

Drug Class Review on Second Generation Antidepressants

Update #5: Preliminary Scan Report #1

November 2009

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. RTI-UNC Evidence-based Practice Center does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Report

October 2008 (searches through April 2008)

Scope and Key Questions

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 key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

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?

Inclusion criteria**Populations**

- Outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders

Interventions

Eleven antidepressant agents are being evaluated:

- Citalopram
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline
- Mirtazapine
- Duloxetine
- Venlafaxine
- Bupropion
- Nefazodone

Additional antidepressant agents being evaluated:

- Desvenlafaxine (FDA approved February 2008)

Efficacy/Effectiveness outcomes

- Response
- Remission
- Speed of response/remission
- Relapse
- Quality of life
- Functional capacity
- Hospitalization

Harms outcomes

- 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

METHODS

Literature Search

To identify relevant citations, we searched PubMed from April 2008 through November 11, 2009 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/index_e.html) Web sites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X.02) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 127 citations. Of those, there are 26 new potentially relevant RCTs (Appendix A).

A supplemental search was conducted for Desvenlafaxine, resulting in 26 citations. Three of the citations were captured in the initial search and are potentially relevant RCTs. Of the remaining 23 citations, there are 6 new potentially relevant RCTs (Appendix B).

New Drugs

Desvenlafaxine (Pristiq™), a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD). Pristiq extended-release oral tablets are available as 50 and 100 mg doses. Each tablet contains 76 or 152 mg of desvenlafaxine succinate equivalent to 50 or 100 mg of desvenlafaxine, respectively. Pristiq is not approved for use in pediatric patients.

New Safety Alerts

None at this time.

Appendix A. Abstracts of potentially relevant new studies of Second Generation Antidepressants

1. Allgulander, C., D. Nutt, et al. (2008). "A non-inferiority comparison of duloxetine and venlafaxine in the treatment of adult patients with generalized anxiety disorder." *J Psychopharmacol* 22(4): 417-25.

The present study is a non-inferiority comparison of duloxetine 60-120 mg/day and venlafaxine extended-release (XR) 75-225 mg/day for the treatment of adults with generalized anxiety disorder (GAD). The non-inferiority test was a prespecified plan to pool data from two nearly identical 10-week, multicentre, randomized, placebo-controlled, double-blind studies of duloxetine 60-120 mg/day and venlafaxine 75-225 mg/day for the treatment of GAD. An independent expert consensus panel provided six statistical and clinical criteria for determining non-inferiority between treatments. Response was defined as $>$ or $=50\%$ reduction in Hamilton Anxiety Rating Scale (HAMA) total score. In the pooled sample, patients were randomly assigned to duloxetine ($n = 320$), venlafaxine XR ($n = 333$) or placebo ($n = 331$). For the non-inferiority analysis, the per-protocol patients who were treated with duloxetine ($n = 239$) or venlafaxine XR ($n = 262$) improved significantly more (mean HAMA reductions were -15.4 and -15.2 , respectively) than placebo-treated patients ($n = 267$; -11.6 , $P < \text{or} = 0.001$, both comparisons). Response rates were 56% , 58% and 40% , respectively. Discontinuation rate because of AEs was significantly higher for duloxetine (13.4% , $P < \text{or} = 0.001$) and venlafaxine XR (11.4% , $P < \text{or} = 0.01$) groups compared with placebo (5.4%). Duloxetine 60-120 mg/day met all statistical and clinical criteria for non-inferiority and exhibited a similar tolerability profile compared with venlafaxine XR 75-225 mg/day for the treatment of adults with GAD.

2. Altamura, A. C., B. Dell'Osso, et al. (2008). "Intravenous augmentative citalopram versus clomipramine in partial/nonresponder depressed patients: a short-term, low dose, randomized, placebo-controlled study." *J Clin Psychopharmacol* 28(4): 406-10.

The aim of the present study was to evaluate the efficacy of short-term low-dose intravenous augmentative citalopram (10 mg/d) versus clomipramine (25 mg/d) versus placebo in a sample of patients with MDE and partial or no response to selective serotonin reuptake inhibitors (SSRIs). Fifty-four patients with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, MDE and partial or no response to SSRIs per os (21-item Hamilton Depression Rating Scale [HAM-D21] score reduction, $<50\%$ or $<$ or $=25\%$, respectively, compared with pretreatment scores) were selected and randomized to citalopram ($n = 18$), clomipramine ($n = 18$), or placebo ($n = 18$) intravenous augmentation. The augmentation regimen lasted 5 days during which patients were maintained on their previous treatment with oral SSRIs. Analyses of variance with repeated measures on HAM-D(21), collected daily in blind-raters design, were performed to detect any change of depressive symptoms between the 3 groups. In addition, the number of responders and remitters was computed in the 3 groups of treatment. At end point, a significant treatment effect ($F = 4.57$; $P = 0.015$) and time-by-treatment effect ($F = 11.22$; $P < 0.0001$) were found on HAM-D21 total scores in favor of citalopram and clomipramine versus placebo, with a superiority of citalopram over clomipramine on overall symptoms ($P = 0.05$) as well as on anxiety-somatization symptoms ($P = 0.027$). The number of responders was significantly superior in the active treatment groups versus the placebo group ($[\chi^2](2) = 16.36$; $P < 0.0001$). The same result was found, considering the number of

remitters ($[\chi^2](2) = 13.50; P < 0.0001$). Present findings suggest that both clomipramine and citalopram intravenous augmentation at low doses and for a short period are well tolerated and superior to placebo in major depressives with partial or no response to oral SSRIs with a possible superiority of citalopram over clomipramine with regard to anxiety-somatization symptoms. The lack of double-blind conditions and the limited sample size may limit the confidence in the reported results, and larger randomized controlled trials are warranted to confirm the present findings.

3. Boyer, P., S. Montgomery, et al. (2008). "Efficacy, safety, and tolerability of fixed-dose desvenlafaxine 50 and 100 mg/day for major depressive disorder in a placebo-controlled trial." *Int Clin Psychopharmacol* 23(5): 243-53.

The objective of this study was to assess the efficacy, safety, and tolerability of desvenlafaxine (administered as desvenlafaxine succinate) 50 and 100 mg/day for major depressive disorder (MDD). A multicenter, randomized, double-blind, placebo-controlled trial was conducted in Europe and South Africa. Outpatients with MDD received fixed-dose desvenlafaxine (50 or 100 mg/day) or placebo for 8 weeks. The primary efficacy variable was the 17-item Hamilton Rating Scale for Depression total score; secondary measures included Clinical Global Impressions-Improvement scores. The intent-to-treat population included 483 patients: desvenlafaxine 50 mg (n=164), desvenlafaxine 100 mg (n=158), and placebo (n=161). At the last-observation-carried-forward analysis (final evaluation) using analysis of covariance, adjusted mean changes from baseline on the Hamilton Rating Scale for Depression were significantly greater for both desvenlafaxine 50 mg (-13.2; P=0.002) and 100 mg (-13.7; P<0.001) versus placebo (-10.7). Significant differences on the Clinical Global Impressions-Improvement scores were observed for desvenlafaxine 50 mg (P=0.002) and 100 mg (P<0.001) versus placebo. Both doses of desvenlafaxine were generally well tolerated. The most common treatment-emergent adverse events were nausea, dizziness, insomnia, constipation, fatigue, anxiety, and decreased appetite. Fixed doses of desvenlafaxine 50 and 100 mg/day are safe, generally well tolerated, and effective at a clinically relevant level for the treatment of MDD.

4. Cipriani, A., T. A. Furukawa, et al. (2008). "Does randomized evidence support sertraline as first-line antidepressant for adults with acute major depression? A systematic review and meta-analysis." *J Clin Psychiatry* 69(11): 1732-42.

OBJECTIVE: Preliminary evidence suggested that sertraline might be slightly superior to other antidepressant medications in terms of efficacy. The aim of this study was to carry out a systematic review and meta-analysis to compare sertraline with any other antidepressant in the acute phase treatment of major depression at 8 weeks. **DATA SOURCES:** MEDLINE; EMBASE; the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register; and the Cochrane Central Register of Controlled Trials up to August 2007. No language restriction. The following search strategy was used: diagnosis = depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms, and intervention (or free text) = sertraline. Reference lists of relevant papers and previous systematic reviews were hand-searched. Pharmaceutical companies and experts in this field were contacted for supplemental data. **STUDY SELECTION:** Only randomized controlled trials allocating patients with major depression to sertraline versus any other antidepressant agent. **DATA EXTRACTION:** Three reviewers independently extracted data. A double-entry procedure was employed by 2 reviewers. To analyze data, a very conservative approach with a 99% confidence

interval (CI) and a random effects model was used. Information extracted included study characteristics, participant characteristics, intervention details, and outcome measures, such as the number of patients who responded to treatment and the number of patients who failed to complete the study by any cause at 8 weeks. **DATA SYNTHESIS:** This systematic review and meta-analysis found that sertraline is statistically significantly better than fluoxetine (relative risk [RR] = 0.85, 99% CI = 0.74 to 0.98; number needed to treat [NNT] = 12) and other SSRIs as a class (RR = 0.88, 99% CI = 0.78 to 0.99; NNT = 17) and highlighted a consistent even though not statistically significant trend in favor of sertraline over many other antidepressants both in terms of efficacy and acceptability in a homogeneous and clinically relevant time frame of 8 weeks. **CONCLUSIONS:** The results of this review suggest that sertraline may be a candidate as the initial choice of antidepressant for people with major depression.

5. Cipriani, A., T. A. Furukawa, et al. (2009). "Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis." *Lancet* 373(9665): 746-58.

BACKGROUND: Conventional meta-analyses have shown inconsistent results for efficacy of second-generation antidepressants. We therefore did a multiple-treatments meta-analysis, which accounts for both direct and indirect comparisons, to assess the effects of 12 new-generation antidepressants on major depression. **METHODS:** We systematically reviewed 117 randomised controlled trials (25 928 participants) from 1991 up to Nov 30, 2007, which compared any of the following antidepressants at therapeutic dose range for the acute treatment of unipolar major depression in adults: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine. The main outcomes were the proportion of patients who responded to or dropped out of the allocated treatment. Analysis was done on an intention-to-treat basis. **FINDINGS:** Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine (odds ratios [OR] 1.39, 1.33, 1.30 and 1.27, respectively), fluoxetine (1.37, 1.32, 1.28, and 1.25, respectively), fluvoxamine (1.41, 1.35, 1.30, and 1.27, respectively), paroxetine (1.35, 1.30, 1.27, and 1.22, respectively), and reboxetine (2.03, 1.95, 1.89, and 1.85, respectively). Reboxetine was significantly less efficacious than all the other antidepressants tested. Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine. **INTERPRETATION:** Clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline. Sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it has the most favourable balance between benefits, acceptability, and acquisition cost.

6. Clayton, A. H., S. G. Kornstein, et al. (2009). "An integrated analysis of the safety and tolerability of desvenlafaxine compared with placebo in the treatment of major depressive disorder." *CNS Spectr* 14(4): 183-95.

INTRODUCTION: The safety and tolerability profiles of antidepressants can often influence the treatment choices of clinicians treating major depressive disorder. The purpose of this investigation was to characterize the safety and tolerability of desvenlafaxine (administered as desvenlafaxine succinate) in treating depression. **METHODS:** An integrated analysis of all short-term, randomized, double-blind, placebo-controlled registration studies for major

depressive disorder (four flexible-dose and five fixed-dose studies) was performed. Adult outpatients with major depressive disorder received desvenlafaxine doses ranging from 50-400 mg/day or placebo for 8 weeks. Treatment-emergent adverse events, laboratory values, vital signs, and discontinuation symptoms were evaluated. In the subset of fixed-dose studies, dose-related effects were analyzed. **RESULTS:** In the overall population (placebo: n=1,116; desvenlafaxine: n=1,834), adverse events resulted in discontinuations in 3% of placebo-treated patients and 12% of desvenlafaxine-treated patients; in the subset of fixed-dose studies, the rates were 4% with placebo and increased with desvenlafaxine dose (50 mg/day: 4%; 400 mg/day: 18%). The most common treatment-emergent adverse event was transient nausea that was generally mild to moderate. The most common sexual dysfunction associated with desvenlafaxine treatment was erectile dysfunction in men (7% vs 1% with placebo) and anorgasmia in women (1% and 0%). One desvenlafaxine-treated patient died of a completed suicide; there were four suicide attempts (three desvenlafaxine, one placebo) and eight cases of suicidal ideation (five desvenlafaxine, three placebo) during the on-therapy period. Small but statistically significant changes in mean blood pressure occurred at all desvenlafaxine doses; clinically meaningful changes were observed in 1% of placebo-treated patients and 2% of desvenlafaxine-treated patients. Desvenlafaxine was associated with small but statistically significant mean changes in laboratory assessments, particularly lipid and liver enzyme elevations, and electrocardiograms; few cases of these changes were clinically relevant. **CONCLUSION:** Desvenlafaxine in the treatment of major depressive disorder exhibited a safety and tolerability profile generally consistent with the serotonin-norepinephrine reuptake inhibitor class. The most common adverse event was transient nausea. At the recommended therapeutic dose of 50 mg/day, discontinuation due to adverse events was similar to placebo.

7. Cutler, A. J., S. A. Montgomery, et al. (2009). "Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study." *J Clin Psychiatry* 70(4): 526-39.

OBJECTIVE: To evaluate the efficacy and tolerability of once-daily extended release quetiapine fumarate (quetiapine XR) as monotherapy treatment for major depressive disorder (MDD). **METHOD:** This 8-week (6-week active-treatment, randomized phase; 2-week posttreatment drug-discontinuation/tapering phase), multicenter, double-blind, randomized, parallel-group, placebo- and active-controlled, phase 3 study was conducted between April 2006 and May 2007. In total, 612 patients with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-defined MDD were randomly assigned to quetiapine XR 150 mg/day or 300 mg/day, duloxetine 60 mg/day (active control), or placebo. The primary endpoint was the change from baseline to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total score. **RESULTS:** At week 6, both doses of quetiapine XR ($p < .001$) and duloxetine ($p < .01$) significantly reduced mean MADRS total score versus placebo. A significant reduction was seen at week 1 with quetiapine XR 150 mg/day and 300 mg/day versus placebo ($p < .01$), but not with duloxetine. Response rates ($\geq 50\%$ reduction in MADRS total score) at week 6 were significantly higher for both doses of quetiapine XR ($p < .01$) and duloxetine ($p < .05$) versus placebo. Remission rates (MADRS score ≤ 8) were significantly higher for quetiapine XR 300 mg/day and duloxetine versus placebo ($p < .05$), but not for quetiapine XR 150 mg/day. Hamilton Rating Scale for Depression, Hamilton Rating Scale for Anxiety, and Clinical Global Impressions-Severity of Illness total scores and the proportion of patients with Clinical Global Impressions-Improvement scores of 1 or 2 ("much/very much improved") were significantly

improved with both doses of quetiapine XR and duloxetine versus placebo. The most common adverse events reported were dry mouth, sedation, and somnolence for quetiapine XR and nausea, headache, dizziness, and dry mouth for duloxetine. CONCLUSION: Quetiapine XR monotherapy (150 mg/day and 300 mg/day) is effective, with safety and tolerability consistent with the known profile of quetiapine XR, in the treatment of patients with MDD, with onset of symptom improvement demonstrated at week 1. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00321490.

8. Davidson, J., C. Allgulander, et al. (2008). "Efficacy and tolerability of duloxetine in elderly patients with generalized anxiety disorder: a pooled analysis of four randomized, double-blind, placebo-controlled studies." *Hum Psychopharmacol* 23(6): 519-26.

OBJECTIVE: To assess the efficacy and tolerability of duloxetine in elderly patients with generalized anxiety disorder (GAD). METHODS: Acute-phase data from a subset of patients (≥ 65 years) with GAD were pooled from four randomized, double-blind, placebo-controlled trials of duloxetine (3 flexible, 1 fixed dosing). Patients were treated with duloxetine 60-120 mg once daily or placebo for 9-10 weeks. The primary outcome measure was the mean baseline-to-endpoint change in Hamilton anxiety scale (HAMA) total score. Secondary measures included the HAMA psychic and somatic anxiety subscales and the Hospital Anxiety Depression Scale (HADS). RESULTS: Of 1491 patients randomly assigned to treatment, 4.9% (duloxetine, $n = 45$; placebo, $n = 28$) were ≥ 65 years old. Compared with placebo-treated patients, duloxetine-treated patients experienced significantly greater improvements on the HAMA-total ($p = 0.029$), the HAMA-psychic anxiety factor ($p = 0.034$), HADS-anxiety ($p = 0.049$) and -depression scales ($p = 0.026$), but not the HAMA somatic anxiety factor ($p = 0.074$). Nausea was reported significantly more often in duloxetine-treated patients (30.0% vs. 7.1%, $p = 0.023$); duloxetine-treated patients experienced greater weight loss ($p = 0.018$). More duloxetine-treated patients discontinued treatment due to an adverse event (22.2% vs. 0%; $p = 0.006$). CONCLUSION: Duloxetine was effective in an elderly patient subset with GAD, although there was a high rate of discontinuations due to adverse events.

9. Davidson, J. R., H. U. Wittchen, et al. (2008). "Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial." *Eur Neuropsychopharmacol* 18(9): 673-81.

The objective was to examine duloxetine 60-120 mg/day treatment for relapse prevention in adults with generalized anxiety disorder (GAD). Adult patients ($N=887$; mean age=43.3 years; 61.0% female) with DSM-IV-TR-defined GAD diagnosis were treated with duloxetine for 26 weeks. Patients who completed open-label phase and were treatment responders ($\geq 50\%$ reduction in Hamilton Anxiety Rating Scale total score to ≤ 11 and "much"/"very much improved" ratings for the last 2 visits of open-label phase) were randomly assigned to receive duloxetine or placebo for a 26-week double-blind continuation phase. Relapse was defined as ≥ 2 -point increase in illness severity ratings or by discontinuation due to lack of efficacy. During the double-blind phase, placebo-treated patients ($N=201$) relapsed more frequently (41.8%) than duloxetine-treated patients (13.7%, $N=204$, $P < 0.001$) and worsened on each outcome measure ($P < 0.001$, all comparisons). Duloxetine 60-120 mg/day treatment was efficacious and reduced risk of relapse in patients with GAD.

10. Demyttenaere, K., H. F. Andersen, et al. (2008). "Impact of escitalopram treatment on Quality of Life Enjoyment and Satisfaction Questionnaire scores in major depressive disorder and generalized anxiety disorder." *Int Clin Psychopharmacol* 23(5): 276-86.

Administration of the same Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) in major depressive disorder (MDD) and in generalized anxiety disorder (GAD) before and after treatment allowed us to compare quality of life enjoyment and satisfaction in these two disorders and to compare outcome based on symptoms versus functioning. Q-LES-Q and symptom-specific Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Anxiety Scale (HAMA) data from eight randomized, 8-week, double-blind, placebo-controlled clinical trials with escitalopram were used. MDD (n=1,140) or GAD (n=1,045) patients report a substantial degree of quality of life enjoyment and satisfaction impairment (baseline scores 64% and 76% of community norm, respectively). Treatment resulted in statistically and clinically significant improvement in quality of life enjoyment and satisfaction. The improvement was greater in patients treated with escitalopram than with placebo. In MDD, the majority of remitters (MADRS \leq 12) reached 'normal' quality of life enjoyment and satisfaction levels, whereas in GAD, 67% of remitters (HAMA \leq 7) reached 'normal' quality of life, enjoyment, and satisfaction. A strong correlation between the symptom-specific scales and the Q-LES-Q was observed. These analyses suggest that remission with scores of 6 on the MADRS and 5 on the HAMA correspond with a quality of life enjoyment and satisfaction found in community comparison patients (Q-LES-Q score of 58 \pm 10%). Treatment with escitalopram results in a significant improvement of quality of life enjoyment and satisfaction in patients with MDD or GAD. Both response and remission in patients with GAD and remission in patients with MDD are correlated with a 'normal' quality of life enjoyment and satisfaction.

11. Emslie, G. J., D. Ventura, et al. (2009). "Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial." *J Am Acad Child Adolesc Psychiatry* 48(7): 721-9.

OBJECTIVE: This article presents the results from a prospective, randomized, double-blind, placebo-controlled trial of escitalopram in adolescent patients with major depressive disorder. **METHOD:** Male and female adolescents (aged 12-17 years) with DSM-IV-defined major depressive disorder were randomly assigned to 8 weeks of double-blind treatment with escitalopram 10 to 20 mg/day (n = 155) or placebo (n = 157). The primary efficacy parameter was change from baseline to week 8 in Children's Depression Rating Scale-Revised (CDRS-R) score using the last observation carried forward approach. **RESULTS:** A total of 83% patients (259/312) completed 8 weeks of double-blind treatment. Mean CDRS-R score at baseline was 57.6 for escitalopram and 56.0 for placebo. Significant improvement was seen in the escitalopram group relative to the placebo group at endpoint in CDRS-R score (-22.1 versus -18.8, p = .022; last observation carried forward). Adverse events occurring in at least 10% of escitalopram patients were headache, menstrual cramps, insomnia, and nausea; only influenza-like symptoms occurred in at least 5% of escitalopram patients and at least twice the incidence of placebo (7.1% versus 3.2%). Discontinuation rates due to adverse events were 2.6% for escitalopram and 0.6% for placebo. Serious adverse events were reported by 2.6% and 1.3% of escitalopram and placebo patients, respectively, and incidence of suicidality was similar for both groups. **CONCLUSIONS:** In this study, escitalopram was effective and well tolerated in the treatment of depressed adolescents.

12. Fava, M., C. Wiltse, et al. (2009). "Predictors of relapse in a study of duloxetine treatment in patients with major depressive disorder." *J Affect Disord* 113(3): 263-71.

BACKGROUND: Using data from a relapse prevention study of duloxetine treatment for adults with major depressive disorder (MDD), we examined demographic- and illness-related variables to identify factors that may predict relapse of MDD. **METHODS:** Post-hoc analyses, using the Cox proportional hazards model, were performed on data from a study designed to compare the time to relapse of MDD in duloxetine- and placebo-treated patients. Patients received open-label duloxetine 60 mg/day during a 12-week acute phase, and those who met response criteria were randomly assigned to duloxetine 60 mg/day (N=136) or placebo (N=142) during a 26-week double-blind continuation phase. **RESULTS:** Significant predictors of relapse were VAS back pain score at entry >30, HAMD(17) total score at randomization >7, and geography (Europe vs. US). Four significant treatment-by-predictor interactions were identified: the SQ-SS pain subscale score at entry >median of 4, VAS overall pain score at entry >30, VAS overall pain score at entry >median of 26, and VAS overall pain score at randomization >median of 7. In the "greater severity" category, the risk of relapse was significantly lower for duloxetine-treated patients compared with placebo-treated patients. **LIMITATIONS:** These were post-hoc analyses. **CONCLUSIONS:** Higher levels of pain severity and depressive symptoms and a US geographical location were significant predictors of relapse in patients with MDD.

13. Freeman, E. W., K. Rickels, et al. (2009). "Time to relapse after short- or long-term treatment of severe premenstrual syndrome with sertraline." *Arch Gen Psychiatry* 66(5): 537-44.

CONTEXT: The duration of treatment after achieving a satisfactory response is unknown in the treatment of premenstrual syndrome. This information is needed in view of the improvement provided by medication vs the adverse effects and costs of drugs. **OBJECTIVE:** To compare rates of relapse and time to relapse between short- and long-term treatment with sertraline hydrochloride administered in the luteal phase of the menstrual cycle. **DESIGN:** Eighteen-month survival study with a randomized double-blind switch to placebo after 4 or 12 months of sertraline treatment. **SETTING:** Academic medical center. **PARTICIPANTS:** One hundred seventy-four patients with premenstrual syndrome or premenstrual dysphoric disorder. **MAIN OUTCOME MEASURE:** Relapse, defined as symptoms returning to the entry criterion level as assessed with daily ratings. **RESULTS:** The relapse rate was 41% during long-term treatment compared with 60% after short-term sertraline therapy, with a median time to relapse of 8 months vs 4 months (hazard ratio, 0.58; 95% confidence interval, 0.34-0.98; $P = .04$). Patients with severe symptoms at baseline were more likely to experience relapse compared with patients in the lower symptom severity group (hazard ratio, 2.02; 95% confidence interval, 1.18-3.41; $P = .01$) and were more likely to experience relapse with short-term treatment ($P = .03$). Duration of treatment did not affect relapse in patients in the lower symptom severity group ($P = .50$). Patients who demonstrated remission were least likely to experience relapse (hazard ratio, 0.22; 95% confidence interval, 0.10-0.45; $P < .001$). Further analysis comparing relapse in the first 6 months of placebo treatment in each group yielded similar results. **CONCLUSIONS:** The relapse rate was significantly greater after short-term treatment compared with long-term treatment. The relapse rate was also high during extended drug treatment. Subjects with severe symptoms at baseline were most likely to experience relapse, and relapse occurred more swiftly regardless of treatment duration. These findings suggest that the severity of symptoms at baseline and symptom remission with treatment should be considered in determining the duration of treatment. **TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00318773.

14. Glassman, A. H., J. T. Bigger, Jr., et al. (2009). "Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: seven-year follow-up of SADHART participants." *Arch Gen Psychiatry* 66(9): 1022-9.

CONTEXT: Major depressive disorder (MDD) after acute coronary syndrome (ACS) is associated with an increased mortality rate. We observed the participants of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) to establish features of MDD associated with long-term mortality. **OBJECTIVES:** To determine whether the following variables were associated with long-term mortality: baseline depression severity, previous MDD episodes, onset of MDD before or after the ACS event, 6 months of sertraline hydrochloride therapy, and mood improvement independent of treatment. **DESIGN:** SADHART was a double-blind, placebo-controlled, randomized trial comparing the safety and antidepressant efficacy of sertraline vs placebo in 369 patients with ACS who met criteria for MDD. The trial was completed in June 2000, and follow-up for vital status was completed in September 2007. **SETTING:** Academic research. **PARTICIPANTS:** SADHART participants. **MAIN OUTCOME MEASURES:** Vital status was determined in 361 participants (97.8%) during a median follow-up of 6.7 years. **RESULTS:** During the study, 75 participants (20.9%) died. Neither previous episodes of MDD, nor onset before or after the index ACS, nor an initial 6 months of sertraline treatment was associated with long-term mortality. Cox proportional hazards regression models showed that baseline MDD severity (hazard ratio, 2.30; 95% confidence interval, 1.28-4.14; $P < .006$) and failure of MDD to improve substantially during treatment with either sertraline or placebo (hazard ratio, 2.39; 95% confidence interval, 1.39-2.44; $P < .001$) were strongly and independently associated with long-term mortality. Marked improvement in depression (Clinical Global Impression-Improvement subscale score of 1) was associated with improved adherence to study medication. **CONCLUSIONS:** Severity of MDD measured within a few weeks of hospitalization for ACS or failure of MDD to improve during the 6 months following ACS predicted more than a doubling of mortality over 6.7 years of follow-up. Because persistent depression increases mortality and decreases medication adherence, physicians need to aggressively treat depression and be diligent in promoting adherence to guideline cardiovascular drug therapy.

15. Hansen, R., B. Gaynes, et al. (2008). "Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants." *Psychiatr Serv* 59(10): 1121-30.

OBJECTIVE: This meta-analysis reviewed data on the efficacy and effectiveness of second-generation antidepressants for preventing major depression relapse and recurrence during continuation and maintenance phases of treatment, respectively. **METHODS:** MEDLINE, EMBASE, and PsycINFO, the Cochrane Library, and International Pharmaceutical Abstracts were searched for the period of January 1980 through April 2007 for reviews, randomized controlled trials, meta-analyses, and observational studies on the topic. Two persons independently reviewed abstracts and full-text articles using a structured data abstraction form to ensure consistency in appraisal and data extraction. **RESULTS:** Four comparative trials and 23 placebo-controlled trials that addressed relapse or recurrence prevention were included. Results of comparative trials have not demonstrated statistically significant differences between duloxetine and paroxetine, fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine. Pooled data for the class of second-generation antidepressants compared with

placebo suggested a relatively large effect size that persists over time. For preventing both relapse and recurrence, the number of patients needed to treat is five (95% confidence interval of 4 to 6). Differences in the length of open-label treatment before randomization, drug type, and trial duration did not affect pooled estimates of relapse rates. Across all trials, 7% of patients randomly assigned to receive active treatment and 5% of patients randomly assigned to receive a placebo discontinued treatment because of adverse events. **CONCLUSIONS:** This review demonstrates the overall benefits of continuation- and maintenance-phase treatment of major depression with second-generation antidepressants and emphasizes the need for additional studies of comparative differences among drugs.

16. Kang, E. H., I. S. Lee, et al. (2009). "Mirtazapine versus venlafaxine for the treatment of somatic symptoms associated with major depressive disorder: a randomized, open-labeled trial." *Psychiatry Res* 169(2): 118-23.

Somatic symptoms are often important in the treatment of major depressive disorder (MDD). The aim of this open-labeled trial was to examine the efficacy of mirtazapine for the treatment of MDD with clinically significant somatic symptoms, as compared with venlafaxine. A total of 126 patients with MDD (score ≥ 18 on the Hamilton Rating Scale for Depression-17) were included in both the intent-to-treat (n=73 in the mirtazapine group and n=53 in the venlafaxine group) and completer analysis (n=51 and n=37, respectively). After treatment, both treatment groups showed similar improvements in depressive symptoms. Repeated measures analysis of variance for the intent-to-treat population revealed that there were no significant differences in mean change of the Symptom Check List-90-Revised (SCL-90-R) somatization subscores between the two groups. For completers, there was a significant time \times treatment interaction in the SCL-90-R somatization subscores, but the differences between the two groups at endpoint did not reach statistical significance in post-hoc analysis. In conclusion, this study suggests that overall efficacies of mirtazapine and venlafaxine are similar for the treatment of overall symptoms in MDD, and both drugs may be useful for the treatment of somatic symptoms in MDD patients.

17. Kilts, C. D., A. G. Wade, et al. (2009). "Baseline severity of depression predicts antidepressant drug response relative to escitalopram." *Expert Opin Pharmacother* 10(6): 927-36.

OBJECTIVE: The intent of this pooled analysis was to determine the relationship between baseline depression symptom severity and treatment response for escitalopram compared to that for other pooled antidepressant medications (citalopram, duloxetine, fluoxetine, paroxetine, sertraline and venlafaxine). **METHODS:** Data were pooled from controlled clinical trials comparing escitalopram with other antidepressants for the treatment of major depression. The 15 trials meeting the inclusion criteria comprised 2,216 patients treated with escitalopram and 2,085 treated with one of the other antidepressants. The primary outcome measure of change from baseline to week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score was analyzed by an analysis of covariance, using the method of last-observation-carried-forward for missing values and adjusting for baseline and center values. **RESULTS:** There was a significant interaction between baseline MADRS total score and treatment group ($p = 0.0208$). Response to escitalopram was stable regardless of baseline severity. For the pooled active comparators, response decreased with increasing baseline symptom severity. This differential efficacy of escitalopram with increasing symptom severity was confirmed by the analyses of the pooled 24-item Hamilton Depression Rating Scale (HAM-D-24) results. A HAM-D-24 single item

analysis indicated that the sum of the baseline psychomotor retardation and hopelessness item scores significantly predicted which patients would benefit from treatment with escitalopram versus a comparator. CONCLUSION: Newer generation antidepressant medications clearly differ in their efficacy as a function of baseline symptom severity. The selective serotonin reuptake inhibitor escitalopram had superior efficacy in the treatment of more severe depression, perhaps attributable to differential efficacy related to symptoms of negativistic thinking.

18. Lam, R. W., H. F. Andersen, et al. (2008). "Escitalopram and duloxetine in the treatment of major depressive disorder: a pooled analysis of two trials." *Int Clin Psychopharmacol* 23(4): 181-7.

Pooled analyses have shown that escitalopram has superior effectiveness versus all comparators, including selective serotonin reuptake inhibitors and venlafaxine. Recent studies have compared escitalopram with duloxetine. Data from two randomized, double-blind studies that compared escitalopram (10-20 mg/day) and duloxetine (60 mg/day) were pooled and analysed for all patients and for the subsample of severely depressed patients [baseline Montgomery-Asberg Depression Rating Scale (MADRS) score \geq 30]. Escitalopram (n=280) was superior to duloxetine (n=284) with respect to mean change from baseline in MADRS score at weeks 1, 2, 4 and 8 with a mean treatment difference at week 8 of 2.6 points ($P < 0.01$). Similar results were seen for severely depressed patients, with a mean treatment difference of 3.7 points ($P < 0.01$). Response and remission rates at week 8 were significantly higher for patients treated with escitalopram [response 67.1% for escitalopram compared with 53.2% for duloxetine, $P < 0.001$; remission (MADRS \leq 12) 54.3% for escitalopram compared with 44.4% for duloxetine, $P < 0.05$]. The numbers needed to treat based on response and remission rates, in favour of escitalopram, were 8 and 11, respectively, for all patients (6 and 7, respectively, for severely depressed patients). Significantly fewer ($P < 0.001$) patients (all cause and owing to adverse events) withdrew from the escitalopram group. This pooled analysis shows that over an 8-week treatment period, escitalopram (10-20 mg/day) is superior in both effectiveness and tolerability compared with duloxetine (60 mg/day).

19. Liebowitz, M. R., G. Asnis, et al. (2009). "A double-blind, placebo-controlled, parallel-group, flexible-dose study of venlafaxine extended release capsules in adult outpatients with panic disorder." *J Clin Psychiatry* 70(4): 550-61.

OBJECTIVE: To evaluate the efficacy, safety, and tolerability of venlafaxine extended release (ER) in short-term treatment of panic disorder. **METHOD:** In this multicenter, double-blind study, conducted from April 2001 to December 2002, 343 adult outpatients who met criteria for panic disorder (with and without agoraphobia) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, were randomly assigned to flexible-dose venlafaxine ER (75-225 mg/d) or placebo for 10 weeks (N = 155 per group, intent-to-treat population). The primary outcome measure was the percentage of panic-free patients as assessed using the Sheehan Panic and Anticipatory Anxiety Scale. Key secondary measures included the Panic Disorder Severity Scale (PDSS) score and Clinical Global Impressions-Improvement (CGI-I) scale response (score = 1 or 2). Last-observation-carried-forward data were analyzed, and statistical significance was set at $p \leq .05$. **RESULTS:** At week 10, the percentage of patients who were free from full-symptom panic attacks was 52% in the venlafaxine ER group and 43% in the placebo group ($p = .11$). Mean change from baseline in PDSS total score was significantly ($p = .006$) greater for the venlafaxine ER group (-9.3) than for the placebo group (-

7.5), and significantly ($p = .03$) more venlafaxine ER-treated patients achieved CGI-I response (71%) than did those receiving placebo (59%) at week 10. Treatment with venlafaxine ER was generally safe and well tolerated. Adverse events were the primary or secondary cause for discontinuation for 7 placebo patients (4%) and 12 venlafaxine ER patients (7%).

CONCLUSIONS: Venlafaxine ER appears to be effective, safe, and well tolerated in short-term treatment of panic disorder, although the results fell just short of significance on the primary outcome measure. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00038896.

20. Perahia, D. G., G. Maina, et al. (2009). "Duloxetine in the prevention of depressive recurrences: a randomized, double-blind, placebo-controlled trial." *J Clin Psychiatry* 70(5): 706-16.

OBJECTIVE: To assess the efficacy of duloxetine 60-120 mg once daily in the prevention of depressive recurrence in outpatients with recurrent major depressive disorder (MDD). METHOD: Eligible patients with at least 3 episodes of MDD (DSM-IV diagnosis) in the past 5 years received open-label duloxetine 60-120 mg/day for up to 34 weeks. Patients meeting response criteria were then randomly assigned to either duloxetine or placebo for up to 52 weeks of double-blind maintenance treatment. The primary outcome measure was time to recurrence of a major depressive episode. Safety and tolerability were assessed via analysis of treatment-emergent adverse events (TEAEs), vital signs, weight, and laboratory measures. Patients were recruited from 43 study centers in 5 European countries (France, Germany, Italy, Russia, and Sweden) and the United States. The study was conducted from March 2005 to January 2008. RESULTS: A total of 288 patients were randomly assigned to duloxetine or placebo. Time to a depressive recurrence was significantly longer in duloxetine-treated patients compared with placebo-treated patients ($p < .001$). During the double-blind maintenance phase, 33.1% of placebo-treated patients experienced a depressive recurrence compared with 14.4% of duloxetine-treated patients ($p < .001$). There were no significant differences between treatment groups in TEAEs, discontinuations due to adverse events, vital signs, or weight.

CONCLUSIONS: Treatment with duloxetine was associated with a longer time to depressive recurrence and a significantly lower recurrence rate compared with placebo. TRIALS REGISTRATION: (ClinicalTrials.gov) Identifier: NCT00105989.

21. Rapaport, M. H., R. B. Lydiard, et al. (2009). "Low doses of controlled-release paroxetine in the treatment of late-life depression: a randomized, placebo-controlled trial." *J Clin Psychiatry* 70(1): 46-57.

OBJECTIVE: To evaluate the efficacy and tolerability of low daily doses of controlled-release (CR) paroxetine in patients with late-life depression. METHOD: This was a 10-week, multicenter, placebo-controlled, double-blind, fixed-dose trial randomly assigning patients ≥ 60 years old to daily doses of paroxetine CR 12.5 mg ($N = 168$), paroxetine CR 25 mg ($N = 177$), or placebo ($N = 180$). Patients had major depressive disorder (DSM-IV criteria) and 17-item Hamilton Rating Scale for Depression (HAM-D) total scores of ≥ 18 . The primary efficacy variable was the change from baseline to study endpoint in total HAM-D scores. The study was conducted from June 2003 to October 2004. RESULTS: The drug/placebo difference in HAM-D change from baseline at study endpoint was -1.8 (95% CI = -3.41 to -0.19, $p = .029$) for paroxetine CR 12.5 mg, and -3.3 (95% CI = -4.84 to -1.68, $p < .001$) for paroxetine CR 25 mg. A significantly larger percentage of patients achieved remission (HAM-D total score ≤ 7 at endpoint) with paroxetine CR 25 mg (41%), but not with 12.5 mg (31%), as compared with

placebo (28%) ($p = .008$). Both doses of paroxetine CR also achieved statistical significance compared to placebo for the Clinical Global Impressions-Severity of Illness scale ($p < .01$) and the patient-rated measures of depression severity ($p < .05$) and quality of life ($p \leq .001$). Both active treatments were generally well tolerated, with adverse event withdrawal rates of 6%, 8%, and 7% for paroxetine CR 12.5 mg, paroxetine CR 25 mg, and placebo, respectively. CONCLUSION: These data demonstrate that paroxetine CR 12.5 mg and 25 mg daily are efficacious and well tolerated in the treatment of major depressive disorder in patients ≥ 60 years of age, although effect sizes are relatively smaller with the 12.5 mg/day dose.

22. Rothbaum, B. O., J. R. Davidson, et al. (2008). "A pooled analysis of gender and trauma-type effects on responsiveness to treatment of PTSD with venlafaxine extended release or placebo." *J Clin Psychiatry* 69(10): 1529-39.

OBJECTIVE: To examine effects of gender and trauma type on response to treatment with venlafaxine extended release (ER) or placebo in patients with posttraumatic stress disorder (PTSD). **METHOD:** Data were pooled from 2 flexible-dose, parallel-group, randomized, double-blind, placebo-controlled trials: a 12-week trial conducted in the United States (March 2001 to December 2002) and a 24-week trial conducted in 12 countries outside the United States (October 2001 to December 2003). Six hundred eighty-seven outpatients with DSM-IV-diagnosed PTSD and a 17-item Clinician-Administered PTSD Scale abbreviated 1-week Symptom Status version (CAPS-SX-17) score ≥ 60 were randomly assigned to treatment with venlafaxine ER (37.5 mg/day-300 mg/day, $N = 340$) or placebo ($N = 347$). The primary efficacy end point was the CAPS-SX-17 total score at week 12. Secondary end points included CAPS-SX-17 cluster scores for reexperiencing, avoidance/numbing, and hyperarousal and scores on the Connor-Davidson Resilience Scale (CD-RISC), Clinical Global Impressions-Severity of Illness scale, Sheehan Disability Scale (SDS), and 17-item Hamilton Rating Scale for Depression (HAM-D-17). Analysis-of-covariance models were used to test for differences by gender and trauma type (accidental injury, combat, nonsexual abuse, adult sexual abuse, childhood sexual abuse, unexpected death, and other), treatment (venlafaxine ER vs. placebo), and the treatment-by-trauma-type interaction. **RESULTS:** Using last-observation-carried-forward analysis, significant effects of treatment with venlafaxine ER were found on the CAPS-SX-17 total score and on all CAPS-SX-17 cluster scores and most other secondary measures. No significant treatment-by-gender interactions were observed. Trauma type significantly affected treatment responsiveness on symptom-related disability (SDS, $p = .0057$) and resilience (CD-RISC, $p = .0012$), with a nearly significant effect on depression (HAM-D-17, $p = .0625$). **CONCLUSION:** Overall, there does not appear to be a significant effect of gender on the efficacy of venlafaxine ER in the treatment of PTSD. Trauma type may affect treatment outcome but seems to affect domains such as disability and resilience more than core PTSD symptoms.

23. Stein, D. J., P. D. Carey, et al. (2008). "Escitalopram in obsessive-compulsive disorder: response of symptom dimensions to pharmacotherapy." *CNS Spectr* 13(6): 492-8.

INTRODUCTION: There is a substantial body of evidence that obsessive-compulsive disorder (OCD) symptoms can be grouped into a series of discrete dimensions, and some evidence that not all OCD symptom dimensions respond equally well to pharmacologic or psychotherapeutic intervention. The response of OCD symptom dimensions to 12 weeks of treatment with escitalopram or placebo was investigated. **METHODS:** Data from a randomized, double-blind, placebo-controlled study of escitalopram in 466 adults with OCD were analyzed.

Exploratory factor analysis of individual items of the Yale-Brown Obsessive-Compulsive Scale checklist was performed and subscale scores based on the extracted factors were determined. Analyses of covariance were undertaken to determine whether inclusion of each subscale score in these models impacted on the efficacy of escitalopram versus placebo. **RESULTS:** Exploratory factor analysis of individual Yale-Brown Obsessive-Compulsive Scale items yielded 5 factors (contamination/cleaning, harm/checking, hoarding/symmetry, religious/sexual, and somatic/hypochondriacal). Analyses of covariance including all the subscales demonstrated that escitalopram was more effective than placebo. There was a significant interaction for the hoarding/symmetry factor, which was associated with a poor treatment response. **CONCLUSION:** Escitalopram shows good efficacy across the range of OCD symptom dimensions. Nevertheless, hoarding/symmetry was associated with a poorer treatment response. Hoarding/symmetry may be particularly characteristic of an early-onset group of OCD patients, with the involvement of neurotransmitters other than serotonin. Further work is needed to delineate fully the subtypes of OCD, and their correlates with underlying psychobiology and treatment responsiveness.

24. Thase, M. E., S. G. Kornstein, et al. (2009). "An integrated analysis of the efficacy of desvenlafaxine compared with placebo in patients with major depressive disorder." *CNS Spectr* 14(3): 144-54.

Introduction: To assess the efficacy of desvenlafaxine (administered as desvenlafaxine succinate) in outpatients with major depressive disorder. **Methods:** A meta-analysis of individual patient data was performed on the complete set of registration trials (nine randomized, double-blind, placebo-controlled 8-week studies) of desvenlafaxine. Patients received fixed (50, 100, 200, or 400 mg/day; n=1,342) or flexible doses (100-400 mg/day; n=463) of desvenlafaxine or placebo (n=1,108). The primary efficacy variable was the 17-item Hamilton Rating Scale for Depression (HAM-D(17)); the primary intent to treat analyses used the last-observation-carried-forward method. **Results:** Significantly greater improvement with desvenlafaxine versus placebo on the HAM-D(17) total score was observed for the full data set (difference in adjusted means: -1.9; P<.001), each fixed-dose group (all P<.001), and the flexible-dose group (P=.024). Overall rates of HAM-D(17) response (> or =150% decrease from baseline score: 53% vs 41%) and remission (HAM-D(17) < or =7: 32% vs 23%) were significantly greater for desvenlafaxine versus placebo (all P<.001). Discontinuation rates due to adverse events increased with dose (4% to 18%; placebo: 3%). **Conclusion:** Desvenlafaxine demonstrated short-term efficacy for treating major depressive disorder across the range of doses studied. No evidence of greater efficacy was observed with doses >50 mg/day; a strong dose-response effect on tolerability was observed.

25. Wade, A. G., T. E. Schlaepfer, et al. (2009). "Clinical milestones predict symptom remission over 6-month and choice of treatment of patients with major depressive disorder (MDD)." *J Psychiatr Res* 43(5): 568-75.

BACKGROUND: It is uncertain as to what short-term outcomes predict long-term treatment compliance and outcomes in patients with MDD. **AIMS:** To determine what treatment milestones predict symptom remission with long-term treatment with antidepressant medication. **METHOD:** Pooled analysis of four randomised, double-blind, active comparator, 6-month trials in MDD. **RESULTS:** Patients received double-blind treatment with escitalopram (N=699) or a comparator (citalopram, duloxetine, or paroxetine) (N=699). Onset of effect at week 2 was correlated with response at week 8, and response at week 8 with completion of 6-month

treatment. Week 8 response was associated with a greater probability of achieving later remission. Week 24 remission (MADRS \geq 10) was significantly ($p < 0.01$) higher for patients treated with escitalopram (70.7%) than for the pooled comparators (64.7%). Week 24 complete remission (MADRS \leq 5) was significantly ($p < 0.01$) higher for escitalopram (51.7%) than for the pooled comparators (45.6%). Fewer patients discontinued treatment with escitalopram (15.9%) than with the pooled comparators (23.9%) ($p < 0.001$). CONCLUSION: A higher probability of achieving remission is associated with responding after 8 weeks and with completing 6 months of treatment.

26. Watanabe, N., I. M. Omori, et al. (2008). "Mirtazapine versus other antidepressants in the acute-phase treatment of adults with major depression: systematic review and meta-analysis." *J Clin Psychiatry* 69(9): 1404-15.

OBJECTIVE: To conduct a comprehensive, systematic review and meta-analysis of the efficacy and tolerability of mirtazapine over other antidepressants in the acute-phase treatment of major depression. **DATA SOURCES:** Studies were initially identified through electronic searches of the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register up to June 2006. The following search terms were used: depress*, dysthymi*, adjustment disorder*, mood disorder*, affective disorder, affective symptoms, and mirtazapine. No language restriction was imposed. The reference lists of the included studies, previous relevant systematic reviews, and trial registers were also hand searched. Pharmaceutical companies and experts in the field were contacted for more studies. **STUDY SELECTION:** Twenty-five randomized controlled trials were included. **DATA EXTRACTION:** Two independent assessors examined the quality of the trials and extracted data on an intention-to-treat basis. **DATA SYNTHESIS:** The primary outcome measure was the relative risk (RR) of response (99% CIs) at the conclusion of acute-phase treatment. In relation to the early phase of treatment (at 2 weeks), there were no statistically significant differences between mirtazapine and the tricyclics in terms of the response (RR = 0.90, 99% CI = 0.69 to 1.18, $p = .30$ [8 trials contributed to this outcome]) or remission (RR = 0.87, 99% CI = 0.52 to 1.47, $p = .50$ [8 trials]) outcomes, but mirtazapine was superior to the selective serotonin reuptake inhibitors (SSRIs) in terms of both the response (RR = 1.36, 99% CI = 1.13 to 1.64, $p < .0001$ [12 trials]) and remission (RR = 1.68, 99% CI = 1.20 to 2.36, $p < .0001$ [12 trials]). In the subgroup analyses, mirtazapine significantly produced more response than paroxetine (RR = 2.02, 99% CI = 1.09 to 3.75, $p = .003$ [3 trials]) and venlafaxine (RR = 1.77, 99% CI = 1.08 to 2.89, $p = .003$ [2 trials]). At the end of acute-phase treatment (6-12 weeks, all trials), no significant differences were observed in the efficacy outcomes. No significant differences were observed between mirtazapine and the other antidepressants in terms of either the total number of dropouts due to any reason (21 trials) or the total number of dropouts due to the development of side effect (23 trials) during the trials. **CONCLUSIONS:** Although mirtazapine is likely to have a faster onset of action than SSRIs, no significant differences were observed at the end of 6 to 12 weeks' treatment. Clinicians should focus on other practically relevant considerations to tailor treatment to best fit the needs of individual patients.

Appendix B. Abstracts of potentially relevant new studies of Desvenlafaxine

1. DeMartinis, N. A., P. P. Yeung, et al. (2007). "A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder." *J Clin Psychiatry* 68(5): 677-88.

OBJECTIVE: This study evaluated the efficacy and safety of desvenlafaxine succinate extended-release in major depressive disorder (MDD). **METHOD:** Adult outpatients with DSM-IV-defined MDD were randomly assigned to desvenlafaxine 100 mg/day (N = 114), 200 mg/day (N = 116), or 400 mg/day (N = 113) or placebo (N = 118) for 8 weeks. Efficacy variables included change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D(17), the primary efficacy measure), Clinical Global Impressions-Improvement scale (CGI-I), Montgomery-Asberg Depression Rating Scale, Clinical Global Impressions-Severity of Illness scale (CGI-S), rates of response (> or = 50% decrease from baseline HAM-D(17) score) and remission (HAM-D(17) score < or =7), and Visual Analog Scale-Pain Intensity overall score. The study was conducted from November 2003 to November 2004. **RESULTS:** At the final on-therapy evaluation, the mean HAM-D(17) scores for desvenlafaxine 100 mg/day (12.75) and 400 mg/day (12.50) were significantly lower than for placebo (15.31; $p = .0038$ and $p = .0023$, respectively); for desvenlafaxine 200 mg/day, the mean score was 13.31 ($p = .0764$). CGI-I and Montgomery-Asberg Depression Rating Scale results were significant for all groups; CGI-S results were significant with 100 mg/day and 400 mg/day. Response rates were significantly greater for desvenlafaxine 100 mg/day (51%) and 400 mg/day (48%) versus placebo (35%; $p = .017$ and $p = .046$, respectively); the response rate for desvenlafaxine 200 mg/day was 45% ($p = .142$). Remission rates were significantly greater for desvenlafaxine 400 mg/day (32%) versus placebo (19%; $p = .035$); remission rates were 30% for desvenlafaxine 100 mg/day ($p = .093$) and 28% for desvenlafaxine 200 mg/day ($p = .126$). Visual Analog Scale-Pain Intensity results were significant for desvenlafaxine 100 mg/day versus placebo ($p = .002$), but not for the higher doses. The most commonly reported adverse events were nausea, insomnia, somnolence, dry mouth, dizziness, sweating, nervousness, anorexia, constipation, asthenia, and abnormal ejaculation/orgasm. **CONCLUSIONS:** Desvenlafaxine is effective and well tolerated in the short-term treatment of MDD.

2. Feiger, A. D., K. A. Tourian, et al. (2009). "A placebo-controlled study evaluating the efficacy and safety of flexible-dose desvenlafaxine treatment in outpatients with major depressive disorder." *CNS Spectr* 14(1): 41-50.

INTRODUCTION: This research compares the efficacy and safety of desvenlafaxine (administered as desvenlafaxine succinate) versus placebo in treating major depressive disorder. **METHODS:** In this randomized, double-blind study, outpatients with major depressive disorder > or =18 years of age received desvenlafaxine 200-400 mg/day or placebo for 8 weeks. Efficacy endpoints included (primary) change in 17-item Hamilton Rating Scale for Depression score at the final evaluation (last observation carried forward, analysis of covariance) and (secondary) Clinical Global Impressions-Improvement and -Severity of Illness scales. **RESULTS:** The difference between desvenlafaxine (n==) and placebo (n==) on the primary endpoint was not significant (-9.1 vs -7.5, $P=.078$). Week 8 observed cases (desvenlafaxine, n=80; placebo, n=94) results were significant (-10.7 vs -7.9, $P=.008$). Differences at the final evaluation (last

observation carried forward) were significant for Clinical Global Impressions-Improvement (2.9 vs 2.5, $P=.037$) and Clinical Global Impressions-Severity of Illness (-1.9 vs -1.2, $P=.041$). Discontinuation rates due to adverse events (AEs) were 12% and 3% for desvenlafaxine and placebo, respectively ($P=.008$). The most frequently reported AE associated with desvenlafaxine was nausea (36% vs 9% [placebo]). **CONCLUSION:** In this study, the primary analysis did not show significant differences between desvenlafaxine and placebo; discontinuations due to AEs associated with the desvenlafaxine dose range may have contributed to the lack of statistical separation.

3. Liebowitz, M. R., A. L. Manley, et al. (2008). "Efficacy, safety, and tolerability of desvenlafaxine 50 mg/day and 100 mg/day in outpatients with major depressive disorder." *Curr Med Res Opin* 24(7): 1877-90.

OBJECTIVE: To assess the efficacy, safety, and tolerability of 50- and 100-mg/day doses of desvenlafaxine (administered as desvenlafaxine succinate), a serotonin-norepinephrine reuptake inhibitor, for the treatment of major depressive disorder (MDD). **RESEARCH DESIGN AND METHODS:** Patients with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) MDD and 17-item Hamilton Rating Scale for Depression (HAM-D(17)) scores ≥ 20 were randomly assigned to double-blind placebo or desvenlafaxine treatment (fixed dose of 50 mg/day or 100 mg/day) for 8 weeks. The primary efficacy measure was the HAM-D(17). Changes from baseline in HAM-D(17) scores were analyzed using analysis of covariance. The final on-therapy evaluation was the primary endpoint for efficacy analyses, using last-observation-carried-forward data. **MAIN OUTCOMES MEASURES AND RESULTS:** The intent-to-treat population included 447 patients. Desvenlafaxine 50 mg was associated with a significantly greater adjusted mean change from baseline on the HAM-D(17) (-11.5) compared with placebo (-9.5, $p=0.018$); the 100-mg dose group (-11.0) did not achieve statistical significance ($p=0.065$). The 100-mg dose group experienced significant improvements compared with placebo on several secondary efficacy measures, including the 6-item Hamilton Depression Rating Scale ($p=0.038$) and the Visual Analog Scale-Pain Intensity total score ($p=0.041$). Both desvenlafaxine doses were generally well-tolerated. The most common adverse events (incidence $\geq 10\%$ in either desvenlafaxine group and twice the rate of placebo) were dry mouth, constipation, insomnia, decreased appetite, hyperhidrosis, and dizziness. **CONCLUSIONS:** These results demonstrate efficacy, safety, and tolerability of desvenlafaxine 50 mg/day for treating MDD. The significant findings on secondary measures support the efficacy of desvenlafaxine 100 mg, as seen in other trials. Conclusions may be limited by the exclusion of MDD patients with comorbid conditions and the short-term desvenlafaxine treatment duration.

4. Liebowitz, M. R., P. P. Yeung, et al. (2007). "A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder." *J Clin Psychiatry* 68(11): 1663-72.

OBJECTIVE: This study evaluated the efficacy and tolerability of desvenlafaxine succinate (desvenlafaxine) in the treatment of major depressive disorder (MDD). **METHOD:** In this 8-week, multicenter, randomized, double-blind, placebo-controlled trial, adult outpatients (aged 18-75 years) with a primary diagnosis of MDD (DSM-IV criteria) were randomly assigned to treatment with desvenlafaxine (100-200 mg/day) or placebo. The primary outcome measure was the 17-item Hamilton Rating Scale for Depression (HAM-D(17)) score at final on-therapy

evaluation. The Clinical Global Impressions-Improvement scale (CGI-I) was the key secondary measure. Other secondary measures included the Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impressions-Severity of Illness scale, Visual Analog Scale-Pain Intensity (VAS-PI) overall and subcomponent scores, and HAM-D(17) response and remission rates. The study was conducted from June 2003 to May 2004. **RESULTS:** Of the 247 patients randomly assigned to treatment, 234 comprised the intent-to-treat population. Following titration, mean daily desvenlafaxine doses ranged from 179 to 195 mg/day. At endpoint, there were no significant differences in scores between the desvenlafaxine (N = 120) and placebo (N = 114) groups on the HAM-D(17) or CGI-I. However, the desvenlafaxine group had significantly greater improvement in MADRS scores ($p = .047$) and in VAS-PI overall pain ($p = .008$), back pain ($p = .006$), and arm, leg, or joint pain ($p < .001$) scores than the placebo group. The most common treatment-emergent adverse events (at least 10% and twice the rate of placebo) were nausea, dry mouth, constipation, anorexia, somnolence, and nervousness. **CONCLUSION:** Desvenlafaxine was generally safe and well tolerated. In this study, it did not show significantly greater efficacy than placebo on the primary or key secondary efficacy endpoints, but it did demonstrate efficacy on an alternate depression scale and pain measure associated with MDD. **CLINICAL TRIALS REGISTRATION:** ClinicalTrials.gov identifier NCT00063206.

5. Septien-Velez, L., B. Pitrosky, et al. (2007). "A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder." *Int Clin Psychopharmacol* 22(6): 338-47.

The antidepressant efficacy and safety of desvenlafaxine succinate (desvenlafaxine) were evaluated in a phase III, double-blind, placebo-controlled study. Outpatients with a primary diagnosis of major depressive disorder were treated with fixed once-daily doses of desvenlafaxine 200 or 400 mg for 8 weeks. The primary efficacy measure was change from baseline on the 17-item Hamilton Rating Scale for Depression. At the final on-therapy evaluation, adjusted mean change from baseline in 17-item Hamilton Rating Scale for Depression total score was greater for desvenlafaxine 200 and 400 mg/day vs. placebo. Both desvenlafaxine doses showed greater efficacy than placebo on the secondary efficacy measures, including the Clinical Global Impressions-Improvement scale scores, Montgomery-Asberg Depression Rating Scale scores, CGI-Severity, and 17-item Hamilton Rating Scale for Depression response rate. Desvenlafaxine 200 mg/day was also significantly better than placebo on remission, Visual Analog Scale-Pain Intensity overall scores, and some Visual Analog Scale-Pain Intensity subscale scores. Desvenlafaxine 400 mg/day was significantly better than placebo on selected Visual Analog Scale-Pain Intensity subscale scores. Most adverse events were mild or moderate in severity, and safety assessments revealed few clinically significant changes in vital signs, laboratory tests, and electrocardiogram results. These data provide support for the efficacy and safety of desvenlafaxine in the treatment of major depressive disorder.

6. Tourian, K. A., S. K. Padmanabhan, et al. (2009). "Desvenlafaxine 50 and 100 mg/d in the treatment of major depressive disorder: an 8-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial and a post hoc pooled analysis of three studies." *Clin Ther* 31(Pt 1): 1405-23.

BACKGROUND: Major depressive disorder (MDD) is a common, chronic illness associated with substantial disability and economic burden. Although a number of effective antidepressants are available, the need for new medications that are effective and well tolerated

remains. **OBJECTIVE:** The aim of this study was to compare the efficacy and tolerability of fixed-dose desvenlafaxine 50 and 100 mg/d with placebo for MDD. A post hoc pooled analysis was conducted to evaluate this study in the context of all similarly designed, completed studies with the 2 doses. **METHODS:** This was an 8-week, Phase III, randomized, double-blind, duloxetine-referenced, placebo-controlled, parallel-group trial conducted in 21 centers across the United States. Duloxetine was included for assay sensitivity as a positive control; the study was not designed or powered to compare desvenlafaxine with duloxetine. Participants were outpatients aged ≥ 18 years with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-defined MDD and a 17-item Hamilton Rating Scale for Depression (HAM-D(17)) score ≥ 20 . Patients were randomly assigned at baseline to fixed-dose desvenlafaxine (50 or 100 mg/d), fixed-dose duloxetine (60 mg/d), or placebo. The primary outcome measure was HAM-D(17) total score at the final evaluation. Additional measures included the Clinical Global Impressions-Improvement (CGI-I) score, Montgomery Asberg Depression Rating Scale (MADRS) score, Clinical Global Impressions-Severity (CGI-S) score, and 6-item Hamilton Rating Scale for Depression, Bech version (HAM-D(6)). Tolerability assessments included discontinuation rates, adverse events (AEs), vital signs, and laboratory tests. The post hoc pooled analysis was performed using data from the current study and 2 previously published, positive studies that compared the efficacy and tolerability of desvenlafaxine 50 and 100 mg/d with placebo for MDD. The design and methodologies of the 2 studies were similar to the methodology of the current trial, other than not including a reference compound. **RESULTS:** Of the 925 patients who were screened, 287 did not meet entry criteria, and 638 patients enrolled in the study; the intent-to-treat (ITT) population included 615 patients who were evaluated for efficacy (mean [SD] age range, 38.8-40.7 [12.1-13.2] years; mean weight range, 83.3-87.0 [22.8-23.9] kg; female sex, 398 [64.7%]; white race, 458 [74.5%]). The primary end point did not reach significance based on the global F test for controlling multiplicity of the desvenlafaxine doses. Based on pairwise comparison, significantly greater improvements on the HAM-D(17) were observed in the desvenlafaxine 100 mg/d (-10.5; $P = 0.028$, unadjusted for multiple comparisons) and duloxetine 60 mg/d groups (-10.3; $P = 0.047$) compared with placebo (-8.7). Desvenlafaxine 100 mg/d and duloxetine 60 mg/d were associated with significantly better scores compared with placebo on the CGI-I, MADRS, CGI-S, and HAM-D(6). No significant differences were observed in any scale between the desvenlafaxine 50 mg/d and placebo groups. Discontinuation rates due to AEs were 5%, 7%, 13%, and 6% for the desvenlafaxine 50-mg/d, desvenlafaxine 100-mg/d, duloxetine 60-mg/d, and placebo groups, respectively. The ITT population from all 3 studies in the pooled analysis consisted of 1388 patients (mean [SD] age range, 38.8-45.7 [12.1-12.6] years; mean weight range, 73.1-87.0 [17.6-23.9] kg; female sex, 896 [64.6%]; white race, 1136 [81.8%]). Significantly greater improvements on the HAM-D(17) were observed for desvenlafaxine 50 mg/d (-11.5; $P < 0.001$) and 100 mg/d (-11.8; $P < 0.001$) versus placebo (-9.6). Both doses were significantly better than placebo on the CGI-I, MADRS, and HAM-D(6). **CONCLUSIONS:** The current study failed to meet its primary efficacy end point based on the a priori analysis plan. Desvenlafaxine was generally well tolerated. A post hoc pooled analysis of this trial and 2 previously published trials with both desvenlafaxine 50 and 100 mg/d found both doses to be effective for MDD compared with placebo. ClinicalTrials.gov Identifier: 00384033.