td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>Ages 12-17; ability to receive care as an outpatient; a DSM-IV diagnosis of MDD at consent and again at baseline; a CDRS-R total score of 45 or higher at baseline; a full scale IQ of 80 or higher; not taking antidepressants prior to consent; depressive mood present in at least 2 or 3 contexts (home, school, among peers) for a least 6 wks prior to consent</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>Current or past diagnosis of bipolar disorder, severe conduct disorder, current substance abuse or dependence; pervasive developmental disorders, thought disorder; concurrent treatment with psychotropic medication or psychotherapy outside the study; 2 failed SSRI trials; a poor response to clinical treatment containing CBT for depression; intolerance to fluoxetine; confounding medical condition, non-English speaking patient or parent; pregnancy or refusal to use birth control; suicidal in the past 6 months; patients considered to be a danger to themselves or others</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>Concurrent stable psychostimulant treatment (methylphenidate or mixed amphetamine salts) for attention deficit hyperactivity disorder permitted</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: 14.6 (treatment-specific numbers not reported)</td>
</tr>
<tr>
<td></td>
<td>Gender (% female): 54.4% (treatment-specific numbers not reported)</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: White: 73.8%; black: 12.5%; Hispanic: 8.9% (treatment-specific numbers not reported)</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: None significant</td>
</tr>
<tr>
<td>Authors: March JS</td>
<td>Year: 2004</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Country: US</td>
<td></td>
</tr>
<tr>
<td>OUTCOME ASSESSMENT:</td>
<td>Measures: CDRS-R total score; CGI-I; RADS; SIQ-Jr</td>
</tr>
<tr>
<td>Timing of assessments: Baseline and weeks 6 and 12</td>
<td></td>
</tr>
<tr>
<td>RESULTS:</td>
<td></td>
</tr>
<tr>
<td>• Fluoxetine with CBT was statistically significantly better than placebo (p = 0.001) on the CDRS-R</td>
<td></td>
</tr>
<tr>
<td>• Compared to fluoxetine alone (p = 0.02) and CBT alone (p = 0.01), treatment with fluoxetine and CBT was statistically significantly superior on the CDRS-R</td>
<td></td>
</tr>
<tr>
<td>• Fluoxetine alone was superior to CBT alone (p = 0.01) on the CDRS-R</td>
<td></td>
</tr>
<tr>
<td>• Fluoxetine with CBT (p &lt; 0.001) and fluoxetine alone (p &lt; 0.001) demonstrated significant improvement on the CGI-I compared to placebo; CBT alone was not significantly better than placebo (p = 0.20)</td>
<td></td>
</tr>
<tr>
<td>• Fluoxetine plus CBT were significantly better than placebo, fluoxetine alone, or CBT alone (p &lt; 0.01) on the RADS</td>
<td></td>
</tr>
<tr>
<td>• Clinically significant suicidal thinking improved significantly in all four treatment groups (SIQ-Jr), with fluoxetine plus CBT showing the greatest reduction (p = 0.02)</td>
<td></td>
</tr>
<tr>
<td>ANALYSIS:</td>
<td></td>
</tr>
<tr>
<td>ITT: Yes</td>
<td></td>
</tr>
<tr>
<td>Post randomization exclusions: Yes</td>
<td></td>
</tr>
<tr>
<td>ATTRITION:</td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up: 18.2%; fluoxetine+CBT: 14%; fluoxetine: 17%; CBT: 22%; placebo: 21%</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to adverse events: Not reported</td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up differential high: No</td>
<td></td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td></td>
</tr>
<tr>
<td>Adverse events reported as harm-related, psychiatric, or other</td>
<td></td>
</tr>
<tr>
<td>• 7.5% of patients had a harm-related adverse event; by FDA definition 69.7% of these had a serious adverse event: fluoxetine alone: 11.9%; fluoxetine with CBT: 8.4%; CBT alone: 4.5%; placebo: 5.4%</td>
<td></td>
</tr>
<tr>
<td>• Psychiatric adverse events: fluoxetine+CBT: 15%; fluoxetine alone: 21%; CBT alone: 1%; placebo: 9.8%</td>
<td></td>
</tr>
<tr>
<td>• Headache was most common: fluoxetine+CBT 5.6%, fluoxetine alone 12%, CBT alone 0%, placebo 9%</td>
<td></td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Evidence Table 3</strong></td>
<td><strong>Major Depressive Disorder Pediatrics</strong></td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------</td>
</tr>
</tbody>
</table>
| **STUDY:**          | Authors: Wagner, et. al.\(^{100}\)  
                     | Year: 2003  
                     | Country: Multinational |
| **FUNDING:**        | Pfizer, Inc. |
| **DESIGN:**         | Study design: Pooled analysis of 2 multi-center, double-blind, placebo-controlled trials  
                     | Setting: 53 hospital, general practice, academic centers in the US, India, Canada, Costa Rica and Mexico.  
                     | Sample size: 376 |
| **INTERVENTION:**   | Drug: Sertraline  
                     | Dose: 50-200 mg/d  
                     | Duration: 10 weeks  
                     | Placebo  
                     | N/A  
                     | 10 weeks |
| **INCLUSION:**      | Ages 6-17 years; met DSM-IV criteria for MDD (as determined by Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, present and lifetime version); current episode of at least 6 weeks duration; minimum score on CDRS-R of 45 and CGI of 4 |
| **EXCLUSION:**      | Current and primary diagnoses of ADHD; conduct disorder; OCD; panic disorder; history of bipolar disorder; current psychotic features; history of psychotic disorder or autistic spectrum disorder; previous suicide attempts or high suicidal or homicidal risk; abnormal screening EKG, labs, vital signs or body weight; pregnancy; prior enrollment in a sertraline study; medical contraindications to SSRI; history of failure on SSRI; no other psychotropic meds for at least 2 weeks (4 weeks for fluoxetine) |
| **ALLOWED OTHER MEDICATIONS/ INTERVENTIONS:** | Chloral hydrate, diphenhydramine as sleep aids |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
                     | Mean age: Not reported  
                     | Gender (% female): sertraline: 57.1%, placebo: 44.9% (p = 0.02)  
                     | Ethnicity: sertraline: white, 71.4%; Asian, 13.8%; Hispanic, 7.9%; black, 3.7%; other, 3.2%  
                     | placebo: white, 69.5%; Asian, 12.3%; Hispanic, 10.2%; black, 4.8%; other, 3.2%  
<pre><code>                 | Other population characteristics: Comorbid psychiatric diagnosis: 38 % |
</code></pre>
<table>
<thead>
<tr>
<th>Authors: Wagner et. al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2003</td>
</tr>
<tr>
<td>Country: Multinational</td>
</tr>
</tbody>
</table>

**OUTCOME ASSESSMENT:**

| Measures: Change in CDRS-R, CDRS-R response ≥ 40% change from baseline, CGI-S score, CGI-I score, and CGI-response (score of 1 or 2), MASC, CGAS, PQ-LES-Q |
| Timing of assessments: Baseline, weeks 1, 2, 3, 4, 6, 8, 10 |

**RESULTS:**

- Mean CDRS-R change (ITT): sertraline: 22.84, placebo: 20.19 (p = 0.007)
- Mean CDRS-R change (completers): sertraline: 30.24, placebo: 25.83 (p = 0.001)
- CDRS-responder: sertraline: 69%, placebo: 59% (p = 0.05)
- Mean CGI: sertraline: 2.56, placebo: 2.75 (p = 0.009)
- CGI responder: sertraline: 63%, placebo: 53% (p = 0.05)
- Change in CGI-S: sertraline: 1.22, placebo: 1.01 (p = 0.005)

**ANALYSIS:**

- ITT: Yes
- Post randomization exclusions: Yes

**ATTRITION:**

- Loss to follow-up: 20%; sertraline: 24.4%; placebo: 16.6%
- Withdrawals due to adverse events: 5.9%; sertraline: 9%; placebo: 2.7%
- Loss to follow-up differential high: No

**ADVERSE EVENTS:**

- Adverse events that occurred in at least 5% of sertraline treated patients with an incidence at least twice that of placebo: insomnia (19.8% vs. 8%), diarrhea (15.1% vs. 4.5%), vomiting (9.3% vs. 4.5%), anorexia (10.5% vs. 2.3%), agitation (8.1% vs. 2.3%)
- Serious adverse events (based on pre-defined criteria): sertraline: 7, placebo: 6
- Mean change in body weight: sertraline: -0.38 kg, placebo: 0.78 kg (p = 0.001)

**QUALITY RATING:** Fair
### Evidence Table 3  
**Major Depressive Disorder Pediatrics**

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

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Children’s Depression Rating Scale-Revised |
| | Secondary Outcome Measures: CGI-I; CGI-S |
| | Timing of assessments: Baseline and weeks 1, 2, 4, 6, and 8. |

| RESULTS: |
| - Compared to placebo, citalopram showed significantly more improvement on the Children’s Depression Rating Scale-Revised (p < 0.05) |
| - 47% of citalopram-treated patients had a CGI-I rating ≤ 2 compared to 47% of placebo-treated patients (p = not reported) |
| - Mean change in CGI-S was -1.3 for citalopram and -1 for placebo (p = not reported) |

| ANALYSIS: |
| ITT: Yes |
| Post randomization exclusions: Yes |

| ATTRITION: |
| Loss to follow-up: 22% (40); citalopram: 24% (22); placebo: 21% (18) |
| Withdrawals due to adverse events: 5.7%; citalopram: 5.6%; placebo: 5.9% |
| Loss to follow-up differential high: No |

| ADVERSE EVENTS: |
| Events occurring in greater than 10% of patients (p = NR): |
| - Rhinitis: Citalopram: 13.5%; placebo: 5.9% |
| - Nausea: Citalopram: 13.5%; placebo: 3.5% |
| - Abdominal Pain: Citalopram: 11.2%; placebo: 7.1% |

| QUALITY RATING: | Fair |
Evidence Table 3  Major Depressive Disorder Pediatrics

| STUDY: | Authors: Whittington CJ, et. al.<sup>80</sup>  
|        | Year: 2004  
|        | Country: UK |
| FUNDING: | NICE (National Institute for Clinical Excellence) |
| DESIGN: | Study design: Systematic review, SSRI versus placebo  
|        | Number of patients: 2145 |
| AIMS OF REVIEW: | To evaluate the risk versus benefit of SSRI's when used to treat childhood depression |
| STUDIES INCLUDED IN META-ANALYSIS | Emslie GJ et al., 1997, Emslie GJ et al., 2002, Keller MB et al., 2001, Wagner, KD et al., 2003 ; unpublished results included in a report by the Committee on Safety of Medicines (UK) |
| TIME PERIOD COVERED: | All studies up to 2003 |
| CHARACTERISTICS OF INCLUDED STUDIES: | Patients randomized to either an SSRI or placebo |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Included trials had patients aged 5-18 years old; no other population information given |
**Authors:** Whittington CJ, et. al.  
**Year:** 2004  
**Country:** UK

| CHARACTERISTICS OF INCLUDED INTERVENTIONS: | Fluoxetine vs. placebo (2 trials); paroxetine vs. placebo (3 trials); sertraline vs. placebo (2 trials); citalopram vs. placebo (1 trial); venlafaxine vs. placebo (3 trials) |
| MAIN RESULTS: | • Both published and unpublished data demonstrated fluoxetine has a favorable risk-benefit profile  
• Published and unpublished data combined on paroxetine demonstrated it does not improve depressive symptoms and has little effect on response  
• One paroxetine study reported an increased risk of serious adverse events (11.8% vs 2.3%; NNTH 10 [95% CI 6-50]) and suicidal ideation or attempting suicide (5.4% vs 0%; NNTH 20 [10 to ∞])  
• Unpublished data on sertraline in children indicate it is not as effective as reported in published trials  
• One unpublished study of citalopram suggested a negative risk-benefit profile  
• Combined, published and unpublished data of venlafaxine suggested a negative risk-benefit profile |
| ADVERSE EVENTS: | Paroxetine, sertraline, citalopram, and venlafaxine all indicated an increased risk of adverse events |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Yes |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING: | Fair |
# Evidence Table 4: General Anxiety Disorder

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

| OUTCOME ASSESSMENT: | **Primary Outcome Measures:** HAM-A  
**Secondary Outcome Measures:** CGI-I, CGI-S, MADRS, HADS, QoL enjoyment and satisfaction questionnaire, Endicott Work Productivity Scale, VAS for perceived health  
**Timing of assessments:** Baseline, weeks 1, 2, 4, 6, 8, and 12 |
| --- | --- |

| RESULTS: | • Mean change in HAM-A total score significantly greater among sertraline-treated patients (-11.7) compared to placebo-treated patients (-8.0); (p < 0.0001)  
• Significantly greater improvement for sertraline in the anxiety and depression component of the HADS (p < 0.0001)  
• Sertraline significantly better than placebo as assessed by change in the MADRS, CGI-I, CGI-S, QoL, and Endicott Work Productivity Scales  
• VAS not reported |

| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** Yes |

| ATTRITION: | **Loss to follow-up:** 23%; sertraline: 20%; placebo: 26%  
**Withdrawals due to adverse events:** 9%; sertraline: 8%; placebo: 10%  
**Loss to follow-up differential high:** No |

| ADVERSE EVENTS: | Discontinuations due to adverse events were 8% for sertraline and 10% for placebo; the incidence of severe adverse events was ≥ 3% with sertraline for the following: sweating (3.8% vs 0.0% for placebo), headache (3.3% vs 4.8%), nausea (4.3% vs 1.6%), insomnia (4.3% vs 3.7%), anxiety (3.3% vs 4.2%), and decreased libido in women (4.6% vs 0.0%); Significantly more nausea (28% vs. 13%), insomnia (20% vs. 15%), decreased libido in men (17% vs. 5%), diarrhea (11% vs. 5%), and fatigue (10% vs. 5%) |

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

**Primary Outcome Measures**: HAM-A; Remission rate (defined as CGI-S score of 1)

**Secondary Outcome Measures**: IU-GAMS (Indiana University Generalized Anxiety Measurement Scale); BAI (Beck Anxiety Inventory); Q-LES-Q

**Timing of assessments**: Baseline and weekly during the study

RESULTS:

- There was no significant difference between SR and PX patients in HAM-A score reduction ($F=0.37$, df=1,51)
- There was no significant difference between SR and PX patients in remission rate ($\chi^2=0.22$, df=1)
- Quality of life scores did not differ significantly between treatment groups

ANALYSIS:

**ITT**: Yes

**Post randomization exclusions**: Yes (2)

<table>
<thead>
<tr>
<th>ATTRITION:</th>
<th>Overall</th>
<th>Paroxetine</th>
<th>Sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>12 (22%)</td>
<td>5 (20%) NR</td>
<td>5 (18%) NR</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>6 (11%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>1 (2%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADVERSE EVENTS:

- Paroxetine: dizziness, nausea, sexual dysfunction, and constipation
- Sertraline: sexual dysfunction, diarrhea

QUALITY RATING: Fair
### Evidence Table 4  
**General Anxiety Disorder**

| STUDY: | Authors: Bielski RJ, et al.  
Year: 2005  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Forest Laboratories, Inc</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: 24-wk randomized, double-blind, flexible dose, head-to-head trial (with 1-wk single blind placebo lead-in period and 2-wk double blind down-titration period)  
Setting: Multi-center, outpatient  
Sample size: 123 |
| INTERVENTION: only for RCT | **Drug:** Escitalopram  
Dose: 10-20 mg/d  
Duration: 24 wks  
Sample size: 61  
Paroxetine  
Dose: 20-50 mg/d  
Duration: 24 wks  
Sample size: 62 |
| INCLUSION: | Male/female outpatients aged 18-65 years; DSM-IV criteria for generalized anxiety disorder (GAD); screening and baseline HAM-A > 18, HAM-D ≤ 17, and Covi Anxiety Scale score greater than Raskin Depression Scale score. |
| EXCLUSION: | DSM-IV criteria of any Axis I disorder other than GAD or history of DSM-IV defined psychotic disorders; any psychotic features; personality disorder; substance abuse / dependency; suicidal tendency; pregnant or breastfeeding; nonreliable contraception if female of childbearing age. |
| OTHER MEDICATIONS/ INTERVENTIONS: | N/A |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes, with exception of gender  
Mean age: 36.8 +/- 10.9 (escitalopram); 37.4 +/- 9.6 (paroxetine)  
Gender: 55.7% female (escitalopram); 67.7% female (paroxetine)  
Ethnicity: 72.1% white (escitalopram); 79.0% white (paroxetine)  
Other population characteristics: Mean weight 168.7 +/- 37.1 lbs (escitalopram) vs. 167.9 +/- 39.5 lbs (paroxetine) |
### Authors: Bielski RJ, et al.  
Year: 2005  
Country: US

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
</tr>
</thead>
</table>
| **Primary Outcome Measures:** HAM-A total score change from baseline to wk 24.  
**Secondary Outcome Measures:** CGI-I, CGI-S, short form of Quality of Life (QOL)  
**Timing of assessments:** HAM-A and safety assessed at week 1,2,4,6,8,12,16,20, and 24. Secondary outcome measures assessed at baseline (except CGI-I), week 8, & week 24.  

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
</table>
| • Both drugs led to improvement in all efficacy measures over time.  
• Efficacy analyses at weeks 8 & 24 showed no statistically significant difference b/w treatment groups.  
• Response rates = 78.3% (escitalopram) and 62.3% (paroxetine) at week 24  
• Week 24 HAM-A total score: -15.3 +/- 0.8 (escitalopram) vs. -13.3 +/- 1.0 (paroxetine)  
• Baseline CGI-S score: 4.3 +/- 0.1 (escitalopram) vs. 4.3 +/- 0.1 (paroxetine)  
• Week 24 CGI-S score: -2.1 +/- 0.2 (escitalopram) vs. -1.8 +/- 0.2 (paroxetine)  
• Baseline QOL score: 47.1 +/- 1.3 (escitalopram) vs. 48.9 +/- 1.3 (paroxetine)  
• Week 24 QOL score: 10.2 +/- 1.4 (escitalopram) vs. 7.5 +/- 1.7 (paroxetine)  
• Week 24 CGI-I score: 1.8 +/- 0.1 (escitalopram) vs. 2.1 +/- 0.2 (paroxetine)  

| ITT: Yes  
**Post randomization exclusions:** Cannot tell  

<table>
<thead>
<tr>
<th>ATTRITION:</th>
</tr>
</thead>
</table>
| **Loss to follow-up:** Overall: 11%  
**Attrition:** Escitalopram: 36%, paroxetine: 47%  
**Withdrawals due to adverse events:** Escitalopram: 6.6%, paroxetine: 22.6%  
**Withdrawals due to lack of efficacy:** Not reported  
**Loss to follow-up differential high:** Not reported  

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
</table>
| • Significantly more withdrawals due to adverse events (AEs) in paroxetine group (p = 0.02)  
• Overall incidence of AEs = 77.0% (escitalopram) vs. 88.7% (paroxetine)  
• Ejaculation disorder = 14.8% (escitalopram); 30.0% (paroxetine)  
• Anorgasmia = 5.9% (escitalopram); 26.2% (paroxetine)  
• Insomnia = 14.8% (escitalopram); 25.8% (paroxetine)  
• Decreased libido = 4.9% (escitalopram); 22.6% (paroxetine)  
• Headache = 11.5% (escitalopram); 21.0% (paroxetine)  
• Somnolence = 13.1% (escitalopram); 16.1% (paroxetine)  
• Dry mouth = 13.1% (escitalopram); 16.1% (paroxetine)  
• Constipation = 1.6% (escitalopram); 14.5% (paroxetine)  
• Nausea = 14.8% (escitalopram); 12.9% (paroxetine)  
• Inflicted injury = 4.9% (escitalopram); 11.3% (paroxetine)  
• Increased sweating = 3.3% (escitalopram); 11.3% (paroxetine)  
• Diarrhea = 21.3% (escitalopram); 8.1% (paroxetine)  
• Fatigue = 11.5% (escitalopram); 8.1% (paroxetine)  
• Upper respiratory tract infection = 14.8% (escitalopram); 4.8% (paroxetine)  

| QUALITY RATING: | Poor |
## Evidence Table 4  General Anxiety Disorder

| STUDY: | Authors: Dahl AA, et al.¹⁷¹⁵  
Year: 2005  
Country: Multinational |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer, Inc.</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multinational, outpatient “investigational sites”  
Sample size: 373 |
| INTERVENTION: only for RCT |  
**Drug:**  
Sertraline  
Dose:  
50-150 mg/d  
12 wks  
184  
Placebo  
N/A  
12 wks  
189 |
| Sample size: |  
Sertraline  
184  
Placebo  
189 |
| INCLUSION: | Adult outpatients; DSM-IV diagnosis of GAD; screening & baseline HAM-A scores ≥ 18; score ≥ 2 on HAM-A item 1 (anxious mood) & item 2 (tension) at baseline |
| EXCLUSION: | Current or history of bipolar, schizophrenia, or OCD; dysthymia, social anxiety, substance abuse or major depressive / panic / eating / body dysmorphic / or post-traumatic stress disorders within last 6 months; MADRS score >16; psychotropic drug treatment within 2 wks of randomization |
| OTHER MEDICATIONS/ INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes, except significantly later mean onset of GAD symptoms in placebo (25.6y) vs. sertraline (22.9y) (p = 0.04).  
Mean age (sd): sertraline: 40.3 (11.1), placebo: 42.4 (11.5) placebo  
Gender (% female): sertraline: 59%, placebo: 51%  
Ethnicity(% white): sertraline: 98%, placebo: 97%  
Other population characteristics: Both groups similar in highest education level achieved, current marital status, and current employment status |
Authors: Dahl AA, et al.
Year: 2005
Country: Multinational

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures: HAM-A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary Outcome Measures: CGI-S &amp; CGI-I, MADRS, Q-LES-Q</td>
</tr>
<tr>
<td>Timing of assessments: Screening, baseline, and weeks 1, 2, 4, 6, 8, and 12</td>
<td></td>
</tr>
</tbody>
</table>

**RESULTS:**

- Sertraline group improved significantly more than placebo group across both primary & secondary measures, including HAM-A somatic and psychic anxiety factors.
- From week 4 to endpoint, HAM-A psychic factor improved at somewhat faster rate (slope -0.39+/-.05 [95% CI: -0.48 to -0.29]) than somatic factor (slope -0.25+/-.05 [95% CI: -0.34 to -0.15]) (F=12.51; d.f = 1,170;p = 0.005)
- LOCF endpoint mean HAM-A total score (sd) = -11.7(0.6) in sertraline vs. -8.0(0.6) in placebo; p < 0.001
- LOCF endpoint mean CGI-S score (sd) = -1.6(0.1) in sertraline vs. -0.9(0.1) in placebo; p < 0.001
- LOCF endpoint mean CGI-I score (sd) = 2.3(0.1) in sertraline vs. 3.0(0.1) in placebo; p < 0.001
- LOCF endpoint mean MADRS score (sd) = -4.8(0.4) in sertraline vs. -1.1(0.4) in placebo; p < 0.001
- 51% of sertraline group compared to 35% of placebo group had a QLESQ score within normal range.
- LOCF endpoint mean QLESQ score (sd) = 9.1(1.0) in sertraline vs. 2.4(0.9) in placebo; p < 0.001

**ANALYSIS:**

- ITT: yes (defined as patients who took at least one dose of double-blind medication and had a baseline and at least 1 post-baseline HAM-A assessment)
- Post randomization exclusions: Cannot tell

**ATTRITION:**

- Loss to follow-up: NR
- Withdrawals due to adverse events: NR
- Withdrawals due to lack of efficacy: NR
- Loss to follow-up differential high: NR

**ADVERSE EVENTS:**

- NR

**QUALITY RATING:**

- Fair
<table>
<thead>
<tr>
<th>Evidence Table 4</th>
<th>General Anxiety Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Davidson JR, et al.  
Year: 2004  
Country: US |
| **FUNDING:**     | Forest Laboratories |
| **DESIGN:**      | Study design: RCT  
Setting: Multi-center (number of centers NR)  
Sample size: 315 |
| **INTERVENTION:**| Drug: Escitalopram  
Dose: 10-20 mg/d (mean 12.3 mg/d)  
Duration: 8 weeks  
Sample size: 158 |
|                  | Placebo  
N/A  
8 weeks  
157 |
| **INCLUSION:**   | Male/female outpatients 18-80 yrs old who met DMS-IV criteria for GAD and had normal physical and laboratory exams and ECG results at screening visit; patients required to have a minimum score of 18 on the HAMA and minimum score of 2 on HAM-A tension and anxiety items |
| **EXCLUSION:**   | HAM-D scores of >17; lower scores on the Covi Anxiety Scale than the Raskin Depression Scale; current bipolar disorder, schizophrenia or any psychotic disorder, OCD, mental retardation or any pervasive developmental disorder or cognitive disorder; principal diagnosis for any DSM-IV defined Axis I disorder other than GAD; substance abuse or dependence within the past 6 months; depot neuroleptics within 6 months; any neuroleptic, antidepressant, or anxiolytic within 2 weeks (5 weeks for fluoxetine); daily benzodiazepine therapy within 1 month, and concomitant treatment with any psychotropic drug (except zolpidem for sleep) or any drug with a psychotropic component; pregnant, breastfeeding, and not practicing a reliable method of birth control |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Not Reported |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: Escitalopram: 39.5; placebo: 39.5  
Gender (% female): Escitalopram: 52.5%; placebo: 52.9%  
Ethnicity: Escitalopram: 70.9% white; placebo: 71.3% white  
Other population characteristics: HAM-A total score 23.4; HAM-D score 12.15; CGI severity score 4.25 |
| Authors: Davidson JR, et al.  
Year: 2004  
Country: US |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
</tr>
</tbody>
</table>
**Primary Outcome Measures:** HAM-A total score  
**Secondary Outcome Measures:** CGI-S; CGI-I; HAD; Covi and Raskin scales; Q-LES-Q  
**Timing of assessments:** screening, baseline and visits at weeks 1, 2, 4, 6, and 8 |
| **RESULTS:** |  
- Mean change in HAM-A total score –11.3 for escitalopram and –7.4 for placebo (p < 0.001)  
- Significantly greater improvement for escitalopram compared to placebo on all secondary outcome measures (p < 0.001) |
| **ANALYSIS:** |  
**ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:** |  
**Loss to follow-up:** 23%; escitalopram: 25%; placebo: 22%  
**Withdrawals due to adverse events:** 7%; escitalopram: 8.9%; placebo: 5.1%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** |  
- Only four adverse events were reported with an incidence exceeding 10%: headache, nausea, somnolence, and upper respiratory tract infection (p = NR); rate of discontinuation due to adverse events not significantly different (escitalopram 8.9% vs. placebo 5.1%, p = 0.27) |
| **QUALITY RATING:** |  
Fair |
# General Anxiety Disorder

| STUDY: | Authors: Meoni P, et al.  
Year: 2004  
Country: UK and France |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Wyeth</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Number of patients: 1,841 |
<p>| AIMS OF REVIEW: | To examine the relative efficacy of venlafaxine XR on the somatic and psychic factors of HAM-A |
| STUDIES INCLUDED IN META-ANALYSIS | Pooled data from five placebo-controlled studies available at the time of this review (Kelsey, 2000) |
| TIME PERIOD COVERED: | 8 weeks to 6 months |
| CHARACTERISTICS OF INCLUDED STUDIES: | DSM-IV criteria for GAD; RCT-double blind with a 4-10 day washout period |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | ≥ 18 yrs old and met DSM-IV criteria for GAD; HAM-A baseline score ≥ 18 or 20 and baseline scores for items 1 and 2 of at least 2; total score on Covi Anxiety Scale greater than total score on the Raskin Depression scale, where the latter score was not &gt;9 |</p>
<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>Venlafaxine XR 37.5 to 225 mg/d vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIN RESULTS:</td>
<td>Mean scores of HAM-A somatic and psychic factors showed different baseline scores of 11.3 and 14.4 respectively, after adjusted by treatment groups; differences in response rates between treatments were greater for the psychic factor of the HAM-A (66.6% vs 35% for venlafaxine and placebo respectively (p &lt; 0.001) than for the somatic factor of HAM-A (67% vs 47% for venlafaxine and placebo respectively (p &lt; 0.001); comparison within treatments of response rates for the two factors of HAM-A by treatment revealed a significant interaction between treatment and factors (p = 0.027).</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>Not reported</td>
</tr>
<tr>
<td>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</td>
<td>Not reported</td>
</tr>
<tr>
<td>STANDARD METHOD OF APPRAISAL OF STUDIES:</td>
<td>Not reported</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
</tbody>
</table>
**Evidence Table 4**

**General Anxiety Disorder**

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

| **OUTCOME ASSESSMENT:**  
**Measures:** Change from baseline on HAM-A, change in anxious mood and tension scales of HAM-A, anxiety subscale of HAD, CGI-I responders (score of 1 or 2), CGI-S, Sheenan Disability Scale  
**Timing of assessments:** Weeks 1, 2, 3, 4, 5, 6, 8 |
|---|

| **RESULTS:**  
- There was a significantly greater reduction in the total HAM-A score, the anxious mood item, and the tension item in the paroxetine group compared to placebo group at week-6 (p < 0.05) and week-8 (p < 0.01)  
- CGI-I responders LOCF: paroxetine: 62%, placebo: 36% (p = 0.007)  
- CGI-I responders (completers): paroxetine: 70%, placebo: 40% (p = 0.005) |
|---|

| **ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** Yes |
|---|

| **ATTRITION:**  
**Loss to follow-up:** 21%  
**Withdrawals due to adverse events:** Paroxetine: 10.5%; placebo: 3.7%  
**Loss to follow-up differential high:** No |
|---|

| **ADVERSE EVENTS:**  
- Asthenia; constipation; abnormal ejaculation; decreased libido; nausea; somnolence (> 10% and at least twice placebo rate)  
- All adverse effects were experienced by more paroxetine than placebo patients |
|---|

| **QUALITY RATING:**  
Fair |
### Evidence Table 4  
**General Anxiety Disorder**

<table>
<thead>
<tr>
<th>STUDY:</th>
</tr>
</thead>
</table>
| **Authors:** Rickels K, et al.  
**Year:** 2003  
**Country:** US and Canada |

<table>
<thead>
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<th>FUNDING:</th>
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</thead>
<tbody>
<tr>
<td>GSK</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DESIGN:</th>
</tr>
</thead>
</table>
| **Study design:** RCT  
**Setting:** Multi-center  
**Sample size:** 566 |

<table>
<thead>
<tr>
<th>INTERVENTION:</th>
</tr>
</thead>
</table>
| **Drug:** | Paroxetine  
**Dose:** 20 mg/d  
**Duration:** 8 weeks | Paroxetine  
**Dose:** 40 mg/d  
**Duration:** 8 weeks | Placebo  
**Duration:** 8 weeks |

<table>
<thead>
<tr>
<th>INCLUSION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-IV criteria for GAD; HAM-A score ≥ 20; score of 2 or more on item 1 &amp; 2 (anxious mood, tension); mean age ≥ 18 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXCLUSION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER MEDICATIONS/INTERVENTIONS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>POPULATION CHARACTERISTICS:</th>
</tr>
</thead>
</table>
| **Groups similar at baseline:** Yes  
**Mean age:** Paroxetine 20mg/d: 40.2; paroxetine 40 mg/d: 40.5; placebo: 40.8  
**Gender** (% female): Paroxetine 20 mg/d: 54%; paroxetine 40 mg/d: 56%; placebo: 56%  
**Ethnicity:** Paroxetine 20 mg/d: black: 5%, Asian: 3%, white: 82%, other: 5%, Hispanic: 5%; paroxetine 40 mg/d: black: 4%, Asian: 1%, white: 89%, other: 4%; Hispanic: 3%; placebo: black: 6%, Asian: 2%, white: 82%, other: 5%, Hispanic: 6%  
**Other population characteristics:** Not reported |
### Authors: Rickels K, et al.
**Year:** 2003  
**Country:** US and Canada

| OUTCOME ASSESSMENT: | Measures: HAM-A, HADS, CGI-S, Remission = HAM-A < 7, Sheehan disability scale  
Timing of assessments: Weeks 1, 2, 3, 4, 6, 8 |
|---------------------|--------------------------------------------------------------------------------------|
| RESULTS:            | • Paroxetine as a group (20 mg/d and 40 mg/d) had a significantly greater mean change from baseline on all outcome measures except the HAM-A somatic anxiety subscale  
• Statistically more subjects on sertraline (53% vs. 29% on placebo) were much or very much improved at the end of treatment based on the CGI-I |
| ANALYSIS:           | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| ATTRITION:          | **Loss to follow-up:** 24.7%; paroxetine 20mg: 24% (143); paroxetine 40mg: 27% (143); placebo: 22% (140)  
**Withdrawals due to adverse events:** Paroxetine 20mg: 10.1%; paroxetine 40mg: 12.2%; placebo: 6.7%  
**Loss to follow-up differential high:** No |
| ADVERSE EVENTS:     | • At least one adverse event: placebo: 74%, paroxetine: 20mg 88%, paroxetine 40mg: 86%  
• Paroxetine: nausea: 32.6%, insomnia: 30.4%, dyspepsia: 25.2%, diarrhea: 20.7%  
• Placebo: diarrhea: 15.9%, nausea: 14.5%, insomnia: 14.5%, asthenia: 11.6%  
• Significantly more subjects in the Paroxetine group reported nausea: (32.6% vs. 14.55), insomnia: (30.4% vs. 14.5%), dyspepsia: (25.2% vs. 7.2%), flu syndrome (17.8% vs. 5.5%), delayed ejaculation (11.4% vs. 4.3%), sweating (11.1% vs. 5.9%) |
| QUALITY RATING:     | Fair |
### Evidence Table 5: Obsessive-compulsive Disorder

| STUDY: | **Authors:** Ackerman, et al.  
**Year:** 2002  
**Country:** US |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>NIMH</td>
</tr>
<tr>
<td>DESIGN:</td>
<td><strong>Study design:</strong> Meta-analysis (meta regression)</td>
</tr>
<tr>
<td>AIMS OF REVIEW:</td>
<td>Meta-analysis with meta regression for treatment of OCD to explain the apparent discrepancy in the literature that makes it seem that CMI is superior to SSRI’s in placebo trials vs. in head/head comparison</td>
</tr>
<tr>
<td>TIME PERIOD COVERED:</td>
<td>Not explicitly reported, studies included spanned 1992-1997 for head to head comparisons and 1989-1999 for placebo comparisons</td>
</tr>
<tr>
<td>CHARACTERISTICS OF INCLUDED STUDIES:</td>
<td>RCTs, double-blinded; 8 weeks or longer; efficacy assessed with Y-BOCS; point estimates and SD(or SE) provided or calculable from report</td>
</tr>
<tr>
<td>CHARACTERISTICS OF INCLUDED POPULATIONS:</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
**Authors:** Ackerman, et al.  
**Year:** 2002

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</th>
<th>Clomipramine, fluvoxamine, fluoxetine, sertraline, paroxetine, placebo</th>
</tr>
</thead>
</table>
| 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 -0.86, 9.16), where a number significantly greater than 1.00 would represent greater efficacy for the SSRIs  
- Effect size was estimated as the difference in improvement (decrease in Y-BOCS) between active drug and placebo. Negative pooled difference represents greater improvement (greater decrease in Y-BOCS) across studies for the active drug compared to placebo  
- Pooled Difference:  
  - Fluvoxamine vs. placebo (4 studies): -4.84 (-7.78, -1.83)  
  - Fluoxetine vs. placebo (3 studies): -1.61 (-2.18, -1.04)  
  - Sertraline vs. placebo (4 studies): -2.47 (-6.13, 1.20)  
  - Paroxetine vs. placebo (1 study): -3.00 (-4.91, -1.09) |

| ADVERSE EVENTS:                                     | None reported                                                        |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY:          | Yes                                                                  |
| STANDARD METHOD OF APPRAISAL OF STUDIES:           | No                                                                   |
| QUALITY RATING:                                     | Fair                                                                 |
**Evidence Table 5**

**Obsessive-compulsive Disorder**

| STUDY: | Authors: Bergeron, et al.\textsuperscript{125}  
Year: 2002  
Country: Canada |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 150 |
| INTERVENTION: | Drug:  
Sertraline  
Dose: 50-200 mg/d  
Duration: 24 weeks  
Fluoxetine  
Dose: 20-80 mg/d  
Duration: 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  
<table>
<thead>
<tr>
<th>Country: Canada</th>
</tr>
</thead>
</table>
| **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  
| • No significant differences in body weight change between groups  
| --- |
| **QUALITY RATING:**  
| Fair  

Second Generation Antidepressants

Page 266 of 534
### Evidence Table 5

**Obsessive-compulsive Disorder**

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

<table>
<thead>
<tr>
<th><strong>OUTCOME ASSESSMENT:</strong></th>
<th><strong>Measures:</strong> Yale-Brown Obsessive Compulsive scale (Y-BOCS), Hamilton Anxiety Scale (HAS), HAM-D-17, Global Assessment of Functioning, Lancashire Quality of Life Profile (LQoLP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of assessments:</strong></td>
<td>Baseline, weeks 1, 3, 5, 8, 10, 12</td>
</tr>
</tbody>
</table>

| **RESULTS:** | • Paroxetine showed significantly greater improvement in HAM-D at endpoint (p < 0.05)  
• Both treatment groups had a significant improvement in Y-BOCS score but there was no significant difference between treatment groups; no differences in HAS  
• Paroxetine and venlafaxine groups improved on all QoL measures  
• Paroxetine and venlafaxine were equally effective based on LQoLP improvement scores |

| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes |

| **ATTRITION:** | **Loss to follow-up:** 16 (11%)  
**Withdrawals due to adverse events:** 5%; venlafaxine: 2%, paroxetine: 6%  
**Loss to follow-up differential high:** No |

| **ADVERSE EVENTS:** | • Somnolence, sweating, insomnia, nausea, dry mouth, dizziness, constipation, sexual dysfunction  
• No differences reported |

<p>| <strong>QUALITY RATING:</strong> | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 5</th>
<th>Obsessive-compulsive Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Denys D, et al.  
Year: 2004  
Country: The Netherlands |
| **FUNDING:**     | Wyeth and GlaxoSmithKline |
| **DESIGN:**      | Study design: RCT  
Setting: Single center  
Sample size: 43 (of 150) continued in switch study |
| **INTERVENTION:**| Paroxetine  
Dose: 60 mg/d  
Duration: 12 weeks (switch study)  
Sample Size: 27  
Venlafaxine XR  
Dose: 300 mg/d  
Duration: 12 weeks (switch study)  
Sample Size: 16 |
| **INCLUSION:**   | Outpatients ages 18-65 with a primary OCD according to DSM-IV criteria; only patients with a score of at least 18 on the Y-BOCS or at least 12 if only obsessions or compulsions were included; nonresponse in the first phase of the study defined as less than a 25% decrease in Y-BOCS |
| **EXCLUSION:**   | Patients with significant depression as determined by a total score of 15 or more on the HAM-D on admission were excluded; pregnant women, childbearing potential not using adequate methods of contraception; patients with organic mental disorders, epilepsy, any structural central nervous system disorder or stroke within the last year; primary DSM–IV diagnoses of major depression, bipolar disorder, schizophrenia, or any other psychotic condition; substance-related disorders within the past 6 months; primary anxiety disorders or obvious personality disorders; use of antidepressants or antipsychotics 1 month before screening visit; use of a concomitant psychotropic drug, behavioral or cognitive therapy 3 months prior to the screening visit |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Not reported |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: 35  
Gender (% female): 54.5%  
Ethnicity: Not reported  
Other population characteristics: YBOCS total score 27.7; HAM-A score 11.0; HAM-D score 7.6 |
<table>
<thead>
<tr>
<th>Authors: Denys D, et al.</th>
<th>Year: 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: The Netherlands</td>
<td></td>
</tr>
</tbody>
</table>

**OUTCOME ASSESSMENT:**
- **Measures:** Y-BOCS; HAM-D; HAM-A; GAF
- **Timing of assessments:** 0, 1, 3, 5, 8, 10, 12 weeks

**RESULTS:**
- LOCF analysis demonstrated a mean decrease of 1.8 (+/-3.5) in the venlafaxine XR group and 6.5 (+/-7.1) in the paroxetine group as measured by the reduction in total Y-BOCS scores; significant decrease in total Y-BOCS score from baseline was found in the paroxetine group (t=4.7, df=26, p < 0.0001) but not in the venlafaxine group (t = 2.0, df = 15, p = .065)
- No significant differences between baseline and endpoint for venlafaxine XR- or paroxetine-treated patients on the HAM-D or HAM-A
- GAF not reported

**ANALYSIS:**
- **ITT:** Yes
- **Post randomization exclusions:** Not reported

**ATTRITION:**
- **Loss to follow-up:** Paroxetine 0 (0%); Venlafaxine XR 1 (6%) (numbers reported for 43 patients switching)
- **Withdrawals due to adverse events:** Yes
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**
- 98% of patients reported adverse events;
- Paroxetine: somnolence 54%, sweating 25%, headache 21%, constipation 21%, insomnia 18%, nausea 18%, change in mood 18%, loss of libido 18%
- Venlafaxine: somnolence 38%, sweating 31%, constipation 31%, dry mouth 19%, headache 13%, insomnia 13%, nausea 13%, loss of libido 13%
- p-values not reported

**QUALITY RATING:** Fair
<table>
<thead>
<tr>
<th>Evidence Table 5</th>
<th>Obsessive-Compulsive Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**      | Authors: Montgomery SA, et. al. 126  
Year: 2001  
Country: Europe, South Africa |
| **FUNDING:**    | Lundbeck A/S |
| **DESIGN:**     | Study design: RCT  
Setting: Multi-center  
Sample size: 401 |
| **INTERVENTION:** | Drug:  
Dose:  
Duration:  
Citalopram  
20 mg/d  
12 weeks  
Citalopram  
40 mg/d  
12 weeks  
Citalopram  
60 mg/d  
12 weeks  
Placebo  
N/A  
12 weeks |
| **INCLUSION:**  | 18-65 years; DSM-IV criteria for OCD; Y-BOCS ≥ 20; symptoms stable for the preceding 6 months |
| **EXCLUSION:**  | MADRS ≥ 22; other Axis I disorders; suicidal risk; recent treatment with fluoxetine or MAOI; hypersensitivity to SSRIs; hepatic impairment; drug/alcohol dependence; pregnancy/lactation; Tourette’s syndrome in family; concomitant therapy with anticonvulsive and psychoactive drugs |
| **OTHER MEDICATIONS/INTERVENTIONS:** | 55.4% received concomitant medication |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean Age: 38; citalopram: 37.6, placebo: 38.6  
Gender (% female): citalopram: 55%, placebo: 50.1%  
Ethnicity: Not reported  
Other population characteristics: Mean duration of illness greater than 15 years for all groups |
| **Authors:** Montgomery SA, et al.  
**Year:** 2001  
**Country:** Europe, South Africa |
<table>
<thead>
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</thead>
<tbody>
<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
</tr>
</tbody>
</table>
| **Measures:** Y-BOCS, MADRS, CGI-I, NIMH-OC  
**Timing of assessments:** Baseline, weeks 1, 3, 5, 7, 9, 12 |
| **RESULTS:** |
| • A significant reduction in Y-BOCS scores for all 3 citalopram groups (p < 0.01) compared to placebo  
• Citalopram 60 mg reached statistical significance at week 3, citalopram 20 mg and 40 mg at week 7  
• Changes in NIMH-OC scores were also significantly greater in the citalopram groups (p < 0.001)  
• All 3 treatment groups had significantly more responders than placebo |
| **ANALYSIS:** |
| **ITT:** Yes  
**Post randomization exclusions:** Not reported |
| **ATTRITION:** |
| **Loss to follow-up:** 16%; citalopram 20 mg: 16%; citalopram 40 mg: 15%; citalopram 60 mg: 15%; placebo: 17%  
**Withdrawals due to adverse events:** 4%; citalopram 20 mg: 4%; citalopram 40 mg: 6%; citalopram 60 mg: 4%; placebo: 2%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** |
| • Treatment emergent adverse events: citalopram 20 mg: 73%; citalopram 40 mg: 68%; citalopram 60 mg: 72%; placebo: 58%  
• The incidence of nausea, insomnia, fatigue, increased sweating, dry mouth, ejaculation failure, and diarrhea was significantly higher in one or more citalopram groups compared to placebo |
| **QUALITY RATING:** |
| Fair |
### Evidence Table 5  
**Obsessive-compulsive Disorder**

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

| OUTCOME ASSESSMENT: | **Primary Outcome Measures**: Yale-Brown Obsessive Compulsive Scale (YBOCS)  
**Secondary Outcome Measures**: HAM-D19; CGI-I, Arizona Sexual Experience Scale  
**Timing of assessments**: At baseline and weekly thereafter. |
|---------------------|------------------------------------------------------------------------------------------------------------------|

**RESULTS:**
- The citalopram/mirtazapine group showed an earlier response than the citalopram/placebo on reduction in mean YBOCS score; a significant between group difference was observed during weeks 2 through 6 ($p < 0.05$)
- No significant between group difference in YBOCS score observed at endpoint.
- No differences in CGI-I at endpoint
- HAM-D not reported

**ANALYSIS:**  
**ITT**: Yes  
**Post randomization exclusions**: No

**ATTRITION:**  
**Loss to follow-up**: 8.2% (4): Citalopram/placebo: 7.1% (2); citalopram/mirtazapine: 9.5% (2)  
**Withdrawals due to adverse events**: 2% (1); citalopram/placebo: 3.6% (1); citalopram/mirtazapine: 0%  
**Loss to follow-up differential high**: No

**ADVERSE EVENTS:**
- Mean Arizona Sexual Experience Scale score at endpoint was significantly worse in citalopram/placebo group than the citalopram/mirtazapine (p < 0.01)
- Significantly greater weight gain among citalopram/mirtazapine group.

**QUALITY RATING**: Fair
### Evidence Table 5

#### Obsessive-compulsive Disorder

| STUDY: | Authors: Piccinelli M, et. al.  
Year: 1995  
Country: Italy |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>University of Verona</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Meta-analysis  
Number of patients: 1076 |
| AIMS OF REVIEW: | Efficacy of drug treatment in OCD; subgroup analysis: SSRIs vs. placebo |
| 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

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</th>
<th>13 trials of SSRI vs. placebo (fluoxetine, fluvoxamine, sertraline)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>MAIN RESULTS:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine vs. placebo:</td>
<td></td>
</tr>
<tr>
<td>Y-BOCS: 0.57 (95% CI: 0.37-0.77)</td>
<td></td>
</tr>
<tr>
<td>NIMH-OC: 0.29 (95% CI 0.07-0.51)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine vs. placebo:</td>
<td></td>
</tr>
<tr>
<td>Y-BOCS: 0.57 (95% CI: 0.33-0.81)</td>
<td></td>
</tr>
<tr>
<td>NIMH-OC: N/A</td>
<td></td>
</tr>
<tr>
<td>Sertraline vs. placebo:</td>
<td></td>
</tr>
<tr>
<td>Y-BOCS: 0.52 (95% CI: 0.27-0.77)</td>
<td></td>
</tr>
<tr>
<td>NIMH-OC: 0.55 (95% CI: 0.30-0.80)</td>
<td></td>
</tr>
<tr>
<td>Improvement rate over placebo (binominal effect size display, Rosenthal 1984):</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine: 28.2%</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine: 28.5%</td>
<td></td>
</tr>
<tr>
<td>Sertraline: 21.6%</td>
<td></td>
</tr>
<tr>
<td>No statistically significant differences between study drugs</td>
<td></td>
</tr>
</tbody>
</table>

| ADVERSE EVENTS: | Not reported |

| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Yes |

| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |

| QUALITY RATING: | Good |
## Evidence Table 5

### Obsessive-compulsive Disorder

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

**CHARACTERISTICS OF INCLUDED INTERVENTIONS:**

| Fluvoxamine (2 studies), fluoxetine (1 study), sertraline (2 studies) |

**MAIN RESULTS:**

- There were no differences in effect sizes between the SSRIs.
- Effect size was calculated in comparison to placebo:
  - Fluvoxamine: 0.69 ± 0.47
  - Sertraline: 0.55
  - Fluoxetine: 0.51 ± 0.12

**ADVERSE EVENTS:**

| N/A |

**COMPREHENSIVE LITERATURE SEARCH STRATEGY:**

| Yes |

**STANDARD METHOD OF APPRAISAL OF STUDIES:**

| No |

**QUALITY RATING:**

| Fair |
Evidence Table 6: Panic Disorder

| STUDY:          | Authors: Asnis G, et al. 148  
|                | Year: 2001  
|                | Country: US  
| FUNDING:       | Not reported  
| DESIGN:        | Study design: RCT  
|                | Setting: Multi-center  
|                | Sample size: 188  
| INTERVENTION:  | Drug:  
|                | Dose:  
|                | Duration:  
|                | Fluvoxamine 50-300 mg/d 8 weeks  
|                | Placebo N/A 8 weeks  
| INCLUSION:     | DSM-III-R diagnosis; age 18-65; at least 1 panic attack per week for at least 4 weeks prior to study  
| EXCLUSION:     | Concurrent systematic illness; other Axis I psychiatric disorder; clinical significant lab abnormalities or ECG; pregnant or lactating women without adequate birth control  
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate or lorazepam for sleep  
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
|                | Mean Age: Fluvoxamine: 34.2, placebo: 36.7  
|                | Gender (% female): fluvoxamine 64.4%, placebo 64.1%  
|                | Ethnicity: Not reported  
|                | Other population characteristics:  
|                | Number of full panic attacks per week at baseline: fluvoxamine: 2.7, paroxetine: 3.3  

**Authors:** Asnis G, et al.  
**Year:** 2001  
**Country:** US

| **OUTCOME ASSESSMENT:** | **Measures:** Primary daily panic attack inventory (DPAI), CAS, SDS, CGI-I, CGI  
**Timing of assessments:** Baseline, weekly intervals thereafter for a maximum of 8 weeks of treatment |
|-------------------------|----------------------------------------------------------------------------------------------------------|

| **RESULTS:** |  
- Significantly more fluvoxamine patients were free from full panic attacks ($p = 0.002$)  
- Reduction of panic disorder severity was significantly greater in the fluvoxamine group ($p = 0.003$)  
- Significantly more fluvoxamine patients were CGI-I responders at endpoint (64% vs. 42%; $p = 0.002$) |

| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes |

| **ATTRITION:** | **Loss to follow-up:** fluoxetine 37.6%, placebo 33.6%  
**Withdrawals due to adverse events:** fluvoxamine: 9.6%; placebo: 5.9%  
**Loss to follow-up differential high:** No |

| **ADVERSE EVENTS:** |  
- Fluvoxamine: nausea: 43%, insomnia: 25%, somnolence: 24%, asthenia: 22%  
- Placebo: nausea: 33%, headache: 22%, anxiety: 16%  
- No significant difference in the number of withdrawals due to adverse events |

<p>| <strong>QUALITY RATING:</strong> | <strong>Fair</strong> |</p>
<table>
<thead>
<tr>
<th>Evidence Table 6</th>
<th>Panic Disorder</th>
</tr>
</thead>
</table>
| STUDY:           | Authors: Bandelow B, et al.<sup>143</sup>  
Country: Germany |
|                  | Year: 2004  
FUNDING: Pfizer |
| DESIGN:          | Study design: RCT  
Setting: Multi-center  
Sample size: 225 |
| INTERVENTION:    | Drug: Sertraline  
Dose: 50 – 150 mg/d  
Duration: 12 weeks  
Paroxetine  
Dose: 40 – 60 mg/d  
Duration: 12 weeks |
| INCLUSION:       | Male or female outpatients; aged 18-65; primary DSM-IV and ICD-10 disease of PD with or without agoraphobia; minimum of 4 panic attacks during the 4 weeks prior to screening; total score > 18 at baseline on the PAS (clinician-rated) |
| EXCLUSION:       | Primary disease other than panic disorder; MADRS rating scale total score > 14; clinically significant and unstable medical illness; current diagnosis of bipolar disorder, schizophrenic disorder, delusional disorder, epilepsy, MDD, OCD, social phobia; history of alcoholism or drug abuse within the past three years; serious risk for suicide; pregnancy or lactation or not using reliable contraceptive methods |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate; zolpidem; zopiclone could be given for severe insomnia on limited basis (< 3 times/wk) |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 38.6  
Gender (% female): sertraline: 60%; paroxetine: 66%  
Ethnicity: Not reported  
Other population characteristics: Patients with agoraphobia subtype: sertraline, 68%; paroxetine, 63%; patients with non-agoraphobia subtype: sertraline, 32%; paroxetine, 66% |
<table>
<thead>
<tr>
<th>Authors: Bandelow B, et al.</th>
<th>Year: 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: Germany</td>
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</table>

**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
<table>
<thead>
<tr>
<th>Evidence Table 6</th>
<th>Panic Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**      | **Authors:** Black DW, et al. 149  
|                 | **Year:** 1993  
|                 | **Country:** US |
| **FUNDING:**    | Reid Rowell Pharma |
| **DESIGN:**     | **Study design:** RCT  
|                 | **Setting:** Multi-center  
|                 | **Sample size:** 75 |
| **INTERVENTION:** | **Drug:** Fluvoxamine  
|                  | **Dose:** Up to 300 mg/d  
|                  | **Duration:** 8 weeks  
|                  | **Cognitive therapy:** Arm 2  
|                  | **Duration:** 8 weeks  
|                  | **Placebo:** N/A  
|                  | **Duration:** 8 weeks |
| **INCLUSION:**  | Age 18-65 yrs; DSM III-R criteria for panic disorder; in good physical health |
| **EXCLUSION:**  | Pregnant, lactating; psychotic; suicidal or demented subjects excluded |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | Not reported |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Not reported  
|                               | **Mean Age:** 36.5  
|                               | **Gender (% female):** Not reported  
|                               | **Ethnicity:** Not reported  
|                               | **Other population characteristics:** No prior psychiatric treatment: fluvoxamine: 40%, cognitive therapy: 32%, placebo: 20% |
|---------------------------------------------|--------------------------------------|---------------------------------|
| **OUTCOME ASSESSMENT:**                     | **Measures:** Number of panic attacks and severity as estimated from a patient log, Clinical Anxiety Scale (CAS), CGI-S, CGI-I, Sheehan Disability Scale, MADRS  |
| **Timing of assessments:** Baseline, during treatment and at endpoint (some were assessed weekly) |                                      |                                 |
| **RESULTS:**                                | • Significantly greater improvement for fluvoxamine on CAS (p = 0.003) and CGI (p = 0.004), Panic Severity Score (p = 0.003) than placebo |
|                                             | • Sheehan Disability Ratings: work (p = 0.01) and social/leisure (p = 0.02) components were significantly better with fluvoxamine than placebo |
|                                             | • MADRS score was significantly more improved with fluvoxamine than placebo |
| **ANALYSIS:**                               | **ITT:** No                           | **Post randomization exclusions:** Yes |
| **ATTRITION:**                              | **Loss to follow-up:** fluvoxamine: 16%, cognitive therapy: 36%, placebo: 28% |
|                                             | **Withdrawals due to adverse events:** fluvoxamine: 8%, cognitive therapy: 0%, placebo: 0% |
|                                             | **Loss to follow-up differential high:** Yes |
| **ADVERSE EVENTS:**                         | • Fluvoxamine-treated patients reported significantly more adverse events than placebo–treated patients (p = 0.005) |
|                                             | • 1 person in the fluvoxamine group attempted suicide |
| **QUALITY RATING:**                         | **Fair**                             |                                 |
### Evidence Table 6

#### Panic Disorder

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

### OUTCOME ASSESSMENT:

**Primary Outcome Measures:** Percentage of participants who were free from full-symptom panic attacks (> 4 symptoms) based on Panic and Anticipatory Anxiety Scale (PAAS)

**Secondary Outcome Measures:** change from baseline in full-symptom panic attack frequency; response; remission; CGI-I, CGI-S, Phobia scale, Sheehan Disability Scale, Q-LES-Q

**Timing of assessments:** screening visit & study days -1,7,14,21,28,42,56, and 70

### RESULTS:

**ITT:**
- No significant differences in number of patients free from panic attacks between treatment groups (data NR)
- Significantly more venlafaxine ER – treated patients responded (data NR; p < 0.05) and remitted (data NR; p < 0.05) compared to placebo group.

**On therapy evaluation:**
- At final evaluations, 55% (venlafaxine) vs. 52.4% (placebo) of patients were free from full-symptom panic attacks (statistically non significant)
- Significantly more venlafaxine ER – treated patients responded (68.1% vs. 55.4%; p = 0.023) and remitted 35.6% vs. 24.4%; p = 0.030) compared to placebo group.
- Venlafaxine ER also associated with lower mean panic attack frequency, improvement in fear and avoidance factors of the Phobia Scale, and higher proportion free from limited-symptom panic attacks.

**ITT:** Yes  
**Post randomization exclusions:** Yes, 9%

### ATTRITION:

**Loss to follow-up:**
- Overall 26.6% attrition

**Withdrawals due to adverse events:**
- Overall NR
- Venlafaxine 9%
- Placebo NR

**Withdrawals due to lack of efficacy:**
- Overall NR
- Venlafaxine NR
- Placebo 10%

**Loss to follow-up differential high:** Cannot determine

### ADVERSE EVENTS:

- No significant differences b/w treatment groups in primary reasons for withdrawal during the double-blind period.
- Overall, adverse events were reported by 86% of venlafaxine ER group and 78% placebo group.
- Most frequent AEs causing discontinuation in venlafaxine ER group were anorexia, nausea, insomnia, and sweating.

### QUALITY RATING:

Fair
### Evidence Table 6  
**Panic Disorder**

| STUDY: | Authors: Hoehn-Saric R, et al.  
Year: 1993  
Country: US |
<table>
<thead>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
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</table>
| DESIGN: | Study design: RCT  
Setting: Single center  
Sample size: 50 |
| INTERVENTION: |  
**Drug:** Fluvaxamine  
**Dose:** 50–300 mg/day  
**Duration:** 8 weeks  
**Placebo:** N/A  
**Duration:** 8 weeks |
| INCLUSION: | Diagnosis by DMS III-R and the SCID; 1 panic attack per week for at least 4 weeks; severity score of 25 or greater on diary (during run in) to enter randomization phase as well as at least one major panic attack (major panic attack = attack with at least 4 symptoms) one week before randomization |
| EXCLUSION: | No medication that could affect the CNS for past 3 weeks before study; abnormal lab values; ECG and hypertension; history of major mental illness; depression; OCD; substance abuse |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
**Mean Age:** 38.0  
**Gender (% female):** 55.6%  
**Ethnicity:** Not reported |
|  | **Other population characteristics:** Education 13.7 yr, 78% with mild agoraphobia, age of onset 26.2 years |
| OUTCOME ASSESSMENT: | Measures: Number of panic attacks per week and severity of attacks, MADRS, Clinical Anxiety Scale (CAS), Sheehan Disability Scale, symptoms from diary  
|                   | Timing of assessments: Weekly for 8 weeks |
| RESULTS:          | Fluvoxamine group had significantly fewer major panic attacks than placebo group  
|                   | Significantly more fluvoxamine treated patients were free of panic attacks at endpoint (p < 0.02)  
|                   | Significantly lower scores in the fluvoxamine group on CAS and MADRS (CAS significant at week 6; MADRS significant at week 7)  
|                   | There was no difference between groups in terms of minor panic attacks or Sheehan Disability Scale |
| ANALYSIS:         | ITT: No  
|                   | Post randomization exclusions: Yes |
| ATTRITION:        | Loss to follow-up: 24%; fluvoxamine: 24%, placebo: 24%  
|                   | Withdrawals due to adverse events: 12%; fluvoxamine: 16%, placebo: 8%  
|                   | Loss to follow-up differential high: No |
| ADVERSE EVENTS:   | Fluvoxamine: drowsiness: 28%, dyspepsia: 17%, headache: 11%  
|                   | Fewer side effects at week 8 than week 3 |
| QUALITY RATING:   | Fair |
# Evidence Table 6

## Panic Disorder

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

| OUTCOME ASSESSMENT: | Measures: Multi-center Panic Anxiety Scale, HAM-A, CGI  
Timing of assessments: Weekly for 4 weeks then biweekly |
|---|---|
| RESULTS: | • The number of panic attacks decreased significantly for sertraline treated patients compared to placebo (77% vs. 51%; p = 0.03)  
• Sertraline treated patients showed significantly greater improvements in the HAM-A scale than placebo treated patients (p = 0.03)  
• Quality of life and CGI scales had significantly higher ratings in the sertraline group (p = 0.006; p < 0.001) |
| ANALYSIS: | ITT: Yes  
Post randomization exclusions: Yes |
| ATTRITION: | Loss to follow-up: 21.4%; sertraline: 26%, placebo: 17%  
Withdrawals due to adverse events: sertraline: 9%, placebo: 1%  
Loss to follow-up differential high: No |
| ADVERSE EVENTS: | Nausea (33% vs. 17%), diarrhea (24% vs. 11%), dry mouth (19% vs. 8%), ejaculation failure (11% vs. 0%), and decreased libido (10% vs. 0%) were significantly more frequent in the sertraline than in the placebo group |
| QUALITY RATING: | Fair |
## Evidence Table 6  
### Panic Disorder

| STUDY: | Authors: Stahl SM, et al.  
Year: 2003  
Country: US |
| FUNDING: | Forest Laboratories |
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 366 |
| INTERVENTION: | Drug: Escitalopram  
Dose: 5-20 mg/d  
10 weeks  
Placebo  
Duration: 10 weeks |
| | Citalopram  
Dose: 10-40 mg/d  
10 weeks |
| | Placebo  
Dose: N/A  
Duration: 10 weeks |
| INCLUSION: | DSM-IV criteria for panic disorder with or without agoraphobia; minimum of 4 DSM-IV defined panic attacks during the 4 weeks prior to the screening visit; 3 panic attacks during the 2 week placebo lead in; 18-80 years of age |
| EXCLUSION: | Score > 17 HAM-D; bipolar disorder; schizophrenia; OCD or other psychotic disorders; pregnancy; clinically significant abnormalities |
| OTHER MEDICATIONS/ INTERVENTIONS: | Zolpidem as needed for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
Mean Age: Escitalopram: 37.5, citalopram: 37.1, placebo: 38.6  
Gender (% female): Escitalopram: 57.6 %, citalopram: 61.6%, placebo: 55.3%  
Ethnicity: Escitalopram: 70.4 % white, citalopram: 75.9% white, placebo: 71.1% white  
Other population characteristics: No significant population differences; mean 5 panic attacks per week and estimated 44% of waking hours worrying about future attacks |
<table>
<thead>
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<tbody>
<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
<td>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)</td>
<td></td>
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<tr>
<td>Timing of assessments: Screening, baseline, weeks 1, 2, 4, 6, 8, 10</td>
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<tr>
<td><strong>RESULTS:</strong></td>
<td>• The frequency of panic attacks was statistically improved in the escitalopram group relative to placebo (p = 0.04)</td>
<td></td>
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<tr>
<td></td>
<td>• 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 &lt; 0.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Escitalopram was not compared to citalopram</td>
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<tr>
<td><strong>ANALYSIS:</strong></td>
<td><strong>ITT:</strong> Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Post randomization exclusions:</strong> Yes</td>
<td></td>
</tr>
<tr>
<td><strong>ATTRITION:</strong></td>
<td><strong>Loss to follow-up:</strong> 32%</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Withdrawals due to adverse events:</strong> 7.4%; escitalopram: 6.3%, citalopram: 8.4%, placebo: 7.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Loss to follow-up differential high:</strong> No</td>
<td></td>
</tr>
<tr>
<td><strong>ADVERSE EVENTS:</strong></td>
<td>No significant differences between study groups</td>
<td></td>
</tr>
<tr>
<td><strong>QUALITY RATING:</strong></td>
<td>Fair</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 7: Post-Traumatic Stress Disorder

| STUDY: | Authors: Brady K, et al., 2000, (1 of 2 acute phase)\(^{152}\)  
Londborg PD, et al., 2001 (24 week open label)\(^{157}\)  
Rapaport MH, et al., 2002 (64 weeks qoI)\(^{154}\)  
Davidson JRT, Pearlstein T, et al., 2001 (28 week continuation)\(^{158}\)  
Country: US |
| FUNDING: | Pfizer |
| DESIGN: | Study design:  
1) 2 RCTs (Brady 2000, Davidson 2001; acute phase); NOTE: Davidson 2001 for acute phase in different evidence table  
2) Open label (continuation)  
3) RCT (maintenance)  
4) QOL study over full 64 weeks  
Setting: Multi-center  
Sample size: Brady 187, continuation 252, maintenance 96, Rapaport 359 |
| INTERVENTION: | Drug: Sertraline  
Dose: 50-200 mg/d  
Duration: 12 weeks  
Open-label continuation treatment:  
24 weeks  
Maintenance:  
28 weeks  
Placebo  
N/A  
12 weeks  
Open-label continuation treatment:  
24 weeks  
Maintenance:  
28 weeks |
**Country:** US |
|---|
| **INCLUSION:** 18 yrs or older; DSM-III-R criteria for PTSD; minimum of 6 months duration; ≥ 50 on CAPS-2 (Clinician Administered PTSD Scale); free of psychotropic medication for at least 2 weeks  
Open-label continuation treatment: patients who completed acute phase trials (Brady 2000 or Davidson 2001) (only results from sertraline group reported in article)  
Maintenance: patients who completed acute and continuation study |
| **EXCLUSION:** Other psychiatric diseases; hepatic or renal disease; current psychotherapy; alcohol or substance abuse; pregnancy or lactation; previously failed to respond to SSRI therapy; clinically relevant progressive disease |
| **OTHER MEDICATIONS/INTERVENTIONS:** Chloral hydrate (not more than 2 nights per week) |
| **POPULATION CHARACTERISTICS:** Groups similar at baseline: Yes  
**Mean age:** Brady et al: sertraline: 40.2, placebo: 39.5  
**Gender:** (% female) sertraline: 75.5%, placebo: 71.0%  
**Ethnicity:** (white) sertraline: 80.9%, placebo: 88.2%; (black) sertraline: 14.9%, placebo: 8.6%; (other) sertraline: 4.3%, placebo: 3.2%  
**Other population characteristics:** Brady et al: current major depression: sertraline: 36%, placebo: 30%; current anxiety disorder: sertraline: 18%, placebo: 14%; history of alcohol abuse: sertraline: 22%, placebo: 30%; history of drug abuse: sertraline: 14%, placebo: 14% |
| **OUTCOME ASSESSMENT:** Measures and timing of assessment CAPS-2, CGI-I, IES weeks 1, 2, 3, 4, 6, 8, 10, 12  
Open-label continuation treatment: weekly for 4 weeks, then biweekly  
Maintenance: rate of relapse measured by: CGI > 3, PTSD increase > 30%, investigator judged clinical worsening, biweekly  
QOL measures: Q-LES-Q, SF36, occupational & social impairment items of CAPS-2 |
**Authors:** Brady K, et al. 2000, Londberg PD, et al., 2001
- Rapaport MH, et al., 2002
- Davidson JRT, Pearlstein T, 2001

**Country:** US

### RESULTS:

- **Brady et al.** (acute) treatment with sertraline yielded statistically significantly greater efficacy on 3 of 4 primary outcome measures:
  - CAPS-2: $p = 0.02$
  - CGI-S: $p = 0.01$
  - CGI-I: $p = 0.02$
  - IES: $p = 0.07$

- 53% of patients were much or very much improved in sertraline group ($p = 0.008$ vs. placebo)

**Quality of life (pooled data from Brady 2000 and Davidson 2001):**

- Sertraline treated patients showed a significantly greater improvement in Q-LES-Q total scores ($p = 0.01$) and SF-36 emotional role functioning subscale scores ($p = 0.002$) than placebo
- Sertraline treated patients also showed a significantly greater improvement in social and occupational functioning on CAPS-2 compared to placebo ($p = 0.038$)

**Open-label continuation treatment**

- 92% of acute phase responders sustained treatment response, 54% of acute phase non-responders become responders
- There was a modest overall improvement of Quality of Life scores during continuation treatment

**Maintenance**

- Continued treatment with sertraline yielded lower PTSD relapse rates (5% vs. 26%; $p < 0.02$) than placebo, lower acute exacerbation rates (15.8% vs. 52.2%; $p < 0.01$) and lower discontinuation due to clinical deterioration rates (15.8% vs. 45.7%; $p = 0.005$)
- Placebo led to a significant clinical deterioration of quality of life scores. Kaplan Meier analysis showed a highly significant relapse prevention for sertraline ($p = 0.0002$)
**Country:** US |
<table>
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<tbody>
<tr>
<td><strong>ANALYSIS:</strong></td>
</tr>
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</table>
**ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:** |  
**Loss to follow-up:** Brady et al. (acute): 28.9%, sertraline: 30.9%, placebo: 27.2%.  
Open-label continuation treatment: Not reported  
Maintenance: 50%  
**Withdrawals due to adverse events:** Brady et al.: sertraline: 5.3%, placebo: 5.4%  
Open-label continuation treatment: sertraline: 8.6%.  
Maintenance: sertraline: 8.7%, placebo: 6.0%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** |  
• There were no statistically significant differences in adverse events between study groups except: Brady et al. insomnia (p = 0.01), sertraline: 16%, placebo: 4.3%  
Open-label continuation treatment:  
• No serious abnormalities in ECG, lab tests, or vital signs were attributed to sertraline treatment  
Maintenance:  
• 6.8% gained 7% or more in body weight, no treatment-emergent or treatment-related adverse events reported at 10% or higher |
| **QUALITY RATING:** | Fair |
# Evidence Table 7

## Post-Traumatic Stress Disorder

| STUDY: | Authors: Connor K, et al.¹³⁶  
Year: 1999  
Country: US |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>NIMH</td>
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</tbody>
</table>
| DESIGN: | Study design: RCT; 12 week acute with 12 week continuation  
Setting: Not reported  
Sample size: 54 |
| INTERVENTION: | *Drug:*  
Fluoxetine  
10-60 mg/d  
12 weeks for acute treatment;  
12 weeks for continuation phase  
Placebo  
N/A  
12 weeks for acute treatment;  
12 weeks for continuation phase |
| INCLUSION: | Age 18-55; DSM-III-R criteria for PTSD according to the SCI for DSM-III-R and were civilians |
| EXCLUSION: | Determined by SCID: history of psychosis; bipolar disorder; antisocial personality disorder; current/recurrent/recent risk of suicide; homicide; and drug or alcohol abuse within previous 6 months |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
Mean age: 37; fluoxetine: 36, placebo: 38  
Gender (% female): 91%, fluoxetine: 89%, placebo: 93%  
Ethnicity: 93% white; fluoxetine: 100%, placebo: 85%  
Other population characteristics: 41% married; 93% high school graduates; 43% employed out of home; median age of PTSD onset 25.5; median years of PTSD 6 |
**Authors:** Connor K, et al.  
**Year:** 1999  
**Country:** US

### OUTCOME ASSESSMENT:

**Measures:** Duke Global Rating for PTSD, SIP (Structured Interview for PTSD), self-rating sales: DTS (Davidson Trauma Scale), SDS (Sheehan Disability Scale), VS (Vulnerability to Effects of Stress Scale)

**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8, 10, 12

### RESULTS:

- Using Duke cut off score of 1 (no symptoms) to define responders, the fluoxetine group had significantly more responders than the placebo group (59% vs.19%; p < 0.005)
- Using Duke cut off score of 1 (no symptoms) or 2 (minimal symptoms) to define responders, no statistically significant difference could be seen (85% vs. 62%; p < 0.06)
- The SIP showed significant improvements for fluoxetine: SIP: p < 0.005
- Fluoxetine subjects responded in significantly less time than placebo treated subjects; Kaplan Meier: p < 0.005
- Fluoxetine was also associated with significantly greater effects on the disability and stress subscales (SDS, VS, DTS) at 12 weeks (p < 0.05; p < 0.01; p < 0.005)

### ANALYSIS:

**ITT:** Yes  
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 31.5%; fluoxetine: 22.2%, placebo: 40.7%  
**Withdrawals due to adverse events:** 0%  
**Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:

Not reported

### QUALITY RATING:

Fair
## Evidence Table 7: Post-Traumatic Stress Disorder

| STUDY: | Authors: Davidson JRT, et al. <sup>153</sup>  
|        | Year: 2001  
|        | Country: US |
| FUNDING: | Pfizer |
| DESIGN: | **Study design:** RCT  
|         | **Setting:** Multi-center  
|         | **Sample size:** 208 |
| INTERVENTION: |  
| *Drug:* | Sertraline  
| *Dose:* | 50-200 mg/d  
| *Duration:* | 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% |
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
- \( Post\ \text{randomization\ exclusions}: \) Yes

ATTRITION:

- \( Loss\ to\ follow-up: \) 32.3%
- \( Withdrawals\ due\ to\ adverse\ events: \) sertraline: 9.1%, placebo: 4.7%
- \( Loss\ to\ follow-up\ differential\ high: \) No

ADVERSE EVENTS:

Adverse events that were significantly more common in sertraline subjects compared with placebo consisted of insomnia (35% vs. 22%), diarrhea (28% vs. 11%), nausea (23% vs 11%), fatigue (13% vs. 5%), and decreased appetite (12% vs. 1%)

QUALITY RATING: Fair
# Evidence Table 7: Post-Traumatic Stress Disorder

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

| **OUTCOME ASSESSMENT:** | **Measures:** Change in CAPS-2, CGI-I, both measured at study endpoint which was 12 weeks, secondary outcomes: change in Davidson Trauma Scale symptom clusters and Treatment Outcome PTSD Scale, Sheehan Disability Scale  
**Timing of assessments:** Weeks 1, 2, 4, 6, 8, 12 |
|--------------------------|----------------------------------------------------------|

| **RESULTS:** | • Paroxetine patients in both treatment groups demonstrated significantly greater improvement on primary outcome measures compared to placebo (CAPS, CGI-I)  
• Treatment response did not vary by trauma type, time since trauma, or severity of baseline PTSD |
|-----------------|---------------------------------------------------------|

| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes |
|-----------------|------------------------------------------|

| **ATTRITION:** | **Loss to follow-up:** 11.2%  
**Withdrawals due to adverse events:** 12.2%; paroxetine (20mg): 11.2%, paroxetine (40 mg): 15 %, placebo: 9.6%  
**Loss to follow-up differential high:** Not reported |
|-----------------|-------------------------------------------------|

| **ADVERSE EVENTS:** | • Side effects reported at least 10% and twice that of placebo: asthenia, diarrhea, abnormal ejaculation, impotence, nausea, somnolence  
• 9 serious adverse experiences in paroxetine treated subjects; 7 of 9 rated by investigators as unrelated or probably unrelated to treatment |
|---------------------|------------------------------------------------|

<table>
<thead>
<tr>
<th><strong>QUALITY RATING:</strong></th>
<th><strong>Fair</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence Table 7</td>
<td>Post-Traumatic Stress Disorder</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------</td>
</tr>
</tbody>
</table>
| **STUDY:**       | Authors: McRae A, et al.  
|                  | Year: 2004  
|                  | Country: US |
| **FUNDING:**     | Bristol-Myers Squibb |
| **DESIGN:**      | Study design: RCT  
|                  | Setting: Multi-center (2 medical centers)  
|                  | Sample size: 37 |
| **INTERVENTION:**| Drug:  
|                  | Nefazodone  
|                  | Sertraline  
| Dose:            | 463 mg/d (mean)  
|                  | 153 mg/d (mean)  
| Duration:        | 12 weeks  
|                  | 12 weeks  
| Sample size:     | 18  
|                  | 19 |
| **INCLUSION:**   | Male and female outpatients aged 18-65; met DSM-IV criteria for PTSD; minimum of 3 months duration of PTSD; severity of at least 50 on the CAPS-2 |
| **EXCLUSION:**   | Any clinically significant medical condition or laboratory abnormality; history of seizure disorder or organic brain disease; pregnancy or breastfeeding; psychotic, eating disorder, or OCD; substance abuse; current diagnosis of major depression; psychotropic medication; drug hypersensitivity; history of non-responsiveness to treatment drugs |
| **OTHER MEDICATIONS/INTERVENTIONS:** | No other psychotropic medications allowed |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
|                  | Mean age: 40  
|                  | Gender (% female): 77%  
|                  | Ethnicity: Not reported  
|                  | Other population characteristics: Time since trauma: 22 years |
### Authors: McRae A, et al.
Year: 2004
Country: US

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
<th>17 item PTSD scale; Part 2 CAPS-2; CGI-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures:</td>
<td>17 item Davidson Trauma Scale; MADRS; HAM-A; Pittsburg Sleep Quality Index; Sheehan Disability Scale</td>
</tr>
<tr>
<td>Timing of assessments:</td>
<td>Baseline, weeks 4, 8, and 12</td>
</tr>
</tbody>
</table>

### RESULTS:

- No statistically significant differences between the sertraline and the nefazodone treatment groups on any of the outcome measures.
- Both treatment groups had statistically significant within-group improvements on all outcome measures from baseline to endpoint:
  - CAPS-2: sertraline: 29.08 (p < 0.001); nefazodone: 28.77 (p < 0.001)
  - CGI: sertraline 2 (p < 0.001); nefazodone: 2 (p < 0.001)

### ANALYSIS:

- ITT: Yes
- Post randomization exclusions: Yes

### ATTRITION:

- Loss to follow-up: 38%; nefazodone: not reported; sertraline: not reported
- Withdrawals due to adverse events: 11%; nefazodone: 11%; sertraline: 10.5%
- Loss to follow-up differential high: not reported

### ADVERSE EVENTS:

- No significant differences in adverse events reported between treatment groups:
  - Drowsiness: Nefazodone: 26.3%; sertraline: 27.8%
  - Headache: Nefazodone: 26.3%; sertraline: 22.2%
  - Insomnia: Nefazodone: 21.1%; sertraline: 16.7%
  - Dizziness: Nefazodone: 21.1%; sertraline: 0%
  - Fatigue: Nefazodone: 5.3%; sertraline: 16.7%
  - Anorgasmia: Nefazodone: 0%; sertraline: 16.7%

### QUALITY RATING:

- Fair
<table>
<thead>
<tr>
<th>Evidence Table 7</th>
<th>Post Traumatic Stress Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Tucker P, et al.  
                   Year: 2005  
                   Country: US |
| **FUNDING:**     | Forest Pharmaceuticals |
| **DESIGN:**      | Study design: RCT  
                   Setting: University hospital outpatient  
                   Sample size: 59 |
| **INTERVENTION:**| Drug: 
                   Citalopram  
                   Dose: 36.2 mg/day  
                   Duration: 10 weeks  
                   Sample size: 25 |
|                  | Sertraline  
                   Dose: 134.1 mg/day  
                   Duration: 10 weeks  
                   Sample size: 23 |
|                  | Placebo  
                   Dose: N/A  
                   Duration: 10 weeks  
                   Sample size: 10 |
| **INCLUSION:**   | 18-64 years old; PTSD symptoms |
| **EXCLUSION:**   | Medical condition precluded use of an SSRI; previous intolerance or lack of response to an adequate trial of citalopram or sertraline; possible placebo treatment was unsafe; psychotherapy was indicated; current alcohol or substance abuse |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | Diphenhydramine for sleep |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
                   Mean age: citalopram: 39.2, sertraline: 39.1, placebo: 36.8  
                   Gender (% female): citalopram: 68%, sertraline: 78.3%, placebo: 80%  
                   Ethnicity (% white): citalopram: 76%, sertraline: 91.3%, placebo 100%  
                   Other population characteristics: Not reported |
Authors: Tucker P, et al.  
Year: 2003  
Country: US

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures:</th>
<th>Clinician administered PTSD scale (CAPS) and BDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments:</td>
<td>CAPS: Baseline and weeks 1, 6, and 10; BDI: baseline and weeks 1, 2, 3, 4, 6, 8, and 10</td>
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</table>

| RESULTS: |  
|----------|--------------------------------------------------|
| • No differences in efficacy between sertraline and citalopram treated patients  
• No differences in efficacy between active treatments and placebo |

<table>
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<tr>
<th>ANALYSIS:</th>
<th>ITT: Yes</th>
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<tbody>
<tr>
<td>Post randomization exclusions:</td>
<td>No</td>
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</tbody>
</table>

| ATTRITION: | Overall  
|-----------|---------|
| Loss to follow-up: | 14  
| Withdrawals due to adverse events: | 2 known  
| Withdrawals due to lack of efficacy: | NR  
| Loss to follow-up differential high: | No |
| Citalopram | 5  
| Sertraline | 6  
| Placebo | 3  

| ADVERSE EVENTS: |  
|----------------|--------------------------------------------------|
| • Fatigue: citalopram: 44%, sertraline: 29%, placebo: 30%  
• GI distress: citalopram: 16%, sertraline: 38%, placebo: 30%  
• Insomnia: citalopram: 60%, sertraline: 33%, placebo: 70%  
• Sexual dysfunction: citalopram: 16%, sertraline: 4%, placebo: 20% |

| QUALITY RATING: | Fair |

<table>
<thead>
<tr>
<th></th>
<th>Citalopram</th>
<th>Sertraline</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>NR</td>
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<td>NR</td>
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<td>N/A</td>
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</table>
Evidence Table 8: Social Anxiety Disorder

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

| OUTCOME ASSESSMENT: | **Primary Outcome Measures:** LSAS  
**Secondary Outcome Measures:** CGI-S; CGI-IM; SPIN; SDI  
**Timing of assessments:** Baseline, and days 7, 14, 21, 28, 42, 56, 70 and 84 |
|---------------------|--------------------------------------------------------------------------------|

**RESULTS:**
- No significant differences in any outcome measures between venlafaxine ER and paroxetine.
- Treatment with venlafaxine ER and paroxetine was associated with significantly greater improvement than treatment with placebo for all primary and secondary efficacy variables (p < 0.05).
- LSAS total scores significantly improved for venlafaxine ER or paroxetine vs. placebo –primary endpoint, the baseline adjusted mean change in LSAS total score was –36.0 (SE 2.35) for venlafaxine, –35.4 (SE 2.46) for paroxetine and –19.1 (SE 2.40) for the placebo group.
- SPIN scores significantly improved for venlafaxine ER and paroxetine groups than for placebo group at weeks 3-12 (both p < 0.05 week 3; both p < 0.01 week 4; both p < 0.001 weeks 6-12).

**ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** Yes

**ATTRITION:**  
**Loss to follow-up:** 16.8%; venlafaxine ER: 16%; paroxetine: 16%; placebo: 18.5%  
**Withdrawals due to adverse events:** 7.6%, venlafaxine: not reported; paroxetine: not reported  
**Loss to follow-up differential high:** No

**ADVERSE EVENTS:**
- During the double-blind treatment period, 90% venlafaxine ER, 89% paroxetine, and 82% placebo treated patients reported treatment emergent adverse events; the most common (incidence ≥5%) adverse events among venlafaxine ER treated patients were headache (10%), nausea (7%), dizziness (14%), insomnia (6%), and vertigo (10%); among paroxetine-treated patients were headache (12%), dizziness (13%), and insomnia (6%); among placebo treated patients, no taper/post study emergent adverse event occurred at an incidence of ≥5% and the differences between groups were not statistically significant.

**QUALITY RATING:** Fair
## Evidence Table 8  Social Anxiety Disorder

| **STUDY:** | **Authors:** Baldwin et. al.  
**Year:** 1999  
**Country:** Belgium, France, Germany, Ireland, South Africa, Spain, United Kingdom |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Smith Kline Beecham</td>
</tr>
</tbody>
</table>
| **DESIGN:** | **Study design:** RCT  
**Setting:** Multi-center (39)  
**Sample size:** 290 |
| **INTERVENTION:** | **Drug:** Paroxetine  
**Dose:** 20-50 mg/d  
**Duration:** 12-weeks  
**Placebo:** N/A  
**Duration:** 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:** | Chlora hydrate for sleep |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Yes  
**Mean Age:** 36  
**Gender (% female):** 53%  
**Ethnicity:** White: 89%  
**Other population characteristics:** Mean HAM-D = 6.5 |
| **Authors:** Baldwin D, et. al.  
**Year:** 1999  
**Country:** Belgium, France, Germany, Ireland, South Africa, Spain, United Kingdom  
**OUTCOME ASSESSMENT:**  
**Measures:** (Primary) mean change from baseline in LSAS; CGI-I responders  
(Secondary) SADS; SDS; CGI-S  
**Timing of assessments:** Weeks 1, 2, 3, 4, 6, 8, 12  
**RESULTS:**  
- Mean change from baseline in LSAS: paroxetine -29.4 vs. placebo -15.6 (p < 0.001 from week-4 through week-12)  
- CGI-I responders: paroxetine 65.7% vs. placebo 32.4% (p < 0.001 from week-4 through week-12)  
- Paroxetine was statistically superior to placebo on all secondary outcome measures (SADS; SDS; CGI-S) (p < 0.05)  
**ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** No  
**ATTRITION:**  
**Loss to follow-up:** 27%; paroxetine 25%; placebo 28%  
**Withdrawals due to adverse events:** 6%; paroxetine 7%; placebo 4%  
**Loss to follow-up differential high:** No  
**ADVERSE EVENTS:**  
- Any adverse event: paroxetine 74.1% vs. placebo 68.2%  
- Nausea: paroxetine 28.1% vs. placebo 7.9%  
- Abnormal ejaculation: paroxetine 14.1% vs. placebo 1.4%  
- Dizziness: paroxetine 12.9% vs. placebo 5.3%  
- Sweating: paroxetine 12.2% vs. placebo 2.6%  
**QUALITY RATING:** Fair
**Evidence Table 8**  
**Social Anxiety Disorder**

| STUDY:                  | Authors: Blomhoff S, et. al.  
|                        | Year: 2001  
|                        | Country: Norway and Sweden |
| FUNDING:               | Pfizer |
| DESIGN:                | Study design: RCT  
|                        | Setting: Multi-center  
|                        | Sample size: 387 |
| INTERVENTION:          | Drug: Sertraline  
|                        | Dose: 50-150 mg/d  
|                        | Duration: 24 weeks  
|                        | Placebo  
|                        | N/A  
|                        | 24 weeks  
|                        | Patients also were randomized to receive either exposure therapy or general care |
| INCLUSION:             | 18-65 years of age; DSM-IV criteria for generalized social phobia; duration of at least one year; ≥ 4 on the CGI-SP scale |
| EXCLUSION:             | Panic disorder; current anxiety; major depressive; substance use; eating disorder; lifetime history of bipolar disorder or psychosis |
| OTHER MEDICATIONS/     | Not reported |
| INTERVENTIONS:         | |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
|                        | Mean age: 40.4  
|                        | Gender (% female): 60.5%  
|                        | Ethnicity: Not reported  
|                        | Other population characteristics: No significant population differences reported |
| Authors: Blomhoff S, et. al.  
Year: 2001  
Country: Norway and Sweden |
|----------------------------------|
| **OUTCOME ASSESSMENT:** | **Measures:** CGI-Social Phobia scale (CGI-SP), social phobia scale, brief social phobia scale, social phobia subscale of the Marks Fear Questionnaire, Sheenan Disability Inventory, Fear of Negative Evaluation Scale, MOS 36 Short-Form Health Survey  
**Timing of assessments:** Weeks 4, 8, 12, 16, 24 |
| **RESULTS:** | • Significantly more sertraline than placebo patients responded to therapy based on a 50% or greater reduction in SPS symptoms (p < 0.001)  
• No significant difference was observed between exposure therapy and non-exposure therapy treated patients |
| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:** | **Loss to follow-up:** 35%  
**Withdrawals due to adverse events:** 2.6%  
**Loss to follow-up differential high:** Not reported |
| **ADVERSE EVENTS:** | Nausea (p = 0.002), malaise (p = 0.022), and sexual dysfunction (p = 0.002) were observed significantly more in the sertraline group than in the placebo group |
| **QUALITY RATING:** | Fair |
### Evidence Table 8  
**Social Anxiety Disorder**

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

**OUTCOME ASSESSMENT:**  
**Primary Outcome Measures:** LSAS total score  
**Secondary Outcome Measures:** LSAS subscales; CGI-S; CGI-I; SDS; MADRS  
**Timing of assessments:** Baseline and weeks 1, 2, 3, 4, 6, 8, 12

**RESULTS:**
- LSAS at 12 weeks: placebo 68.8, escitalopram 62.2 with a treatment difference of 7.3 (p < 0.01)  
- Mean reduction in LSAS fear/anxiety subscale: escitalopram -16.9, placebo -12.7 (p < 0.001)  
- Mean reduction in LSAS avoidance subscale: escitalopram -17.6, placebo -14.4 (p < 0.05)  
- Escitalopram showed significant improvements over placebo in CGI-S (p < 0.01); CGI-I responders 39% for placebo and 54% for escitalopram (p < 0.01)  
- Significantly more improvement in SDS work (p < 0.001) and social (p < 0.05) subscales  
- MADRS not reported

**ANALYSIS:**
- ITT: Yes  
- **Post randomization exclusions:** Yes- 5 had no post-baseline assessment

**ATTRITION:**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Placebo</th>
<th>Escitalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>19%</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>6.8%</td>
<td>4.5%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>4.2%</td>
<td>6.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**
- Headache: placebo: 25%, escitalopram: 25%  
- Nausea: placebo: 12%, escitalopram: 22%  
- Fatigue: placebo: 9%, escitalopram: 14%  
- Somnolence: placebo: 5%, escitalopram: 10%  
- Diarrhea: placebo: 5%, escitalopram: 9%  
- Insomnia: placebo: 6%, escitalopram: 9%

**QUALITY RATING:** Fair
<table>
<thead>
<tr>
<th>Evidence Table 8</th>
<th>Social Anxiety Disorder</th>
</tr>
</thead>
</table>
| **STUDY:** | **Authors:** Kobak KA, et. al.  
**Year:** 2002  
**Country:** US |
| **FUNDING:** | Eli Lilly & Co. |
| **DESIGN:** | **Study design:** RCT  
**Setting:** Single center  
**Sample size:** 60 |
| **INTERVENTION:** |  
**Drug:**  
**Dose:**  
**Duration:**  |
| | Fluoxetine  
20-60 mg/d  
14 weeks |
| | Placebo  
N/A  
14 weeks |
| **INCLUSION:** | DSM-IV criteria for social phobia for at least 6 months; a score of at least 50 on the Liebowitz Social Anxiety Scale (LSAS) before and after the lead–in; score could not decrease by more than 20% |
| **EXCLUSION:** | Non-response to fluoxetine treatment; pregnancy; previous participation in a fluoxetine study; concurrent use of psychotropic or centrally acting drugs, anticonvulsants, corticosteroids, or tryptophan; serious illness; suicidal; concurrent Axis I disorders in past 12 months; psychotherapy; seizure disorder |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Not reported |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Not reported  
**Mean age:** 39.5  
**Gender** (% female): 58%  
**Ethnicity:** Not reported  
**Other population characteristics:** Not reported |
**Authors:** Kobak KA, et. al.  
**Year:** 2002  
**Country:** US

| OUTCOME ASSESSMENT: | **Measures:** Liebowitz Social Anxiety Scale (LSAS) (primary), Social Phobia Subscale of Fear Questionnaire, CGI-S, CGI-I, Patient Global Improvement Scales, HAM-A, Brief Social Phobia Scale, HAM-D (did not report which scale), Global Assessment of Functioning Scale, QOL  
**Timing of assessments:** Weeks 1, 2, 4, 6, 8, 10, 12, 14 |
|---|---|

| RESULTS: | • Fluoxetine was not significantly different from placebo on the LSAS score (p = 0.901)  
• Similar results in secondary outcome measures with no significant difference between fluoxetine and placebo  
• A significant change was found on all outcome measures from baseline to endpoint with both fluoxetine (p < 0.001) and placebo (p < 0.001) |
|---|---|

| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** No |
|---|---|

| ATTRITION: | **Loss to follow-up:** 20%; fluoxetine 16%; placebo 23%  
**Withdrawals due to adverse events:** 7%; fluoxetine 3%, placebo 10%  
**Loss to follow-up differential high:** No |
|---|---|

| ADVERSE EVENTS: | • For fluoxetine: headache, insomnia, asthenia, and nervousness  
• For placebo: headache, insomnia, nervousness, and myalgia  
• Significantly more fluoxetine than placebo patients had asthenia (p = 0.02)  
• Significantly more placebo than fluoxetine patients had myalgia (p = 0.04) |
|---|---|

<p>| QUALITY RATING: | Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 8</th>
<th>Social Anxiety Disorder</th>
</tr>
</thead>
</table>
| **STUDY:**      | Authors: Lader M, et al. 18th  
|                 | Year: 2004  
|                 | Country: Multinational (11 countries) |
| **FUNDING:**    | H. Lundbeck A/S |
| **DESIGN:**     | Study design: RCT  
|                 | Setting: Multi-center (47 centers)  
|                 | Sample size: 839 |
| **INTERVENTION:** | Escitalopram 5  
| **Drug:**       | Dose: 5 mg/d  
|                 | Duration: 24 weeks  
| **Sample size:** | 167 |
|                 | Escitalopram 10  
| **Drug:**       | Dose: 10 mg/d  
|                 | Duration: 24 weeks  
| **Sample size:** | 167 |
|                 | Escitalopram 20  
| **Drug:**       | Dose: 20 mg/d  
|                 | Duration: 24 weeks  
| **Sample size:** | 170 |
|                 | Paroxetine 20  
| **Drug:**       | Dose: 20 mg/d  
|                 | Duration: 24 weeks  
| **Sample size:** | 170 |
|                 | Placebo  
| **Drug:**       | N/A  
|                 | Duration: 24 weeks  
| **Sample size:** | 166 |
| **INCLUSION:**  | Healthy female and male outpatients 18-65 years of age; primary diagnosis of generalized SAD according to DSM-IV criteria; score ≥ 70 on the Liebowitz Social Anxiety Scale (LSAS); score > 5 on one or more of the Sheehan Disability Scale (SDS) subscales |
| **EXCLUSION:**  | Another Axis I disorder primary diagnosis within 6 months; MADRS total score ≥ 18; DSM-IV diagnosis of schizophrenia/other psychotic disorder; Axis II Cluster B diagnosis; learning difficulties or other cognitive disorder; suicidal tendencies; no therapeutic response to SSRIs; drug hypersensitivities; taken a psychoactive drug within 2 weeks of screening; receiving formal psychotherapy |
| **OTHER MEDICATIONS/INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
| **Mean age:**   | Escitalopram 5: 36.3; escitalopram 10: 37.2; escitalopram 20: 37; paroxetine 20: 37.4; placebo: 37  
| **Gender (% female):** | Escitalopram 5: 50%; escitalopram 10: 57%; escitalopram 20: 53%; paroxetine: 54%; placebo: 49%  
| **Ethnicity:**  | 99.3% white  
| **Other population characteristics:** | Mean duration of disorder (yrs): 19.5 |
### Authors: Lader M, et al.
Year: 2004
Country: Multinational

| OUTCOME ASSESSMENT: | **Primary Outcome Measures**: Mean change from baseline to week 12 in LSAS total score (LOCF)  
**Secondary Outcome Measures**: LSAS subscale scores; CGI-S; CGI-I; change in SDS  
**Timing of assessments**: Baseline and after weeks 1,2,4,6,8,10,12,16,20,24,25, and 26. |
|---------------------|------------------------------------------------------------------------------------------------------------------|

### RESULTS:  
- No significant difference observed between any escitalopram treatment groups and the paroxetine group in the LOCF analysis of LSAS total score.  
- At weeks 16, 20, and 24 (observed case analysis), compared to the paroxetine group (p < 0.05) the 20 mg/d escitalopram group had significantly superior LSAS scores.  
- Escitalopram 20mg/d was superior to paroxetine 20mg/d on CGI-S at week 24.  
- Escitalopram 20mg/d was superior to paroxetine 20mg/d on some SDS subscales during weeks 16 and 20, but no significant differences were noted at week 24.

### ANALYSIS:  
**ITT**: Yes  
**Post randomization exclusions**: Not reported

### ATTRITION:  
**Loss to follow-up**: 29%; escitalopram 5: 25.1%; escitalopram 10: 33.5%; escitalopram 20: 28.8%; paroxetine: 26.6%; placebo: 30.1%  
**Withdrawals due to adverse events**: 9%; escitalopram 5: 4.8%; escitalopram 10: 9.6%; escitalopram 20: 11.8%; paroxetine: 13.6%; placebo: 6%  
**Loss to follow-up differential high**: No

### ADVERSE EVENTS:  
- Percentage patients experiencing any adverse effect: Escitalopram 5: 68.9%; escitalopram 10: 72.5%; escitalopram 20: 78.2%; paroxetine 20: 79.3%; placebo: 60.8%  
- Nausea: Escitalopram 5: 20.4%; escitalopram 10: 19.8%; escitalopram 20: 28.8%; paroxetine 20: 29%; placebo: 10.2%  
- Fatigue: 9% placebo; Escitalopram 5: 11.4%; escitalopram 10: 12%; escitalopram 20: 14.1%; paroxetine 20: 17.8%; placebo: 9%  
- Increased sweating: Escitalopram 5: 5.4%; escitalopram 10: 10.8%; escitalopram 20: 11.8%; paroxetine 20: 14.2%; placebo: 1.8%

### QUALITY RATING:  
Fair
## Evidence Table 8: Social Anxiety Disorder

| STUDY: | Authors: Lepola et al.  
Year: 2004  
Country: Multinational |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>GlaxoSmithKline</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multinational (35 academic centers and private clinics in Europe and South Africa)  
Sample size: 375 |
| INTERVENTION: | **Drug:** Paroxetine CR  
Dose: 12.5-37.5 mg/d  
Duration: 12 weeks  
Placebo  
Dose: N/A  
Duration: 12 weeks |
| INCLUSION: | Outpatients with DSM-IV primary diagnosis SAD; ≥ 18 years of age; patients older than 65 included if they did not have renal or hepatic impairment |
| EXCLUSION: | CGI score of 1 or 2 or score of ≥ 15 on 17-item HAM-D at baseline; other Axis I disorders currently or within 6 months prior to screening; substance abuse; current homicidal or suicidal risk; history of seizures (except febrile seizures); schizophrenia or bipolar disorder or current diagnosis of body dismorphic disorder or serious medical disorder; treatment with psychotropic medications or antidepressants within 14 days of screening; monoamine oxidase inhibitors or fluoxetine within 4 weeks of screening; depot neuroleptics within 12 weeks of screening or electroconvulsive therapy within past 3 months; patients requiring concomitant therapy with beta-adrenergic blockers, monoamine oxidase inhibitors, benzodiazepines or other psychoactive medications; pregnant, lactating or of childbearing potential and not practicing clinically accepted contraceptive method |
| OTHER MEDICATIONS/INTERVENTIONS: | Concomitant use of other psychotropic medications prohibited except for chloral betaine (up to 828 mg) or chloral hydrate (up to 1000 mg) for insomnia |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Yes  
**Mean age:** paroxetine CR: 38.7, placebo: 39.0  
**Gender:** (% female): paroxetine CR: 53%, placebo: 47%  
**Ethnicity:** (% white) paroxetine CR: 93.5%, placebo: 95.1% |
**Authors:** Lepola U, et al.  
**Year:** 2003  
**Country:** Multinational

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th><strong>Measures:</strong> Liebowitz Social Anxiety Scale (LSAS), CGI-Global Improvement, CGI-S, Social Avoidance and Distress Scale, Sheenan Disability Scale (SDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of assessments:</strong> Baseline, weeks 1, 2, 3, 4, 6, 8, 12 (or at time of early withdrawal)</td>
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</tr>
</tbody>
</table>

**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 (OR = 2.95, 95% CI: 1.67 to 5.20, p < 0.001)
- Paroxetine significantly superior to placebo on LSAS fear or anxiety and avoidance subscales (p < 0.001), social avoidance distress scale (p < 0.001), and SDS total score (p < 0.001)

**ANALYSIS:**

- **ITT:** Yes  
- **Post randomization exclusions:** Yes

**ATTRITION:**

- **Loss to follow-up:** 21.9%; paroxetine CR: 16.1%, placebo: 25.5%
- **Withdrawals due to adverse events:** paroxetine CR: 2.7%, placebo: 1.6%
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**

- Treatment-emergent associated with paroxetine CR (incidence of ≥ 5% in paroxetine CR) were mild to moderate in intensity with incidence greater during first 14 days of treatment
- Headache, nausea, diarrhea reported in paroxetine CR patients that stopped treatment
- Serious adverse events were reported during treatment phase in 2 patients in paroxetine CR group and 2 in placebo group

**QUALITY RATING:** Fair
## Evidence Table 8

### Social Anxiety Disorder

| STUDY: | Authors: Liebowitz MR, et al.  
Year: 2003  
Country: US |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center  
Sample size: 415 |
| INTERVENTION: | Drug: Sertraline  
Dose: 50-200 mg/day  
Duration: 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 OCD; 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; serious medical illness; pregnant, nursing or lactating; concomitant psychotropics |
| 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% |
<table>
<thead>
<tr>
<th>Authors: Liebowitz MR, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 2003</td>
</tr>
</tbody>
</table>

**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 effect 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
  - Mean change Endicott Work: p = 0.07

**Analysis:**
- **ITT:** Yes
- **Post randomization exclusions:** Yes

**Attrition:**
- **Loss to follow-up:** overall: 29%; sertraline: 28%, placebo: 31%
- **Withdrawals due to adverse events:** 5.3%, sertraline: 7.6%, placebo: 2.9%
- **Loss to follow-up differential high:** No

**Adverse Events:**
- Insomnia: sertraline 24.4%, placebo 10.1%
- Loose stools: sertraline 20.6%, placebo 4%
- Nausea: sertraline 16.7%, placebo 6.5%
- Dizziness: sertraline 16.7%, placebo 5.5%
- Dry mouth: sertraline 14.4%, placebo 3.5%
- Ejaculatory dysfunction: sertraline 14.3%, placebo 0%
- No differences in laboratory parameters, ECG, vital signs, or weight change

**Quality Rating:** Fair
### Evidence Table 8: Social Anxiety Disorder

| STUDY: | Authors: Liebowitz MR, et al.<sup>101</sup>  
| Year: 2005  
| Country: US |
| FUNDING: | Wyeth Research, Collegeville PA |
| DESIGN: | Study design: RCT  
| Setting: Multi-center (26 centers)  
| Sample size: 440 |
| INTERVENTION: |  
| Drug: | Venlafaxine  
| Dose: | 75-225 mg/d  
| Duration: | 12 weeks  
| Sample size: | 146 |
| Paroxetine |  
| Dose: | 20-50 mg/d  
| Duration: | 12 weeks  
| Sample size: | 147 |
| Placebo |  
| N/A |  
| Duration: | 12 weeks  
| Sample size: | 147 |
| INCLUSION: | Outpatients ≥ 18 years who fulfilled DSM-IV criteria for SAD for ≥ 6 months at screening; LSAS ≥ 50 at screening and baseline with ≤ 30% decrease between prestudy and baseline; ≥ 4 on the CGI-S; Covi Anxiety Score total > Raskin Depression Scale total score; HAM-D < 15 with ≤ 2 on depressed mood item. |
| EXCLUSION: | Patients with a clinically important Axis I or Axis II disorder other than SAD or avoidant personality disorder; history or current psychotic illness; Suicidal; history of drug or alcohol dependence within 1 year of the study; used anti-depressants (other than fluoxetine), anxiolytics, or herbal products within 14 days of the study; ECT within 6 months of the study; used antipsychotic medications or fluoxetine treatment within 30 days of the study; clinically significant abnormal findings on laboratory tests; pregnant or breastfeeding |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
| Mean age: | venlafaxine: 35.7, paroxetine: 35.8, placebo: 37.3  
| Gender (% female): | venlafaxine: 46.6%, paroxetine: 45.6%, placebo: 47.2%  
| Ethnicity: | White: VX: 71.4% PX: 72.8% Placebo: 70.1%  
| African American: VX: 11.3% PX: 8.8% Placebo: 8.3%  
| Hispanic: VX: 15.0% PX: 12.5% Placebo: 13.2%  
| Other population characteristics: | Baseline LSAS: VX: 86.2 PX: 87.2 Placebo: 86.1 |
Authors: Liebowitz MR, et al.  
Year: 2005  
Country: US

**OUTCOME ASSESSMENT:**  
Primary Outcome Measures: Reduction in Liebowitz Social Anxiety Scale (LSAS) total score  
Secondary Outcome Measures: CGI-I; CGI-S; Social Phobia Inventory Scores, SDS  
Timing of assessments: Weekly

**RESULTS:**  
- No significant difference in LSAS improvement was observed between the venlafaxine and paroxetine groups at endpoint. Both were significantly improved from placebo (p < 0.05).
- No significant difference in CGI-I improvement was observed between the venlafaxine and paroxetine groups at endpoint. Both were significantly improved from placebo (p < 0.05).
- No significant difference in Social Phobia Inventory improvement was observed between the venlafaxine and paroxetine groups at endpoint; both significantly improved from placebo (p < 0.05).
- No significant difference in CGI-S improvement was observed between the venlafaxine and paroxetine groups at endpoint. Both were significantly improved from placebo (p < 0.05).
- No significant differences in SDS domains between venlafaxine and placebo.

**ANALYSIS:**  
ITT: Yes  
Post randomization exclusions: Yes

**ATTRITION:**  
<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Venlafaxine</th>
<th>Paroxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td>26%</td>
<td>27.0%</td>
<td>28.2%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td>10.4%</td>
<td>14.2%</td>
<td>13.4%</td>
<td>4.1%</td>
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<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td>2.3%</td>
<td>0.7%</td>
<td>0.7%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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**ADVERSE EVENTS:**  
<table>
<thead>
<tr>
<th></th>
<th>Venlafaxine</th>
<th>Paroxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>32.6%</td>
<td>26.1%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>27.7%</td>
<td>18.3%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>27%</td>
<td>26.8%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20.6%</td>
<td>23.9%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>17.7%</td>
<td>16.2%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>14.2%</td>
<td>10.6%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Abnormal ejaculation (men)</td>
<td>10.5%</td>
<td>20.8%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**QUALITY RATING:** Fair
### Evidence Table 8  
#### Social Anxiety Disorder

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

| OUTCOME ASSESSMENT: | Primary Outcome Measures: survival analysis estimate of time to relapse in the double-blind period. (Relapse defined as LSAS score increase ≥ 10 or withdrawal of patient due to lack of efficacy.)  
Secondary Outcome Measures: LSAS total score; LSAS avoidance and fear/anxiety subscale; SDS  
Timing of assessments: 1,2,4,8,12,16,20, & 24 weeks after randomization; also safety follow-up at 4 weeks after last dose of double-blind treatment |
|---|---|

| RESULTS: | • Significant advantage in survival for escitalopram vs. placebo in primary efficacy analysis (log rank test p < 0.001)  
• Relapse rates = 22% (escitalopram) vs. 50% (placebo)  
• Risk of relapse was 2.8 times higher with placebo than escitalopram  
• Median time to relapse = 407 days (escitalopram) vs. 144 days (placebo)  
• Significant advantage for escitalopram on all secondary measures (LSAS, CGI-S, SDS, and MADRS)  
• Improvement on LSAS in escitalopram group (8.3 points), deterioration in placebo group (4.5 points)  
• Mean MADRS score change = +0.8 (escitalopram) and +2.6 (placebo)  
• Mean CGI-S score change = -0.3 (escitalopram) and +0.3 (placebo) |

| ANALYSIS: | ITT: Yes, defined as all randomized patients who took at least 1 dose of double-blind medication and had at least 1 valid post baseline assessment of LSAS total score  
Post randomization exclusions: |

| ATTRITION: | Loss to follow-up: Escitalopram: 25 (13%), placebo: 15 (8.3%)  
Withdrawals due to adverse events: Escitalopram: 5 (2.6%), placebo: 6 (3.3%)  
Withdrawals due to lack of efficacy: N/A  
Loss to follow-up differential high: No |

| ADVERSE EVENTS: | • Assessed via spontaneous report, various clinical exam/lab reports, and 43-item Discontinuation Emergent Signs and Symptoms (DESS) checklist at randomization and 1 and 2 wks after.  
• Treatment emergent adverse events (TEAEs) with incidence ≥ 5% in either group were: headache, dizziness, increased sweating, nervousness, fatigue, insomnia, nausea, rhinitis, and influenza-like symptoms  
• Incidence of TEAEs was lower in escitalopram group (62.6%) vs. placebo group (71.8%)  
• Dizziness, increased sweating, and nervousness were significantly higher in placebo group in 1st 2 weeks following discontinuation of escitalopram (p < 0.05). Excluding these TEAEs in 1st 2 weeks post-randomization, adverse events were similar in both treatment groups  
• After 1 and 2 weeks of double-blind treatment, mean total DESS score was significantly lower in escitalopram group (week 1: escitalopram =1.17 vs. placebo = 2.61; week 2: escitalopram =1.02 vs. placebo = 1.78) (p < 0.01) |

| QUALITY RATING: | Fair |
### Evidence Table 8  
#### Social Anxiety Disorder

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

| OUTCOME ASSESSMENT: | **Primary Outcome Measures:** Change in social anxiety measured w/ social phobia inventory (SPIN) and LSAS  
**Secondary Outcome Measures:** SF-36 Health Survey  
**Timing of assessments:** Weekly for 10 weeks, although intermediate results were not analyzed |

| RESULTS: |  
| • Mirtazapine group experienced significantly greater rate of change on both SPIN and LSAS scales  
• Initial SPIN scores = 32.5 +/- 4.7 (mirtazapine) vs. 29.0 +/- 4.6 (placebo)  
• Final SPIN scores = 24.1 +/- 4.3 (mirtazapine) vs. 28.7 +/- 5.1 (placebo)  
• SPIN: Difference in change b/w both groups = -8.1 (95% CI -9.6 to 4.1; p < 0.001)  
• Initial LSAS scores = 71.9 +/- 8.3 (mirtazapine) vs. 72.5 +/- 8.0 (placebo)  
• Final LSAS scores= 46.3 +/- 7.0 (mirtazapine) vs. 67.1 +/- 7.4 (placebo)  
• LSAS: Difference in change b/w both groups = -20.2 (95% CI -27.5 to -4.1; p < 0.001)  
• Mirtazapine group experienced significantly greater rate of change on SF-36 (on general health perceptions, vitality, social functioning, role-emotional, and mental health scales) |

| ANALYSIS: | ITT: No  
**Post randomization exclusions:** Cannot tell |

| ATTRITION: | Loss to follow-up: NR  
Withdrawals due to adverse events: NR  
Withdrawals due to lack of efficacy: NR  
Loss to follow-up differential high: NR |

| ADVERSE EVENTS: |  
| • Most frequently reported adverse events in mirtazapine vs. placebo were: dry mouth (21.2% vs. 12.1%), drowsiness (18.2% vs. 9.1%), sedation (18.2% vs. 6.1%), increased appetite (12.1% vs. 3.0%), and weight gain (21.2% vs. 6.1%) |

| QUALITY RATING: | Fair |
### Evidence Table 8  Social Anxiety Disorder

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

**OUTCOME ASSESSMENT:**
- **Measures:** Proportion of CGI-I responders (1 or 2), Brief Social Phobia Scale, Social Phobia Inventory, Liebowitz Social Anxiety Scale, Sheenan Disability Scale
- **Timing of assessments:** Weeks 1, 2, 3, 4, 6, 8, 10, 12

**RESULTS:**
- Significantly higher proportion of responders in the fluvoxamine than the placebo group (fluvoxamine: 42.9%, placebo: 22.7%; p = 0.04)
- Fluvoxamine better than placebo on all social anxiety scales from week 8 to endpoint

**ANALYSIS:**
- **ITT:** Yes
- **Post randomization exclusions:** Yes

**ATTRITION:**
- **Loss to follow-up:** Not reported
- **Withdrawals due to adverse events:** 17%; fluvoxamine: 25%, placebo: 9.1%
- **Loss to follow-up differential high:** Not reported

**ADVERSE EVENTS:**
- Difference between fluvoxamine and placebo greater than 10 percentage points: nausea, insomnia, dizziness, reduced libido, nervousness, and somnolence

**QUALITY RATING:**
- Fair
### Evidence Table 8  
**Social Anxiety Disorder**

| STUDY: | Authors: Stein MB, et. al.  
Year: 1998  
Country: US, Canada |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>SmithKline Beecham</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (13 US, 1 Canada)  
Sample size: 187 |
| INTERVENTION: |  
**Drug:** Paroxetine  
**Dose:** 20-50 mg/d  
**Duration:** 12 weeks  
**Placebo:** N/A  
**Duration:** 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 sulfonyleureas; psychotropic agent or beta-blocker within 14 days; depot neuroleptics within 12 weeks; other Axis I diagnosis; substance abuse or dependence; suicidal or homicidal risk; dysmorphic disorder, schizophrenia, bipolar affective disorder, uncontrolled medical illness; other clinical trial within 12 months; pregnant, lactating, or no clinically acceptable method of birth control |
| OTHER MEDICATIONS/ INTERVENTIONS: | Chloral hydrate for sleep |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes  
**Mean Age:** 36  
**Gender** (% female): 53%  
**Ethnicity:** 81% white  
**Other population characteristics:** Not reported |
### Authors: Stein MB, et al.
Year: 1998
Country: US, Canada

### OUTCOME ASSESSMENT:

**Measures:**
- (Primary) Percentage of CGI-I responders; mean change from baseline on LSAS
- (Secondary) Mean change from baseline on SADS; SDI; fear, anxiety and avoidance subscale of the LSAS

**Timing of assessments:** Weeks 1, 2, 3, 4, 6, 8, 12

### RESULTS:

- CGI-I Responders: paroxetine 55%; placebo 24% (p < 0.001 from week 4 through week 12)
- Mean change from baseline in LSAS: paroxetine -30.5; placebo -14.5 (p < 0.001 from week 2 through week 12)
- Paroxetine superior to placebo on all secondary efficacy measures except family life item of SDI (p < 0.05)

### ANALYSIS:

**ITT:** Yes
**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 28.3%; paroxetine 34%, placebo 23%
**Withdrawals due to adverse events:** 9%; paroxetine 14.9%, placebo 5.45%
**Loss to follow-up differential high:** Yes

### ADVERSE EVENTS:

- Abnormal ejaculation: paroxetine 36% vs. placebo 0%
- Somnolence: paroxetine 27% vs. placebo 10%
- Nausea: paroxetine 26% vs. placebo 12%

### QUALITY RATING:

Fair
### Evidence Table 8  Social Anxiety Disorder

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

| OUTCOME ASSESSMENT: | Measures: Proportion of patients relapsing during maintenance stage (increase in CGI-S of 2 points from week 12, score of 4 or >, or withdrawal because of lack of efficacy). Time to relapse % of improvers, CGI-I, Liebowitz Social anxiety Scale (LSAS), social phobia inventory scale, Sheehan disability scale, Symptom checklist-90 (SCL-90), EQ-5D  
Timing of assessments: Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36

| RESULTS: |  
- Significantly fewer patients relapsed on paroxetine; OR = 2.78 (p < 0.001)  
- Time to relapse was significantly longer in paroxetine group  
- Hazard ratio for relapse time = 3.29  
- Significantly more paroxetine subjects were much improved or very much improved on the CGI-I  
- Significantly greater improvement with paroxetine on LSAS, Sheehan, SCL-90, EQ-5D, VAS

| ANALYSIS: | ITT: Yes  
Post randomization exclusions: No

| ATTRITION: | Loss to follow-up: 20.5%; paroxetine: 16%, placebo: 25%  
Withdrawals due to adverse events: Paroxetine: 2%, placebo: 5%  
Loss to follow-up differential high: Yes

| ADVERSE EVENTS: |  
- Paroxetine during acute phase (all patients): nausea 24%, somnolence 17%, insomnia 17%, abnormal ejaculation 26%, headache 20%.  
- Continuation phase: paroxetine: headache 11%; placebo: headache 16%, dizziness 15%  
- Significantly more subjects in the paroxetine group experienced weight gain (23% vs. 9%)

| QUALITY RATING: | Fair
## Evidence Table 8  Social Anxiety Disorder

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

| OUTCOME ASSESSMENT: | Measures: CGI-S, CGI-I, MADRS, Liebowitz Panic & Social Phobic Disorders Rating Scale; Social Phobia & Anxiety Inventory Social Phobia Subscale; Social Avoidance & Distress Scale; Fear of Negative Evaluation Scale, Clinical Anxiety Scale, Sheehan Disability Scale  
**Timing of assessments:** Weeks 1, 2, 4, 7, 10, 13, 16, 20 |
| --- | --- |
| RESULTS: | • Difference in change from baseline to end of treatment was significantly better for sertraline on all scales measured  
• Statistically more subjects on sertraline (53% vs. 29% on placebo) were much or very much improved at the end of treatment based on the CGI-I |
| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| ATTRITION: | **Loss to follow-up:** Sertraline: 23%, placebo: 22%  
**Withdrawals due to adverse events:** sertraline: 12%; placebo: 1%  
**Loss to follow-up differential high:** No |
| ADVERSE EVENTS: | • Sertraline: nausea 32.6%, insomnia 30.4%, dyspepsia 25.2%, diarrhea 20.7%.  
• Placebo: diarrhea 15.9%, nausea 14.5%, insomnia 14.5%, asthenia: 11.6%.  
• Significantly more subjects in the sertraline group reported nausea (32.6% vs. 14.55), insomnia (30.4% vs. 14.5%), dyspepsia (25.2% vs. 7.2%), flu syndrome (17.8% vs. 5.5%), delayed ejaculation (11.4% vs. 4.3%), sweating (11.1% vs. 5.9%) |
| QUALITY RATING: | Fair |
## Evidence Table 8: Social Anxiety Disorder

| STUDY: | Authors: van der Linden et al.  
Year: 2000  
Country: South Africa, the Netherlands |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FUNDING:</td>
<td>MRC Research Unit on Anxiety and Stress Disorders; Harry Crossley Trust; Cochrane review collaborators</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Meta-analysis  
Number of patients: 1482 |
| AIMS OF REVIEW: | To review all available SSRI studies for social anxiety disorder |
| 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:**

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</th>
<th>RCT data were analyzed for fluvoxamine, paroxetine, and sertraline</th>
</tr>
</thead>
</table>
| MAIN RESULTS:                             | • Odds ratio of responder status for SSRI vs. placebo varied between 2.1 and 26.2  
|                                          | • The NNT varied from 1.6 to 4.2  
|                                          | • LSAS effect size varied from 0.3 to 2.2  
|                                          | • No difference in efficacy between SSRIs was reported |
| ADVERSE EVENTS:                           | Not reported |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Not defined in article but described to be consistent with methods of a Cochrane review |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Not defined in article but described to be consistent with methods of a Cochrane review |
| QUALITY RATING:                           | Fair |
### Evidence Table 8  Social Anxiety Disorder

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

**OUTCOME ASSESSMENT:**

<table>
<thead>
<tr>
<th>Primary Outcome Measures: LSAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcome Measures: CGI-S, SDS, CGI-I, PGI</td>
</tr>
<tr>
<td>Timing of assessments: Screening, baseline and weeks 2,4,6,8,10,12</td>
</tr>
</tbody>
</table>

**RESULTS:**

<table>
<thead>
<tr>
<th>LSAS- mean change from baseline</th>
<th>fluvoxamine -36.1 (± 2.7) placebo -27.3 (± 2.4) (p = 0.02)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI-S- mean change from baseline</td>
<td>fluvoxamine -1.5 (± 0.1) placebo -1.0 (± 0.1) (p = 0.022)</td>
</tr>
<tr>
<td>SDS- mean change from baseline fluvoxamine -7.8 (± 0.7) placebo -5.8 (± 0.6) (p = 0.036)</td>
<td></td>
</tr>
<tr>
<td>CGI-I- endpoint score fluvoxamine 2.5 (± 0.1) placebo 2.9 (± 0.1) (p = 0.026)</td>
<td></td>
</tr>
<tr>
<td>Responders – CGI-I of very much or much improved fluvoxamine 48% placebo 44% (p = 0.078)</td>
<td></td>
</tr>
<tr>
<td>PGI- endpoint score fluvoxamine 2.6 (± 0.1) placebo 3.0 (± 0.1) (p = 0.051)</td>
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</tr>
</tbody>
</table>

**ANALYSIS:**

| ITT: Yes | Post randomization exclusions: Yes- 6 had no post baseline assessments |

**ATTRITION:**

<table>
<thead>
<tr>
<th>Overall</th>
<th>Fluvoxamine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>32%</td>
<td>38%</td>
<td>29%</td>
</tr>
<tr>
<td>15%</td>
<td>26%</td>
<td>5%</td>
</tr>
<tr>
<td>5%</td>
<td>0%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**ADVERSE EVENTS:**

- All AEs: fluvoxamine 92%, placebo 83%
- Nausea: fluvoxamine 47%, placebo 15%
- Headache: fluvoxamine 35%, placebo 32%
- Insomnia: fluvoxamine 32%, placebo 15%
- Asthenia: fluvoxamine 28%, placebo 13%
- Somnolence: fluvoxamine 22%, placebo 7%

**QUALITY RATING:**

Fair
### Evidence Table 9: Premenstrual Dysphoric Disorder

| STUDY: | Authors: Dimmock PW, et al.177  
| Year: 2000 |  
| Country: |  
| FUNDING: | No external funding |  
| DESIGN: | Study design: Meta-analysis  
| Number of patients: 904 |  
| AIMS OF REVIEW: | To determine the efficacy of SSRIs in severe premenstrual syndrome |  
| TIME PERIOD COVERED: | 1966-1999 |  
| CHARACTERISTICS OF INCLUDED STUDIES: | RCTs; 1 head-to-head; all placebo controlled |  
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Women with PMS |
**Authors:** Dimmock PW, et al.  
**Year:** 2000

| CHARACTERISTICS OF INCLUDED INTERVENTIONS: | Fluoxetine, sertraline, citalopram, paroxetine, fluvoxamine |
| MAIN RESULTS: | • Overall standardized mean difference showed a significant reduction of PMS symptoms in SSRI group compared to placebo  
• -1.066 (95% CI -1.381 to -0.750) = OR 6.91 (3.90-12.2)  
• SSRIs were effective in physical and behavioral symptoms; there was no significant variation in the overall standardized mean differences (p = 0.386) |
| ADVERSE EVENTS: | Insufficient data; some trials did not quote a complete breakdown |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Yes |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING: | Good |
# Evidence Table 9  
## Premenstrual Dysphoric Disorder

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

### OUTCOME ASSESSMENT:
- **Measures:** Premenstrual daily symptom report (maintained by subject), 21 item HAM-D, CGI scale
- **Timing of assessments:** Scales administered twice a cycle: once during the premenstrual phase and once during the postmenstrual phase

### RESULTS:
- Premenstrual Daily Symptom Report scores were significantly more improved in the venlafaxine group than in the placebo group at each time point and at endpoint ($p < 0.001$)
- Venlafaxine showed significantly greater improvement than placebo in four of the factors of the DSR: emotion ($p < 0.001$), function ($p = 0.011$), pain ($p = 0.016$), and physical symptoms ($p = 0.003$)
- The venlafaxine group was significantly more improved on the 21 item HAM-D ($p = 0.001$)
- DSR response (> 50% reduction): venlafaxine 60%, placebo: 35% ($p = 0.003$)

### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 36%; venlafaxine: 35%, placebo: 36%
- **Withdrawals due to adverse events:** 12.8%; venlafaxine: 9%, placebo: 6.25%
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Nausea 45% vs. 13% (venlafaxine vs. placebo $p < 0.001$)
- Insomnia 34 % vs. 16% (venlafaxine vs. placebo $p = 0.05$)
- Dizziness 32% vs. 5% (venlafaxine vs. placebo $p < 0.001$)
- Decreased libido (venlafaxine vs. placebo $p < 0.001$)
- Fatigue (not significant)
- Headache (not significant)
- Dry mouth (not significant)
- Dysmenorrhea (not significant)

### QUALITY RATING:
- Fair
## Evidence Table 9: Premenstrual Dysphoric Disorder

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

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome Measures:</strong> Total score on the premenstrual Daily Symptom Rating Form</td>
</tr>
<tr>
<td><strong>Secondary Outcome Measures:</strong> Subject Global Ratings of Functioning</td>
</tr>
<tr>
<td><strong>Timing of assessments:</strong> Symptoms were recorded daily and patients were seen at the start of each cycle</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Both sertraline treatment groups showed greater improvement than placebo on the Premenstrual Daily Symptom Scores: full cycle dosing (p = 0.055); Luteal phase dosing (p = 0.009)</td>
</tr>
<tr>
<td>• Clinical response rate (&gt;50% reduction on Daily Symptom Rating Form): continuous: 63%; intermittent: 51%; placebo: 36% (p = 0.03)</td>
</tr>
<tr>
<td>• No significant difference was observed between the two sertraline groups (p = 0.44)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT:</strong> Yes</td>
</tr>
<tr>
<td><strong>Post randomization exclusions:</strong> yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTRITION:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loss to follow-up:</strong> 49%; full cycle dosing: 28.6%; luteal phase dosing: 37.5%</td>
</tr>
<tr>
<td><strong>Withdrawals due to adverse events:</strong> 13%; full cycle dosing: 12/5%; luteal phase dosing: 9%</td>
</tr>
<tr>
<td><strong>Loss to follow-up differential high:</strong> N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Most frequent adverse events for sertraline: gastrointestinal (19%), decreased libido or orgasm (15%), headache (14%), insomnia (13%), dry mouth (13%), nausea (13%), nightmares (12%)</td>
</tr>
<tr>
<td>• Adverse event reporting in the third cycle did not differ between the full-cycle dosing group and placebo (p = 0.38), but did differ between the luteal phase dosing group and placebo (p = 0.03).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
</tr>
</tbody>
</table>
### Evidence Table 9: Premenstrual Dysphoric Disorder

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

**OUTCOME ASSESSMENT:**

- **Measures:** CGI-S, CGI-I, total score from the Daily Record of Severity of Problems, Patient Global Evaluation, Social Adjustment Scale, Quality of Life Enjoyment and Satisfaction questionnaire
- **Timing of assessments:** Not reported

**RESULTS:**

At endpoint, sertraline had significantly lower scores than placebo on the CGI-I scale (p < 0.001), the CGI-S scale (p < 0.001), and the Daily Record of Severity of Problems (p < 0.002)

**ANALYSIS:**

- **ITT:** Yes
- **Post randomization exclusions:** Yes

**ATTRITION:**

- **Loss to follow-up:** 21%
- **Withdrawals due to adverse events:** 4%; sertraline: 7.7%, placebo: 0.7%
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**

- Headache, nausea (sertraline vs. placebo; p = 0.006)
- Insomnia, diarrhea, dry mouth (sertraline vs. placebo; p = 0.027)
- More patients experienced severe adverse events with sertraline (16.9%) than placebo (7.1%); p = 0.022

**QUALITY RATING:**

- Fair
## Evidence Table 9  
### Premenstrual Dysphoric Disorder

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

**OUTCOME ASSESSMENT:**  
*Measures:* Daily symptom ratings using a visual analogue scale for the following symptoms: irritability, depressed mood, tension, affect lability, food craving, bloating, breast tenderness. CGI scale after last treatment cycle or after dropout  
*Timing of assessments:* Daily

**RESULTS:**  
- Nefazodone was not significantly different from placebo on the CGI score (p = 0.22)  
- Nefazodone did not significantly improve irritability, depressed mood, or tension at any time point  
- After the second cycle of the intermittent phase, nefazodone was significantly better than placebo for affect lability (p = 0.05); significance was not maintained after the continuous treatment

**ANALYSIS:**  
*ITT:* Yes  
*Post randomization exclusions:* Yes

**ATTRITION:**  
*Loss to follow-up:* 22%  
*Withdrawals due to adverse events:* 14.5%  
*Loss to follow-up differential high:* No

**ADVERSE EVENTS:**  
Dizziness, blurred vision, insomnia, abnormal dreams, somnolence, and flu-like symptoms were reported more often in nefazodone than placebo (p < 0.05)

**QUALITY RATING:**  
Fair
### Evidence Table 9: Premenstrual Dysphoric Disorder

**STUDY:**
- **Authors:** Steiner M, et al.  
- **Year:** 2005  
- **Country:** Multinational

**FUNDING:**
- **NR**

**DESIGN:**
- **Study design:** RCT  
- **Setting:** Multi-center  
- **Sample size:** 373

**INTERVENTION:**
- **Drug:**
  - Paroxetine CR
  - Dose: 12.5 mg
  - Duration: 3 months
  - Sample size: 131
  - Paroxetine CR
  - Dose: 25 mg
  - Duration: 3 months
  - Sample size: 119
  - Placebo
  - N/A
  - Duration: 3 months
  - Sample size: 123

**INCLUSION:**
- Female outpatients; 18 to 45 years; regular menstrual cycles; PMDD as outlined in the DSM-IV; have had the condition for at least 1 year, during which symptoms of the disorder needed to have been present in at least 9 of 12 menstrual cycles; baseline rating of at least “mildly ill” according to the CGI-S

**EXCLUSION:**
- Other Axis I disorders (except specific phobias) within 6 months; gynecologic or other clinically significant disease; clinically significant depressive symptomatology during the follicular phase; significant risk for suicide; medications that could interfere with their PMDD symptoms or with the assessment of their symptoms; oral or systemic contraceptives; previous adequate treatment for PMDD, had participated in a clinical trial with an SSRI for PMDD; pregnant or breastfeeding

**OTHER MEDICATIONS/INTERVENTIONS:**
- **NR**

**POPULATION CHARACTERISTICS:**
- **Groups similar at baseline:**
  - **Mean age:** paroxetine (25 mg): 37.2; paroxetine (12.5 mg): 35.9; placebo: 36.9
  - **Gender (% female):** 100%
  - **Ethnicity (% white):** paroxetine (25 mg): 100%; paroxetine (12.5 mg): 96.2%; placebo: 98.3%
  - **Duration of PMDD (years):** paroxetine (25mg): 10.5; paroxetine (12.5 mg): 10.5; placebo: 10.4
| Authors: Steiner M, et al.  
| Year: 2005  
| **OUTCOME ASSESSMENT:**  
| Primary Outcome Measures: VAS-Mood score at treatment cycle 3  
| Secondary Outcome Measures: Premenstrual Tension Scale (PMTS-O); CGI-S and CGI-I; patient global evaluation (PGE); SDS  
| Timing of assessments: First 3 days of the onset of menses for up to 3 treatment cycles  
| **RESULTS:**  
| • VAS- Mood score  
| paroxetine CR 25 mg vs. placebo: −10.79 (95% CI: −16.46 to −5.12) *p* < 0.001  
| paroxetine CR 12.5 mg vs. placebo: −7.66 (95% CI: −13.25 to −2.08) *p* = 0.007  
| • VAS-total  
| paroxetine CR 25 mg vs placebo: −77.82 (95% CI: −133.47 to −22.16) *p* = 0.006  
| paroxetine CR 12.5 mg vs placebo: −73.13 (95% CI: −127.91 to −18.36) *p* = 0.009  
| • PMTS-O total score  
| paroxetine CR 25 mg vs placebo: −3.21 (95% CI: −5.42 to −0.99) *p* = 0.005  
| paroxetine CR 12.5 mg vs placebo: −1.78 (95% CI: −3.86 to 0.30) *p* = 0.093  
| • CGI-S  
| paroxetine CR 25 mg vs placebo: −0.61 (95% CI: −1.03 to −0.20) *p* = 0.004  
| paroxetine CR 12.5 mg vs placebo: −0.27 (95% CI: −0.67 to 0.12) *p* = 0.177  
| • SDS total  
| paroxetine CR 25 mg vs placebo: −2.74 (95% CI: −4.97 to −0.51) *p* = 0.016  
| paroxetine CR 12.5 mg vs placebo: −2.33 (95% CI: −4.40 to −0.26) *p* = 0.028  
| **ANALYSIS:**  
| ITT: Yes  
| Post randomization exclusions: Yes -7  
| **ATTRITION:**  
| Loss to follow-up:  
| Paroxetine 12.5 mg | Paroxetine 25 mg | Placebo  
| 26 (19.8%) | 29 (24.4%) | 19 (15.4%)  
| 13 (9.9%) | 16 (13.4%) | 5 (4.1%)  
| Withdrawals due to adverse events:  
| 2 (1.7%) | 2 (1.5%) | 6 (5%)  
| Withdrawals due to lack of efficacy:  
| No | No | No  
| Loss to follow-up differential high:  
| No | No | No  
| **ADVERSE EVENTS:**  
| • 9 AEs occurred at a frequency > 5% and at an incidence in either paroxetine CR group of at least twice that of placebo: nausea, asthenia, libido decreased, sweating, diarrhea, dizziness, tremor, insomnia, and sinusitis; all but insomnia and sinusitis were observed more frequently in the 25 mg paroxetine CR- than in the 12.5-mg paroxetine CR treatment group; the majority were rated as mild or moderate in severity  
| **QUALITY RATING:** Fair
### Evidence Table 9: Premenstrual Dysphoric Disorder

| STUDY: | **Authors:** Wyatt KM, et al.  
|        | **Year:** 2004  
|        | **Country:** UK |
| FUNDING: | Cochrane Collaboration |
| DESIGN: | **Study design:** Meta-analysis  
|        | **Number of patients:** 844 |
| AIMS OF REVIEW: | To evaluate the effectiveness of SSRIs in reducing symptoms in women diagnosed with severe premenstrual syndrome |
| TIME PERIOD COVERED: | Not reported |
| CHARACTERISTICS OF INCLUDED STUDIES: | RCTs; quasi-randomized controlled trials; controlled trials |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Women of any age who met the diagnostic criteria for premenstrual syndrome, premenstrual dysphoria, PMDD, or LLPDD; diagnosis must have been established by a clinician prior to inclusion in the trial |
**Authors:** Wyatt KM, et al.  
**Year:** 2004  
**Country:** UK

<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</th>
<th>SSRIs at any dosage and any dosing regimen for any duration longer than one menstrual cycle versus placebo</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>MAIN RESULTS:</th>
<th>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)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
<th>Withdrawals: higher drop-out rate in SSRI group due to side effects: OR 2.42 (95% CI = 1.59 to 3.67)</th>
</tr>
</thead>
</table>

| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Yes |

| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |

| QUALITY RATING: | Good |
## Evidence Table 10: Adverse Events

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

| **OUTCOME ASSESSMENT:** | **Measures:** HAM-D-17, HAM-A, CGI-S, CGI-I, BDI-II, Welzel-Kohnen Colored Scales, Short Form 36  
**Timing of assessments:** Screening, baseline, weeks 1, 2, 3, 4, 6 |
|-------------------------|------------------------------------------------------------------|

| **RESULTS:** | • Mirtazapine and paroxetine were equally effective in reducing mean HAM-D-17 score (58.3% vs. 53.7%)  
• Significantly more mirtazapine patients responded at weeks 1 & 4 on the HAM-D-17 than paroxetine patients; week 1 response: mirtazapine: 23.2%, paroxetine: 8.9% (p < 0.002). |
|------------------|-----------------------------------------------------------------|

| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes |
|-----------------|---------------------------------|

| **ATTRITION:** | **Loss to follow-up:** 23%; mirtazapine: 21.6%, paroxetine: 24.2%  
**Withdrawals due to adverse events:** 8%; mirtazapine: 8.6%, paroxetine: 7.4%  
**Loss to follow-up differential high:** No |
|----------------|-------------------------------------------------|

| **ADVERSE EVENTS:** | • Significantly more mirtazapine patients experienced weight increase (p < 0.05)  
• At least one adverse event reported: mirtazapine: 68.1%, paroxetine: 63.4%  
• Dry mouth: mirtazapine: 14.1%, paroxetine: 8.2%  
• Headache: mirtazapine: 9.6%, paroxetine: 10.4%  
• Nausea: mirtazapine: 4.4%, paroxetine: 11.2%  
• Flu-like symptoms: mirtazapine: 9.6%, paroxetine: 3.7%  
• Differences all p < 0.1 |
|---------------------|------------------------------------------------------------|

<table>
<thead>
<tr>
<th><strong>QUALITY RATING:</strong></th>
<th><strong>Fair</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence Table 10</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
</tr>
</tbody>
</table>
| **STUDY:** | **Authors:** Brambilla P, et al.\(^{18}\)  
**Year:** 2005  
**Country:** Multinational |
| **FUNDING:** | NR |
| **DESIGN:** | **Study design:** Meta-analysis  
**Number of patients:** 15,920 |
<p>| <strong>AIMS OF REVIEW:</strong> | To assess the frequency of side-effects in fluoxetine compared to other SSRIs, TCAs and other anti-depressants |
| <strong>STUDIES INCLUDED IN META-ANALYSIS</strong> | 131 studies |
| <strong>TIME PERIOD COVERED:</strong> | Not reported |
| <strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong> | All studies with random assigned patients that received fluoxetine or any other anti-depressant. Cross-over studies and those with patients with concomitant medical illness were excluded. |
| <strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong> | Patients with MDD |</p>
<table>
<thead>
<tr>
<th>Authors: Brambilla P, et al.</th>
<th>Year: 2005</th>
<th>Country: Multinational</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARACTERISTICS OF INTERVENTIONS:</td>
<td>Fluoxetine vs. TCA (65 studies); fluoxetine vs. SSRI (22 studies); fluoxetine vs. another AD (44 studies)</td>
<td></td>
</tr>
</tbody>
</table>
| MAIN RESULTS: | • Fluoxetine less withdrawals due to side effects than TCAs and other related Ads RR 0.61 95% CI 0.52, 0.71 but not in comparison to other SSRIs RR 1.04 95% CI 0.84, 1.29  
• Fluoxetine less side effects (50.9%) than TCAs (60.3%) RR= 0.84 95% CI 0.76 to 0.94 (p = 0.03) but not in comparison to other SSRIs RR 1.00 95% CI 0.95, 1.04  
• Fluoxetine patients had more activating and GI adverse effects and less cholinergic side effects than other ADs |
| ADVERSE EVENTS: | N/A |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | Yes |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING: | Good |
**Evidence Table 10**

| **STUDY:** | Authors: Buckley NA, et al.\(^{10}\)  
Year: 2002  
Country: UK |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>FUNDING:</strong></td>
<td>None</td>
</tr>
</tbody>
</table>
| **DESIGN:** | Study design: Retrospective database analysis  
Setting: General practice  
Sample size: 121,927 |
| **INTERVENTION:** | | |
| Drug: | TCAs and related drugs  
Dose: Varied  
Duration: N/A  
Sample size: 74,598 |
| | Serotoninergic drugs  
Dose: Varied  
Duration: N/A  
Sample size: 47,329 |
| **INCLUSION:** | Used TCAs or SSRIs |
| **EXCLUSION:** | N/A |
| **OTHER MEDICATIONS/INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: N/A  
Mean age: NR  
Gender (% female): NR  
Ethnicity: NR  
Other population characteristics: NR |
**Authors:** Buckley NA, et al.  
**Year:** 2002  
**Country:** UK

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures: Death due to acute poisoning by a single drug w/ or w/o co-ingestion of alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments:</td>
<td></td>
</tr>
</tbody>
</table>

| RESULTS: | Among second generation antidepressants, venlafaxine had the highest fatal toxicity index (deaths/million prescriptions):  
Venlafaxine: 13.2 (9.2-18.5)  
Fluvoxamine: 3.0 (0.3-10.9)  
Citalopram: 1.9 (0.6-4.5)  
Sertraline: 1.2 (0.5-2.4)  
Fluoxetine: 0.9 (0.5-1.4)  
Paroxetine: 0.7 (0.4-1.3)  
Nefazodone: 0 (0-6.4) |

| ANALYSIS: | ITT: N/A  
Post randomization exclusions: N/A |

| ATTRITION: | Loss to follow-up: N/A  
Withdrawals due to adverse events: N/A  
Withdrawals due to lack of efficacy: N/A  
Loss to follow-up differential high: N/A |

| ADVERSE EVENTS: | See above |

<p>| QUALITY RATING: | N/A |</p>
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:** | **Authors:** Clayton AH, et al.<sup>200</sup>  
**Year:** 2002  
**Country:** US |
| **FUNDING:** | Glaxo Wellcome Inc. |
| **DESIGN:** | **Study design:** Cross sectional survey  
**Setting:** Multi-center  
**Sample size:** 6297 |
| **INTERVENTION:** | Second generation antidepressants  
**Dose:** Variable  
**Duration:** 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. |
| **Year:** 2002 |
| **OUTCOME ASSESSMENT:** | **Measures:** Changes in sexual functioning questionnaire |
| | **Timing of assessments:** Completed at one visit |
| **RESULTS:** | In the overall clinical population: |
| | • Patients taking bupropion SR or nefazodone had a lower prevalence of sexual dysfunction than patients taking fluoxetine, paroxetine, sertraline, or venlafaxine XR |
| | • Patients taking bupropion 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 bupropion SR or nefazodone had a lower prevalence of sexual dysfunction than patients taking citalopram, paroxetine, sertraline, or venlafaxine XR |
| **ANALYSIS:** | **ITT:** N/A |
| | **Post randomization exclusions:** N/A |
| **ATTRITION:** | **Loss to follow-up:** N/A |
| | **Withdrawals due to adverse events:** N/A |
| | **Loss to follow-up differential high:** N/A |
| **ADVERSE EVENTS:** | N/A |
| **QUALITY RATING:** | N/A |
**Evidence Table 10**

<table>
<thead>
<tr>
<th><strong>Adverse Events</strong></th>
</tr>
</thead>
</table>

**STUDY:**
- **Authors:** Coleman CC, et al.**1**
- **Year:** 1999
- **Country:** US

**FUNDING:** Glaxo Wellcome

**DESIGN:**
- **Study design:** RCT
- **Setting:** Multi-center (9 centers)
- **Sample size:** 364

**INTERVENTION:**
- **Drug:**
  - **Sertraline:** 50-200 mg/d
  - **Bupropion:** 150-400 mg/d
  - **Placebo:** N/A
- **Duration:**
  - 8 weeks

**INCLUSION:**
- DSM-IV criteria for major depression; minimum score of 18 on the first 21 items of the 31 item HAM-D; 18 years of age or older; be in a stable relationship, have normal sexual functioning, and sexual activity at least once every 2 weeks; currently experiencing recurrent major episode of duration 2-24 months

**EXCLUSION:**
- Predisposition to seizure or taking med that lowers seizure threshold; anorexia or bulimia; pregnancy; alcohol or substance abuse; eating disorder; suicidal tendencies; prior treatment with bupropion 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, bupropion: 38.1, placebo: 38.5
- **Gender** (% female): 59%; sertraline: 54%, bupropion: 56%, placebo: 59%
- **Ethnicity:** Sertraline: white: 92%, black: 8%, other: < 1%; bupropion: white: 87%, black: 11%, other: 2%; placebo: white: 88%, black: 9%, other: 3%
- **Other population characteristics:** No significant differences at diagnosis
| **Authors:** Coleman CC, et al. |
| **Year:** 1999 |
| **Country:** US |

### OUTCOME ASSESSMENT:

**Measures:** 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual functioning by investigator questions: sexual desire disorder, sexual arousal disorder, orgasm dysfunction, premature ejaculation, patient rated overall sexual function

**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8

### RESULTS:

- Mean HAM-D scores in the buproprion but not the sertraline group were statistically better than placebo (by day 28 p < 0.05)
- There was no significant difference between the buproprion and sertraline groups
- CGI-I and CGI-S for buproprion significantly better than placebo but not better than sertraline
- Sertraline not statistically better than placebo
- No differences in HAM-A; significantly fewer buproprion patients had sexual desire disorder than sertraline patients (p < 0.05)
- There was no significant difference between either active treatment group and placebo
- Orgasm dysfunction occurred significantly more in sertraline patients compared with placebo or buproprion patients (p < 0.05)
- Diagnosed with at least one sexual dysfunction: sertraline: 39%, buproprion: 13%, placebo: 17%

### ANALYSIS:

**ITT:** Yes

**Post randomization exclusions:** Yes

### ATTRITION:

**Loss to follow-up:** 30%; sertraline: 36%, buproprion sr: 22%, placebo: 32%

**Withdrawals due to adverse events:** 18.5%; sertraline: 8%, buproprion: 6%, placebo: 2%

**Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- Headache was the most commonly reported event in all treatment groups
- Nausea, diarrhea, dyspepsia occurred more frequently in sertraline patients than buproprion or placebo
- Insomnia and agitation were reported more frequently in buproprion patients than sertraline or placebo

### QUALITY RATING:

Fair
### Evidence Table 10  Adverse Events

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Funding</td>
<td>Glaxo Wellcome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Design | Study design: RCT  
Setting: Multi-center (15 centers)  
Sample size: 456 |
| Intervention | Drug:  
Bupropion 150-400 mg/d  
8 weeks  
Fluoxetine 150-400 mg/d  
8 weeks  
Placebo N/A  
8 weeks |
| Inclusion | DSM-IV criteria for major depression; minimum score of 20 on the 21-item HAM-D; ≥18 years of age; have sexual activity at least once every 2 weeks; currently experiencing episode lasting 2-24 months |
| Exclusion | Predisposition to seizure; pregnancy; alcohol or substance abuse; eating disorder; suicidal; treatment with bupropion 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, bupropion sr: 36.6, placebo: 36.7  
Gender: (% female) Fluoxetine: 66%, bupropion: 63%, placebo: 61%  
Ethnicity: Fluoxetine: white 82%, black 11%, other 7%; bupropion: white 83%, black 11%, other 5%; placebo: white 82%, black 14%, other 4%  
Other population characteristics: At baseline more patients in the fluoxetine and bupropion groups than the placebo group had sexual desire disorder |
Authors: Coleman CC, et al.  
Year: 2001  
Country: US

### OUTCOME ASSESSMENT:
- **Measures:** 21item HAM-D, sexual function assessment, substance-induced arousal disorder and orgasm dysfunction. Assessed: orgasm dysfunction, sexual desire disorder, sexual arousal disorder, overall patient sexual functioning (1-6 scale)  
- **Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 5, 6, 7, 8

### RESULTS:
- Mean HAM-D scores were not statistically different between the three groups (in ITT analysis)  
- No difference in responders (> 50 decrease in HAM-D), remitters (HAMD < 8)  
- More buproprion remitters (47%) compared to placebo (32%).  
- Orgasm dysfunction occurred significantly more in fluoxetine patients compared with placebo or buproprion patients ($p < 0.001$)  
- At endpoint more fluoxetine treated patients had sexual desire disorder than buproprion-treated patients ($p < 0.05$).  
- More fluoxetine-treated patients dissatisfied with sexual function beginning at week 1 ($p < 0.05$)

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 34%  
- **Withdrawals due to adverse events:** fluoxetine: 4%, buproprion: 9%, placebo: 3%  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Headache was the most commonly reported event in all treatment groups  
- Headache, diarrhea, and somnolence occurred more frequently in fluoxetine than buproprion or placebo groups  
- Dry mouth, nausea, and insomnia were reported more frequently in buproprion than fluoxetine or placebo groups  
- Buproprion group had mean increases in DBP and heart rate, authors state these were not clinically significant  
- Fluoxetine treated patients had a mean decrease in both DBP and heart rate

### QUALITY RATING:
- Fair
<table>
<thead>
<tr>
<th>Evidence Table 10 Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Coogan PF, et al.¹⁶⁴  
Year: 2005  
Country: US |
| **FUNDING:** | NR |
| **DESIGN:** | Study design: Case-control  
Setting: 3 centers  
Sample size: 4996 |
| **INTERVENTION:** | Cases | Controls |
| Drug: | SSRIs | None |
| Dose: | Various | N/A |
| Duration: | N/A | N/A |
| Sample size: | 2138 | 2858 |
| **INCLUSION:** | Cases: women with a first occurrence of primary invasive breast cancer diagnosed within the last year and no concurrent or previous cancer other than nonmelanoma skin cancer  
Controls: women admitted for nonmalignant diagnoses, unrelated to the use of SSRIs and no history of cancer other than nonmelanoma skin cancer |
| **EXCLUSION:** | N/A |
| **OTHER MEDICATIONS/INTERVENTIONS:** | N/A |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Range of age: 24-73  
Gender (% female): 100%  
Ethnicity: NR |
<table>
<thead>
<tr>
<th>Authors: Coogan PF, et al.</th>
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<tbody>
<tr>
<td>Year: 2005</td>
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<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome Measures:</strong> Increased risk of breast cancer due to use of SSRIs</td>
</tr>
<tr>
<td>Risk factors other than SSRI use that were taken into account include alcohol consumption, religion, family history of breast cancer, center, age and race</td>
</tr>
<tr>
<td><strong>Secondary Outcome Measures:</strong></td>
</tr>
<tr>
<td><strong>Timing of Assessments:</strong></td>
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<table>
<thead>
<tr>
<th>RESULTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Regular use of SSRIs was not associated with breast cancer risk after adjustment for other risk factors OR 1.1 95% 0.8, 1.7</td>
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<table>
<thead>
<tr>
<th>ANALYSIS:</th>
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<tbody>
<tr>
<td>ITT: N/A</td>
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<tr>
<td>Post randomization exclusions: N/A</td>
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<table>
<thead>
<tr>
<th>ATTRITION:</th>
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<tbody>
<tr>
<td>Loss to follow-up: N/A</td>
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<tr>
<td>Withdrawals due to adverse events: N/A</td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy: N/A</td>
</tr>
<tr>
<td>Loss to follow-up differential high: N/A</td>
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<thead>
<tr>
<th>ADVERSE EVENTS:</th>
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<tr>
<td>• N/A</td>
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<thead>
<tr>
<th>QUALITY RATING:</th>
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<tr>
<td>Fair</td>
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# Evidence Table 10: Adverse Events

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<tbody>
<tr>
<td>FUNDING:</td>
<td>Glaxo Wellcome</td>
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<tr>
<td>DESIGN:</td>
<td>Study design: RCT (active and placebo control)</td>
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<tr>
<td></td>
<td>Setting: Multi-center (8 centers)</td>
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<tr>
<td></td>
<td>Sample size: 360</td>
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<tr>
<td>INTERVENTION:</td>
<td><strong>Drug:</strong> Sertraline 50-200 mg/d, Bupropion 150-400 mg/d, Placebo N/A</td>
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<tr>
<td></td>
<td><strong>Dose:</strong> 8 weeks</td>
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<tr>
<td></td>
<td><strong>Duration:</strong> 8 weeks</td>
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<tr>
<td>INCLUSION:</td>
<td>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</td>
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<tr>
<td>EXCLUSION:</td>
<td>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</td>
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<td></td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS:</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td><strong>Groups similar at baseline:</strong> Yes</td>
<td></td>
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<tr>
<td></td>
<td><strong>Mean age:</strong> Sertraline: 36.0, bupropion: 35.9, placebo: 37.4</td>
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<tr>
<td></td>
<td><strong>Gender (% female):</strong> Sertraline: 50%, bupropion: 51%, placebo: 50%</td>
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<tr>
<td></td>
<td><strong>Ethnicity:</strong> Sertraline: white: 87%, black: 8%, other: 4%; bupropion: white: 86%, black: 9%, other: 5%; placebo: white: 88%, black: 8%, other: 3%</td>
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<tr>
<td></td>
<td><strong>Other population characteristics:</strong> Not reported</td>
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</tbody>
</table>
### Authors: Croft H, et al.
### Year: 1999
### Country: US

#### OUTCOME ASSESSMENT:
- **Measures:** 31 item HAM-D, HAM-A, CGI-S, CGI-I, sexual function assessment by investigator interview-sexual desire disorder, sexual arousal disorder, orgasmic dysfunction, premature ejaculation (men only), overall patient satisfaction with sexual functioning, vital signs
- **Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8

#### RESULTS:
- Mean HAM-D scores in both the bupropion and sertraline group were statistically better than placebo ($p < 0.05$)
- No significant difference in HAM-D scores between the bupropion 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 bupropion sr-treated patients had sexual desire disorder than sertraline- or placebo-treated patients ($p < 0.05$)
- At day 56 both bupropion and sertraline groups had higher sexual arousal disorder ($p < 0.05$) than placebo
- Orgasmic dysfunction occurred significantly more in sertraline group compared with placebo or bupropion groups ($p < 0.001$)
- At day 56 no difference in overall satisfaction with sexual function between treatment groups

#### ANALYSIS:
- **ITT:** Yes
- **Post randomization exclusions:** Yes

#### ATTRITION:
- **Loss to follow-up:** 32%
- **Withdrawals due to adverse events:** sertraline: 3%, bupropion sr: 3%, placebo: 7%

#### ADVERSE EVENTS:
- Headache was the most commonly reported event in all treatment groups
- Somnolence and insomnia occurred more frequently in sertraline group than bupropion group
- Nausea and diarrhea occurred more frequently with sertraline than bupropion or placebo

#### QUALITY RATING:
- Fair
<table>
<thead>
<tr>
<th><strong>Evidence Table 10</strong></th>
<th><strong>Adverse Events</strong></th>
</tr>
</thead>
</table>
| **STUDY:**           | Authors: Didham RC, et al.  
Year: 2005  
Country: New Zealand |
| **FUNDING:**         | The Royal NZ College of General Practitioners Research Unit which receives funding from the NZ government |
| **DESIGN:**          | Study design: Retrospective cohort and nested case control study  
Setting: General practice  
Sample size: 57,361 |
| **INTERVENTION:**    | Drug: SSRIs and other ADS  
Dose: Varied  
Duration: 120 days  
Cases: Suicides: 26  
Self-harms: 330 |
| **INCLUSION:**       | Patients that received a prescription for an anti-depressant from 1996 to 2001 |
| **EXCLUSION:**       | Patients under 10 years old; additional concurrent anti-depressants |
| **OTHER MEDICATIONS/INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Median age: 46  
Gender (% female): 68.1%  
Ethnicity: NR |
<table>
<thead>
<tr>
<th>Authors: Didham RC, et al. Year: 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
</tr>
<tr>
<td><em>Primary Outcome Measures:</em> Suicides or self-harm within 120 days of a prescription</td>
</tr>
<tr>
<td><em>Timing of assessments:</em> N/A</td>
</tr>
<tr>
<td><strong>RESULTS:</strong></td>
</tr>
<tr>
<td>• No significant increase in suicides for SSRIs as a group: OR 1.28; 95% CI 0.38-4.35</td>
</tr>
<tr>
<td>• No significant difference in suicides between drugs</td>
</tr>
<tr>
<td>Fluoxetine: 0.80 (0.22-2.89)</td>
</tr>
<tr>
<td>Paroxetine: 2.25 (0.47-10.72)</td>
</tr>
<tr>
<td>• Self-harm SSRIs vs. TCAs incidence rate 2.57 95% CI 2.03-3.28</td>
</tr>
<tr>
<td>• Increased risk of self-harm for SSRIs as a group OR 1.66 95% CI 1.23-2.23</td>
</tr>
<tr>
<td>• No significant differences in self-harm between drugs</td>
</tr>
<tr>
<td>Fluoxetine: 1.30 (0.96-1.75)</td>
</tr>
<tr>
<td>Paroxetine 1.21 (0.84-1.72)</td>
</tr>
<tr>
<td><strong>ANALYSIS:</strong></td>
</tr>
<tr>
<td><em>ITT:</em> N/A</td>
</tr>
<tr>
<td><em>Post randomization exclusions:</em> N/A</td>
</tr>
<tr>
<td><strong>ATTRITION:</strong></td>
</tr>
<tr>
<td><em>Loss to follow-up:</em> N/A</td>
</tr>
<tr>
<td><em>Withdrawals due to adverse events:</em> N/A</td>
</tr>
<tr>
<td><em>Withdrawals due to lack of efficacy:</em> N/A</td>
</tr>
<tr>
<td><em>Loss to follow-up differential high:</em> N/A</td>
</tr>
<tr>
<td><strong>ADVERSE EVENTS:</strong></td>
</tr>
<tr>
<td>• N/A</td>
</tr>
<tr>
<td><strong>QUALITY RATING:</strong></td>
</tr>
<tr>
<td>Fair</td>
</tr>
</tbody>
</table>
### Evidence Table 10

**Adverse Events**

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

| **Authors**: Dunner et al.  
| **Year**: 1998  
| **Country**: US  

| **OUTCOME ASSESSMENT:** | **Primary Outcome Measures**: Number of seizures; seizure rate  
| **Secondary Outcome Measures**: N/A  
| **Timing of assessments**: Biweekly during the study  

| **RESULTS:** | During the 8 week acute phase of the trial, 2 patients (0.06% -- Upper 1-sided CL of 0.14%) experienced seizures out of 3094 patients.  

| **ANALYSIS:** | ITT: N/A  
| Post randomization exclusions: N/A  

| **ATTRITION:** | Overall  
| Loss to follow-up:  
| Withdrawals due to adverse events:  
| Withdrawals due to lack of efficacy:  
| Loss to follow-up differential high:  
| 34%  
| NR  
| NR  
| N/A  

| **ADVERSE EVENTS:** | 54 serious adverse events (other than seizure) occurred during the study. Suicide attempt or overdose: 9 patients; accidental injury: 4 patients; myocardial function: 3 patients  

| **QUALITY RATING:** | Fair  

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Evidence Table 10: Adverse Events

| STUDY: Authors: Ekselius, et al.¹⁹⁷  
Year: 2001  
Country: Sweden |
|-----------------|

<table>
<thead>
<tr>
<th>FUNDING: Swedish Medical Research Council and Pfizer AB</th>
</tr>
</thead>
</table>

| 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 |
|-----------------|

<table>
<thead>
<tr>
<th>INCLUSION: DSM-III-R criteria for major depression; MADRS score ≥ 21</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>OTHER MEDICATIONS/INTERVENTIONS: Hypnotics for insomnia or daytime anxiolytics</th>
</tr>
</thead>
</table>

| POPULATION CHARACTERISTICS: Groups similar at baseline: Yes  
Gender (% female): Sertraline: 72%, citalopram: 71%  
Ethnicity: Not reported  
Mean age: Sertraline: 47.3, citalopram: 48.1  
Other population characteristics: No significant population differences |
|-----------------|
**Outcomes Assessment:**

**Measures:** MADRS, CGI-S, CGI-I, sexual function assessed by five items in the Utvalg for Kliniske Undersøgelser Side Effect Scale (UKU-SES); increased or decreased sexual desire, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction

**Timing of assessments:** Not reported

**Results:**

- No statistically significant differences between sertraline and citalopram in the magnitude or frequency of adverse sexual side effects
- For both groups sexual desire and mean total score of UKU significantly improved in women; sexual desire improved in men, but not mean score of UKU.
- In female patients reporting no sexual dysfunction at baseline, 11.8% reported decreased sexual desire and 14.3% reported orgasmic dysfunction
- In male patients reporting no sexual dysfunction at baseline, 16.7% reported decreased sexual desire, 18.9% reported orgasmic dysfunction, 25% experienced ejaculatory dysfunction

**Analysis:**

**ITT:** Not reported

**Post randomization exclusions:** Not reported

**Attrition:**

- **Loss to follow-up:** 23%; sertraline: not reported, citalopram: not reported
- **Withdrawals due to adverse events:** 11%; sertraline: not reported, citalopram: not reported
- **Loss to follow-up differential high:** Not reported

**Adverse Events:**

Not reported

**Quality Rating:**

Fair
## Evidence Table 10

<table>
<thead>
<tr>
<th><strong>STUDY:</strong></th>
<th><strong>Adverse Events</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Fava M, et al.</td>
<td></td>
</tr>
<tr>
<td><strong>Year:</strong> 2002</td>
<td></td>
</tr>
<tr>
<td><strong>Country:</strong> US</td>
<td></td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Eli Lilly Research</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
<td><strong>Study design:</strong> RCT</td>
</tr>
<tr>
<td></td>
<td><strong>Setting:</strong> Multi-center</td>
</tr>
<tr>
<td></td>
<td><strong>Sample size:</strong> 284</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Drug:</strong></td>
<td>Fluooxetine</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>20-60 mg/day</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>10-16 weeks</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
<td>≥ 18 years of age; DSM-V criteria for major depression; DSM-IV for atypical MDD; HAM-D-17 ≥ 16; episode ≥ 1month</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
<td>Thyroid medications, chloral hydrate</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
<td>Groups similar at baseline: Yes</td>
</tr>
<tr>
<td></td>
<td>Mean age: Fluooxetine: 42.1, sertraline: 44.0, paroxetine: 42.5</td>
</tr>
<tr>
<td></td>
<td>Gender (female%): Fluooxetine: 63.0, sertraline: 57.3, paroxetine: 58.3</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Not reported</td>
</tr>
<tr>
<td></td>
<td>Other population characteristics: Not reported</td>
</tr>
</tbody>
</table>
### Authors: Fava M, et al.
Year: 2002
Country: US

### Outcome Assessment:
**Measures:** HAM-D-17, CGI-S, HAM-D sleep disturbance  
**Timing of assessments:** Not reported  

### Results:
- No statistical differences between fluoxetine, sertraline and paroxetine in all outcome measures  
- Response rate: 64.8%, 72.9%, and 68.8% respectively  
- Remission rates: 54.4%, 59.4%, and 57.0% respectively  
- No statistical differences in sleep disturbance factor scores; no significant differences of treatment groups in patients with high or low insomnia  

#### Subgroup analysis (Fava 2000): Anxious depression
- No significant differences between treatment groups and changes over time  
- Response: fluoxetine: 73%, sertraline: 86%, paroxetine: 77%, overall p = 0.405  
- Remission: fluoxetine: 53%, sertraline: 62%, paroxetine: 50%, overall p = 0.588  
- Fluoxetine and sertraline had a significantly greater improvement than paroxetine in week 1 on the HAM-D anxiety score

### Analysis:
**ITT:** Yes  
**Post randomization exclusions:** Not reported

### Attrition:
**Loss to follow-up:** 27.1%; fluoxetine: 26.1%, sertraline: 27.1%, paroxetine: 28.1%  
**Withdrawals due to adverse events:** Fluoxetine: 8.7%, sertraline: 6.3%, paroxetine: 11.5%  
**Loss to follow-up differential high:** No

### Adverse Events:
- Pairwise comparisons indicated that the paroxetine-treated patients reported more constipation than the fluoxetine-treated patients; the fluoxetine-treated patients reported more twitching and cough increase than the sertraline-treated patients  
- Most common adverse events: Fluoxetine: headache (25%); sertraline: headache (28.1%), diarrhea (26.0%), insomnia (26%), nausea (20.8%); paroxetine: nausea (25.0%), headache (21.9%), insomnia (20.8%), abnormal ejaculation (20.8%)  
- There was a significant increase in weight for the paroxetine group; fluoxetine treated patients showed a significant decrease in weight and the sertraline group a non-significant decrease in weight from baseline to endpoint  

#### Subgroup analysis (Fava 1999)
- Adverse events were similar among treatments; only flu-like syndrome was significantly higher in the sertraline treated group overall (p = 0.021)

### Quality Rating:
Fair
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Fergusson D, et al.  
Year: 2005  
Country: Canada |
| **FUNDING:**      | Canadian Institutes of Health Research |
| **DESIGN:**       | Study design: Meta-analysis  
Number of patients: 36,445 |
<p>| <strong>AIMS OF REVIEW:</strong> | To establish if an association exists between SSRI use and suicide attempts. |
| <strong>STUDIES INCLUDED IN META-ANALYSIS</strong> | 345 trials included in analysis |
| <strong>TIME PERIOD COVERED:</strong> | 1967 – June 2003 |
| <strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong> | RCTs comparing an SSRI with either placebo or an active non-SSRI control |
| <strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong> | All patients included in trials comparing SSRIs to either placebo or non-SSRI control; no age, gender, or diagnosis restrictions |</p>
<table>
<thead>
<tr>
<th><strong>CHARACTERISTICS OF INTERVENTIONS:</strong></th>
<th>Patients randomized to either an SSRI, placebo, or non-SSRI control</th>
</tr>
</thead>
</table>
| **MAIN RESULTS:** | • A significant increase in the odds of suicide attempts was found in patients receiving SSRIs compared to patients receiving placebo (OR: 2.28; CI: 1.144 to 4.55; p = 0.02)  
• No significant difference found in the odds of suicide attempts between patients receiving SSRIs and patients receiving TCAs (OR: 0.88 (CI: 0.54 to 1.42)) |
<p>| <strong>ADVERSE EVENTS:</strong> | • No other adverse events reported. |
| <strong>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</strong> | Yes |
| <strong>STANDARD METHOD OF APPRAISAL OF STUDIES:</strong> | Yes |
| <strong>QUALITY RATING:</strong> | Good |</p>
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | **Authors:** Greist J, et al.  
                   | **Year:** 2004  
                   | **Country:** US |
| **FUNDING:**      | Eli Lilly |
| **DESIGN:**       | **Study design:** Pooled analysis  
<pre><code>               | **Number of patients:** 2,345 |
</code></pre>
<p>| <strong>AIMS OF REVIEW:</strong> | To assess the incidence, severity and onset of nausea among MDD patients treated with duloxetine |
| <strong>STUDIES INCLUDED IN META-ANALYSIS</strong> | Detke et al. 2002; Detke et al. 2002; Goldstein et al 2002; Goldstein et al. 2004; 4 unpublished studies submitted for FDA approval of duloxetine |
| <strong>TIME PERIOD COVERED:</strong> | Not reported |
| <strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong> | Double blinded, placebo or active controlled trials of duloxetine |
| <strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong> | Adult outpatients with MDD |</p>
<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>Duloxetine vs. placebo (8 studies); duloxetine vs. paroxetine (4 studies); duloxetine vs. fluoxetine (2 studies)</th>
</tr>
</thead>
</table>
| MAIN RESULTS:                   | • No significant differences in nausea between duloxetine (40-120mg/d) and paroxetine (20mg/d) (14.4% vs. 12%; p = not reported)  
• No significant differences between duloxetine (120mg/d) and fluoxetine (20mg/d) (17.1% vs. 15.7%; p = not reported)  
• Significantly more patients on duloxetine than on placebo reported nausea (19% vs. 6.9%; p < 0.001) |
<p>| ADVERSE EVENTS:                  | N/A                                                                                               |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | No; analysis of published and unpublished trials                                                  |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Not reported                                                                                      |
| QUALITY RATING:                  | Fair                                                                                             |</p>
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:** | **Authors:** Gunnell D, et al.  
**Year:** 2005  
**Country:** UK |
| **FUNDING:** | Not Reported |
| **DESIGN:** | **Study design:** Meta-analysis  
**Number of patients:** 40,826 |
| **AIMS OF REVIEW:** | To investigate whether SSRIs are associated with an increased risk of suicide related outcomes in adults. |
| **STUDIES INCLUDED IN META-ANALYSIS** | Published and unpublished data submitted by pharmaceutical companies to the Medicine and Healthcare Products Regulatory Agency (MHRA) (2004)  
342 placebo controlled trials included in report – citations not given in bibliography |
<p>| <strong>TIME PERIOD COVERED:</strong> | NR |
| <strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong> | Randomized, placebo controlled trials of SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) submitted by pharmaceutical companies |
| <strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong> | Adult patients with various indications included in trials comparing SSRIs to placebo. |</p>
<table>
<thead>
<tr>
<th><strong>CHARACTERISTICS OF INTERVENTIONS:</strong></th>
<th>Patients randomized to either SSRI or placebo.</th>
</tr>
</thead>
</table>
| **MAIN RESULTS:**                   | • No significant difference was found between SSRI treatment and placebo treatment in the odds ratios for suicide (OR: 0.85 CI: 0.2 to 3.4), non-fatal self harm (OR: 1.57 CI: 0.99 to 2.55), or suicidal thought (OR: 0.77 CI: 0.37 to 1.55).  
• For non-fatal self-harm the NNT to harm is 759 |
| **ADVERSE EVENTS:**                 | • No other adverse events reported. |
| **COMPREHENSIVE LITERATURE SEARCH STRATEGY:** | No (published and unpublished data submitted by pharmaceutical companies; review does not include studies from sources other than pharmaceutical companies) |
| **STANDARD METHOD OF APPRAISAL OF STUDIES:** | Yes |
| **QUALITY RATING:**                 | Good |
## Evidence Table 10: Adverse Events

| STUDY: | **Authors:** Haffmans, et al.  
**Year:** 1996  
**Country:** The Netherlands |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Lundbeck</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design:** RCT  
**Setting:** Multi-center  
**Sample size:** 217 |
| INTERVENTION: | **Drug:**  
**Dose:** Citalopram: 20-40 mg/d  
6 weeks  
Fluvoxamine: 100–200 mg/d  
6 weeks |
| INCLUSION: | Ages 18-70 years; met DSM III-R criteria for major depression (single episode or recurrent) or bipolar disorder; score of > 16 on HAM-D-17; reasonable knowledge of the Dutch language |
| EXCLUSION: | MAOI or fluoxetine use within 3 weeks or other psychotropic drugs within 1 week (except for benzos); other primary psychiatric diagnosis (other than MDD); history of epilepsy, alcohol or drug abuse; pregnancy, lactation, or not using contraception; renal, hepatic, cardiovascular, neurological or somatic disorders and/or significant abnormal lab findings |
| OTHER MEDICATIONS/INTERVENTIONS: | Selected benzodiazepines; oxazepam, lormetazepam, temazepam, lorazepam, or flurazepam, all non-psychotropic medications were allowed, domperidone for nausea/vomiting allowed |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** No  
**Mean age:** Citalopram: 44.2, fluvoxamine: 40.2  
**Gender (% female):** 58%; citalopram: 58%, fluvoxamine: 60%  
**Ethnicity:** Not reported  
**Other population characteristics:** Previous depressive disorder: citalopram: 43%; fluvoxamine: 54%; previous antidepressant therapy (within 3 weeks of starting trial): citalopram: 65%, fluvoxamine: 73% |
| **Authors:** Haffmans, et al.  
**Year:** 1996  
**Country:** The Netherlands |
|---|
| **OUTCOME ASSESSMENT:**  
*Measures:* Primary: HAM-D-17; secondary: CGI, UKU side effect rating scale, Zung self-rating depression scale  
*Timing of assessments:* Baseline, weeks 1, 2, 4, 6 |
| **RESULTS:**  
- No difference in mean HAM-D-17 scores after 6 weeks  
- Complete Response (HAM-D17) ≤ 7: citalopram: 14%, fluvoxamine: 18%; no significant difference  
- Mean % reduction in score at week 6: citalopram: 33%, fluvoxamine: 26%  
- Responders (reduction in score from baseline > 50%): citalopram: 30.5%, fluvoxamine: 28.4% |
| **ANALYSIS:**  
*ITT:* Yes  
*Post randomization exclusions:* Yes |
| **ATTRITION:**  
*Loss to follow-up:* 23%; citalopram: 19.4%, fluvoxamine: 26.6%  
*Withdrawals due to adverse events:* Citalopram: 13.9%, fluvoxamine: 21.1%  
*Loss to follow-up differential high:* No |
| **ADVERSE EVENTS:**  
- No differences between groups in laboratory values or vital signs  
- 10 serious adverse events (4 in citalopram and 6 in fluvoxamine) none of which were deemed to be causally related to treatment  
- Similar UKU side effect scale measured impact on functioning between groups  
- Fluvoxamine had the following excess incidence of adverse events as compared to citalopram:  
  - Diarrhea: 13.6% (p = 0.026)  
  - Nausea: 16.0% (p = 0.017)  
  - Vomiting: 9.1% (p = 0.052)  
  - Suicide attempt: 4.6%  
  - Citalopram had the following excess incidence of adverse events as compared to fluvoxamine: paraesthesia: 10.4% |
| **QUALITY RATING:**  
Fair |
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**       | Authors: Jick H, et al.\(^2\)\(^5\)\(^1\)  
Year: 2004  
Country: UK |
| **FUNDING:**     | Boston Collaborative Drug Surveillance Program |
| **DESIGN:**      | Study design: Matched case-control; post-hoc database analysis  
Setting: General practices in the UK using VAMP database (General Practice Research Database)  
Sample size: 159,810 (555 cases, 2062 controls) |
| **INTERVENTION:**| Drug: Dothiepin, amitriptyline, fluoxetine, paroxetine  
Dose: Not reported  
Duration: Not reported |
| **INCLUSION:**   | Received a prescription for at least 1 antidepressant in the VAMP database during the 1993-1999 years; all patients who had a first-time recorded diagnosis of nonfatal suicidal ideation or attempted suicide at age 10-69 years during the 1993-1999 time period; had received at least 1 prescription for a study drug within 90 days before their index date |
| **EXCLUSION:**   | Received prescription for another antidepressant or more than one study drug prior to their index date; history of psychosis, panic disorders, phobias, obsessive-compulsive neurosis, manic-depressive disease, drug abuse, alcohol abuse, epilepsy, anorexia, bulimia, and attention-deficit disorder |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Not reported |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: not reported  
Gender (% female): 65.4% female (cases only)  
Ethnicity: Not reported  
Other population characteristics: ~85% of cases had attempted suicide while 15% had suicidal ideation |
<table>
<thead>
<tr>
<th>Authors:</th>
<th>Jick H, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year:</td>
<td>2004</td>
</tr>
<tr>
<td>Country:</td>
<td>UK</td>
</tr>
</tbody>
</table>

**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 amitriptyline (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 dothiepin
- 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
<table>
<thead>
<tr>
<th><strong>Evidence Table 10</strong></th>
<th><strong>Adverse Events</strong></th>
</tr>
</thead>
</table>
| **STUDY:**            | **Authors:** Jick, et al.  
**Year:** 1995  
**Country:** UK |
| **FUNDING:**          | Various pharmaceutical companies (Berlex, Boots, Burroughs Wellcome, Ciba-Geigy, Hoeschst, Hoffman-LaRoche, RW Johnson, Pfizer, Proctor and Gamble, Sanofi Winthrop) |
| **DESIGN:**           | **Study design:** Cohort study with nested case-control analysis  
**Setting:** General practices in the UK using VAMP database  
**Sample size:** 172,598 |
| **INTERVENTION:**     | **Drug:** Drugs studies in this cohort: dothiepin, amitryptyline, clomipramine, imipramine, flupenthixol, lofepramine, mianserin, fluoxetine, doxepin, trazodone, maprotiline, desipramine |
|                       | **Dose:** Not reported  
**Duration:** 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 |
<table>
<thead>
<tr>
<th>Authors: Jick, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year: 1995</td>
</tr>
<tr>
<td>Country: UK</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Measures: Suicide completion rate, suicides/person time at risk, relative risks of suicide reported with dothiepin as reference group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments: N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS:</th>
<th>• 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</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 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)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
<th>ITT: N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post randomization exclusions: N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTRITION:</th>
<th>Loss to follow-up: Not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Withdrawals due to adverse events: N/A</td>
</tr>
<tr>
<td></td>
<td>Loss to follow-up differential high: N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
<th>Not reported</th>
</tr>
</thead>
</table>

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

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Number of seizures  
| | Secondary Outcome Measures: N/A  
| | Timing of assessments: Biweekly |

| RESULTS: | Eight seizures were reported in the 3277 patients analyzed during the treatment phase. This is a seizure rate of 0.24%. A survival analysis showed a cumulative seizure rate of 0.36% during the 8 week trial. |

| ANALYSIS: | ITT: No  
| | Post randomization exclusions: N/A |

| ATTRITION: | Overall  
| | NR  
| | 613 (19%)  
| | NR  
| | N/A  
| | Loss to follow-up differential high: |

| ADVERSE EVENTS: | 82 (2.5%) patients experienced major adverse events (life threatening or requiring hospitalization)  
| | Most common adverse events were nausea (3.6%), agitation (2.4%), anxiety (1.7%), headache (1.5%), insomnia (1.3%), and rash (1.3%) |

<p>| QUALITY RATING: | N/A |</p>
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| STUDY: | Authors: Khan, et al.<sup>194</sup>  
Year: 2003  
Country: US |
| FUNDING: | Not reported |
| DESIGN: | Study design: Meta-analysis  
Number of patients: 48,277 |
| AIMS OF REVIEW: | Compare suicide rates among depressed patients |
| STUDIES INCLUDED IN META-ANALYSIS | Pooled analysis of FDA clinical trial data from 1985-2000 for 9 SSRIs  
2000 publication reports on 1987 to 1997 (same data) |
| TIME PERIOD COVERED: | 1985-2000 |
| CHARACTERISTICS OF INCLUDED STUDIES: | FDA clinical trial data |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Major depression according to DSM-II-R criteria; minimum score of 18 or 20 on HAM-D-17 or HAM-D-21 |
**Authors:** Khan, et al.  
**Year:** 2003  
**Country:** US

**CHARACTERISTICS OF INCLUDED INTERVENTIONS:** Fluoxetine, sertaline, paroxetine, citalopram, fluvoxamine, nefazodone, mirtazapine, bupropion, venlafaxine, imipramine, amitryptiline, maprotiline, trazadone, mianserin, dothiepin

**MAIN RESULTS:**

- **Absolute Suicide Rate**
  - SSRI: 0.15% (0.10-0.20% 95% CI)
  - "Other": 0.20% (0.09-0.27% 95% CI)
  - Placebo: 0.10% (0.01-0.19% 95% CI)
  - p > 0.05 for difference

- **Suicide Rate by Patient Exposure Years (PEY)**
  - SSRI: 0.59%/PEY (0.31-0.87 95% CI)
  - "Other": 0.76%/PEY (0.49-1.03 95% CI)
  - Placebo: 0.45%/PEY (0.01-0.89 95% CI)
  - p > 0.05 for difference

- 2000 study: looked at suicide attempts and completion and found no difference

**ADVERSE EVENTS:** N/A

**COMPREHENSIVE LITERATURE SEARCH STRATEGY:** No

**STANDARD METHOD OF APPRAISAL OF STUDIES:** Not reported

**QUALITY RATING:** Fair
## Evidence Table 10: Adverse Events

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>FUNDING: Solvay Pharma, Upjohn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DESIGN: Study design: RCT</td>
<td>Setting: Single center</td>
<td>Sample size: 60</td>
</tr>
<tr>
<td>INTERVENTION:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug:</strong></td>
<td>Fluvoxamine</td>
<td>Paroxetine</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>50-150 mg/d</td>
<td>20-50 mg/d</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>7 weeks</td>
<td>7 weeks</td>
</tr>
<tr>
<td>INCLUSION:</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>EXCLUSION:</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>OTHER MEDICATIONS/INTERVENTIONS:</td>
<td>Antacids, laxatives, acetaminophen, aspirin, ibuprofen, chloral hydrate, other meds only with permission of study physician</td>
<td></td>
</tr>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: Yes</td>
<td>Mean age: Fluvoxamine: 42.7, paroxetine: 39</td>
</tr>
</tbody>
</table>
| Authors: Kiev, et al.  
Year: 1997 | OUTCOME ASSESSMENT: | Measures: HAM-D-21, HAM-A, SCL-56, CGI  
Timing of assessments: Baseline, weeks 1, 2, 3, 5, 7 |
|-----------------|-----------------|--------------------------|
| RESULTS: | • Mean change in HAM-D score: fluvoxamine: -13.45, paroxetine: -12.86 (p = 0.763)  
• No significant differences between groups on HAM-D-21, CGI, HAM-A, or SCL56 |
| ANALYSIS: | ITT: Yes  
Post randomization exclusions: Yes |
| ATTRITION: | Loss to follow-up: 31%  
Withdrawals due to adverse events: fluvoxamine: 6.8%, paroxetine: 13.8%  
Loss to follow-up differential high: No |
| ADVERSE EVENTS: | • Sweating (p = 0.028); fluvoxamine: 10%, paroxetine: 33%  
• Headache: fluvoxamine: 40%, paroxetine: 57%  
• Nausea: fluvoxamine: 37%, paroxetine: 47%  
• No clinically significant labs or vital sign changes in either group |
| QUALITY RATING: | Fair |
### Evidence Table 10

#### Adverse Events

| STUDY: | Authors: Landen M, et al. 
Year: 2005
Country: Sweden and Norway |
| FUNDING: | Bristol-Myers Squibb, Sweden |
| OBJECTIVE: | To determine: 1) concordance of sexual dysfunction adverse event rates between open-ended questioning and directed questioning; 2) the incidence of sexual side effects of citalopram and paroxetine; 3) the correlation between sexual side effects and illness severity, treatment duration and drug/dose combination |
| DESIGN: | Study design: Non-randomized trial of adverse event elicitation methods embedded in a RCT (Landen et al 1998 – patients who had not responded to CP or PX were randomized to receive buspirone or placebo)
Setting: Multi-center (13 centers)
Sample size: 119 |
| INTERVENTION: | Drug: Citalopram at least 40 mg/d 4 weeks 77
Paroxetine at least 30 mg/d 4 weeks 42 |
| INCLUSION: | Patients 18 years or older; met criteria for a major depressive episode according to DSM-IV criteria; has not responded to CP or PX for a minimum of 4 weeks prior to start of study |
| EXCLUSION: | Pregnancy; epilepsy; severe somatic disease; mental disorder due to a general medical condition; substance abuse; highly suicidal status |
| OTHER MEDICATIONS/INTERVENTIONS: | Patients received either buspirone or placebo for 4 week study duration |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Yes
Mean age: 46
Gender (% female): 69%
Ethnicity: NR
Other population characteristics: NR |
| **OUTCOME ASSESSMENT:** | **Primary Outcome Measures:** Sexual dysfunction score (0-6); Percent patients reporting any sexual side effect based on open and direct questioning  
**Secondary Outcome Measures:** N/A  
**Timing of assessments:** Before and after the 4 week trial |
|-------------------------|--------------------------------------------------|
| **RESULTS:** | By objective  
1. Side effect elicitation method  
   - Significantly more patients (49 versus 6) reported sexual side effects in response to direct questioning than open questioning (p < 0.001).  
2. Incidence of side effects by drug  
   - There were no statistically significant differences between the paroxetine and paroxetine groups in sexual side effects reported or sexual dysfunction score.  
   - Open-ended questioning: citalopram 5%, paroxetine 7% (p = 0.98)  
   - Direct questioning: citalopram 44%, paroxetine 36% (p = 0.37)  
3. Correlations with illness severity and treatment parameters  
   - Only weak correlation with duration of current depression episode (p = 0.043) |
| **ANALYSIS:** | **ITT:** N/A  
**Post randomization exclusions:** N/A |
| **ATTRITION:** | **Loss to follow-up:** N/A  
**Withdrawals due to adverse events:** N/A  
**Withdrawals due to lack of efficacy:** N/A  
**Loss to follow-up differential high:** N/A |
| **ADVERSE EVENTS:** | • Decreased desire reported by 43% of men and 32% of women  
• Orgasmic dysfunction reported by 23% women and 32% men |
<p>| <strong>QUALITY RATING:</strong> | Good |</p>
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| STUDY:           | Authors: Lopez-Ibor JJ<sup>13</sup>  
|                  | Year: 1993  
|                  | Country: Spain |
| FUNDING:         | N/A |
| DESIGN:          | Study design: Retrospective database analysis  
|                  | Setting: Not reported  
|                  | Sample size: 4,668 |
| INTERVENTION:    | Paroxetine  
|                  | Not reported  
|                  | Up to 6 weeks  
|                  | Placebo  
|                  | N/A  
|                  | Up to 6 weeks  
|                  | Active control  
|                  | N/A  
|                  | Up to 6 weeks |
| INCLUSION:       | Depressed patients enrolled in a clinical trial |
| EXCLUSION:       | Not reported |
| OTHER MEDICATIONS/INTERVENTIONS: | Not reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: Not reported  
|                  | Mean age: Not reported  
|                  | Gender: Not reported  
|                  | Ethnicity: Not reported  
|                  | Other population characteristics: Not reported |
**Authors:** Lopez-Ibor, JJ  
**Year:** 1993  
**Country:** Spain

### OUTCOME ASSESSMENT:

**Measures:** Suicide item of HAM-D, emergence of suicidal ideation, assessed by the development of HAM-D suicide item score  
**Timing of assessments:** N/A

### RESULTS:

Paroxetine and active control were significantly better than placebo in reducing suicidal thoughts and behavior from week 1 onwards

### ANALYSIS:

**ITT:** N/A  
**Post randomization exclusions:** Not reported

### ATTRITION:

**Loss to follow-up:** N/A  
**Withdrawals due to adverse events:** N/A  
**Loss to follow-up differential high:** N/A

### ADVERSE EVENTS:

- There were no differences among the groups with regards to suicidality as an adverse event.  
- 0.4% of each group reported suicidality.  
- There were 10 suicides overall and 58 attempts overall.

### QUALITY RATING:

N/A
### Evidence Table 10

| **STUDY:** | **Authors:** Mackay, et al.\(^{184, 185}\)  
**Year:** 1997  
**Country:** UK |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>FUNDING:</strong></td>
<td>Drug Safety Research Unit, UK, various unnamed pharmaceutical companies</td>
</tr>
</tbody>
</table>
| **DESIGN:** | **Study design:** Cohort study (prescription event monitoring)  
**Setting:** General practice in the UK  
**Sample size:** Number identified as getting a first prescription: fluvoxamine: 20,504, fluoxetine: 24,738, sertraline: 24,632, paroxetine: 26,194 |
| **INTERVENTION:** | **Drugs:** fluvoxamine, fluoxetine, sertraline, paroxetine  
**Dose:** N/A  
**Duration:** Outcomes assessed after approximately 6 months for all but fluvoxamine (which was 12 months) |
| **EXCLUSION:** | Not reported |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Not reported |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** Yes; some differences existed between groups as far as indication for prescription  
**Mean age:** 50  
**Gender (% female):** 70%  
**Ethnicity:** Not reported  
**Other population characteristics:** Not reported |
Authors: Mackay, et al.
Year: 1997
Country: UK

OUTCOME ASSESSMENT:

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

Timing of assessments: Mailed 6-12 months after initial prescription written

RESULTS:

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

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

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

- Adverse Effects Reported:

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

- 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)
<table>
<thead>
<tr>
<th>RESULTS:</th>
<th>SSRIs and nefazodone:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 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</td>
</tr>
<tr>
<td></td>
<td>• Sertraline and fluoxetine had a significantly lower rate ratio of agitation and anxiety than the remaining drugs</td>
</tr>
<tr>
<td></td>
<td>• Drowsiness and sedation were reported most frequently with nefazodone and paroxetine</td>
</tr>
<tr>
<td></td>
<td>• 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)</td>
</tr>
<tr>
<td></td>
<td>• There were more reports of mania during 90 days with fluoxetine than with the other drugs</td>
</tr>
<tr>
<td></td>
<td>• There was no significant difference in deaths between drugs</td>
</tr>
<tr>
<td>ANALYSIS:</td>
<td>ITT: N/A</td>
</tr>
<tr>
<td></td>
<td>Post randomization exclusions: N/A</td>
</tr>
<tr>
<td>ATTRITION:</td>
<td>Loss to follow-up: N/A</td>
</tr>
<tr>
<td></td>
<td>Completion rates of surveys: 60%</td>
</tr>
<tr>
<td></td>
<td>Withdrawals due to adverse events: N/A</td>
</tr>
<tr>
<td></td>
<td>Loss to follow-up differential high: N/A</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>N/A</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
</tbody>
</table>
**Evidence Table 10**

### Adverse Events

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

**OUTCOME ASSESSMENT:**

- **Primary Outcome Measures:** Percentage weight gain
- **Secondary Outcome Measures:** Number of patients with extreme weight gain
- **Timing of assessments:** Weight recorded at the beginning of treatment and at six months intervals thereafter.

**RESULTS:**

- An ANOVA analysis showed significant between group differences in weight gain ($p = 0.009$). Clomipramine had the highest increase in weight and fluoxetine and sertraline had the lowest increase in weight.
- Clomipramine (+2.6 kg; $p < 0.001$), citalopram (+1.5kg; $p = 0.002$), paroxetine (+1.7kg; $p = 0.001$), fluvoxamine (+1.7kg; $p < 0.001$), and sertraline (+ 1.0kg; $p = 0.01$) showed significant increases in weight from baseline. No significant increase in weight was observed in the fluoxetine group (+0.5kg; $p = NR$).
- Patients with significant weight gain ($\geq 7\%$): clomipramine 34.8%; citalopram 14.3%; paroxetine 14.3%; fluvoxamine 10.7%; sertraline 4.5%; fluoxetine 8.7%.

**ANALYSIS:**

- **ITT:** No
- **Post randomization exclusions:** N/A: above results are reported only for patients who completed the 2 year extension phase of the trial

**ATTRITION:**

- **Loss to follow-up:** 7%
- **Withdrawals due to adverse events:** NR
- **Loss to follow-up differential high:** NR

**ADVERSE EVENTS:**

- NR

**QUALITY RATING:**

- Fair
**Evidence Table 10**

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

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Primary Outcome Measures</th>
<th>Secondary Outcome Measures</th>
<th>Timing of assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of non-fatal self harm and completed suicide</td>
<td>none</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### RESULTS:
- No difference in risk of non-fatal self harm among the different SSRIs (p = 0.35). The greatest risk of self harm was found in patients taking paroxetine.
- No difference in the risk of self-harm between SSRIs and TCAs (OR: 0.99 CI: 0.86 to 1.14).
- Significantly higher risk of self-harm among SSRI patients younger than 18 years compared to those on TCAs (OR 1.59; 95% CI 1.01-2.50). Among SSRIs, the greatest risk of self harm was found in patients taking paroxetine.
- No difference in the risk of suicide between SSRIs and TCAs (OR: 0.57 CI: 0.26 to 1.25).

### ANALYSIS:
- ITT: N/A  
- Post randomization exclusions: N/A

### ATTRITION:
- Loss to follow-up: N/A  
- Withdrawals due to adverse events: N/A  
- Loss to follow-up differential high: N/A

### ADVERSE EVENTS:
- N/A

### QUALITY RATING:
- Good
## Evidence Table 10

### Adverse Events

| STUDY: | Authors: Meijer WE, et. al.  
Year: 2002  
Country: The Netherlands |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Observational study of adverse effects  
Setting: Multi-center (109 psychiatrists)  
Sample size: 1,251 |
| INTERVENTION: | Drug:  
Sertraline or fluoxetine, fluvoxamine, or paroxetine  
Any administered dose  
12 month observation period |
| INCLUSION: | All patients with a new sertraline prescription; patients taking fluoxetine, fluvoxamine, or paroxetine were used as controls |
| EXCLUSION: | None reported |
| ALLOWED OTHER MEDICATIONS/INTERVENTIONS: | None reported |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: N/A  
Mean age: 41  
Gender (% female): 64.1%  
Ethnicity: Not reported  
Other population characteristics: Significantly more sertraline patients had a diagnosis of depressive disorder than patients on other SSRIs (p < 0.001); anxiety disorder was significantly less in sertraline patients than patients with other SSRIs (p < 0.001); MDD: 77.9%, anxiety: 15.5%, multiple diagnoses: 37.8%. |
<table>
<thead>
<tr>
<th><strong>Authors:</strong> Meijer WE, et al.</th>
<th><strong>Year:</strong> 2002</th>
</tr>
</thead>
</table>
| **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 |
<p>| <strong>ADVERSE EVENTS:</strong> N/A |
| <strong>QUALITY RATING:</strong> Fair |</p>
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| STUDY:            | Authors: Montejo et al.¹⁹⁹  
Year: 2001  
Country: Spain |
| FUNDING:          | Bristol-Myers Squibb |
| DESIGN:           | Study design: Observational  
Setting: Multi-center  
Sample size: 1022 |
| INTERVENTION:     | Drug: |
|                   | Dose (mean): |
|                   | Duration: |
|                   | Sample size: |
| fluoxetine        | 24.5 mg  
NR  
279 |
| paroxetine        | 23.4 mg  
NR  
208 |
| fluvoxamine       | 115.7 mg  
NR  
77 |
| sertraline        | 90.4 mg  
NR  
159 |
| citalopram        | 28.7 mg  
NR  
66 |
| venlafaxine       | 159.5 mg  
NR  
55 |
| mirtazapine       | 37.7 mg  
NR  
49 |
| nefazodone        | 324.6 mg  
NR  
50 |
| INCLUSION:        | Normal sexual functioning prior to taking antidepressants; treatment with an antidepressant alone or in combination with a benzodiazepine; previous regular and satisfactory sexual practices; occurrence of sexual dysfunction within the two months after introduction of an antidepressant |
| EXCLUSION:        | Prior sexual dysfunction; combination of antidepressant and neuroleptic treatment; treatment with hormones or any other drug capable of interfering with sexual intercourse; significant intercurrent diseases affecting sexual function; substance abuse |
| OTHER MEDICATIONS/INTERVENTIONS: | NR |
| POPULATION CHARACTERISTICS: | Groups similar at baseline: NR  
Mean age: Overall: 39.8  
Gender (% female): Overall: 60%  
Ethnicity: NR  
Other population characteristics: MDD: 60.1%; dysthymic disorder: 17.3%; panic disorder: 12.1%; OCD: 5.9%; other disorders: 3.7% |
| Authors: Montejo et al.  
Year: 2001  
Country: Spain |
|---|
| **OUTCOME ASSESSMENT:** | **Primary Outcome Measures:** PRSexDQ (Psychotropic-Related Sexual Dysfunction Questionnaire)  
**Secondary Outcome Measures:** None  
**Timing of assessments:** Each clinic visit |
| **RESULTS:** | **•** Overall incidence of sexual dysfunction was 59.1% (604/1022) when all antidepressants were considered as a whole  
**•** There were relevant differences when the incidence of any type of sexual dysfunction was compared among different drugs: fluoxetine: 57.7%; sertraline: 62.9%; fluvoxamine: 62.3%; paroxetine: 70.7%; citalopram: 72.7%; venlafaxine: 67.3%; mirtazapine: 24.4%; nefazodone: 8%  
**•** Men had a higher frequency of sexual dysfunction (62.4%) than women (56.9%), although women had higher severity |
| **ANALYSIS:** | **ITT:** N/A  
**Post randomization exclusions:** N/A |
| **ATTRITION:** | **Loss to follow-up:** N/A  
**Withdrawals due to adverse events:** N/A  
**Withdrawals due to lack of efficacy:** N/A  
**Loss to follow-up differential high:** N/A |
| **ADVERSE EVENTS:** | **N/A** |
| **QUALITY RATING:** | **Fair** |
**Evidence Table 10**

### Adverse Events

| STUDY: | Authors: Nieuwstraten C, et al.  
Year: 2001  
Country: Canada |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: Meta-analysis  
Number of patients: 1332 |
<p>| AIMS OF REVIEW: | To assess the benefits and risks of bupropion vs. SSRIs in major depression |
| TIME PERIOD COVERED: | 1966-1999 |
| CHARACTERISTICS OF INCLUDED STUDIES: | RCTs, study durations: 6-16 weeks, median 7 weeks |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Age: 36 to 70 yrs; proportion of females: 48.0% to 61.8% |</p>
<table>
<thead>
<tr>
<th><strong>Authors</strong></th>
<th>Nieuwstraten C, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td>2001</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>Canada</td>
</tr>
</tbody>
</table>

**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:
  - Nausea: RR: 0.6 (95%CI: 0.41-0.89)
  - Diarrhea: RR: 0.31 (95%CI: 0.16-0.57)
  - Somnolence: RR: 0.27 (95%CI: 0.15-0.48)
- Satisfaction with sexual function was significantly less in the SSRI group: RR: 1.28 (95%CI: 1.16-1.41)

**COMPREHENSIVE LITERATURE SEARCH STRATEGY:**
- Yes

**STANDARD METHOD OF APPRAISAL OF STUDIES:**
- Yes

**QUALITY RATING:**
- Good
### Evidence Table 10  
#### Adverse Events

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

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Rates of suicide and self-harm  
Secondary Outcome Measures: |  
Timing of assessments: N/A |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RESULTS:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- MADRS item 10 (suicidal thoughts) escitalopram patients had less suicidal thoughts than placebo from weeks 1 (p < 0.05) to 8 (p < 0.001).  
- Suicides in placebo-controlled studies escitalopram n- 0 rate- 0 incidence- 0 Placebo n-1 rate-0.003 incidence- 0.1  
- Non-fatal self harm in placebo-controlled studies: escitalopram n- 5 rate- 0.011 incidence- 0.2 Placebo n-1 rate-0.003 incidence- 0.1 |
| ANALYSIS: | ITT: N/A  
Post randomization exclusions: N/A |
| ATTRITION: | Overall  
Loss to follow-up: NR  
Withdrawals due to adverse events: NR  
Withdrawals due to lack of efficacy: NR  
Loss to follow-up differential high: Not enough information |
| ADVERSE EVENTS: | N/A |
| QUALITY RATING: | Fair |
# Evidence Table 10: Adverse Events

| STUDY: | Authors: Rapaport ME, et. al.  
Year: 1996  
Country: US |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Solvay Pharmaceuticals, Upjohn</td>
</tr>
</tbody>
</table>
| DESIGN: | Study design: RCT  
Setting: Multi-center (6 sites)  
Sample size: 100 |
| INTERVENTION: |  
**Drug:**  
**Dose:**  
**Duration:**  
Fluvoxamine 100-150 mg/d  
7 weeks |
|  |  
Fluoxetine 20-80 mg/d  
7 weeks |
| INCLUSION: | Male and female outpatients; 18-65 years; met DSM-III-R criteria for MDD; minimum HAM-D (21-item) score of 20; minimum score of 2 on the depressed mood item |
| EXCLUSION: | Any primary DSM-IV Axis I disorder diagnosis other than MDD; acute suicidality; unstable medical conditions; history of seizure; had been treated with study medications; history of substance abuse or dependence; pregnancy and lack of appropriate birth control for women of child-bearing age |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** Yes  
**Mean age:** fluoxetine: 38.6; fluvoxamine: 40.0  
**Gender** (% female): fluoxetine: 63; fluvoxamine: 61  
**Ethnicity:** 95% white; 5% other  
**Other population characteristics:** NR |
| **Authors:** Rapaport ME, et al.  
**Year:** 1996  
**Country:** US |
|---|
| **OUTCOME ASSESSMENT:** | **Measures:** HAM-D-21, HAM-A, CGI-S, Raskin–Covi Scale, Hopkins Symptom Checklist, TESS (Specific treatment-emergent signs and symptoms) Barnes Akathisia Scale, Modified Scale for Suicidal Ideation  
**Timing of assessments:** Primary outcome measures weekly; secondary outcome measures at baseline and endpoint |
| **RESULTS:** | • No statistically significant differences between fluvoxamine and fluoxetine in all outcome measures  
• Both drugs significantly improved scores on HAM-D (<10 for both groups at endpoint) |
| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes (7) |
| **ATTRITION:** | **Loss to follow-up:** 11%  
**Withdrawals due to adverse events:** 4%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** | • Overall, no difference in the rate of adverse events were reported between fluvoxamine and fluoxetine and there were no differences in the average event severity (1.12 vs. 1.13; p = NR)  
• Significantly more patients on fluoxetine than on fluvoxamine reported nausea (42.5% vs. NR; p = 0.03)  
• Other frequent adverse events:  
  - headache: fluoxetine 53%, fluvoxamine 50% (p not significant)  
  - vomiting: fluoxetine 13%, fluvoxamine 4% (p not significant)  
  - daytime agitation: fluoxetine 47%, fluvoxamine 32% (p not significant) |
| **QUALITY RATING:** | Fair |
**Evidence Table 10**

### Adverse Events

| STUDY: | Authors: Schatzberg et al.
| Year: 2002 |
| Country: US |
| FUNDING: | Organon Pharma |
| DESIGN: | Study design: RCT |
| Setting: Multi-center |
| Sample size: 255 |
| INTERVENTION: | Mirtazapine 15-45 mg/d 8 weeks |
| Paroxetine 20-40 mg/d 8 weeks |
| (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 |
| EXCLUSION: | HAMD decrease > 20% between screening and baseline; untreated or unstable clinically significant medical condition or lab/physical exam abnormality; history of seizures; recent drug or alcohol abuse or any principal psych condition other than MDD; presence of psychotic features; suicide attempt in current episode; use of MAOI within 2 weeks, or other psychotropics or herbal treatments within 1 week; use of paroxetine or mirtazpine for the current episode; ECT therapy within 6 months; use of treatment for memory deficits; prior intolerance or lack of efficacy to mirtazapine or paroxetine in the past; patients who failed more than one adequate trial of an antidepressant for the current episode |
| OTHER MEDICATIONS/INTERVENTIONS: | Chloral hydrate or zolpidem for sleep induction; therapy for conditions like DM, hypothyroidism, high blood pressure, chronic respiratory conditions was allowed if they had been receiving for at least 1 month prior to screening visit. |
### Authors: Schatzberg, et al.
**Year:** 2002  
**Country:** US

### POPULATION CHARACTERISTICS:
- **Groups similar at baseline:** Yes  
- **Mean age:** 72  
- **Gender (% female):** Mirtazapine: 63%, paroxetine: 64%  
- **Ethnicity:** Not reported  
- **Other population characteristics:** Not reported

### OUTCOME ASSESSMENT:
- **Measures:** HAM-D-17, CGI-S, CGI-I  
- **Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8

### RESULTS:
- Mean Ham-D-17 scores significantly lower with mirtazapine at week 1, 2, 3, 6 but no difference at 8 week endpoint  
- Trend towards higher response and remission rates with mirtazapine but only significant difference at 2 weeks (response) and 6 weeks (remission)  
- Time to response: mirtazapine mean 26 days, paroxetine 40 days; p = -0.016 for Kaplan-Meier plot comparing the two  
- No difference in CGI Improvement response

### ANALYSIS:
- **ITT:** Yes  
- **Post randomization exclusions:** Yes

### ATTRITION:
- **Loss to follow-up:** 26.8%  
- **Withdrawals due to adverse events:** 20.4%; mirtazapine 14.8%, paroxetine 26.2% (p < 0.05)  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:
- Frequency of treatment related adverse events: mirtazapine: 79.7%, paroxetine: 82.5%  
- Significant differences: dry mouth: mirtazapine 26.6%, paroxetine 10.3%; weight gain: mirtazapine 10.9%, paroxetine 0%; nausea: mirtazapine 6.3%, paroxetine 19.0%

### QUALITY RATING:
- Fair
# Evidence Table 10

<table>
<thead>
<tr>
<th>Study</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:** | *Authors:* Segraves, et al.  
*Year:* 2000  
*Country:* US |
| **FUNDING:** | Glaxo Wellcome Inc |
| **DESIGN:** | *Study design:* RCT  
*Setting:* Multi-center  
*Sample size:* 248 |
| **INTERVENTION:** |  
*Drug:* Sertraline  
*Dose:* 50-200 mg/d  
*Duration:* 16 weeks  
*Bupropion:*  
*Dose:* 100-300 mg/d  
*Duration:* 16 weeks |
<p>| <strong>INCLUSION:</strong> | Received a DSM-IV diagnosis of moderate to severe depression with a minimum duration of 4 weeks and a maximum duration of 24 months; ≥ 18 years of age; in a stable relationship, have normal sexual functioning and sexual activity at least once every 2 weeks |
| <strong>EXCLUSION:</strong> | 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 |
| <strong>OTHER MEDICATIONS/INTERVENTIONS:</strong> | None reported |</p>
<table>
<thead>
<tr>
<th>Authors: Segraves et al.</th>
<th>Year: 2000</th>
<th>Country: US</th>
</tr>
</thead>
<tbody>
<tr>
<td>POPULATION CHARACTERISTICS:</td>
<td>Groups similar at baseline: Yes</td>
<td></td>
</tr>
<tr>
<td>Mean age: 39</td>
<td>Gender (% female): Sertraline: 48%, bupropion: 48%</td>
<td></td>
</tr>
<tr>
<td>Ethnicity: (% white) Sertraline: 94%, bupropion: 93%</td>
<td>Other population characteristics: No significant differences in diagnosis</td>
<td></td>
</tr>
<tr>
<td>OUTCOME ASSESSMENT:</td>
<td>Measures: Sexual function assessment, Sexual desire disorder, Sexual arousal disorder, Orgasm dysfunction, Premature ejaculation, patient rated overall sexual satisfaction on 6 point Likert scale</td>
<td></td>
</tr>
<tr>
<td>Timing of assessments: Baseline, weeks 1, 2, 3, 4, 6, 8, 12, 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RESULTS:</td>
<td>Significantly more sertraline patients developed a sexual dysfunction compared to bupropion patients; p &lt; 0.001 for men and women p &lt; 0.05 for sexual desire disorder</td>
<td></td>
</tr>
<tr>
<td>Overall sexual satisfaction (patient-rated) significantly more improved in bupropion treated patients. Men (p &lt; 0.05) significant difference at day 21, 28, 42, and 56. Women (p &lt; 0.01) beginning at day 56 and continuing to end</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANALYSIS:</td>
<td>ITT: Yes</td>
<td></td>
</tr>
<tr>
<td>Post randomization exclusions: Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTRITION:</td>
<td>Loss to follow-up: 31.5%; bupropion: 29%, sertraline: 34%</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to adverse events: 1.6%; bupropion 0%, sertraline 1.6%</td>
<td>Loss to follow-up differential high: Yes</td>
<td></td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 10

### Adverse Events

| STUDY: | Authors: Thase ME<sup>106</sup>  
|        | Year: 1998  
|        | Country: US  
|        | Study design: Meta-analysis  
|        | Number of patients: 3744  
| FUNDING: | Wyeth-Ayerst Labs; National Institute of Mental Health  
| DESIGN: | To assess the effects of venlafaxine on blood pressure  
| STORIES INCLUDED IN META-ANALYSIS | Original data for the statistical analysis were provided by Wyeth-Ayerst Laboratories.  
| TIME PERIOD COVERED: | Not reported  
| CHARACTERISTICS OF INCLUDED STUDIES: | Acute and continuation phase data from randomized controlled trials comparing venlafaxine with placebo and imipramine. (21 outpatient and 6 inpatient trials at 180 different sites)  
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Meet DSM-III-R criteria for a current principal diagnosis of major depression; score at least 20 on the 21-item HAM-D; have no poorly controlled or serious medical illness |
**CHARACTERISTICS OF INCLUDED INTERVENTIONS:**
- Venlafaxine, imipramine, placebo

**MAIN RESULTS:**

**Acute phase results at 6 weeks:**
- Mean supine DBP: venlafaxine: 78 mmHg, 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 $> 90$ mmHg: venlafaxine: 11.5%, imipramine 7.9 %, placebo 5.7% ($p < 0.001$ venlafaxine vs imipramine and venlafaxine vs placebo, $p = 0.24$ for imipramine vs placebo)

**Continuation Phase Results:**
- Mean supine DBP: no drug effect $p = 0.58$ (actual values not reported)
- 4.5% (21 of 467) of subjects with normal supine DBPs developed elevated readings during this phase and it was significantly higher in the venlafaxine group $p = 0.058$ (actual numbers not reported)
- A significant dose response effect on BP was seen in the venlafaxine group ($p < 0.001$)

**ADVERSE EVENTS:**
- N/A

**COMPREHENSIVE LITERATURE SEARCH STRATEGY:**
- No

**STANDARD METHOD OF APPRAISAL OF STUDIES:**
- No

**QUALITY RATING:**
- Fair
### Evidence Table 10  Adverse Events

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

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures: Supine blood pressure, heart rate and ECG interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of assessments:</td>
<td>Supine BP and heart rate at each study visit, ECG at baseline and last visit</td>
</tr>
</tbody>
</table>

#### RESULTS:
- Greater change in heart rate for duloxetine vs. fluoxetine and paroxetine: mean change of 2.8 bpm for duloxetine vs. -1.0 bpm for fluoxetine (p < 0.01); mean change of 1.0 bpm for duloxetine vs. -1.4 bpm for paroxetine (p < 0.001)
- Duloxetine had slightly lower mean change in systolic BP than fluoxetine (2.3 mm Hg vs. 3.2 mm Hg)
- No statistically significant differences in systolic and diastolic BP for duloxetine vs. fluoxetine or paroxetine
- Mean changes in QTcF and QRS intervals not significantly different for duloxetine vs. paroxetine

<table>
<thead>
<tr>
<th>ANALYSIS:</th>
<th>ITT: Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post randomization exclusions:</td>
<td>at least 7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTRITION:</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up:</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to adverse events:</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy:</td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up differential high:</td>
<td></td>
</tr>
</tbody>
</table>

| ADVERSE EVENTS: | N/A |

<p>| QUALITY RATING: | N/A |</p>
<table>
<thead>
<tr>
<th>Evidence Table 10</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **STUDY:**        | **Authors:** Whyte et al. 2003  
                      **Year:** 2003  
                      **Country:** Australia |
| **FUNDING:**      | NR |
| **DESIGN:**       | **Study design:** Observational-prospective cohort  
                      **Setting:** Hospital (Hunter Area Toxicology Service Database, Australia)  
                      **Sample size:** 538 (284 venlafaxine and other SSRI records) |
| **INTERVENTION:** | **Drug:** Venlafaxine  
                      **Dose:** overdose  
                      **Duration:** N/A  
                      **Sample size:** 51  
                      **Other SSRIs**  
                      **Dose:** overdose  
                      **Duration:** N/A  
                      **Sample size:** 284 |
| **INCLUSION:**    | First time admissions for overdose with an SSRI or TCA |
| **EXCLUSION:**    | Patients who ingested multiple drugs of interest |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | N/A |
| **POPULATION CHARACTERISTICS:** | **Groups similar at baseline:** No, SSRI group was younger and significantly; took more drug; waited longer to present  
                      **Mean age:** VX: 36; SSRI: 29  
                      **Gender:** VX: 68.6%; SSRI: 67% female  
                      **Ethnicity:** NR  
                      **Other population characteristics:** NR |
<table>
<thead>
<tr>
<th>Authors: Whyte et al.</th>
<th>Year: 2003</th>
<th>Country: US</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Primary Outcome Measures: Incidence of seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary Outcome Measures: Serotonin toxicity; ICU admission; life-threatening arrhythmias; heart rate; blood pressure; coma score; ECG measures; time in hospital</td>
</tr>
<tr>
<td>Timing of assessments: N/A</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Significantly more patients overdosing on venlafaxine (13.7%) experienced seizures than patients taking other SSRIs (1.3%) p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>• Significantly more patients overdosing on venlafaxine (29.4%) required ICU admission than patients taking other SSRIs (7.3%) p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>• No other significant differences were found between venlafaxine overdoses and SSRI overdoses</td>
<td></td>
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<table>
<thead>
<tr>
<th>ANALYSIS:</th>
<th>ITT: N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post randomization exclusions: N/A</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTRITION:</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss to follow-up: N/A</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to adverse events: N/A</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to lack of efficacy: N/A</td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up differential high: N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
<th>N/A</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
<th>Good</th>
</tr>
</thead>
</table>
## Evidence Table 11: Subgroups

| STUDY: | **Authors:** Burt VK, et al.  
**Year:** 2005  
**Country:** US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>Eli Lilly</td>
</tr>
</tbody>
</table>
| DESIGN: | **Study design:** Pooled data analysis  
**Number of patients:** 512 (subgroup analysis 114) |
<p>| AIMS OF REVIEW: | To assess the efficacy of duloxetine in depressed women during the years in which most women undergo perimenopause (aged 40-55) |
| STUDIES INCLUDED IN META-ANALYSIS | Two identical but independently conducted double-blinded RCTs |
| TIME PERIOD COVERED: | NR |
| CHARACTERISTICS OF INCLUDED STUDIES: | Randomized, double-blind, parallel-group, placebo controlled trials of duloxetine |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Women 40-55 years of age; MDD; HAM-D score ≥ 15; CGI-S score ≥ 4 |</p>
<table>
<thead>
<tr>
<th>CHARACTERISTICS OF INTERVENTIONS:</th>
<th>Duloxetine 60 mg/d vs. placebo</th>
</tr>
</thead>
</table>
| MAIN RESULTS:                    | • Significantly greater improvement in HAM-D total scores at endpoint for duloxetine vs. placebo (p = 0.001)  
• Estimated probability of response significantly greater for duloxetine vs. placebo: 74.7% vs. 47.0% (p = 0.03)  
• Estimated probabilities of remission were 41.8% vs. 23.4% for duloxetine and placebo, respectively (p < 0.07)  
• Using LOCF analysis, response rates were 58.2% for duloxetine 60 mg/d vs. 32.2% for placebo (p = 0.008); remission rates were 34.6% for duloxetine vs. 18.6% for placebo (p = 0.06) |
<p>| ADVERSE EVENTS:                  | NR                              |
| COMPREHENSIVE LITERATURE SEARCH STRATEGY: | No; analysis of 2 trials |
| STANDARD METHOD OF APPRAISAL OF STUDIES: | Yes |
| QUALITY RATING:                  | Fair                            |</p>
<table>
<thead>
<tr>
<th>Evidence Table 11</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:** | *Authors:* Cassano GB, et al.  
*Year:* 2002  
*Country:* Italy |
| **FUNDING:** | SmithKline Beecham, Ravizza Farmaceutici |
| **DESIGN:** | *Study design:* RCT  
*Setting:* Multi-center (38)  
*Sample size:* 242 |
| **INTERVENTION:** |  
**Drug:**  
**Dose:**  
**Duration:** |  
Paroxetine  
20-40 mg/day  
1 year |  
Fluoxetine  
20-60 mg/day  
1 year |
| **INCLUSION:** | 65 yrs or older; ICD-10 criteria for depression; ≥ 18 on HAM-D-17; mini mental state ≥ 22; Raskin score higher than Covi Anxiety score |
| **EXCLUSION:** | History of seizures; dementia; history of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; clinically relevant progressive disease; depot neuroleptics within 6 months |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Treatments for concomitant systemic diseases; short or intermediate half-life benzodiazepines; temazepam for insomnia |
| **POPULATION CHARACTERISTICS:** | *Groups similar at baseline:* Yes  
*Mean age:* Paroxetine: 75.6, fluoxetine: 74.9  
*Gender* (% female): Paroxetine: 61%, fluoxetine: 50%  
*Ethnicity:* Not reported  
*Other population characteristics:* Duration of present episode was less than 6 months for 60% of patients and more than 1 year for 25%; 40% had already been treated for present episode |
| **Authors:** Cassano GB, et al.  
**Year:** 2002  
**Country:** Italy |
|---|

### OUTCOME ASSESSMENT:

**Measures and timing of assessments:** HAM-D, CGI, Clinical Anxiety Scale at baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52. HAMD responders = score < 10, anxiety responders = CAS score < 8. Cognitive tests: Buschke Selective Reminding Test, Blessed Information and Memory Test, Clifton Assessment Schedule, Cancellation Task Test, Wechsler Paired Word Test, Mini-mental State Examination, baseline, weeks 3, 6, 12, 20, 28, 36, 44, 52.

### RESULTS:

**Cognitive function:**
- Both treatment groups showed significant improvement in cognitive performance on all test scales.
- There were no significant differences between treatment groups and cognitive performance except for the Buschke test at week 3 and 6 where paroxetine showed a significantly greater improvement on a number of tests.

**Depressive symptoms:**
- Both treatment groups significantly improved the HAM-D total scores.
- Paroxetine showed a greater improvement of HAM-D scores during the first 6 weeks (week 3: p < 0.05; week 6: p < 0.002), otherwise there were no differences between the treatment groups.
- A Kaplan Meier analysis evaluating the percentage of responders (HAM-D ≥ 10) over time showed a significant difference in favor of paroxetine (p < 0.03).
- No significant differences on CGI scores.

### ANALYSIS:

**ITT:** No
**Post randomization exclusions:** Not reported.

### ATTRITION:

**Loss to follow-up:** 39.3%; paroxetine: 40.6%, fluoxetine: 37.8%  
**Withdrawals due to adverse events:** 15%  
**Loss to follow-up differential high:** No.

### ADVERSE EVENTS:

- At least 1 adverse event: paroxetine: 27.6%, fluoxetine: 32.8%
- Fluoxetine had significantly more severe adverse events than paroxetine (22 vs. 9; p < 0.02).

### QUALITY RATING:

Fair
<table>
<thead>
<tr>
<th>Evidence Table 11</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Cassano P, et al.  
Year: 2004  
Country: US |
| **FUNDING:**      | NIMH       |
| **DESIGN:**       | Study design: Open trial  
Setting: Not reported  
Sample size: 384 |
| **INTERVENTION:** | Drug: Fluoxetine  
Dose: 20 mg/d  
Duration: 8 weeks |
| **INCLUSION:**    | Outpatients aged 18-65; met criteria for MDD using the DSM-III-R and HAM-D-17 (score 16 or higher at baseline) |
| **EXCLUSION:**    | Pregnancy or lactation, lack of accepted contraceptive method; women of child bearing potential taking a birth control pill; serious suicidal risk; serious and unstable co-morbid illness; seizure disorder with a seizure occurring with the last year; presence of other DSM-III-R diagnoses; schizophrenia; delusional disorder; antisocial personality disorder; mood congruent disorder or mood incongruent disorders |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | Concomitant use of psychotropic drugs |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Not reported  
Mean age: Not reported  
Gender: (% female): 54.6%  
Ethnicity: Not reported  
Other population characteristics: Mean age of onset for MDD was 28.4 +/- 13.1 yrs |
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</thead>
<tbody>
<tr>
<td><strong>OUTCOME ASSESSMENT:</strong></td>
<td><strong>Measures:</strong> HAM-D-17</td>
<td></td>
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<tr>
<td></td>
<td><strong>Timing of assessments:</strong> Baseline and weeks 2, 4, 6, 8</td>
<td></td>
</tr>
<tr>
<td><strong>RESULTS:</strong></td>
<td>• No difference in remission rates between older (&gt; 45 years) and younger (&lt;45 years) women (57.1% vs. 50% ( p = 0.84 ))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No difference in remission rates between older (&gt; 45 years) and younger (&lt;45 years) men (57.2% vs. 49.1% ( p = 0.96 ))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Co-morbid anxiety was a significant predictor of a higher burden of residual depressive symptoms ( p = 0.047 )</td>
<td></td>
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<tr>
<td></td>
<td>• Anxious and non-anxious subtypes of depression did not present age or sex-related differences in outcomes</td>
<td></td>
</tr>
<tr>
<td><strong>ANALYSIS:</strong></td>
<td><strong>ITT:</strong> Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Post randomization exclusions:</strong> Not reported</td>
<td></td>
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<tr>
<td><strong>ATTRITION:</strong></td>
<td><strong>Loss to follow-up:</strong> Not reported</td>
<td></td>
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<tr>
<td></td>
<td><strong>Withdrawals due to adverse events:</strong> Not reported</td>
<td></td>
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<tr>
<td></td>
<td><strong>Loss to follow-up differential high:</strong> Not reported</td>
<td></td>
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<tr>
<td><strong>ADVERSE EVENTS:</strong></td>
<td>Not reported</td>
<td></td>
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<tr>
<td><strong>QUALITY RATING:</strong></td>
<td>Fair</td>
<td></td>
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<tr>
<td>Evidence Table 11</td>
<td>Subgroups</td>
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</tbody>
</table>
| **STUDY:**        | **Authors:** Clayton AH, et al.  
                    **Year:** 2005  
                    **Country:** NR |
| **FUNDING:**      | Pfizer, Inc. |
| **DESIGN:**       | **Study design:** Pooled analysis  
                    **Number of patients:** 673 (338 women, 335 men) |
| **AIMS OF REVIEW:** | To examine the sex differences in efficacy and safety when panic disorder is treated with sertraline or placebo |
| **STUDIES INCLUDED IN POOLED-ANALYSIS** | Four double-blinded RCTs (Pohl et al., 1998; Løndborg et al, 1998; Pollack and Otto, 1998; and Sheikh et al., 2000) |
| **TIME PERIOD COVERED:** | Not reported |
| **CHARACTERISTICS OF INCLUDED STUDIES:** | Double blinded, placebo controlled trials of sertraline: all used a 2-week single-blind period |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** | Adult, 18 years or older, outpatients with panic disorder with or without agoraphobia; at baseline males reported an earlier age of onset (28.1 vs. 30.0 years) shorter duration of disease (8.6 vs. 7.3 years), were younger (36 vs. 40 years) and had higher past histories with alcohol/substance abuse/dependence (substance 14% vs. 6% alcohol 20% vs. 9%) |
| Authors: Clayton AH, et al.  
Year: 2005 |
<table>
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<tbody>
<tr>
<td><strong>CHARACTERISTICS OF INTERVENTIONS:</strong></td>
</tr>
<tr>
<td>2 fixed dose studies 12 weeks in length, 2 flexible dose studies 10 weeks in length</td>
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</table>

<table>
<thead>
<tr>
<th><strong>MAIN RESULTS:</strong></th>
</tr>
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<tbody>
<tr>
<td>• Panic attack frequency- change from baseline males -77% females -82% p = 0.02</td>
</tr>
<tr>
<td>• PDSS total score- change from baseline males -5.79 (0.61) females -6.99 (0.47) p = 0.42</td>
</tr>
<tr>
<td>• Time spent worrying- change from baseline males -61.4% females -72.1% p = 0.01</td>
</tr>
<tr>
<td>• HAM-A total score- change from baseline males -10.74 (0.60) females -10.07 (0.58) p = 0.42</td>
</tr>
<tr>
<td>• Q-LES-Q total score- change from baseline males +8.45 (1.84) females +8.89 (1.43) p = 0.85</td>
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</tbody>
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<tr>
<th><strong>ADVERSE EVENTS:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess over placebo rates of more than 5% in nausea (11% male, 11% female), insomnia (10% male, 5% female), sedation ( 9% male, 2% female) diarrhea (7% male, 14% female) dry mouth (7% male, 3% female) fatigue (5% male, 6% female)</td>
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</table>

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<thead>
<tr>
<th><strong>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</strong></th>
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<tbody>
<tr>
<td>No; analysis of published trials</td>
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<table>
<thead>
<tr>
<th><strong>STANDARD METHOD OF APPRAISAL OF STUDIES:</strong></th>
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<tbody>
<tr>
<td>Not reported</td>
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<tr>
<th><strong>QUALITY RATING:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
</tr>
<tr>
<td>Evidence Table 11</td>
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<tr>
<td>-------------------</td>
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</tbody>
</table>
| STUDY:            | **Authors:** Cornelius JR, et. al.  
**Year:** 1997; Subgroup analysis, 1998; Follow up study, 2000  
**Country:** US |
| FUNDING:          | Not reported |
| DESIGN:           | **Study design:** RCT  
**Setting:** Single-center  
**Sample size:** 51  
  - Subgroup analysis 1998: 17  
  - Follow up study 2000: 31 |
| INTERVENTION:     | **Drug:** Fluoxetine  
**Dose:** 20-40 mg/d  
**Duration:** 12 weeks  
**Placebo:** N/A  
**Duration:** 12 weeks |
| INCLUSION:        | 18-65 years old; DSM-III-R criteria for MDD and alcohol dependence  
  - Subgroup analysis 1998: cocaine abuse by DSM-III |
| EXCLUSION:        | Serious concomitant medical illness; pregnancy; bipolar; schizoaffective; schizophrenia; non-alcohol substance abuse; antidepressant medication within 1 month |
| OTHER MEDICATIONS/INTERVENTIONS: | None reported |
| POPULATION CHARACTERISTICS: | **Groups similar at baseline:** No  
**Mean Age:** 34.8  
**Gender** (female%): 49%  
**Ethnicity:** 47% white, 53% black  
**Other population characteristics:** The fluoxetine group was significantly more depressed on the BDI scale than the placebo group following washout (p < 0.02) |
**Authors:** Cornelius JR, et. al.  
**Year:** 1997, 1998, 2000  
**Country:** US  

| OUTCOME ASSESSMENT: | **Measures:** 24 item HAM-D, BDI, Addiction Severity Index, drinking level  
**Timing of assessments:** Assessments performed weekly  

| RESULTS: |  
- Change in HAM-D score was significantly better for the fluoxetine group than placebo (p < 0.05)  
- Change in BDI score was not significantly different between groups  
- Fluoxetine patients had significantly fewer drinks, number of drinking days, and drinks per day (p < 0.05)  

Subgroup analysis 1998  
- Cocaine abusers showed a significantly worse outcome on HAM-D (p = 0.17) and on BDI (p = 0.001) and multiple measures of alcohol consumption (p = 0.042) compared to non-cocaine abusing alcoholics  

Follow up study 2000  
- HAM-D scores remained significantly lower in the fluoxetine group during the one year follow-up. No additional improvement was reported.  
- Number of days intoxicated decreased in fluoxetine group (p = 0.010)  

| ANALYSIS: | **ITT:** Yes  
**Post randomization exclusions:** No  

| ATTRITION: | **Loss to follow-up:** 10%  
**Withdrawals due to adverse events:** 0  
**Loss to follow-up differential high:** No  

| ADVERSE EVENTS: | No side effects observed  

| QUALITY RATING: | Good  

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<table>
<thead>
<tr>
<th>Evidence Table 11</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:**        | **Authors:** Entsuah AR, et al.  
**Year:** 2001  
**Country:** Not reported |
| **FUNDING:**      | Wyeth |
| **DESIGN:**       | **Study design:** Systematic review  
**Number of patients:** 2045 |
<p>| <strong>AIMS OF REVIEW:</strong> | To detect differences in response and remission rates with respect to age and gender |
| <strong>STUDIES INCLUDED IN META-ANALYSIS</strong> | No systematic literature search |
| <strong>TIME PERIOD COVERED:</strong> | Not reported |
| <strong>CHARACTERISTICS OF INCLUDED STUDIES:</strong> | Double-blind, active-controlled, RCTs |
| <strong>CHARACTERISTICS OF INCLUDED POPULATIONS:</strong> | MDD; ≥ 20 on HAM-D; age 18-85 |</p>
<table>
<thead>
<tr>
<th><strong>Authors:</strong> Entsuah AR, et. al.</th>
<th><strong>Year:</strong> 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country:</strong> Not reported</td>
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</table>

<table>
<thead>
<tr>
<th><strong>CHARACTERISTICS OF INCLUDED INTERVENTIONS:</strong></th>
<th>Venlafaxine, paroxetine, fluoxetine, placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAIN RESULTS:</strong></td>
<td>No significant age by treatment; gender by treatment; or age-by-gender by treatment interactions</td>
</tr>
<tr>
<td><strong>ADVERSE EVENTS:</strong></td>
<td>No differences in adverse events for age or gender subgroups</td>
</tr>
<tr>
<td><strong>COMPREHENSIVE LITERATURE SEARCH STRATEGY:</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>STANDARD METHOD OF APPRAISAL OF STUDIES:</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>QUALITY RATING:</strong></td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Evidence Table 11

### Subgroups

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

| Groups similar at baseline: | Yes |
| HTN (hypertension): VAS (vascular disease); NOVASC (no hypertension, no vascular comorbidity) |
| Mean Age: HTN: 68.6; VASC: 68.9; NOVASC: 67.3 |
| Gender: (% female) HTN: 69%; VASC: 44%; NOVASC: 62% |
| Ethnicity: Not reported |
| Other population characteristics: Not reported |
**Authors:** Krishnan KRR, et. al.
**Year:** 2001
**Country:** US

| **OUTCOME ASSESSMENT:** | **Measures:** HAM-D (change from baseline, > 50% response), HAM-A, CGI-I (1 or 2 = responder), CGI-S  
**Timing of assessments:** Weeks 1, 2, 3, 4, 6, 8, 10, 12 |
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<tbody>
<tr>
<td><strong>RESULTS:</strong></td>
<td>The antidepressant effect of sertraline was not significantly affected by the presence of vascular illness</td>
</tr>
</tbody>
</table>
| **ANALYSIS:**         | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:**        | **Loss to follow-up:** Not reported  
**Withdrawals due to adverse events:** High concomitant medication group: 23.6%; low concomitant medication: 15.7%  
**Loss to follow-up differential high:** Not reported |
| **ADVERSE EVENTS:**   | • Vascular comorbidity was not associated with an increase in the reported severity of adverse events, or premature discontinuation for patients on sertraline  
• Sertraline did not have clinically significant effects on blood pressure or heart rate |
| **QUALITY RATING:**   | **FAIR** (only for subgroup analysis) |
## Evidence Table 11

### 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:
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Paroxetine: 23.5mg</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Fluoxetine: 23.4mg</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td>Sertraline: 72.8mg</td>
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</tbody>
</table>

### INCLUSION:
- 18 years or older; depressive disorder as determined by the primary care physician (PCP); had home telephone

### EXCLUSION:
- Cognitive impairment; lack of reading/writing skills; terminal illness; nursing home resident; actively suicidal; SSRI within past 2 months; other antidepressant therapy; bipolar disorder; pregnancy; lactation

### OTHER MEDICATIONS/INTERVENTIONS:
- Yes

### POPULATION CHARACTERISTICS:
- **Groups similar at baseline:** Yes
- **Mean age:** Paroxetine: 47.2, fluoxetine: 47.1, sertraline: 44.1
- **Gender (% female):** Paroxetine: 76%, fluoxetine: 86%, sertraline: 75%
- **Ethnicity:** (white) Paroxetine: 85%, fluoxetine: 88%, sertraline: 79%; (black) paroxetine: 13%, fluoxetine: 9%, sertraline: 17%; (other) paroxetine: 2%, fluoxetine: 3%, sertraline: 4%
- **Other population characteristics:** (MDD) total: 74%, paroxetine: 71%, fluoxetine: 74%, sertraline: 73%; (dysthymia) total: 18%, paroxetine: 22%, fluoxetine: 17%, sertraline: 18%; (minor depression) total: 8%, paroxetine: 7%, fluoxetine: 9%, sertraline: 9%
| **Authors:** Kroenke K, et al.  
**Year:** 2001  
**Country:**  
**Trial name:** ARTIST |
| --- |
| **OUTCOME ASSESSMENT:** | **Measures:** Computer assisted telephone interview: SF-36, MSC (mental component summary), SCL-20 (symptoms checklist), PRIME-MD (primary care Evaluation of mental disorders), subscales of: medical outcomes study questionnaire (MOS): patient health questionnaire, health and daily living form, quality of social interaction scale, quality of close relationship scale, work limitations questionnaire  
**Timing of assessments:** Months 1, 3, 6, 9 |
| **RESULTS:** | • All 3 treatment groups showed significant improvements in depression and other health related quality of life domains (social function, work function, physical function)  
• There were no significant differences between treatment groups in any of the 3 and 9 months outcome measures  
• Subgroup analysis showed that there were no differences in treatment effects for patients with MDD and for patients older than 60 years  
• Switch rate to other medication: paroxetine: 22%, fluoxetine: 14%, sertraline: 17% |
| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:** | **Loss to follow-up:** 24.3%; paroxetine: 24.8%, fluoxetine: 22.5%, sertraline: 25.7%  
**Withdrawals due to adverse events:** paroxetine: 30%, fluoxetine: 23%, sertraline: 24%  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** | No significant differences in adverse events between treatment groups |
| **QUALITY RATING:** | Fair |
### Evidence Table 11

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

| OUTCOME ASSESSMENT: | **Measures:** HAM-D, Raskin, Covi, CGI, SCL-90  
**Timing of assessments:** Weeks 1, 2, 3, 4, 6, 9, 12 |
| RESULTS: |  
- Subjects with baseline complaints of gastrointestinal symptoms or more severe depression were not more likely to develop gastrointestinal side effects under SSRI treatment  
| ANALYSIS: | **ITT:** No  
**Post randomization exclusions:** Not reported  
| ATTRITION: | **Loss to follow-up:** Not reported  
**Withdrawals due to adverse events:** GI withdrawals: fluoxetine: 5.2%, paroxetine: 0%  
**Loss to follow-up differential high:** No  
| ADVERSE EVENTS: | For this analysis only gastrointestinal side effects were considered  
- Nausea: paroxetine: 28%, fluoxetine: 26%, placebo: 0%  
- Diarrhea: paroxetine: 14%, fluoxetine: 16%, placebo: 7%  
- Weight loss/loss of appetite: paroxetine: 22%, fluoxetine: 8%, placebo: 7%  
| QUALITY RATING: | Fair  |
# Evidence Table 11

## Subgroups

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

### OUTCOME ASSESSMENT:

<table>
<thead>
<tr>
<th>Measures</th>
<th>Timing of assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 item HAM-D, HAM-A, CGI-S, CGI-I, BDI, MADRS, POMS, Q-LES-Q, digit symbol substitution test, SLT</td>
<td>Baseline, week 1, 2, 3, 4, 6, 8, 10, 12</td>
</tr>
</tbody>
</table>

### RESULTS:

- Sertraline and fluoxetine were effective in the relief of depressive symptoms
- There were no significant differences between sertraline and fluoxetine on the primary efficacy measures (HAM-D and CGI)  
  - HAM-D Responders: sertraline: 73%, fluoxetine: 71%
  - HAMD remitters: sertraline: 45%, fluoxetine: 46%
- Overall there was no significant differences between sertraline and fluoxetine on cognitive measures (SLT and digit symbol substitution test)

### ANALYSIS:

- **ITT:** Yes
- **Post randomization exclusions:** Yes

### ATTRITION:

- **Loss to follow-up:** 32.2%; sertraline: 31.6%, fluoxetine: 32.8%
- **Withdrawals due to adverse events:** sertraline: 18.8%, fluoxetine: 24.4%, p = 0.5
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- Weight reduction: sertraline: -1.7lb, fluoxetine: -3.2lb (p = 0.018)
- Otherwise no statistically significant differences between groups
- Headache: sertraline: 33.6%, fluoxetine: 31.4%
- Dizziness: sertraline: 7.8%, fluoxetine: 10.2%
- Dry mouth: sertraline: 15.5%, fluoxetine: 7.6%
- Nausea: sertraline: 14.7%, fluoxetine: 18.6%
- Diarrhea: sertraline: 22.4%, fluoxetine: 16.1%

### QUALITY RATING:

Fair
## Evidence Table 11

### Subgroups

| STUDY: | Authors: Petrakis I, et. al.  
Year: 1998  
Country: US |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNDING:</td>
<td>National Institute on Drug Abuse</td>
</tr>
</tbody>
</table>
| 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:** US

| OUTCOME ASSESSMENT: | Measures: BDI, HAM-D (Hamilton Depression Rating Scale), ASI (addiction severity index)  
Timing of assessments: Weekly, weeks 4, 8, 12, urine samples weekly |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------|

**RESULTS:**
- BDI and HADRS scores decreased significantly in both groups ($z = 2.37; p = 0.01; z = 5.85, p < 0.01$). There were no significant differences between placebo and fluoxetine treated patients.
- Concomitant heroin use and ASI scores decreased significantly for both groups ($z = 2.92, p < 0.01; z = 2.66, p < 0.01$) but there was no significant difference between groups

**ANALYSIS:**

- **ITT:** No  
- **Post randomization exclusions:** Not reported

**ATTRITION:**

- **Loss to follow-up:** 15.9%; fluoxetine: 13%, placebo: 19%  
- **Withdrawals due to adverse events:** Not reported  
- **Loss to follow-up differential high:** No

**ADVERSE EVENTS:**

- All fluoxetine discontinuations due to possible treatment-related adverse events

**QUALITY RATING:**

- Fair
Evidence Table 11  Subgroups

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

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

<table>
<thead>
<tr>
<th>Evidence Table 11</th>
<th>Subgroups</th>
</tr>
</thead>
</table>

| STUDY: | Authors: Rapaport MH, et al.\textsuperscript{217}  
Year: 2003  
Country: US and Canada |
| FUNDING: | GlaxoSmithKline |
| DESIGN: | Study design: RCT  
Setting: Multi-center (29 US and 2 Canadian sites)  
Sample size: 323 |
| INTERVENTION: | Paroxetine CR  
Dose: 12.5-50 mg/d  
Duration: 12 weeks  
Paroxetine IR  
Dose: 10-40 mg/d  
Duration: 12 weeks  
Placebo  
Duration: N/A  
Placebo  
Duration: 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 ≤8 weeks with spontaneous remission; neurologic disorders contributing to secondary depression; dementia; Mini-Mental State Examination score ≤24; serious medical conditions that would preclude paroxetine administration; history of seizure disorders; concomitant treatment with warfarin, phenytoin, 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% |
<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Measures: Change from baseline to endpoint in 17-item HAM-D total score; CGI-S; CGI-I all visits except baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Timing of assessments: Baseline, weeks 1, 2, 3, 4, 6, 8, 10, 12</td>
</tr>
<tr>
<td>RESULTS:</td>
<td>Both paroxetine IR and paroxetine CR had significantly higher rates of response and remission than placebo</td>
</tr>
<tr>
<td></td>
<td>No significant differences in any efficacy measures between paroxetine IR and paroxetine CR (HAM-D, CGI-I)</td>
</tr>
<tr>
<td>ANALYSIS:</td>
<td>ITT: Yes</td>
</tr>
<tr>
<td></td>
<td>Post randomization exclusions: Yes (4)</td>
</tr>
<tr>
<td>ATTRITION:</td>
<td>Loss to follow-up: 24%</td>
</tr>
<tr>
<td></td>
<td>Withdrawals due to adverse events: Paroxetine CR=13 (12.5%); paroxetine IR=17 (16.0%); placebo=9 (8.3%)</td>
</tr>
<tr>
<td></td>
<td>Loss to follow-up differential high: No</td>
</tr>
<tr>
<td>ADVERSE EVENTS:</td>
<td>The most common events reported in &gt; 10% of patients were somnolence, dry mouth, headache, abnormal ejaculation, diarrhea, asthenia, nausea, constipation, dyspepsia and decreased appetite</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>QUALITY RATING:</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Evidence Table 11

<table>
<thead>
<tr>
<th><strong>Subgroups</strong></th>
</tr>
</thead>
</table>
| **STUDY:** | Authors: Razavi D, et. al.  
Year: 1996  
Country: Europe |
| **FUNDING:** | Eli Lilly |
| **DESIGN:** | Study design: RCT  
Setting: Multi-center  
Sample size: 91 |
| **INTERVENTION:** |  
**Drug:**  
Fluoxetine  
Placebo  
**Dose:**  
20 mg/day  
N/A  
5 weeks  
5 weeks  
**Duration:**  
5 weeks  
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 granisetron 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:** US

<table>
<thead>
<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>Measures:</th>
<th>MADRS, HAM-D, Hospital Anxiety Scale (HAS), Hospital Anxiety and depression Scale (HADS), Revised Symptom Checklist (SCL90-R), Spitzer Quality of Life Index (SQOLI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Timing of assessments:</strong></td>
<td>Not reported</td>
</tr>
</tbody>
</table>

| RESULTS: | There were no significant differences in efficacy between treatment groups (observer rated scales)  
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Responders (improvement ≥ 50% on HADS): fluoxetine: 18%, placebo: 20%</td>
</tr>
<tr>
<td></td>
<td>Both treatment groups showed significant improvements on all assessment scales compared to baseline</td>
</tr>
<tr>
<td></td>
<td>The improvements were greater for the fluoxetine group but only statistically significant for SCL90-R (p = 0.02)</td>
</tr>
<tr>
<td></td>
<td>Drop out rate was significantly higher in the fluoxetine group (33% vs. 15%; p = 0.04)</td>
</tr>
</tbody>
</table>

| ANALYSIS: | **ITT:** Yes  
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td><strong>Post randomization exclusions:</strong> Not reported</td>
</tr>
</tbody>
</table>

| ATTRITION: | **Loss to follow-up:** 24.2%; fluoxetine: 33%, placebo: 15%  
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Withdrawals due to adverse events:</strong> Fluoxetine: 15.6%, placebo: 0</td>
</tr>
<tr>
<td></td>
<td><strong>Loss to follow-up differential high:</strong> Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS:</th>
<th>Frequency of adverse events did not differ between treatment groups (p = 0.43)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>QUALITY RATING:</th>
<th>Fair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence Table 11</td>
<td>Subgroups</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
</tr>
</tbody>
</table>
| **STUDY:**       | Authors: Roscoe JA, et al.  
Year: 2005  
Country: US |
| **FUNDING:**     | Department of Defense, SmithKline Beecham provided drug and placebo |
| **OBJECTIVE:**   | To evaluate the effect of a serotonin uptake inhibitor on depression and fatigue (both conditions are postulated to share a serotonin link) in a homogeneous sample of breast cancer patients |
| **DESIGN:**      | Study design: RCT  
Setting: University affiliated hospital and 2 of its affiliated hospitals  
Sample size: 94 |
| **INTERVENTION:**| Paroxetine  
Dose: 20 mg/day  
Duration: At least 6 weeks  
Sample size: 44  
Placebo  
N/A  
At least 6 weeks  
50 |
| **INCLUSION:**   | Female patients about to begin or currently undergoing chemotherapy treatment for breast cancer, with at least 4 cycles to be completed |
| **EXCLUSION:**   | Concurrent radiation or interferon treatment; history of seizures or mania taking psychotropic medications; treatment cycles of less than 2 weeks apart |
| **OTHER MEDICATIONS/INTERVENTIONS:** | NR |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: 51.3  
Gender (% female): 100%  
Ethnicity (% white): paroxetine: 93%, placebo 86%  
Other population characteristics:  
Baseline depression (CES-D of 19 or more): paroxetine: 13 (29%), placebo: 13 (26%) |
| **Authors:** Roscoe JA, et al.  
**Year:** 2005 |
|---|---|
| **OUTCOME ASSESSMENT:** | **Primary Outcome Measures:** Fatigue using the Fatigue Symptom Checklist (FSCL), Multidimensional Assessment of Fatigue (MAF) and the Fatigue/Inertia subscale of the Monopolar Profile of Mood States (POMS-FI)  
**Secondary Outcome Measures:** Depression using the CES-D and the Depression/Dejection subscale of the Monopolar Profile of Mood States (POMS-DD)  
**Timing of assessments:** 7th day after each of the 4 chemotherapy treatments |
| **RESULTS:** | • Cycle 4 comparisons of paroxetine versus placebo: mean (SE)  
• CES-D: 8.8 (1.11) vs. 12.6 (1.24)  
• POMS-DD: 1.2 (0.30) vs. 2.2 (0.34)  
• MAF (question 1): 4.6 (0.38) vs. 5.9 (0.37)  
• POMS-FI: 6.0 (0.70) vs. 7.1 (0.79)  
• FSCL: 44.6 (2.41) vs. 48.0 (2.62) |
| **ANALYSIS:** | ITT: No- 122 were randomized, analysis was done on 94 that completed at least 2 cycles  
**Post randomization exclusions:** Yes – 28/122 (23%) |
| **ATTRITION:** | Loss to follow-up: 14/94 (15%)  
**Withdrawals due to adverse events:** NR except in non-completers  
**Withdrawals due to lack of efficacy:** NR  
**Loss to follow-up differential high:** No |
<p>| <strong>ADVERSE EVENTS:</strong> | • 11 patients not in the analysis withdrew because of AEs, primarily headache and nausea (paroxetine: 6, placebo: 5); no other AEs were reported |
| <strong>QUALITY RATING:</strong> | Poor |</p>
<table>
<thead>
<tr>
<th>Evidence Table 11</th>
<th>Subgroups</th>
</tr>
</thead>
</table>
| **STUDY:**        | Authors: Roy-Byrne PP, et al.  
*Year*: 2005  
*Country*: US |
| **FUNDING:**      | NIMH      |
| **DESIGN:**       | Study design: Pooled analysis  
*Number of patients*: 14,875 |
| **AIMS OF REVIEW:** | To explore differences in minorities response and tolerability to paroxetine |
| **STUDIES INCLUDED IN ANALYSIS** | 104 placebo controlled paroxetine trials |
| **TIME PERIOD COVERED:** | Not reported |
| **CHARACTERISTICS OF INCLUDED STUDIES:** | Double blinded, placebo controlled trials of paroxetine at least 6 weeks in length. |
| **CHARACTERISTICS OF INCLUDED POPULATIONS:** | Adult outpatients with: MDD (7603), anxiety disorders GAD, SAD, OCD, PTSD (6156) and PMDD (1116); 63% were women, 89% white, 4% black, 3% Hispanic, 0.9% Asian, 3% unknown or other, mean age 42.3 years |
### CHARACTERISTICS OF INTERVENTIONS:
Paroxetine vs. placebo (104 studies) 10-40 mg/day

### MAIN RESULTS:
- Significant treatment by ethno-racial groups for response (p = 0.014) and full response (p = 0.012)
- Response rates: white- OR 2.1 95% CI 2.0 to 2.3 (p < 0.001), black- OR 2.1 95% CI 1.5 to 3.0 (p < 0.001), Hispanic- OR 1.1 95% CI 0.5 to 2.4 (p = 0.554), Asian- 1.1 95% CI 0.5 to 2.4 (p = .743)
- Hispanics and Asians had a substantially lower response rate than white and black
- Full response rates: white- OR 2.0 95% CI 1.8 to 2.2 (p < 0.001), black- OR 1.6 95% CI 1.1 to 2.4 (p = 0.016), Hispanic- OR 0.9 95% CI 0.6 to 1.5 (p = 0.554), Asian- 2.7 95% CI 1.0 to 2.0 (p = 0.061)
- Asians had the highest rate of “full response” and Hispanics had the lowest

### ADVERSE EVENTS:
Insomnia was the only event to show a significance difference due to a higher rate shown in Asians

### COMPREHENSIVE LITERATURE SEARCH STRATEGY:
No; analysis of published and unpublished trials in GSK database

### STANDARD METHOD OF APPRAISAL OF STUDIES:
Not reported

### QUALITY RATING:
Fair
## Evidence Table 11

<table>
<thead>
<tr>
<th>Subgroups</th>
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</thead>
<tbody>
<tr>
<td><strong>STUDY:</strong></td>
</tr>
<tr>
<td><strong>Authors:</strong> Schatzberg et al. 48</td>
</tr>
<tr>
<td><strong>Year:</strong> 2002</td>
</tr>
<tr>
<td><strong>Country:</strong> US</td>
</tr>
<tr>
<td><strong>FUNDING:</strong></td>
</tr>
<tr>
<td>Organon Pharma</td>
</tr>
<tr>
<td><strong>DESIGN:</strong></td>
</tr>
<tr>
<td><strong>Study design:</strong> RCT</td>
</tr>
<tr>
<td><strong>Setting:</strong> Multi-center</td>
</tr>
<tr>
<td><strong>Sample size:</strong> 255</td>
</tr>
<tr>
<td><strong>INTERVENTION:</strong></td>
</tr>
<tr>
<td><strong>Drug:</strong> Mirtazapine 15-45 mg/d 8 weeks</td>
</tr>
<tr>
<td><strong>Dose:</strong> Paroxetine 20-40 mg/d 8 weeks</td>
</tr>
<tr>
<td><strong>Duration:</strong> (There was extension phase to 16 weeks but only included subjects who had favorable response during the first part of the study)</td>
</tr>
<tr>
<td><strong>INCLUSION:</strong></td>
</tr>
<tr>
<td>Min. age of 65 years; DSM IV criteria for single or recurrent MDD; MMSE score &gt; 25% for age and education; min. score of 18 on HAM-D 17</td>
</tr>
<tr>
<td><strong>EXCLUSION:</strong></td>
</tr>
<tr>
<td>HAMD decrease &gt; 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</td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong></td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong></td>
</tr>
<tr>
<td><strong>Groups similar at baseline:</strong> Yes</td>
</tr>
<tr>
<td><strong>Gender (% female):</strong> Martazapine: 63%, paroxetine: 64%</td>
</tr>
<tr>
<td><strong>Ethnicity:</strong> Not reported</td>
</tr>
<tr>
<td><strong>Other population characteristics:</strong> Not reported</td>
</tr>
</tbody>
</table>
| **Authors:** Schatzberg et al.  
**Year:** 2002  
**Country:** US |
|---|
| **OUTCOME ASSESSMENT:** | **Measures:** HAM-D 17, CGI-S, CGI-I  
**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8 |
| **RESULTS:** | • Mean Ham-D17 scores significantly lower with mirtazapine at week 1, 2, 3, 6 but no difference at 8 week endpoint  
• Trend towards higher response and remission rates with mirtazapine but only significant difference at 2 weeks (response) and 6 weeks (remission)  
• Time to response: mirtazapine mean 26 days, paroxetine 40 days (p = -.016 for Kaplan-Meier plot comparing the two)  
• No difference in CGI Improvement response |
| **ANALYSIS:** | **ITT:** Yes  
**Post randomization exclusions:** Yes |
| **ATTRITION:** | **Loss to follow-up:** 26.8%; mirtazapine 22.7%, paroxetine 31.0%  
**Withdrawals due to adverse events:** 20.4%; mirtazapine 14.8 paroxetine 26.2% (p < 0.05)  
**Loss to follow-up differential high:** No |
| **ADVERSE EVENTS:** | • Frequency of treatment related adverse events: mirtazapine: 79.7%, paroxetine: 82.5%  
• Significant differences: dry mouth: mirtazapine 26.6%, paroxetine 10.3%; weight gain: mirtazapine 10.9%, paroxetine 0%; nausea: mirtazapine 6.3%, paroxetine 19.0% |
<p>| <strong>QUALITY RATING:</strong> | <strong>Fair</strong> |</p>
<table>
<thead>
<tr>
<th>Evidence Table 11</th>
<th>Subgroups</th>
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</table>
| **STUDY:**       | Authors: Schöne W, et al.  
Year: 1993  
Country: Austria and Germany |
| **FUNDING:**     | SmithKline, Beecham |
| **DESIGN:**      | Study design: Randomized, double-blind trial  
Setting: Geriatric outpatients at 6 centers in Austria and Germany  
Sample size: 108 |
| **INTERVENTION:**| Drug:  
Dose:  
Duration: |
| Paroxetine       | Fluoxetine |
| 20-40 mg/d       | 20-60 mg/d |
| 6 weeks          | 6 weeks    |
| **INCLUSION:**   | Age 65 or more; met DSM-IIR for MDD; HAM-D21 score > 18 at baseline |
| **EXCLUSION:**   | Severe physical illness (not specified further); senile dementia; schizophrenia or organic brain syndrome; known abusers of alcohol; receipt of ECT within prior 3 mos.; MAOI or oral neuroleptics within 14 days; depot neuroleptics with 4 wks.; patients whose baseline HAM-D improved by > 20% or whose score was < 18 after placebo run-in |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Prohibited psychotropic meds except temazapam for sleep; other allowed nonpsychotropic medications not specifically reported. |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes  
Mean age: 74, paroxetine: 74.3, fluoxetine: 73.7  
Gender (% female): 87%, paroxetine: 83%, fluoxetine: 90%  
Ethnicity: Not reported  
Other population characteristics: History of prior depression: paroxetine: 94%, fluoxetine: 88%; duration of present episode > 12 months: paroxetine: 24%, fluoxetine: 27% |
**Authors:** Schöne W, et al.  
**Year:** 1993  
**Country:** Germany

### OUTCOME ASSESSMENT:

- **Measures:** HAM-D 21, MADRS, CGI  
- **Timing of assessments:** Days 7, 21, 42

### RESULTS:

- No significant difference in mean changes on HAM-D score  
- HAM-D responders at week 6 (i.e. reduction > 50% from baseline HAM-D21): paroxetine: 37.5%, fluoxetine: 16% (p = 0.03)  
- MADRS: no significant difference in mean change scores between groups  
- MADRS responders at week 6 (i.e. reduction > 50% from baseline MADRS): paroxetine 37.5%, fluoxetine 17.5% (p = 0.04)

### ANALYSIS:

- **ITT:** Yes  
- **Post randomization exclusions:** Yes

### ATTRITION:

- **Loss to follow-up:** Not reported  
- **Withdrawals due to adverse events:** 12%; paroxetine: 11.1%, fluoxetine: 13.5%  
- **Loss to follow-up differential high:** No

### ADVERSE EVENTS:

- No significant differences between paroxetine and fluoxetine on overall incidence of adverse events or of any specific adverse event

### QUALITY RATING:

- Fair
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<th>Evidence Table 11</th>
<th>Subgroups</th>
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| **STUDY:**        | Authors: Thase et al.\textsuperscript{14}  
                  Year: 2005  
                  Country: Multinational |
| **FUNDING:**      | Not reported |
| **DESIGN:**       | Study design: Pooled data from 8 randomized, double-blind, placebo controlled trials  
                  Setting: Various  
                  Sample size: 2045 |
| **INTERVENTION:** | Drug: Venlafaxine  
                  Dose: 75 - 375mg/d  
                  Duration: 6-12 wks  
                  Sample size: 851 |
|                   | SSRIs (fluoxetine, paroxetine, fluvoxamine)  
                  Dose: varying  
                  Duration: 6-12 wks  
                  Sample size: 748 |
|                   | Placebo  
                  Dose: N/A  
                  Duration: 6-12 weeks  
                  Sample size: 446 |
| **INCLUSION:**    | 18 years or older with DSM-IV diagnosed MDD; HAM-D ≥ 20 |
| **EXCLUSION:**    | Malignancies; history of significant or unstable cardiovascular, renal, endocrine or hepatic diseases, seizure disorders; alcohol or substance abuse; pregnant or nursing; any investigational or anti-psychotic drugs. |
| **OTHER MEDICATIONS/ INTERVENTIONS:** | As required |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes, except within the older group men receiving placebo were younger than those taking anti-depressants and within younger male placebo group CGIS were significantly lower.  
                  Mean age: 42  
                  Gender: 64% female  
                  Ethnicity: NR |
**Authors:** Thase et al.  
**Year:** 2005  
**Country:** Multinational

| OUTCOME ASSESSMENT: | Primary Outcome Measures: Remission (HAM-D ≤ 7)  
Timing of assessments: Study days 7,14,21,28,42,56 |
|-------------------|-----------------------------------------------------|
| RESULTS: | • Remission rates on venlafaxine therapy were not affected by age or sex.  
• Poorer SSRI response in the older age group (Wald chi-square = 4.21, df = 1, p = 0.04)  
• With SSRIs, older women age > 50 had a 28% chance of remission compared to younger women, 36% |
| ANALYSIS: | ITT: N/A  
Post randomization exclusions: Cannot tell |
| ATTRITION: | **Loss to follow-up:**  
Withdrawals due to adverse events:  
Withdrawals due to lack of efficacy:  
Loss to follow-up differential high:  
Overall | Mirtazapine | Placebo |
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<tr>
<td>ADVERSE EVENTS:</td>
<td>NR</td>
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<tr>
<td>QUALITY RATING:</td>
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<td>Evidence Table 11 Subgroups</td>
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<td><strong>STUDY:</strong> Authors: Wagner GJ, et. al. Year: 1998 Country: US</td>
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<tr>
<td><strong>FUNDING:</strong> National Institute for Mental Health</td>
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<tr>
<td><strong>DESIGN:</strong> Study design: RCT Setting: Not reported Sample size: 118</td>
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<tr>
<td><strong>INTERVENTION:</strong> Drug: Dose: Duration:</td>
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<tr>
<td>Fluoxetine 20-80 mg/d 8 weeks</td>
<td>Placebo N/A 8 weeks</td>
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<td><strong>INCLUSION:</strong> HIV pos; DSM-IV diagnosis of major depression; under care of HIV physician</td>
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<td><strong>EXCLUSION:</strong> History of psychotic disorders; bipolar disorder; alcohol or substance abuse; existing suicidal risk; unstable medical condition; severe cognitive impairment</td>
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<td><strong>OTHER MEDICATIONS/INTERVENTIONS:</strong> Not reported</td>
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<tr>
<td><strong>POPULATION CHARACTERISTICS:</strong> Groups similar at baseline: Yes Mean Age: 39 Gender (% female): 2% Ethnicity: White: 67%, black: 19%, Latino: 14% Other population characteristics: All HIV +</td>
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<tr>
<td>Authors: Wagner GJ, et. al.</td>
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<td>Year: 1998</td>
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| OUTCOME ASSESSMENT: | Measures: HAM-D, CGI, BSI (Brief Symptom Inventory) |
| Timing of assessments: Not reported |

| RESULTS: |
| Responders in the fluoxetine group among patients who completed study: white: 84%, black: 50%, Latino: 67% |
| Dosages did not differ significantly comparing whites/blacks (p < 0.05) |
| Responders among patients who completed the placebo group: white: 43%, black: 36%, Latino: 80% |
| In a direct linear regression model ethnicity was not a significant predictor of study completion (p = 0.08) |
| Attrition rate was significantly higher among Latinos (p < 0.05), white: 28%, black: 14%, Latino: 52% |
| When adjusting for covariates HAM-D score was only predictor of attrition |

| ANALYSIS: |
| ITT: No |
| Post randomization exclusions: Not reported |

| ATTRITION: |
| Loss to follow-up: white: 38%, black: 14%, Latino: 52% (p < 0.05) |
| Withdrawals due to adverse events: Not reported |
| Loss to follow-up differential high: Yes |

| ADVERSE EVENTS: |
| There was no significant difference in the frequency of adverse events, white: 53%, black: 50%, Latino: 35% |

<p>| QUALITY RATING: |
| Poor |</p>
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<tr>
<th>Evidence Table 11 Subgroups</th>
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| **STUDY:** Authors: Wagner, et. al.\(^{100}\)  
  Year: 2003  
  Country: Multinational |
| **FUNDING:** Pfizer, Inc. |
| **DESIGN:** Study design: Pooled analysis of 2 multi-center, double-blind, placebo-controlled trials  
  Setting: 53 hospital, general practice, academic centers in the US, India, Canada, Costa Rica and Mexico.  
  Sample size: 376 |
| **INTERVENTION:**  
  **Drug:** Sertraline  
  **Dose:** 50-200 mg/d  
  **Duration:** 10 weeks  
  **Placebo:** N/A  
  **Duration:** 10 weeks |
| **INCLUSION:** Ages 6-17 years; met DSM-IV criteria for MDD (as determined by Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, present and lifetime version); current episode of at least 6 weeks duration; minimum score on CDRS-R of 45 and CGI of 4 |
| **EXCLUSION:** Current and primary diagnoses of ADHD; conduct disorder; OCD; panic disorder; history of bipolar disorder; current psychotic features; history of psychotic disorder or autistic spectrum disorder; previous suicide attempts or high suicidal or homicidal risk; abnormal screening EKG, labs, vital signs or body weight; pregnancy; prior enrollment in a sertraline study; medical contraindications to SSRI; history of failure on SSRI; no other psychotropic meds for at least 2 weeks (4 weeks for fluoxetine) |
| **ALLOWED OTHER MEDICATIONS/ INTERVENTIONS:** Chloral hydrate, diphenhydramine as sleep aids |
| **POPULATION CHARACTERISTICS:** Groups similar at baseline: Yes  
  Mean age: Not reported  
  Gender (% female): sertraline: 57.1%, placebo: 44.9%  
  (p = 0.02)  
  Ethnicity: sertraline: white, 71.4%; Asian, 13.8%; Hispanic, 7.9%; black, 3.7%; other, 3.2%  
  placebo: white, 69.5%; Asian, 12.3%; Hispanic, 10.2%; black, 4.8%; other, 3.2%  
  Other population characteristics: Comorbid psychiatric diagnosis: 38% |
**Authors:** Wagner et. al.  
**Year:** 2003  
**Country:** Multinational

**OUTCOME ASSESSMENT:**  
**Measures:** Change in CDRS-R, CDRS-R response ≥ 40% change from baseline, CGI-S score, CGI-I score, and CGI-response (score of 1 or 2), MASC, CGAS, PQ-LES-Q  
**Timing of assessments:** Baseline, weeks 1, 2, 3, 4, 6, 8, 10

**RESULTS:**  
- Mean CDRS-R change (ITT): sertraline: 22.84, placebo: 20.19 (p = 0.007)  
- Mean CDRS-R change (completers): sertraline: 30.24, placebo: 25.83 (p = 0.001)  
- CDRS-responder: sertraline: 69%, placebo: 59% (p = 0.05)  
- Mean CGI: sertraline: 2.56, placebo: 2.75 (p = 0.009)  
- CGI responder: sertraline: 63%, placebo: 53% (p = 0.05)  
- Change in CGI-S: sertraline: 1.22, placebo: 1.01 (p = 0.005)

**ANALYSIS:**  
**ITT:** Yes  
**Post randomization exclusions:** Yes

**ATTRITION:**  
**Loss to follow-up:** 20%; sertraline: 24.4%; placebo: 16.6%  
**Withdrawals due to adverse events:** 5.9%; sertraline: 9%; placebo: 2.7%  
**Loss to follow-up differential high:** No

**ADVERSE EVENTS:**  
- Adverse events that occurred in at least 5% of sertraline treated patients with an incidence at least twice that of placebo: insomnia (19.8% vs. 8%), diarrhea (15.1% vs. 4.5%), vomiting (9.3% vs. 4.5%), anorexia (10.5% vs. 2.3%), agitation (8.1% vs. 2.3%)  
- Serious adverse events (based on pre-defined criteria): sertraline: 7, placebo: 6  
- Mean change in body weight: sertraline: -0.38 kg, placebo: 0.78 kg (p = 0.001)

**QUALITY RATING:** Fair
### Evidence Table 11

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

<table>
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<tr>
<th>OUTCOME ASSESSMENT:</th>
<th>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</th>
</tr>
</thead>
</table>
| RESULTS:            | • No significant differences in any outcome measures between the treatment groups (LOCF and observed)  
|                     | • Response rates (≥ 50% reduction in HAM-D) were similar in both groups: bupropion sr: 71%, paroxetine: 77%  
|                     | • CGIS, CGIi, and HAMA were all similar at each week of the study  
|                     | • No significant differences in the Quality of Life scales (QLDS, SF-36) between treatment groups at endpoint  
|                     | • Overall significant improvement in QLDS and QOL at day 42 (p < 0.0001)  

| ANALYSIS:           | ITT: Yes  
|                     | Post randomization exclusions: Yes |

| ATTRITION:          | Loss to follow-up: 16%; bupropion sr: 16.6%, paroxetine: 15.4%  
|                     | Withdrawals due to adverse events: Bupropion sr: 8.3%, paroxetine: 5.8%  
|                     | Loss to follow-up differential high: No |

| ADVERSE EVENTS:     | • Significantly more patients treated with paroxetine reported somnolence (27% vs. 6%; p < 0.05), diarrhea (21% vs. 6%; p < 0.05), and constipation (15% vs. 4%; p < 0.05)  
|                     | • More than 10% in either group reported headache, insomnia, dry mouth, nausea, dizziness, and agitation  
|                     | • Neither group showed clinically significant changes in weight or clinically significant cardiovascular effects |

<p>| QUALITY RATING:     | Fair |</p>
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<th>Evidence Table 11</th>
<th>Subgroups</th>
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| STUDY:            | Authors: Whittington CJ, et. al.
|                   | Year: 2004
|                   | Country: UK |
| FUNDING:          | NICE (National Institute for Clinical Excellence) |
| DESIGN:           | Study design: Systematic review, SSRI versus placebo
|                   | Number of patients: 2145 |
| AIMS OF REVIEW:   | To evaluate risk versus benefit of SSRI’s when used to treat childhood depression |
| STUDIES INCLUDED IN META-ANALYSIS | Emslie GJ et. al., 1997, Emslie GJ et. al., 2002, Keller MB et. al., 2001, Wagner, KD et. al., 2003. Also unpublished results included in a report by the Committee on Safety of Medicines (UK) |
| TIME PERIOD COVERED: | All studies up to 2003 |
| CHARACTERISTICS OF INCLUDED STUDIES: | Patients randomized to either an SSRI or placebo |
| CHARACTERISTICS OF INCLUDED POPULATIONS: | Included trials had patients aged 5-18 years old; no other population information given |
**Authors:** Whittington CJ, et. al.  
**Year:** 2004  
**Country:** UK

| CHARACTERISTICS OF INCLUDED INTERVENTIONS: | Fluoxetine vs. placebo (2 trials); paroxetine vs. placebo (3 trials); sertraline vs. placebo (2 trials); citalopram vs. placebo (1 trial); venlafaxine vs. placebo (3 trials) |
| MAIN RESULTS: | • Both published and unpublished data demonstrated fluoxetine has a favorable risk-benefit profile  
• Published and unpublished data combined on paroxetine demonstrated it does not improve depressive symptoms and has little effect on response  
• Unpublished data on sertraline in children indicate it is not as effective as reported in published trials  
• One unpublished study of citalopram a negative risk-benefit profile  
• Combined published and unpublished data of venlafaxine suggested a negative risk-benefit profile |
<p>| 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 |</p>
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<th>Evidence Table 11</th>
<th>Subgroups</th>
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| **STUDY:** | Authors: Williams JW, et. al. 
Year: 2000 
Country: US |
| **FUNDING:** | Hartford Foundation, MacArthur Foundation, Smith Kline Beecham supplied meds and placebo, VA (career award to lead author) |
| **DESIGN:** | Study design: RCT 
Setting: Multi-center (Community, VA, and academic primary care clinics) 
Sample size: 415 |
| **INTERVENTION:** | Drug: 
Peroxetine 
Dose: 10-40 mg/d 
Duration: 11 weeks 
Placebo 
Dose: N/A 
Duration: 11 weeks 
Behavior Therapy 
Dose: N/A 
Duration: 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 ≤ 23); medical illness with prognosis ≤ 6 months to live; patients in current treatment excluded unless willing to discontinue and dose ≤ 50 mg of amitriptyline |
| **OTHER MEDICATIONS/INTERVENTIONS:** | Not reported |
| **POPULATION CHARACTERISTICS:** | Groups similar at baseline: Yes 
Mean age: 71 
Ethnicity: (% white) Paroxetine: 82.5%, placebo: 75.7% 
Gender (% female): Paroxetine: 39%, placebo: 45% 
Other population characteristics: Mean of 3.4 medical conditions per patient |
| Authors: Williams JW, et al.  
Year: 2000  
Country: US |
|-----------------|
| **OUTCOME ASSESSMENT:** Measures: Hopkins Symptom Checklist Depression Scale (HSCL-D-20), HDRS, and functional status, by the Medical Outcomes Study Short-Form 36 (SF-36) physical and mental components  
Timing of assessments: Not reported |
| RESULTS: |
| • Mean (SE) decrease in HSCL-D-20:  
  Paroxetine: 0.61 (p = 0.05)  
  Placebo: 0.40 (p = 0.05)  
  Behavior Therapy 0.52 (p = 0.05)  
  (p = 0.004 for paroxetine vs. placebo)  
• Paroxetine only statistically and clinically significantly better than placebo for subjects with dysthymia and high baseline mental health function.  
• HAM-D results not reported for the ITT population |
| ANALYSIS: |
| **ITT:** Yes  
Post randomization exclusions: Yes |
| ATTRITION: |
| **Loss to follow-up:** 25.1% (all three arms, including behavioral tx)  
**Withdrawals due to adverse events:** Paroxetine 8.8%, placebo: 5.7%  
**Loss to follow-up differential high:** No |
| ADVERSE EVENTS: |
| Not reported |
| QUALITY RATING: |
| Fair |
Appendix A. Search Strategy

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

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

#5 Search #1 OR #4 = 11409


#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


#11 Search #10 AND #7 = 89

Longitudinal Studies


#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


#7 Search #2 AND #6 = 86


# 15 Search #14 AND #2 = 63

Total unduplicated records for children = 295.
Appendix B: Quality Assessment

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

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

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

For Controlled Trials:

Assessment of Internal Validity

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

2. Was the treatment allocation concealed?
   - Adequate approaches to concealment of randomization:
     - Centralized or pharmacy-controlled randomization
     - Serially-numbered identical containers
     - On-site computer based system with a randomization sequence that is not readable until allocation
     - Other approaches sequence to clinicians and patients
   - Inferior approaches to concealment of randomization:
     - Use of alternation, case record numbers, birth dates or week days
     - Open random numbers lists
     - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

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

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

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

Assessment of External Validity

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

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

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

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

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

5. **Are the primary studies summarized appropriately?**
   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).
   For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or...
inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.
## Appendix C. Excluded Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample size</th>
<th>Intervention</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive disorder</td>
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<td></td>
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</tr>
<tr>
<td>Aguglia et al., 1993&lt;sup&gt;237&lt;/sup&gt;</td>
<td>RCT</td>
<td>108</td>
<td>Sertraline vs. fluoxetine</td>
<td>High loss to follow-up; High differential loss to follow-up</td>
</tr>
<tr>
<td>Davidson et al., 2002&lt;sup&gt;238&lt;/sup&gt;</td>
<td>Pooled analysis</td>
<td>1097</td>
<td>Venlafaxine vs. fluoxetine</td>
<td>No systematic literature search</td>
</tr>
<tr>
<td>Feiger et al., 2003&lt;sup&gt;239&lt;/sup&gt;</td>
<td>Pooled analysis</td>
<td>1,088</td>
<td>Sertraline vs. fluoxetine</td>
<td>No systematic literature search</td>
</tr>
<tr>
<td>Goldstein et al., 2004&lt;sup&gt;240&lt;/sup&gt;</td>
<td>RCT</td>
<td>353</td>
<td>Duloxetine vs. Paroxetine</td>
<td>High loss to follow-up</td>
</tr>
<tr>
<td>Gorman et al., 2002&lt;sup&gt;241&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td>1,321</td>
<td>Escitalopram vs. citalopram</td>
<td>No systematic literature search</td>
</tr>
<tr>
<td>Llorca et al., 2005&lt;sup&gt;242&lt;/sup&gt;</td>
<td>Pooled analysis</td>
<td>506</td>
<td>Escitalopram vs. citalopram</td>
<td>No systematic literature search</td>
</tr>
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<td>Oslin et al., 2003&lt;sup&gt;243&lt;/sup&gt;</td>
<td>RCT</td>
<td>52</td>
<td>Venlafaxine vs. sertraline</td>
<td>High loss to follow-up</td>
</tr>
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<td>Schmitz et al., 2001&lt;sup&gt;231&lt;/sup&gt;</td>
<td>RCT</td>
<td>68</td>
<td>Fluoxetine vs. placebo</td>
<td>High loss to follow-up</td>
</tr>
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<td>Shelton et al., 2005&lt;sup&gt;244&lt;/sup&gt;</td>
<td>Pooled analysis</td>
<td>1,391</td>
<td>Venlafaxine vs. Fluoxetine and paroxetine</td>
<td>No systematic literature search</td>
</tr>
<tr>
<td>Stahl et al., 2000&lt;sup&gt;245&lt;/sup&gt;</td>
<td>RCT</td>
<td>323</td>
<td>Citalopram vs. sertraline vs. placebo</td>
<td>High loss to follow-up</td>
</tr>
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<td>Stahl et al., 2002&lt;sup&gt;246&lt;/sup&gt;</td>
<td>Pooled analysis</td>
<td>1,622</td>
<td>Venlafaxine fluoxetine paroxetine placebo</td>
<td>No systematic literature search</td>
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<tr>
<td>Thase et al., 2001&lt;sup&gt;247&lt;/sup&gt;</td>
<td>Pooled analysis</td>
<td>2,117</td>
<td>Venlafaxine vs. SSRI vs. placebo</td>
<td>No systematic literature search</td>
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<td>Thase et al., 2005&lt;sup&gt;248&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td>1,975</td>
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<td>Wade et al., 2003&lt;sup&gt;249&lt;/sup&gt;</td>
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<td>197</td>
<td>Mirtazapine vs. paroxetine</td>
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<td>MDD-Ped</td>
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<tr>
<td>DeVane et al., 1996&lt;sup&gt;250&lt;/sup&gt;</td>
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<td>61</td>
<td>Fluoxetine vs. placebo</td>
<td>No systematic literature search</td>
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<td>96</td>
<td>Fluoxetine vs. placebo</td>
<td>Loss to follow-up differential &gt; 15 percentage points</td>
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<td>Emslie et al., 2002&lt;sup&gt;252&lt;/sup&gt;</td>
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<td>Generalized Anxiety Disorder</td>
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<td>RCT</td>
<td>123</td>
<td>Escitalopram vs. paroxetine</td>
<td>High loss to follow-up</td>
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<td>Kelsey et al., 2000&lt;sup&gt;254&lt;/sup&gt;</td>
<td>Pooled analysis</td>
<td>2000</td>
<td>Venlafaxine vs.</td>
<td>No systematic literature search</td>
</tr>
<tr>
<td>Year</td>
<td>Design</td>
<td>N</td>
<td>Treatment</td>
<td>Notes</td>
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<td>Cox et al., 1993&lt;sup&gt;251&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td></td>
<td>Not reported</td>
<td>Clomipramine vs. fluoxetine vs. behavior therapy</td>
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<tr>
<td>Greist et al., 1995&lt;sup&gt;252&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td>1530</td>
<td>Clomipramine vs. fluoxetine vs. fluvoxamine vs. sertraline</td>
<td>No systematic literature search</td>
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<tr>
<td>Kobak et al., 1998&lt;sup&gt;253&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td></td>
<td>Not reported</td>
<td>Fluoxetine vs. fluvoxamine vs. paroxetine vs. sertraline</td>
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<td>Panic</td>
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<tr>
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<td>RCT</td>
<td>148</td>
<td>Fluvoxamine vs. placebo</td>
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<td>PTSD</td>
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<td></td>
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<td></td>
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<tr>
<td>Chung et al., 2004&lt;sup&gt;255&lt;/sup&gt;</td>
<td>Open-label trial</td>
<td>113</td>
<td>Mirtazapine vs. Sertraline</td>
<td>Significant differences in patient characteristics at baseline</td>
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<td>Davidson et al., 1998&lt;sup&gt;256&lt;/sup&gt;</td>
<td>Open-label trial</td>
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<td>Fluvoxamine</td>
<td>Open-label, high loss to follow-up</td>
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<td>Davidson et al., 1998&lt;sup&gt;257&lt;/sup&gt;</td>
<td>Open-label trial</td>
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<td>Nefazodone</td>
<td>Open-label, high loss to follow-up</td>
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<tr>
<td>De Boer et al., 1992&lt;sup&gt;258&lt;/sup&gt;</td>
<td>Open-label trial</td>
<td>24</td>
<td>Fluvoxamine</td>
<td>Open-label, high loss to follow-up</td>
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<td>Martenyi et al., 2002&lt;sup&gt;259,260&lt;/sup&gt;</td>
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<td>301</td>
<td>Fluoxetine vs. placebo</td>
<td>High loss to follow-up</td>
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<tr>
<td>Smajkic et al., 2001&lt;sup&gt;261&lt;/sup&gt;</td>
<td>RCT</td>
<td>40</td>
<td>Sertraline vs. paroxetine vs. venlafaxine</td>
<td>Small sample size, no ITT analysis</td>
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<td>Tucker et al., 2001&lt;sup&gt;262&lt;/sup&gt;</td>
<td>RCT</td>
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<td>Paroxetine vs. placebo</td>
<td>High loss to follow-up</td>
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<tr>
<td>Social Anxiety Disorder</td>
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<td></td>
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<tr>
<td>Allgulander et al., 2001&lt;sup&gt;116&lt;/sup&gt;</td>
<td>RCT</td>
<td>96</td>
<td>Paroxetine vs. placebo</td>
<td>No ITT analysis, lack of statistical comparisons</td>
</tr>
<tr>
<td>PMDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diegoli et al., 1998&lt;sup&gt;263&lt;/sup&gt;</td>
<td>RCT</td>
<td>120</td>
<td>Pyridoxine, alprazolam, fluoxetine, propanolol</td>
<td>Important information about study methodology not reported</td>
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<td>Carr et al., 2002&lt;sup&gt;264&lt;/sup&gt;</td>
<td>Systematic review</td>
<td>NR</td>
<td>Fluoxetine</td>
<td>No critical appraisal of study quality; no description of review process</td>
</tr>
<tr>
<td>Subgroups</td>
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<td></td>
<td></td>
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<tr>
<td>Beasley et al., 1991&lt;sup&gt;265,266&lt;/sup&gt; and Tollefson et al.,</td>
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<td>3,065</td>
<td>Fluoxetine vs. placebo</td>
<td>No systematic literature search</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Design</td>
<td>n</td>
<td>Comparator</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>--------</td>
<td>---</td>
<td>------------</td>
</tr>
<tr>
<td>1994</td>
<td>Gülseren et al. 2005</td>
<td>RCT</td>
<td>25</td>
<td>Fluoxetine vs. paroxetine</td>
</tr>
<tr>
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<td>Roy-Byrne et al.</td>
<td>RCT</td>
<td>64</td>
<td>Nefazodone vs. placebo</td>
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<td>1998</td>
<td>Wagner et al., 1998</td>
<td>RCT</td>
<td>118</td>
<td>Fluoxetine vs. placebo</td>
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</table>

**Adverse Events**

<table>
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<tr>
<th>Year</th>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Comparator</th>
<th>Notes</th>
</tr>
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<tr>
<td>2002</td>
<td>Croft et al., 2002</td>
<td>RCT</td>
<td>432</td>
<td>Bupropion vs. placebo</td>
<td>High loss to follow-up</td>
</tr>
<tr>
<td>2005</td>
<td>Demyttenaere et al.</td>
<td>RCT</td>
<td>85</td>
<td>Escitalopram vs. placebo</td>
<td>No ITT analysis</td>
</tr>
<tr>
<td>2001</td>
<td>Ferguson et al.,</td>
<td>RCT</td>
<td>72</td>
<td>Nefazodone vs. sertraline</td>
<td>Selection bias</td>
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<td>1996</td>
<td>Letizia et al., 1996</td>
<td>Systematic review</td>
<td>3,828</td>
<td>Fluvoxamine vs. TCA vs. placebo</td>
<td>Search strategy not reported; no critical appraisal of study quality</td>
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<td>1997</td>
<td>Wernicke et al., 1997</td>
<td>Meta-analysis</td>
<td>4016</td>
<td>Fluoxetine, placebo, TCA</td>
<td>No systematic literature search</td>
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</table>
## Appendix D. Pharmacokinetic Properties and Drug Interactions

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein Binding</th>
<th>Major Substrate of</th>
<th>Minor Substrate of</th>
<th>Inhibits</th>
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</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>80%</td>
<td>CYP2C19; CYP3A4</td>
<td>CYP2D6</td>
<td>Weak: CYP1A2; CYP2B6; CYP2C19; CYP2D6</td>
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<tr>
<td>Escitalopram</td>
<td>56%</td>
<td>CYP2C19; CYP3A4</td>
<td></td>
<td>Weak: CYP2D6</td>
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<tr>
<td>Fluoxetine</td>
<td>94.5%</td>
<td>CYP2C8/9; CYP2D6</td>
<td>CYP3A4</td>
<td>Strong: CYP2D6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP1A2; CYP2B6;</td>
<td></td>
<td>Moderate: CYP1A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP2C19; CYP2E1;</td>
<td></td>
<td>Weak: CYP2B6; CYP2C8/9; CYP3A4</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>80%</td>
<td>CYP1A2; CYP2D6</td>
<td></td>
<td>Strong: CYP1A2; CYP2C19; CYP2D6; CYP2C8/9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weak: CYP2B6; CYP3A4; CYP2D6; CYP2C8/9</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>95%</td>
<td>CYP2D6</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate: CYP1A2; CYP2C19; CYP2C8/9; CYP3A4</td>
</tr>
<tr>
<td>Sertraline</td>
<td>98%</td>
<td>CYP2C19; CYP2D6</td>
<td>CYP3A4</td>
<td>Moderate: CYP2C19; CYP2D6; CYP2B6; CYP3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP2C8/9; CYP3A4</td>
<td></td>
<td>Weak: CYP1A2; CYP2C8/9</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>85%</td>
<td>CYP1A2; CYP2D6;</td>
<td>CYP3A4</td>
<td>Weak: CYP1A2; CYP3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP2C8/9</td>
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<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>27%</td>
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<td>Weak: CYP2B6; CYP2D6</td>
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<td></td>
<td>CYP2C8/9; CYP2C19</td>
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<tr>
<td>Bupropion</td>
<td>84%</td>
<td>CYP2C8/9</td>
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<td>Weak: CYP2D6</td>
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<td></td>
<td>CYP2E1; CYP3A4</td>
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<tr>
<td>Nefazodone</td>
<td>&gt;99%</td>
<td>CYP2D6; CYP3A4</td>
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<td></td>
<td></td>
<td></td>
<td>Weak: CYP1A2; CYP2B6; CYP2D6</td>
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</table>

*Pharmacokinetic properties abstracted from Lexi-Comp online (licensed by the University)*
# Clinically Significant Drug Interactions: SSRIs

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Citalopram</th>
<th>Escitalopram</th>
<th>Fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Monitor (1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Monitor (2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Monitor (3)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Cimetidine</td>
<td>Monitor (1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Monitor (2)&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Clozapine</td>
<td></td>
<td>Monitor (3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Monitor (3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>No significant interaction (1)</td>
<td>No significant interaction (2)</td>
<td>Monitor (3)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td>Monitor (3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Ketoconazole</td>
<td>Monitor (1)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Monitor (2)&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Lithium</td>
<td>Monitor (1)</td>
<td>Monitor (2)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Monitor (3)</td>
</tr>
<tr>
<td>MAOIs</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
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<tr>
<td>Metoprolol</td>
<td>Monitor (1)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Monitor (2)&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Phenytoin</td>
<td>Monitor (3)&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Pimozide</td>
<td>Monitor (3)&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Sumatriptan</td>
<td>Monitor (1)</td>
<td>Monitor (2)</td>
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<td>Ritonavir</td>
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<td>Monitor (1)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Monitor (2)</td>
<td>Monitor (3)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>No significant interaction (1)</td>
<td>No significant interaction (2)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Thioridazine</td>
<td></td>
<td></td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Triazolam</td>
<td>No significant interaction (1)</td>
<td>No significant interaction (2)</td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td></td>
<td></td>
<td>Monitor (3)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Monitor (1)</td>
<td>Monitor (2)</td>
<td>Monitor (3)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Decrease in second generation antidepressant plasma levels
<sup>b</sup>Increase in second generation antidepressant plasma levels
<sup>c</sup>Decrease in plasma levels for the interacting drug or its active metabolite
<sup>d</sup>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

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Fluvoxamine</th>
<th>Paroxetine</th>
<th>Sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Monitor (4)^c</td>
<td>Monitor (5)^d</td>
<td>No significant interaction (6)</td>
</tr>
<tr>
<td>Atenolol</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Monitor (4)^c</td>
<td>Monitor (5)^d</td>
<td>Monitor (6)^d</td>
</tr>
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<td>Diazepam</td>
<td>Monitor (5)</td>
<td>Monitor (5)</td>
<td>Monitor (6)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Monitor (5)^c</td>
<td>Monitor (6)^d</td>
<td>Monitor (6)^d</td>
</tr>
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<td>Lithium</td>
<td>Monitor (5)</td>
<td>Monitor (5)</td>
<td>Monitor (6)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>No significant interaction (4)</td>
<td>Monitor (5)</td>
<td>Monitor (6)</td>
</tr>
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<td>MAOIs</td>
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<td>Contraindicated (6)</td>
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<tr>
<td>Phenobarbital</td>
<td>Monitor (5)</td>
<td>Monitor (5)</td>
<td>Monitor (5)</td>
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<tr>
<td>Phenytoin</td>
<td>Monitor (5)</td>
<td>Monitor (5)</td>
<td>Monitor (5)</td>
</tr>
<tr>
<td>Pimozide</td>
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<td>Contraindicated (6)</td>
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<td>Procyclidine</td>
<td>Monitor (5)^d</td>
<td>Monitor (5)^d</td>
<td>Monitor (6)^d</td>
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<td>Propranolol</td>
<td>No significant interaction (5)</td>
<td>Monitor (5)</td>
<td>Monitor (6)</td>
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<td>Triptans</td>
<td>Monitor (5)</td>
<td>Monitor (5)</td>
<td>Monitor (6)</td>
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<td>Monitor (5)</td>
<td>Monitor (5)</td>
<td>Monitor (6)</td>
</tr>
<tr>
<td>Temazepam</td>
<td>No significant interaction (4)</td>
<td>Monitor (5)^d</td>
<td>Monitor (6)^d</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Monitor (4)^c</td>
<td>Monitor (5)^d</td>
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<tr>
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<td>Contraindicated (5)</td>
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<td>Monitor (5)^d</td>
<td>Monitor (6)^d</td>
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<td>Tryptophan</td>
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<td>Monitor (5)</td>
<td>Monitor (6)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Monitor (4)^d</td>
<td>Monitor (5)^d</td>
<td>Monitor (6)^d</td>
</tr>
</tbody>
</table>

^aDecrease in second generation antidepressant plasma levels
^bIncrease in second generation antidepressant plasma levels
^cDecrease in plasma levels for the interacting drug or its active metabolite
^dIncrease in plasma levels for the interacting drug or its active metabolite

1. Fluvoxamine package insert
2. Paroxetine package insert
3. Sertraline package insert
Clinically Significant Drug Interactions: Mirtazapine, Venlafaxine

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Mirtazapine</th>
<th>Venlafaxine</th>
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<tbody>
<tr>
<td>Alprazolam</td>
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<td>Cimetidine</td>
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<td>Ciprofloxacin</td>
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<td>Diazepam</td>
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<td>Erythromycin</td>
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<td>Haloperidol</td>
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<tr>
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<td>Monitor (8)$^c$</td>
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<tr>
<td>Ketoconazole</td>
<td>Monitor (7)$^b$</td>
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<tr>
<td>Lithium</td>
<td></td>
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<tr>
<td>Lorazepam</td>
<td>Monitor (7)</td>
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<tr>
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<td>Contraindicated (7)</td>
<td>Contraindicated (8)</td>
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<tr>
<td>Phenobarbital</td>
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<td>Phenytoin</td>
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<td>Risperidone</td>
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<td>Triazolam</td>
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</table>

$^a$ 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

<table>
<thead>
<tr>
<th>Interacting Drug</th>
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<th>Nefazodone</th>
</tr>
</thead>
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<td>Alprazolam</td>
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<tr>
<td>Amantadine</td>
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<tr>
<td>Atenolol</td>
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<td>Buspirone</td>
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<td>Carbamazepine</td>
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<td>Cimetidine</td>
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<td>Cyclosporine</td>
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<tr>
<td>Digoxin</td>
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<td>Flecaainide</td>
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<td>Haloperidol</td>
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<td>HMG-CoA Reductase Inhibitors</td>
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<tr>
<td>Lorazepam</td>
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<td>MAOIs</td>
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<td>Contraindicated (10)</td>
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<td>Pimozide</td>
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<td>Propafenone</td>
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<td>Propranolol</td>
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<td>Tacrolimus</td>
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<td>Thioridazine</td>
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</tr>
<tr>
<td>Triazolam</td>
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<td>Contraindicated (10)</td>
</tr>
</tbody>
</table>

**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) Bupropion  
(10) Nefazodone
Appendix E. Placebo-controlled Trials (not included)


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the treatment of panic disorder. A multi-site, double-blind, placebo-controlled, fixed-dose

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imipramine, and placebo in the treatment of depressed outpatients: effects on depression.

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Treatment for the Emotional and Physical Symptoms of Depression. Prim Care

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Appendix F. Abstract-only Studies (not included)


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Appendix G: Acknowledgements

Reviewers

We gratefully acknowledge the following individuals who reviewed the initial draft of this report and provided us with valuable and constructive feedback.

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