

Drug Class Review on Second Generation Antidepressants

Update #4: Preliminary Scan Report

August 2007

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 Update

September 2006 (searches through April 2006)

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

Adult outpatients with depressive, anxiety, and/or premenstrual dysphoric disorders and children with major depressive disorder.

Interventions

Eleven different treatments are currently available in the United States:

- Fluoxetine
- Sertraline
- Paroxetine
- Citalopram
- Escitalopram

- Fluvoxamine
- Venlafaxine
- Mirtazapine
- Duloxetine
- Bupropion
- Nefazodone

Efficacy/ Effectiveness outcomes

- Response
- Remission
- Speed and duration of response/remission
- Relapse (on and off treatment)
- Recurrence
- Functional capacity (quality of life, work productivity)
- Hospitalization

Safety outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Danger to self (suicide attempts and completions)
- Specific adverse effects or withdrawals due to specific adverse events (e.g., hyponatremia, activation of mania/hypomania, seizures, suicide, hepatotoxicity, weight gain, GI symptoms, loss of libido, etc.)
- Mortality

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from April 2006 through August 16, 2007 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) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 8.0) 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 258 citations. Of those, there are 90 new potentially relevant studies (see Appendix A, attached). The following table shows the conditions being studied. Seven of the 20 studies in pediatric MDD were results from the Treatment of Adolescent Depression Study (TADS).

Obsessive compulsive disorder 3	Major depressive disorder 30
Social anxiety disorder 1	Pediatric MDD 20 (TADS 7)
General anxiety disorder 6	Perimenopausal dysphoric disorder 3
Post traumatic stress disorder 8	Panic disorder 6
Background/Other 13	

New Drugs

None at this time.

New Safety Alerts

FDA:

5-Hydroxytryptamine Receptor Agonists (Triptans)

Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

Serotonin Syndrome

Audience: Neuropsychiatric and other healthcare professionals, and consumers

[Posted 07/19/2006] FDA notified healthcare professionals and consumers of new safety information regarding taking medications used to treat migraine headaches (triptans) together with certain types of antidepressant and mood disorder medications (selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs)). A life-threatening condition called serotonin syndrome may occur when triptans are used together with a SSRI or a SNRI.

Serotonin syndrome occurs when the body has too much of a chemical found in the nervous system (serotonin). Each of the above medications (triptans, SSRIs, and SNRIs), cause an increase in serotonin levels. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea.

Healthcare professionals prescribing a triptan, SSRI or SNRI should keep in mind that triptans are often used intermittently and either the triptan, SSRI or SNRI may be prescribed by a different physician; weigh the potential risk of serotonin syndrome with the expected benefit of using the above combination; discuss the possibility of serotonin syndrome with patients if a triptan and an SSRI or SNRI will be used together; and follow patients closely during treatment if a triptan and an SSRI or SNRI are used together.

Patients taking a triptan along with an SSRI or SNRI should talk to their doctor before stopping their medication and should immediately seek medical attention if they experience any of the above symptoms. FDA requested that all manufacturers of triptans, SSRIs and SNRIs update their prescribing information to warn of the possibility of serotonin syndrome when these medications are taken together.

SSRIs and Treatment Challenges of Depression in Pregnancy

Audience: Neuropsychiatric and other healthcare professionals, and consumers

[Posted 07/19/2006] FDA notified healthcare professionals and consumers of important information from two recent studies that should be considered when making treatment decisions in pregnant women who take antidepressants. The studies included pregnant women who were treated with selective serotonin reuptake inhibitors (SSRIs), or in a few cases, other antidepressant medications.

One study illustrated the potential risk of relapsed depression after stopping antidepressant medication during pregnancy. In this study, women who stopped their medicine were five times more likely to have a relapse of depression during their pregnancy than were women who continued to take their antidepressant medicine while pregnant.

The second study suggests there may be additional, though rare, risks of taking SSRI medications during pregnancy. This study focused on newborn babies with persistent pulmonary hypertension (PPHN), which is a serious and life-threatening lung condition that occurs soon after birth. Babies born with PPHN have high pressure in their lung blood vessels and are not able to get enough oxygen into their bloodstream. In this study, PPHN was six times more common in babies whose mothers took an SSRI antidepressant after the 20th week of pregnancy compared to babies whose mothers did not take an antidepressant. The study was too small to compare the risk of one drug compared to another. The finding of PPHN in babies of mothers who used a SSRI antidepressant in the second half of pregnancy adds to concerns from previous reports that infants of mothers taking SSRIs late in pregnancy may experience difficulties such as irritability, difficulty feeding and in very rare cases, difficulty breathing. Additionally, the labeling for paroxetine (Paxil) was recently changed to add information about findings in an epidemiologic study that suggests that exposure to the drug in the first trimester of pregnancy may be associated with an increased risk of cardiac birth defects. Women who are pregnant or thinking about becoming pregnant should not stop any antidepressant medication without first consulting their physician. The FDA is seeking additional information about the possible risk of PPHN in newborn babies of mothers who took SSRI antidepressants in pregnancy. FDA has asked the sponsors of all SSRIs to change prescribing information to describe the potential risk for PPHN.

Effexor XR (venlafaxine HCl) Extended-Release Capsules

Effexor (venlafaxine HCl) Tablets

Audience: Neuropsychiatric and other healthcare professionals

[Posted 10/25/2006] Wyeth and FDA notified healthcare professionals of revisions to the OVERDOSAGE/Human Experience section of the prescribing information for Effexor (venlafaxine HCl), indicated for treatment of major depressive disorder. In postmarketing experience, there have been reports of overdose with venlafaxine, occurring predominantly in combination with alcohol and/or other drugs. Published retrospective studies report that venlafaxine overdose may be associated with an increased risk of fatal outcome compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Healthcare professionals are advised to prescribe Effexor and Effexor XR in the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose.

Unsafe, Misrepresented Drugs Purchased Over the Internet:

Ambien (zolpidem tartrate) , Xanax (alprazolam), Lexapro (escitalopram oxalate), and Ativan (lorazepam)

Audience: Consumers, healthcare professionals

[Posted 02/16/2007] FDA informed consumers and healthcare professionals regarding the possible dangers of buying prescription medications online. Individuals who ordered Ambien, Xanax, Lexapro, and Ativan over the internet received a product that contained haloperidol, a powerful anti-psychotic drug. Several consumers experienced difficulty in breathing, muscle spasms and muscle stiffness after ingesting the suspect product and had to seek emergency medical treatment. Haloperidol can cause muscle stiffness, spasms, agitation and sedation.

Taking medication that contains an active ingredient other than what is prescribed by qualified healthcare professionals is generally unsafe. FDA urges consumers to review the FDA website for additional information prior to making purchases of medications over the internet

Antidepressant Medication Products

Audience: Healthcare professionals, consumers

[Posted 05/02/2007] FDA notified healthcare professionals that the Agency proposed that makers of all antidepressant medications update the existing black box warning on the prescribing information for their products to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment. The proposed labeling changes also state that scientific data did not show this increased risk in adults older than 24 years of age and that adults 65 years of age and older taking antidepressants have a decreased risk of suicidality. The proposed updates apply to the entire category of antidepressants. Individuals currently taking prescribed antidepressant medications should not stop taking them and should notify their healthcare professional if they have concerns. Manufacturers of antidepressant medications will have 30 days to submit their revised product labeling and revised Medication Guides to FDA for review.

HealthCanada:

None found at this time

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

1. Alderman, J., R. Wolkow, et al. (2006). "Drug concentration monitoring with tolerability and efficacy assessments during open-label, long-term sertraline treatment of children and adolescents." *J Child Adolesc Psychopharmacol* 16(1-2): 117-29.

OBJECTIVE: The aim of this study was to evaluate the long-term pharmacokinetics, safety, and efficacy of sertraline in children and adolescents with obsessive-compulsive disorder (OCD) or major depressive disorder (MDD). **METHOD:** After 42-day initial treatment and 9-day withdrawal phases, children (6-12 years, n = 16) and adolescents (13-18 years, n = 27) entered a 24-week open-label phase, with sertraline titrated to 200 mg/day. Blood samples for plasma sertraline and N-desmethylsertraline levels were taken at the beginning of the 24-week phase and at weeks 1, 4, 8, 12, and 24. Efficacy and safety data were also collected. **RESULTS:** Mean maximum daily dose at endpoint was 157 +/- 49 mg. For female and male children, mean sertraline/N-desmethylsertraline concentrations normalized to a 200-mg dose were 85.0/160 ng/mL (n = 8) and 79.3/134 ng/mL (n = 8), respectively, and for female and male adolescents, 70.5/109 ng/mL (n = 16) and 76.3/120 ng/mL (n = 8). No significant age or gender effects or age-by-gender interactions were observed in sertraline values. Mean sertraline plasma concentrations normalized for dose and body weight did not differ significantly by age or gender. Three (3) patients (7%) discontinued owing to adverse events. In patients with OCD (n = 10), improvements were observed in Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (p = 0.029) and National Institute of Mental Health (NIMH) Global Obsessive Compulsive Scale (OCS) (p = 0.01). In MDD patients (n = 32), Clinical Global Impression (CGI) Severity (p = 0.002) and Improvement (p = 0.011) improved. **CONCLUSIONS:** Long-term treatment of MDD and OCD with sertraline up to 200 mg/day in children and adolescents results in dose-normalized plasma concentrations comparable to those seen in adults. Sertraline was generally well tolerated, and patients demonstrated clinical improvement over 24 weeks of treatment.

2. Almeida, O. P., A. Waterreus, et al. (2006). "Preventing depression after stroke: Results from a randomized placebo-controlled trial." *J Clin Psychiatry* 67(7): 1104-9.

OBJECTIVE: We designed this study to determine whether the daily treatment of nondepressed acute stroke patients with sertraline reduced the incidence of depression at follow-up. **METHOD:** 111 patients with recent stroke (< 2 weeks; International Classification of Diseases, Tenth Revision criteria) were randomly assigned to treatment with placebo (N = 56) and sertraline (N = 55, 50 mg once daily) in this double-blind, placebo-controlled 24-week clinical trial. Subjects were recruited from the 2 largest teaching hospitals of Western Australia between June 2002 and June 2004. The primary endpoint of interest was development of clinically significant depressive symptoms as assessed by a Hospital Anxiety and Depression Scale-depression subscale score of 8 or above, or as diagnosed by the treating physician during 24 weeks. **RESULTS:** There was no significant difference in the incidence of depressive symptoms during 24 weeks of treatment (16.7% [8/48] sertraline vs. 21.6% [11/51] placebo, rate ratio = 0.8, 95% CI = 0.3 to 2.1, p = .590). The trial medication

was discontinued by 51.8% (29/56) of patients assigned placebo and 47.3% (26/55) assigned sertraline ($p = .634$), most often because of perceived side effects or because the treating physician introduced an antidepressant medication. CONCLUSIONS: Twenty-four-week treatment with 50 mg of sertraline once daily initiated within 2 weeks of onset of acute stroke is not a significantly more effective strategy to prevent 6-month depression than usual care plus placebo among nondepressed stroke patients. New pharmacologic and nonpharmacologic strategies need to be developed to reduce the health and financial burden associated with depression after stroke.

3. 4. Asakura, S., O. Tajima, et al. (2007). "Fluvoxamine treatment of generalized social anxiety disorder in Japan: a randomized double-blind, placebo-controlled study." *Int J Neuropsychopharmacol* 10(2): 263-74.

The efficacy of selective serotonin reuptake inhibitors (SSRIs) for the treatment of social anxiety disorder (SAD) has been reported in the USA and Europe. However, no clinical investigation has been done with SSRIs in Japanese patients with SAD. This study was performed to determine the effectiveness and safety of fluvoxamine for generalized SAD (GSAD) in Japanese patients. In this double-blind study, patients meeting DSM-IV criteria for GSAD were randomized to receive treatment with fluvoxamine or placebo for 10 wk. Fluvoxamine treatment was initiated at 50 mg/d, and increased by 50 mg weekly to a maximum of 150 or 300 mg/d. The primary efficacy outcome was mean change from baseline on the Liebowitz Social Anxiety Scale - Japanese Version (LSAS-J) total score. The secondary outcomes were response according to the Clinical Global Impressions - Global Improvement (CGI-I) score and three domains of the Sheehan Disability Scale (SDS; used to assess psychosocial impairment). A total of 176 fluvoxamine-treated patients and 89 placebo-treated patients were eligible for the efficacy analysis. At week 10, the fluvoxamine-treated patients had a significantly greater reduction in the LSAS-J total score compared with placebo-treated patients ($p=0.0197$), with significantly more fluvoxamine recipients being at least much improved on the CGI-I scale compared with placebo-treated patients ($p=0.024$). Fluvoxamine-treated patients also had better responses on the SDS compared with placebo-treated patients ($p=0.0208$). Fluvoxamine was safe and well tolerated. These results suggest that fluvoxamine is effective for the treatment of Japanese patients with GSAD.

4. 5. Baca, E., M. Roca, et al. (2006). "Venlafaxine extended-release in patients older than 80 years with depressive syndrome." *Int J Geriatr Psychiatry* 21(4): 337-43.

OBJECTIVES: The aim of this evaluation was to assess the efficacy and safety of venlafaxine extended-release (ER) in very old primary care out-patients with depressive syndrome and associated anxiety symptoms. METHODS: This was an observational, naturalistic, multicenter, prospective, open-label study in an outpatient population with a diagnosis of depressive syndrome with anxiety symptoms. Minimum scores of 17 and 10 on the Hamilton Rating Scale for Depression (HAM-D(17)) and Anxiety (HAM-A), respectively, were required. Daily doses of 75 mg to 225 mg of venlafaxine extended release (ER) were administered for 24 weeks. Effectiveness for depressive-anxious symptomatology was assessed using the HAM-D(17) and HAM-A scales. PATIENTS: The 97 patients discussed in this report are a subgroup comprising all elderly patients, aged ≥ 80 years, who were part of the larger observational, naturalistic, multicenter, prospective, open-label

study and who had received venlafaxine ER for a maximum duration of 24 weeks.

RESULTS: At endpoint, remission rates were 57.1% (HAM-D(17) ≤ 7), 66.2% (HAM-A ≤ 7), and 52% (HAM-D(17) ≤ 7 and HAM-A ≤ 7). Twenty patients (20.6%) dropped out or were withdrawn. Adverse events were reported by seven (7.2%) patients, none were reported as serious. **CONCLUSIONS:** Venlafaxine ER was shown to be an effective and safe drug for the treatment of very elderly primary care patients with depressive syndrome and associated anxiety symptoms.

5. Back, S. E., K. T. Brady, et al. (2006). "Symptom improvement in co-occurring PTSD and alcohol dependence." *J Nerv Ment Dis* 194(9): 690-6.

This study investigated the temporal course of improvement in PTSD and alcohol dependence symptoms among individuals participating in a 12-week outpatient treatment study. Participants were 94 individuals with comorbid PTSD and alcohol dependence enrolled in a double-blind, placebo-controlled medication trial. Outcome measures included PTSD symptoms (as measured by the Clinician Administered PTSD Scale, Impact of Events Scale, and Civilian Mississippi Scale for PTSD) and alcohol use severity (as measured by the Time Line Follow Back). Study completion rates were significantly higher for individuals who demonstrated improvement in both disorders. Improvements in PTSD had a greater impact on improvement in alcohol dependence symptoms than the reciprocal relationship. Improvement in hyperarousal PTSD symptoms, in particular, was related to substantially improved alcohol use. Examination of the temporal course of symptom improvement revealed that alcohol symptoms tended to start improving either before or in conjunction with PTSD symptoms. Although preliminary in nature, these findings suggest that co-occurring PTSD symptoms may have a strong impact on alcohol dependence treatment outcome, and that PTSD treatment may be important to optimizing outcomes for patients with comorbid PTSD and alcohol dependence.

6. Baldwin, D. S., J. A. Cooper, et al. (2006). "A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder." *Int Clin Psychopharmacol* 21(3): 159-69.

This multinational, randomized, double-blind, flexible-dose study evaluated the short- and long-term antidepressant tolerability and efficacy of escitalopram and paroxetine. Tolerability was assessed by monitoring adverse events throughout the study, and discontinuation events during brief treatment interruption and tapered withdrawal. Discontinuation-emergent effects were evaluated in two separate double-blind periods. First, to mimic the consequences of non-compliance, patients were randomized to one of two treatment interruption periods (placebo-substitution for 3-5 days). Second, patients were randomized to a 1-2-week tapered withdrawal period randomly scheduled between weeks 28 and 31. The pre-specified primary efficacy endpoint was the mean change from baseline in total Montgomery-Asberg Depression Rating Scale (MADRS) score at week 8, using the principle of last observation carried forward. A total of 323 patients entered 8 weeks of double-blind treatment and received at least one flexible dose of escitalopram (10-20 mg/day) or paroxetine (20-40 mg/day). Patients who demonstrated evidence of a significant clinical improvement (Clinical Global Impression-Improvement of 1 or 2) at week 8 entered

a 19-week, double-blind maintenance period during which they were treated with the same dose they received at week 8, followed by a 1-2-week tapered withdrawal period. A total of 89 patients (28%) withdrew during the study; significantly ($P<0.01$) more patients withdrew from the paroxetine group (34%) than from the escitalopram group (21%), and significantly ($P<0.05$) more paroxetine patients withdrew due to lack of efficacy. The mean MADRS total score improved for both treatment groups from baseline to week 8, with no statistical difference between groups. In severely depressed patients (baseline MADRS total score ≥ 30), escitalopram was superior ($P<0.05$) to paroxetine at week 27 (end of maintenance treatment). There was a high prevalence of sexual dysfunction at baseline: the mean Arizona Sexual Experience Scale (ASEX) score was approximately 20 points in both treatment groups. Mean total ASEX scores increased slightly above baseline values during the acute period and declined slightly below baseline values towards the end of the maintenance period. During taper and cessation of treatment, patients in the paroxetine group demonstrated significantly more discontinuation symptoms relative to escitalopram based on the Discontinuation Emergent Signs and Symptoms scores.

7. Baldwin, D. S., A. K. Huusom, et al. (2006). "Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, double-blind study." *Br J Psychiatry* 189: 264-72.

BACKGROUND: It is uncertain whether higher doses of selective serotonin reuptake inhibitors have greater efficacy in generalised anxiety disorder. **AIMS:** To assess the efficacy of different doses of escitalopram in generalised anxiety disorder. **METHOD:** Randomised, double-blind, placebo-controlled, fixed-dose, parallel-group, 12-week study, with 681 patients: placebo (n=139); escitalopram, 5 mg/day, (n=134); 10 mg/day (n=136); 20 mg/day (n=133); paroxetine, 20 mg/day (n=139). **RESULTS:** Mean change in the primary efficacy measure was greater with escitalopram 10 and 20 mg than with placebo; 10 mg was more efficacious than paroxetine. Paroxetine was superior to placebo on some secondary measures, at some time points. Compared with placebo, more patients withdrew because of adverse events with escitalopram 20 mg and paroxetine. **CONCLUSIONS:** Escitalopram was efficacious in generalised anxiety disorder, 20 was not significantly superior to 10 mg/day. Escitalopram 10 mg was more efficacious than paroxetine.

8. Bandelow, B., H. F. Andersen, et al. (2007). "Escitalopram in the treatment of anxiety symptoms associated with depression." *Depress Anxiety* 24(1): 53-61.

Most patients with depression have symptoms of anxiety associated with their illness. Our aim in this study was to investigate the efficacy of escitalopram, a proven antidepressant, on symptoms of anxiety in patients with major depressive disorder (MDD). Data from five placebo-controlled escitalopram studies in MDD were analyzed. Three of the studies also included a comparison with citalopram. In all studies, anxiety was assessed using the Inner Tension item (item 3) of the Montgomery-Asberg Depression Rating Scale (MADRS). In three studies, anxiety symptoms were also specifically assessed, either continuously over time or at baseline and end point, by using the Hamilton Rating Scale for Anxiety (HAM-A), the Anxious Mood item of the HAM-A (item 1), the Psychic Anxiety subscale of the HAM-A (items 1-6 and 14), the Anxiety Psychic item (item 10) of the Hamilton Rating Scale for Depression (HAM-D-24), and the Anxiety/Somatization subfactor (items 10-13, 15, and 17)

of the HAM-D-24. Escitalopram was significantly superior to placebo in all comparisons. Citalopram was also consistently better than placebo in all comparisons, except in the HAM-D-24 Anxiety/Somatization subfactor. In some comparisons with placebo, escitalopram showed a significantly earlier onset of action or an earlier separation. Escitalopram was significantly more effective compared to placebo in treating both anxiety symptoms and the entire depression in the total depressive population, as well as in depressive patients with a high degree of anxiety.

9. Barbui, C. and M. Percudani (2006). "Epidemiological impact of antidepressant and antipsychotic drugs on the general population." *Curr Opin Psychiatry* 19(4): 405-10.
PURPOSE OF REVIEW: To analyse the prevalence of and sex and age distribution associated with antidepressant and antipsychotic drug exposure in the general population and to highlight recent epidemiological findings concerning specific adverse outcomes associated with drug exposure. RECENT FINDINGS: Epidemiological studies indicate high rates of second-generation antidepressant and antipsychotic drug use in the general population. The use is more prevalent among women than among men, and in older rather than in younger age groups. A new pattern of adverse outcomes has been described in individuals exposed to newer agents, including a possible risk of suicidal acts in adults receiving second-generation antidepressants, the risk of cerebrovascular events in older individuals receiving second-generation antipsychotics and the risk of metabolic disturbances in individuals exposed to specific second-generation antipsychotics. SUMMARY: The assessment of, and attention to, the development of specific adverse reactions in individuals exposed to second-generation psychotropic drugs may improve treatment outcomes.
10. Bauer, M. S., S. R. Wisniewski, et al. (2006). "Brief report: paroxetine in younger and adult individuals at high risk for suicide." *Psychopharmacol Bull* 39(1): 31-7.
Paroxetine has been associated with increased rates of suicidality in adolescents treated in antidepressant clinical trials. Regulatory agencies in the United States and the UK have issued warnings that are already changing clinical practice for adolescents. In a pilot analysis, we characterized the extent of risk by investigating paroxetine-associated suicidality in a related high-risk population, younger and adult individuals with bipolar disorder whose rate of suicide attempts approaches 2 percent per year. A cross-sectional survey and cohort analysis of 1,000 patients followed for at least 1 year under naturalistic conditions in the NIMH-funded STEP-BD network revealed no association of paroxetine with suicidality in those less than or at least 21 years of age. In fact, the younger group showed a trend for decreased suicidality ($P = .13$). Thus, increased suicidality risk with paroxetine exposure does not extend to this other high-risk mood disordered population, even among younger individuals.
11. Becker, M. E., M. A. Hertzberg, et al. (2007). "A placebo-controlled trial of bupropion SR in the treatment of chronic posttraumatic stress disorder." *J Clin Psychopharmacol* 27(2): 193-7.
OBJECTIVE: Although selective serotonin reuptake inhibitors have been the most empirically studied pharmacotherapy for posttraumatic stress disorder (PTSD), a need remains for the investigation of additional pharmacological agents in the treatment of PTSD.

The present study examined the use of bupropion sustained release (SR) as compared with placebo for symptom reduction in patients with PTSD: approximately half who were already prescribed an selective serotonin reuptake inhibitor and half who were not. **METHOD:** Thirty patients (mean age, 50 years) with civilian- or military-related PTSD enrolled in an 8-week evaluation of bupropion SR versus placebo assigned in a 2:1 ratio in addition to their usual pharmacological care. Statistical tests included analyzing both study completers and using an intent-to-treat analysis, as well as post hoc examination of responders versus nonresponders. **RESULTS:** Although no between-group differences were detected, both groups reported a reduction in PTSD symptoms. In a hypothesis-generating post hoc analysis of responders versus nonresponders in the bupropion SR condition (defined as a Clinician Global Improvement score of at least minimally improved), it seemed that younger patients not currently on another antidepressant were more likely to benefit from bupropion. **CONCLUSIONS:** Bupropion SR in the treatment of PTSD had no significant effect in the current sample. Factors contributing to the absence of an effect need further study. Our analysis points to the inclusion of age and concomitant antidepressant treatment as important variables in any future larger-scale study.

12. Berard, R., R. Fong, et al. (2006). "An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder." *J Child Adolesc Psychopharmacol* 16(1-2): 59-75.

OBJECTIVE: The aim of this study was to examine the efficacy, safety, and tolerability of paroxetine in adolescents with unipolar major depression. **METHOD:** Two hundred eighty-six (286) adolescents with unipolar major depression were randomly assigned to receive either paroxetine or placebo for 12 weeks. **RESULTS:** The proportion of Montgomery-Asberg Depression Rating Scale (MADRS) responders (at least 50% reduction from baseline) for paroxetine and placebo were similar and not statistically different at endpoint ($p = 0.702$). A similar result was obtained for change from baseline on the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-L) depression subscale. Among secondary endpoints, only a significantly higher Clinical Global Impression-Improvement (CGI-I) response rate was reported in paroxetine-treated patients versus placebo (69.2% versus 57.3%; $p = 0.045$). In general, results differed by age, with patients older than 16 years demonstrating a greater response to active treatment. This age group also reported more adverse experiences (AEs) relative to placebo than younger adolescents. Overall, paroxetine was generally well tolerated (11% discontinued owing to an AE versus 7% of placebo-treated patients). A post hoc analysis of AEs related to suicidal behavior suggested a greater incidence of these events for paroxetine than for placebo (4.4% versus 2.1%); however, this difference was not statistically significant (odds ratio, 2.15, 95% Confidence Interval 0.45, 10.33; $p = 0.502$). **CONCLUSIONS:** No statistically significant differences were observed for paroxetine compared with placebo on the two prospectively defined primary efficacy variables. Paroxetine at 20-40 mg/day administered over a period of up to 12 weeks was generally well tolerated.

13. Bodnar, L. M., K. R. Sunder, et al. (2006). "Treatment with selective serotonin reuptake inhibitors during pregnancy: deceleration of weight gain because of depression or drug?" *Am J Psychiatry* 163(6): 986-91.

14. Boulenger, J. P., A. K. Huusom, et al. (2006). "A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients." *Curr Med Res Opin* 22(7): 1331-41.

OBJECTIVE: This randomised, double-blind, fixed-dose study evaluated the efficacy of escitalopram and paroxetine in the long-term treatment of severely depressed patients with major depressive disorder (MDD). **RESEARCH DESIGN AND METHODS:** Patients with a primary diagnosis of MDD and baseline Montgomery-Asberg Depression Rating Scale (MADRS) ≥ 30 were randomised to 24 weeks of double-blind treatment with fixed doses of either escitalopram (20 mg) (n = 232) or paroxetine (40 mg) (n = 227). The primary analysis of efficacy was an analysis of covariance (ANCOVA) of change from baseline to endpoint (Week 24) in MADRS total score (last observation carried forward, LOCF). **MAIN OUTCOME MEASURES; RESULTS:** At endpoint (24 weeks), the mean change from baseline in MADRS total score was -25.2 for patients treated with escitalopram (n = 228) and -23.1 for patients with paroxetine (n = 223), resulting in a difference of 2.1 points (p < 0.05). The difference in the change in the MADRS total score (LOCF) was significantly in favour of escitalopram from Week 8 onwards. The proportion of remitters (MADRS ≤ 12) after 24 weeks was 75% for escitalopram and 67% for paroxetine (p < 0.05). The results on the primary efficacy scale were supported by significantly greater differences in favour of escitalopram on the Hamilton Anxiety, Hamilton Depression and Clinical Global Impression-Improvement and -Severity scales. For very severely depressed patients (baseline MADRS ≥ 35), there was a difference of 3.4 points at endpoint in the MADRS total score in favour of escitalopram (p < 0.05). The overall withdrawal rate for patients treated with escitalopram (19%) was significantly lower than with paroxetine (32%) (p < 0.01). The withdrawal rate due to adverse events was significantly lower for escitalopram (8%) compared to paroxetine (16%) (p < 0.05). There were no significant differences in the incidence of individual adverse events during treatment. **CONCLUSION:** Escitalopram is significantly more effective than paroxetine in the long-term treatment of severely depressed patients.

15. Bridge, J. A., S. Iyengar, et al. (2007). "Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials." *Jama* 297(15): 1683-96.

CONTEXT: The US Food and Drug Administration (FDA) has issued warnings that use of antidepressant medications poses a small but significantly increased risk of suicidal ideation/suicide attempt for children and adolescents. **OBJECTIVE:** To assess the efficacy and risk of reported suicidal ideation/suicide attempt of antidepressants for treatment of pediatric major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and non-OCD anxiety disorders. **DATA SOURCES AND STUDY SELECTION:** PubMed (1988 to July 2006), relevant US and British regulatory agency reports, published abstracts of important scientific meetings (1998-2006), clinical trial registries, and information from authors. Studies were published and unpublished randomized, placebo-controlled, parallel-group trials of second-generation antidepressants (selective serotonin reuptake inhibitors,

nefazodone, venlafaxine, and mirtazapine) in participants younger than 19 years with MDD, OCD, or non-OCD anxiety disorders. **DATA EXTRACTION:** Information was extracted on study characteristics, efficacy outcomes, and spontaneously reported suicidal ideation/suicide attempt. **DATA SYNTHESIS:** Twenty-seven trials of pediatric MDD (n = 15), OCD (n = 6), and non-OCD anxiety disorders (n = 6) were selected, and risk differences for response and for suicidal ideation/suicide attempt estimated by random-effects methods. Pooled risk differences in rates of primary study-defined measures of responder status significantly favored antidepressants for MDD (11.0%; [95% confidence interval {CI}, 7.1% to 14.9%]), OCD (19.8% [95% CI, 13.0% to 26.6%]), and non-OCD anxiety disorders (37.1% [22.5% to 51.7%]), corresponding to a number needed to treat (NNT) of 10 (95% CI, 7 to 15), 6 (4 to 8), and 3 (2 to 5), respectively. While there was increased risk difference of suicidal ideation/suicide attempt across all trials and indications for drug vs placebo (0.7%; 95% CI, 0.1% to 1.3%) (number needed to harm, 143 [95% CI, 77 to 1000]), the pooled risk differences within each indication were not statistically significant: 0.9% (95% CI, -0.1% to 1.9%) for MDD, 0.5% (-1.2% to 2.2%) for OCD, and 0.7% (-0.4% to 1.8%) for non-OCD anxiety disorders. There were no completed suicides. Age-stratified analyses showed that for children younger than 12 years with MDD, only fluoxetine showed benefit over placebo. In MDD trials, efficacy was moderated by age, duration of depression, and number of sites in the treatment trial. **CONCLUSIONS:** Relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. Benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.

16. Carandang, C., D. Santor, et al. (2007). "Data safety monitoring boards and other study methodologies that address subject safety in "high-risk" therapeutic trials in youths." *J Am Acad Child Adolesc Psychiatry* 46(4): 489-92.
17. Clayton, A. H., H. A. Croft, et al. (2006). "Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies." *J Clin Psychiatry* 67(5): 736-46.
OBJECTIVE: To compare the effects on sexual functioning and the antidepressant efficacy of once-daily bupropion extended release (XL) and escitalopram in adults with major depressive disorder (MDD). **METHOD:** Adult outpatients with moderate to severe DSM-IV-defined MDD and normal sexual functioning were randomly assigned to receive bupropion XL (300-450 mg/day; N = 276), escitalopram (10-20 mg/day; N = 281), or placebo (N = 273) for up to 8 weeks in 2 identically designed, randomized, double-blind, parallel-group studies (study 1 conducted from February 6, 2003, to June 10, 2004; study 2 conducted from January 21, 2003, to June 15, 2004). Data were analyzed prospectively for each study individually, and pooled data were analyzed retrospectively. **RESULTS:** In both the individual studies and the pooled dataset, the incidence of orgasm dysfunction at week 8 (primary endpoint) and the incidence of worsened sexual functioning at the end of the treatment period were statistically significantly lower with bupropion XL than with escitalopram (p < .05), not statistically

different between bupropion XL and placebo ($p > \text{or} = .067$), and statistically significantly higher with escitalopram than with placebo ($p < \text{or} = .001$). The percentages of patients with orgasm dysfunction at week 8 in study 1, study 2, and the pooled dataset, respectively, were 13%, 16%, and 15% with bupropion XL; 32%, 29%, and 30% with escitalopram; and 11%, 8%, and 9% with placebo. The respective percentages of patients with worsened sexual functioning at the end of the treatment period were 18%, 22%, and 20% with bupropion XL; 37%, 34%, and 36% with escitalopram; and 14%, 16%, and 15% with placebo. Mean changes in Changes in Sexual Functioning Questionnaire scores for all domains at week 8 were statistically significantly worse for escitalopram compared with bupropion XL ($p < \text{or} = .05$). Separation from placebo could not be established at a statistical .05 level for bupropion on 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score. However, escitalopram showed statistical superiority to placebo on HAM-D-17 total score in one of the 2 studies and in the pooled data. Bupropion XL did not statistically differ from escitalopram with respect to mean change in HAM-D-17 total score, HAM-D-17 response or remission rates, percentage of patients much or very much improved on Clinical Global Impressions-Improvement scale scores, or mean changes in the Hospital Anxiety and Depression (HAD) scale total score or Clinical Global Impressions-Severity of Illness scale score at week 8. CONCLUSIONS: Bupropion XL had a sexual tolerability profile significantly better than that of escitalopram with similar HAM-D-17 remission rates and HAD total scores in patients with MDD.

18. Cookson, J., I. Gilaberte, et al. (2006). "Treatment benefits of duloxetine in major depressive disorder as assessed by number needed to treat." *Int Clin Psychopharmacol* 21(5): 267-73.

The efficacy of an antidepressant typically is assessed by comparing it with placebo using a validated rating scale. This type of analysis, however, does not translate well to the clinical settings. For clinicians, a more meaningful measure is the number needed to treat (NNT). The objective of this analysis is to assess the efficacy of duloxetine in terms of NNT. Data were obtained from nine clinical trials designed to assess the efficacy and safety of duloxetine as a treatment for major depressive disorder. These studies examined 8-9 weeks of acute treatment with duloxetine. NNT estimates were determined for duloxetine, selective serotonin reuptake inhibitor comparators from six multi-dose studies, and for duloxetine in patients ≥ 65 years of age. The NNT was based on the Hamilton Depression Rating Scale (HAM-D-17) for response and remission, and improvements defined by the Clinical Global Impression (CGI) were estimated and compared. The NNT was favorable for both duloxetine and selective serotonin reuptake inhibitor compared with placebo. The patients receiving duloxetine had NNT for HAM-D-17 response of 6.0, remission 7-9, and CGI-defined improvement 6-7 by 8 weeks. The NNTs for selective serotonin reuptake inhibitors (fluoxetine or paroxetine, 20 mg/day) were around 7 for response, 11 for remission, and 8 for CGI-defined improvement. The NNTs in the elderly were similar. The NNT for several measures of efficacy including remission consistently demonstrated the treatment benefits of duloxetine as well as of fluoxetine and paroxetine compared with placebo.

19. Curry, J., P. Rohde, et al. (2006). "Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS)." *J Am Acad Child Adolesc Psychiatry* 45(12): 1427-39.

OBJECTIVE: To identify predictors and moderators of response to acute treatments among depressed adolescents (N = 439) randomly assigned to fluoxetine, cognitive-behavioral therapy (CBT), both fluoxetine and CBT, or clinical management with pill placebo in the Treatment for Adolescents With Depression Study (TADS). **METHOD:** Potential baseline predictors and moderators were identified by a literature review. The outcome measure was a week 12 predicted score derived from the Children's Depression Rating Scale-Revised (CDRS-R). For each candidate moderator or predictor, a general linear model was conducted to examine main and interactive effects of treatment and the candidate variable on the CDRS-R predicted scores. **RESULTS:** Adolescents who were younger, less chronically depressed, higher functioning, and less hopeless with less suicidal ideation, fewer melancholic features or comorbid diagnoses, and greater expectations for improvement were more likely to benefit acutely than their counterparts. Combined treatment, under no condition less effective than monotherapy, was more effective than fluoxetine for mild to moderate depression and for depression with high levels of cognitive distortion, but not for severe depression or depression with low levels of cognitive distortion. Adolescents from high-income families were as likely to benefit from CBT alone as from combined treatment. **CONCLUSIONS:** Younger and less severely impaired adolescents are likely to respond better to acute treatment than older, more impaired, or multiply comorbid adolescents. Family income level, cognitive distortions, and severity of depression may help clinicians to choose among acute interventions, but combined treatment proved robust in the presence of moderators.

20. Davidson, J., D. Baldwin, et al. (2006). "Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial." *Arch Gen Psychiatry* 63(10): 1158-65.

CONTEXT: No large-scale posttraumatic stress disorder drug trials have been conducted to evaluate treatment effects beyond 12 weeks outside of those with selective serotonin reuptake inhibitors. **OBJECTIVE:** To evaluate the efficacy of venlafaxine extended release (ER), a serotonin norepinephrine reuptake inhibitor, in posttraumatic stress disorder. **DESIGN:** 6-month, double-blind, placebo-controlled trial. **SETTING:** International study at 56 sites. **Patients** Adult outpatients (N = 329) with a primary diagnosis of posttraumatic stress disorder as defined in the DSM-IV, symptoms for 6 months or longer, and a 17-item Clinician-Administered Posttraumatic Stress Disorder Scale score of 60 or higher. **Intervention** Patients randomly assigned to receive flexible doses of venlafaxine ER (37.5-300 mg/d) or placebo for 24 weeks. **MAIN OUTCOME MEASURES:** Primary measure was the change from baseline in the Clinician-Administered Posttraumatic Stress Disorder Scale score. Secondary measures included remission, defined as a Clinician-Administered Posttraumatic Stress Disorder Scale score of 20 or lower, and changes in symptom cluster scores, frequency of remission, and time to remission. Measures of stress vulnerability, resilience, depression, quality of life, functioning, and global illness severity were also taken. **RESULTS:** Mean changes from baseline in Clinician-Administered Posttraumatic Stress Disorder Scale total scores at end point were -51.7 for venlafaxine ER and -43.9 for placebo (P = .006). Improvement was significantly greater for the venlafaxine

ER group than for the placebo group in cluster scores for reexperiencing ($P = .008$) and avoidance/numbing ($P = .006$), but not for hyperarousal. Remission rates were 50.9% for venlafaxine ER and 37.5% for placebo ($P = .01$). The venlafaxine ER group also showed significantly greater improvement at end point than the placebo group ($P < .05$) on all other reported outcome measures. The mean maximum daily dose of venlafaxine ER was 221.5 mg/d. Withdrawal rates were similar between groups with no significant difference in dropouts attributable to adverse events. **CONCLUSION:** In this study, venlafaxine ER was effective and well tolerated in short-term and continuation treatment of patients with posttraumatic stress disorder.

21. Davidson, J., B. O. Rothbaum, et al. (2006). "Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study." *J Clin Psychopharmacol* 26(3): 259-67.

This 12-week, double-blind, multicenter trial evaluated the efficacy of venlafaxine extended release (ER), sertraline, and placebo in adult outpatients ($N = 538$) with a primary diagnosis of posttraumatic stress disorder (PTSD), as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, symptoms for 6 months or more and 17-item Clinician-administered PTSD Scale (CAPS-SX17) score of 60 or more. Patients were randomly assigned to receive placebo or flexible doses of venlafaxine ER (37.5-300 mg/d) or sertraline (25-200 mg/d) for 12 weeks or less. The primary outcome was the baseline-to-end point change in total CAPS-SX17 score (last observation carried forward). Secondary measures included CAPS-SX17 symptom cluster scores for reexperiencing/intrusion, avoidance/numbing, and hyperarousal; frequency of remission (CAPS-SX17 $<$ or $=20$); and changes in Davidson Trauma Scale total score and symptom cluster scores for avoidance/numbing, hyperarousal, and reexperiencing/intrusion. Mean changes in CAPS-SX17 scores were -41.8, -39.4, and -33.9 for venlafaxine ER ($P < 0.05$ vs. placebo), sertraline, and placebo, respectively. Mean changes for venlafaxine ER, sertraline, and placebo in CAPS-SX17 cluster scores were -13.0, -11.7, and -11.0 for reexperiencing; -17.1, -16.8, and -13.7 ($P < 0.05$ both active treatments vs. placebo) for avoidance/numbing; and -11.8, -10.9, and -9.2 ($P < 0.05$ venlafaxine vs. placebo) for hyperarousal. Week 12 remission rates were venlafaxine ER 30.2% ($P < 0.05$ vs. placebo), sertraline 24.3%, and placebo 19.6%. The venlafaxine ER group had significantly better Davidson Trauma Scale total and cluster scores than placebo. Mean maximum daily doses were 225-mg venlafaxine ER and 151-mg sertraline. Both treatments were generally well tolerated. Study results suggest that venlafaxine ER is effective and well tolerated in the short-term treatment of PTSD.

22. Djulus, J., G. Koren, et al. (2006). "Exposure to mirtazapine during pregnancy: a prospective, comparative study of birth outcomes." *J Clin Psychiatry* 67(8): 1280-4.

BACKGROUND: Mirtazapine is a novel piperazinoazepine antidepressant, unrelated to any known class of antidepressants. Currently, apart from a few case reports and case series in the literature, there are no studies evaluating the safety of this drug during pregnancy.

OBJECTIVE: To determine whether mirtazapine increases the risk for major malformations in newborns when used by pregnant women. **METHOD:** The study design was prospective, with 2 comparison groups: disease-matched pregnant women diagnosed with depression taking other antidepressants and pregnant women exposed to nonteratogens. The primary

outcome was major malformations in neonates; secondary endpoints included spontaneous abortions, therapeutic abortions, gestational age at birth, and mean birth weight. Women were recruited from 5 teratogen information services in Toronto, Canada; Farmington, Conn., U.S.A.; Jerusalem, Israel; Rome, Italy; Sydney, Australia; and from the Drug Safety Research Unit in Southampton, United Kingdom. Women were recruited into the study from June 2002 to August 2005. RESULTS: We were able to follow 104 pregnancy outcomes in each drug group. There were 77 live births, 1 stillbirth, 20 spontaneous abortions, 6 therapeutic abortions, and 2 major malformations in the mirtazapine group. The mean +/- SD birth weight was 3335 +/- 654 g and the mean +/- SD gestational age at delivery was 38.9 +/- 2.5 weeks. Most (95%) of the women took mirtazapine in the first trimester, but only 25% of the women took it throughout pregnancy. The differences among the 3 groups were in the rate of spontaneous abortions, which was higher in both antidepressant groups (19% in the mirtazapine group and 17% in the other antidepressant group) than in the nonteratogen group (11%), but none of the differences were statistically significant. The rate of preterm births (prior to 37 weeks' gestation) was also higher in the mirtazapine group (10%) and in the other antidepressant group (7%) than in the nonteratogen group (2%). The difference was statistically significant between the mirtazapine group and the nonteratogen group ($p = .04$). CONCLUSION: Mirtazapine does not appear to increase the baseline rate of major malformations of 1% to 3%. However, the higher number of spontaneous abortions in the antidepressant groups confirms the higher rates of spontaneous abortions in pregnant women taking antidepressant medications found in previous studies.

23. Donnelly, C. L., K. D. Wagner, et al. (2006). "Sertraline in children and adolescents with major depressive disorder." *J Am Acad Child Adolesc Psychiatry* 45(10): 1162-70. OBJECTIVE: To explore time to first response and time to first persistent response of sertraline versus placebo and compare these parameters between children (6-11 years old, $n = 177$) and adolescents (12-17 years old, $n = 199$) with major depressive disorder. METHOD: A 10-week placebo-controlled treatment was followed by a 24-week open-label sertraline treatment. The double-blind studies were not powered to detect efficacy differences between age groups. A post hoc analysis explored time to first response and first persistent response using the Children's Depression Rating Scale-Revised and Clinical Global Impressions-Improvement predefined criteria. RESULTS: There were no statistically significant differences in time to first response or first persistent response between sertraline and placebo in children, except for time to first response on Clinical Global Impressions-Improvement. Sertraline had a significantly faster time to first persistent response in adolescents compared to placebo. Within treatment groups, children had a significantly faster time to first response than adolescents, whether treated with placebo or sertraline, but not on time to first persistent response. Both age groups showed similar improvement over 34 weeks of treatment. CONCLUSION: In the double-blind studies, children and adolescents had different patterns of response with sertraline vs. placebo.
24. Dusseldorp, E., P. Spinhoven, et al. (2007). "Which panic disorder patients benefit from which treatment: cognitive therapy or antidepressants?" *Psychother Psychosom* 76(3): 154-61.

BACKGROUND: Beliefs about the controllability of a disorder may be relevant in the causation, maintenance and treatment of disorders. We investigated whether congruence between patients' beliefs about controllability of a panic disorder and the type of treatment provided predicted outcome. **METHODS:** The differential effectiveness of cognitive therapy and antidepressant treatment (paroxetine or clomipramine) was investigated in a sample of 129 panic disorder patients in a 12-week, pretest posttest placebo-controlled study. Panic frequency, agoraphobic avoidance, anxiety, depression, and disability were measured with various validated interviewer and self-report measures. Beliefs about controllability were measured with the Multidimensional Anxiety Locus of Control Scale measuring an internal, chance, therapist and medication locus of control. In order to analyze aptitude-treatment interactions a new strategy called the Regression Trunk Approach was used in addition to classical hierarchical multiple regression analysis. **RESULTS:** Using the Regression Trunk Approach we found that locus of control orientation (LOC) predicted the differential effectiveness of cognitive therapy. Those patients with a medium internal LOC who received cognitive therapy performed significantly better than all patients who received a placebo pill on 8 of the 10 outcome variables. We did not find a differential LOC effect for antidepressant treatment. No evidence for aptitude-treatment interactions using hierarchical multiple regression analysis was found. **CONCLUSIONS:** Moderately strong beliefs about self-control of panic disorder congruent with the cognitive intervention provided seem to moderate treatment effectiveness. Future studies must be more attentive to the nonlinear effects of patient characteristics on the outcome of different types of treatments.

25. Eckert, L. and B. Falissard (2006). "Using meta-regression in performing indirect-comparisons: comparing escitalopram with venlafaxine XR." *Curr Med Res Opin* 22(11): 2313-21.

BACKGROUND: In the absence of well-powered, randomised, direct-comparison trials, indirect comparisons are the only option for comparing treatment strategies. Several methodologies have been developed and each has sparked criticism. Using direct comparisons of escitalopram versus venlafaxine extended release (XR), we explore the differences between the two compounds through indirect comparisons. **METHODS:** The CENTRAL, Medline and Embase databases were interrogated, focusing on randomized placebo-controlled clinical trials involving adult patients treated for major depressive disorder in the acute phase. Corresponding authors were contacted to reduce missing data. Effect sizes were derived from each study's primary outcome. For indirect comparisons, a global effect size was computed through meta-regression. For direct comparisons, the studies were considered separately due to missing data. Non-inferiority assessments were employed. The conclusion of the meta-regression was then compared with the conclusions made in direct comparison trials. **RESULTS:** Ten placebo-controlled studies--six assessing escitalopram and four assessing venlafaxine XR--and two direct comparison studies were retrieved. Escitalopram was found to be non-inferior to venlafaxine XR in both indirect and direct comparisons with results of mean -0.02 (unilateral 95% confidence interval [CI] -0.16 to infinity) and 0.23 (95% CI -0.01 to infinity), respectively. Results obtained by both indirect and direct comparisons were similar. Investigating the influence of age, gender repartition and severity at baseline suggests that results are consistent. Results were also considered robust against publication bias. **CONCLUSIONS:** This empirical finding suggests

that escitalopram is non-inferior to venlafaxine XR. This reinforces the evidence found in direct comparisons trials. Indirect comparisons through meta-regression may be suitable to support decision-making. To fully assess its potential, further evaluation of this methodology, using other examples, is needed.

26. Emslie, G., C. Kratochvil, et al. (2006). "Treatment for Adolescents with Depression Study (TADS): safety results." *J Am Acad Child Adolesc Psychiatry* 45(12): 1440-55.

OBJECTIVE: To compare the rates of physical, psychiatric, and suicide-related events in adolescents with MDD treated with fluoxetine alone (FLX), cognitive-behavioral therapy (CBT), combination treatment (COMB), or placebo (PBO). **METHOD:** Safety assessments included adverse events (AEs) collected by spontaneous report, as well as systematic measures for specific physical and psychiatric symptoms. Suicidal ideation and suicidal behavior were systematically assessed by self- and clinician reports. Suicidal events were also reanalyzed by the Columbia Group and expert raters using the Columbia-Classification Algorithm for Suicidal Assessment used in the U.S. Food and Drug Administration reclassification effort. **RESULTS:** Depressed adolescents reported high rates of physical symptoms at baseline, which improved as depression improved. Sedation, insomnia, vomiting, and upper abdominal pain occurred in at least 2% of those treated with FLX and/or COMB and at twice the rate of placebo. The rate of psychiatric AEs was 11% in FLX, 5.6% in COMB, 4.5% in PBO, and 0.9% in CBT. Suicidal ideation improved overall, with greatest improvement in COMB. Twenty-four suicide-related events occurred during the 12-week period: 5 patients (4.7%) in COMB, 10 (9.2%) in FLX, 5 (4.5%) in CBT, and 3 (2.7%) in placebo. Statistically, only FLX had more suicide-related events than PBO ($p = .0402$, odds ratio (OR) = 3.7, 95% CI 1.00-63.7). Only five actual attempts occurred (2 COMB, 2 FLX, 1 CBT, 0 PBO). There were no suicide completions. **CONCLUSIONS:** Different methods for eliciting AEs produce different results. In general, as depression improves, physical complaints and suicidal ideation decrease in proportion to treatment benefit. In this study, psychiatric AEs and suicide-related events are more common in FLX-treated patients. COMB treatment may offer a more favorable safety profile than medication alone in adolescent depression.

27. Emslie, G. J., R. L. Findling, et al. (2007). "Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials." *J Am Acad Child Adolesc Psychiatry* 46(4): 479-88.

OBJECTIVE: The safety, efficacy, and tolerability of venlafaxine extended release (ER) in subjects ages 7 to 17 years with major depressive disorder were evaluated in two multicenter, randomized, double-blind, placebo-controlled trials conducted between October 1997 and August 2001. **METHOD:** Participants received venlafaxine ER (flexible dose, based on body weight; intent to treat, $n = 169$) or placebo (intent to treat, $n = 165$) for up to 8 weeks. The primary efficacy variable was the change from baseline in the Children's Depression Rating Scale-Revised score at week 8. **RESULTS:** There were no statistically significant differences between venlafaxine ER and placebo on the Children's Depression Rating Scale-Revised in either study. A post hoc age subgroup analysis of the pooled data showed greater improvement on the Children's Depression Rating Scale-Revised with venlafaxine ER than with placebo (-24.4 versus -19.9; $p = .022$) among adolescents (ages 12-17), but not among

children (ages 7-11). The most common adverse events were anorexia and abdominal pain. Hostility and suicide-related events were more common in venlafaxine ER-treated participants than in placebo-treated participants. There were no completed suicides. CONCLUSIONS: Venlafaxine ER may be effective in depressed adolescents. However, its safety and efficacy in pediatric patients has not been established. Prescribers should monitor for signs of suicidal ideation and hostility in pediatric patients taking venlafaxine ER.

28. Emslie, G. J., K. D. Wagner, et al. (2006). "Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial." *J Am Acad Child Adolesc Psychiatry* 45(6): 709-19.
OBJECTIVE: To assess the efficacy and tolerability of paroxetine in pediatric major depressive disorder. METHOD: Subjects 7 to 17 years old with major depressive disorder received paroxetine (10-50 mg/day) or placebo for 8 weeks from 2000 to 2001. The primary efficacy measure was change from baseline in the Children's Depression Rating Scale-Revised total score at week 8 last observation carried forward). Safety was primarily assessed by spontaneous reporting of adverse events. RESULTS: A total of 206 patients (intent to treat) were randomized to paroxetine (n = 104) or placebo (n = 102). Week 8 Children's Depression Rating Scale-Revised total score adjusted mean changes from baseline for patients receiving paroxetine and placebo were -22.58 (SE 1.47) and -23.38 points (SE 1.60), respectively (0.80, 95% confidence interval -3.09 to 4.69, p = 0.684). Increased cough (5.9% versus 2.9%), dyspepsia (5.9% versus 2.9%), vomiting (5.9% versus 2.0%), and dizziness (5.0% versus 1.0%) occurred in $\geq 5\%$ of the paroxetine group and at least twice that of the placebo group. Six of 104 (5.8%) paroxetine patients reported serious adverse events compared to 1 placebo patient (1.0%). The incidence of adverse events of suicidal behavior and/or ideation while taking study medication (excluding taper) was 1.92% (2/104) for paroxetine versus 0.98% (1/102) for placebo. CONCLUSIONS: Paroxetine was not shown to be more efficacious than placebo for treating pediatric major depressive disorder.
29. Emslie, G. J., P. P. Yeung, et al. (2007). "Long-term, open-label venlafaxine extended-release treatment in children and adolescents with major depressive disorder." *CNS Spectr* 12(3): 223-33.
INTRODUCTION: Because major depressive disorder (MDD) is often chronic and recurrent, even pediatric patients who are treated successfully during an acute episode may need longer-term treatment. Yet, data on long-term treatment with antidepressants in pediatric MDD are limited. OBJECTIVE: To evaluate long-term effectiveness and safety of treatment with venlafaxine extended-release (ER) in children and adolescents with MDD. METHODS: Subjects (n=86) 7-17 years of age with MDD entered a multicenter, open-label study of flexible-dose venlafaxine ER for 6 weeks of acute treatment, followed by continuation treatment for up to 6 months total treatment. The primary efficacy variable was the Children's Depression Rating Scale-Revised (CDRS-R) total score (intent-to-treat population). RESULTS: Mean CDRS-R total score decreased from 60.1 \pm 10.0 at baseline to 36.3 \pm 13.1 at week 6, and to 33.8 \pm 15.0 at 6 months (last observation carried forward). Among completers (n=36), the mean CDRS-R total score was 24.3 \pm 7.6 at the end of 6 months of treatment. The most frequent treatment-emergent adverse events were headache (53%), nausea (26%), infection (24%), abdominal pain (22%), vomiting (21%), and

pharyngitis (19%). Fifteen (17%) participants discontinued due to adverse events, 9 of whom did so within the first 6 weeks. Serious adverse events (suicide attempt [two], hostility [two], hallucinations, depression, and pharyngitis) occurred in seven patients. There were no suicides. CONCLUSION: Most improvement with venlafaxine ER occurs during the first 6 weeks of treatment. Prescribers should be alert to signs of suicidal ideation and hostility in pediatric patients.

30. Ferguson, J. M., A. Khan, et al. (2007). "Relapse prevention of panic disorder in adult outpatient responders to treatment with venlafaxine extended release." *J Clin Psychiatry* 68(1): 58-68.

OBJECTIVE: To compare the long-term efficacy of venlafaxine extended release (ER) with placebo in preventing panic disorder relapse in out-patient treatment responders. METHOD: Outpatients aged ≥ 18 years who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for panic disorder with or without agoraphobia for at least the previous 3 months, with ≥ 6 full symptom panic attacks in the 2 weeks prior to screening and ≥ 3 in the 2 weeks before baseline and a Clinical Global Impressions-Severity of Illness rating ≥ 4 at screen were eligible to participate. Outpatients received flexible-dose (75-225 mg/day) venlafaxine ER for 12 weeks. Treatment responders were randomly assigned to venlafaxine ER or placebo for 26 weeks. Criteria for response were ≤ 1 panic attack per week during the last 2 weeks of open-label treatment and a Clinical Global Impressions-Improvement score of 1 or 2. The primary endpoint, time to relapse during double-blind treatment, defined as ≥ 2 full symptom panic attacks per week for 2 consecutive weeks or discontinuation due to loss of effectiveness, was evaluated using Kaplan-Meier survival analysis. The study was conducted between December 2001 and August 2003. RESULTS: The intent-to-treat population had 291 patients in the open-label phase and 169 in the double-blind phase (placebo, N = 80; venlafaxine ER, N = 89; mean daily dose 165-171 mg). Time to relapse was significantly longer with venlafaxine ER than placebo ($p < .001$). All secondary measures of panic attack treatment efficacy, quality of life, and disability were significantly better with venlafaxine ER than placebo ($p < \text{or} = .005$). CONCLUSION: Venlafaxine ER was safe, well tolerated, and effective in preventing relapse in outpatients with panic disorder.

31. Fineberg, N. A., B. Tonnoir, et al. (2007). "Escitalopram prevents relapse of obsessive-compulsive disorder." *Eur Neuropsychopharmacol* 17(6-7): 430-9.

To examine the efficacy and tolerability of escitalopram in the prevention of relapse in patients with OCD, 468 patients with OCD were treated with open label escitalopram (10 mg or 20 mg) for 16 weeks, after which the 320 responders (Y-BOCS total score decrease $\geq 25\%$) were randomised to placebo or escitalopram (at the assigned dose) for 24 weeks double-blind treatment. The primary analysis (time to relapse) showed a significant advantage for escitalopram ($p < 0.001$, log-rank test). The proportion of patients who relapsed was statistically significantly higher in the placebo group (52%) than in the escitalopram group (23%) ($p < 0.001$, chi(2)-test). The risk of relapse was 2.74 times higher for placebo compared to escitalopram. Escitalopram was well tolerated and improvements in obsessive-compulsive symptoms reported during the open label period were sustained during the

double-blind extension of treatment with active drug. These results demonstrate that escitalopram is effective for long-term treatment and relapse prevention in OCD.

32. Friedman, M. J., C. R. Marmar, et al. (2007). "Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting." *J Clin Psychiatry* 68(5): 711-20.

OBJECTIVE: To evaluate the efficacy of sertraline in the treatment of posttraumatic stress disorder (PTSD) in a Veterans Affairs (VA) clinic setting involving patients with predominantly combat-related PTSD. **METHOD:** 169 outpatient subjects with a DSM-III-R diagnosis of PTSD and who scored 50 or higher on Part 2 of the Clinician-Administered PTSD Scale (CAPS-2) at the end of a 1-week placebo run-in period participated. Patients recruited from 10 VA medical centers were randomly assigned to 12 weeks of flexibly dosed sertraline (25-200 mg/day) (N = 86; 70% with combat-related PTSD; 79% male) or placebo (N = 83; 72% combat-related PTSD; 81% male) between May 1994 and September 1996. The primary efficacy measures were the mean change in CAPS-2 total severity score from baseline to endpoint, in the total score from the Impact of Event Scale, and in the Clinical Global Impressions-Severity of Illness and Improvement scales. **RESULTS:** There were no significant differences between sertraline and placebo on any of the primary or secondary efficacy measures at endpoint. In order to understand the results, gender, duration of illness, severity of illness, type of trauma, and history of alcohol/substance abuse were explored as potential moderators of outcome, but no consistent effects were uncovered. Sertraline was well tolerated, with 13% of patients discontinuing due to adverse events. **CONCLUSION:** Sertraline was not demonstrated to be efficacious in the treatment of PTSD in the VA clinic settings studied.

33. Gastpar, M., A. Singer, et al. (2006). "Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study." *Pharmacopsychiatry* 39(2): 66-75.

OBJECTIVE: The objective of this double-blind, randomised, placebo-controlled, multicentre clinical study was to demonstrate the non-inferiority and safety of the hypericum extract STW3-VI in a once-daily dosage regime in the treatment of moderate depression. During the 6-week treatment phase, the course of depression was documented by use of HAMD (items 1-17), the von Zerssen's Adjective Mood Scale (BfS) and the CGI scales. The primary objective of this 3-arm design study was to demonstrate the non-inferiority of hypericum extract STW3-VI (900 mg) to the SSRI citalopram (20 mg) and superiority of hypericum over placebo. **METHODS:** Outpatients (N = 388) suffering from moderate depression were enrolled. The safety and tolerability of hypericum extract in comparison to citalopram and placebo was investigated on the basis of CGI, the occurrence of adverse events and the investigation of laboratory parameters and vital signs. **RESULTS:** From almost identical baseline values of 21.9 +/- 1.2 points (hypericum extract), 21.8 +/- 1.2 points (citalopram) and 22.0 +/- 1.2 points (placebo), the HAMD score was reduced to 10.3 +/- 6.4 (hypericum extract), 10.3 +/- 6.4 (citalopram) and 13.0 +/- 6.9 (placebo), respectively. Based on this data, the statistical significant therapeutic equivalence of hypericum extract STW3-VI to citalopram ($p < 0.0001$) and the superiority of this hypericum extract over placebo ($p <$

0.0001) was demonstrated. At the end of treatment 54.2 % (hypericum extract), 55.9 % (citalopram) and 39.2 % (placebo) of the patients were assessed as therapy responders. The secondary efficacy parameters, change in BfS, CGI and amount of therapy responders showed that the hypericum group was not statistically different from the citalopram group, and significantly superior to the placebo group. Significantly more adverse events with "certain", "probable" or "possible" relation to study medication were documented in the citalopram group (hypericum: 17.2 %, citalopram: 53.2 %, placebo: 30 %). In most cases, the investigators assessed the tolerability of hypericum extract, citalopram and placebo as "good" or "very good". **CONCLUSION:** The non-inferiority of hypericum extract as compared to citalopram and the superiority of both active compounds to placebo were demonstrated, as well as a better safety and tolerability of hypericum extract in comparison to citalopram. These results revealed that hypericum extract STW3-VI is a good alternative to chemically defined antidepressants in the treatment of outpatients with moderate depression.

34. Glassman, A. H., J. T. Bigger, et al. (2006). "Onset of major depression associated with acute coronary syndromes: relationship of onset, major depressive disorder history, and episode severity to sertraline benefit." *Arch Gen Psychiatry* 63(3): 283-8.
- CONTEXT:** Depression observed following acute coronary syndrome (ACS) is common and associated with an increased risk of death. The Sertraline Antidepressant Heart Attack Trial (SADHART) tested the safety and efficacy of a selective serotonin reuptake inhibitor in this population. No evidence of harm was seen, and sertraline hydrochloride had an overall beneficial effect on mood that occurred primarily in patients with a history of episodes of major depressive disorder (MDD). **OBJECTIVES:** To determine how frequently the MDD began before ACS and whether onset of the current MDD episode before or after the ACS event influenced response to sertraline. **DESIGN, SETTINGS, AND PARTICIPANTS:** A randomized, double-blind, placebo-controlled treatment of 369 patients with ACS and MDD was conducted in 40 outpatient clinics in 10 countries between April 1, 1997, and April 30, 2001. **MAIN OUTCOME MEASURES:** Diagnosis of MDD, number of previous episodes of depression, and episode onset before or after hospitalization were established using the Diagnostic Interview Schedule. Treatment response was measured with the Clinical Global Impression-Improvement scale. **RESULTS:** Fifty-three percent of MDD episodes began before hospitalization for the index episode of ACS (for 197 of 369 patients), and 94% of the MDD episodes began more than 30 days before the index ACS episode. Episodes of MDD that began prior to ACS responded more frequently to sertraline than to placebo (63% vs 46%, respectively; odds ratio, 2.0; 95% confidence interval, 1.13-3.55) whereas depression with onset beginning after hospitalization showed a high placebo response rate (69% vs 60%, respectively) and low sertraline-placebo response ratio (1.15). Multivariate analysis indicated that time of onset of the current episode, history of MDD, and baseline severity independently predicted the sertraline-placebo response ratio. **CONCLUSIONS:** Half of the episodes of major depression associated with ACS began long before ACS and therefore were not caused by ACS. Patients whose current episodes of MDD begin before ACS, those with a history of MDD, and those whose episodes are severe should be treated because they will benefit considerably from sertraline. Since these 3 predictors of sertraline response are independent, having more than 1 of them substantially increases the benefit of sertraline while reducing the chance of spontaneous recovery.

35. Hall, W. D. and J. Lucke (2006). "How have the selective serotonin reuptake inhibitor antidepressants affected suicide mortality?" *Aust N Z J Psychiatry* 40(11-12): 941-50. **OBJECTIVE:** We review evidence on two claims that have been made about the effects of selective serotonin reuptake inhibitor (SSRI) antidepressants; that they have: (i) decreased suicide rates in the population; and (ii) increased suicide rates in some individuals early in treatment. **METHOD:** We critically review evidence in the English-speaking peer-reviewed medical literature on: (i) meta-analyses of randomized controlled trials (RCTs) of SSRIs; (ii) observational studies of suicide risk in patients prescribed SSRIs and other antidepressants; and (iii) ecological studies of correlations between population use of SSRI use and population suicide rates. **RESULTS:** The largest and most recent meta-analyses of RCTs of SSRIs have found suggestive evidence that SSRIs increase suicidal ideation early in treatment compared with placebo. Observational studies have found an increased risk of self-harm within 9 days of an antidepressant drug being prescribed but the risk has been similar for the older tricyclic antidepressants and the SSRIs. Ecological studies in developed countries have found either that suicide rates have declined as SSRI use has increased, or have found no relationship between suicide rates and increased SSRI use. **CONCLUSIONS:** Meta-analyses of RCTs suggest that SSRIs increase suicide ideation compared with placebo but the observational studies suggest that SSRIs do not increase suicide risk more than older antidepressants. If SSRIs increase suicide risk in some patients, the number of additional deaths is very small because ecological studies have generally found that suicide mortality has declined (or at least not increased) as SSRI use has increased.
36. Hammad, T. A., T. Laughren, et al. (2006). "Suicidality in pediatric patients treated with antidepressant drugs." *Arch Gen Psychiatry* 63(3): 332-9. **CONTEXT:** There has been concern that widely used antidepressant agents might be associated with an increased risk of suicidal ideation and behavior (suicidality) in pediatric patients. **OBJECTIVE:** To investigate the relationship between antidepressant drugs and suicidality in pediatric patients participating in randomized, placebo-controlled trials. **DATA SOURCES:** Data were derived from 23 trials conducted in 9 drug company-supported programs evaluating the effectiveness of antidepressants in pediatric patients and 1 multicenter trial (the Treatment for Adolescents With Depression Study) that evaluated fluoxetine hydrochloride. **STUDY SELECTION:** All placebo-controlled trials submitted to the Food and Drug Administration were eligible for inclusion. Evaluable data were derived from 4582 patients in 24 trials. Sixteen trials studied patients with major depressive disorder, and the remaining 8 studied obsessive-compulsive disorder (n = 4), generalized anxiety disorder (n = 2), attention-deficit/hyperactivity disorder (n = 1), and social anxiety disorder (n = 1). Only 20 trials were included in the risk ratio analysis of suicidality because 4 trials had no events in the drug or placebo groups. **DATA EXTRACTION:** Individual patient data were available for all the trials. **DATA SYNTHESIS:** A meta-analysis was conducted to obtain overall suicidality risk estimates for each drug individually, for selective serotonin reuptake inhibitors in depression trials as a group, and for all evaluable trials combined. There were no completed suicides in any of these trials. The multicenter trial was the only individual trial to show a statistically significant risk ratio (4.62; 95% confidence interval

[CI], 1.02-20.92). The overall risk ratio for selective serotonin reuptake inhibitors in depression trials was 1.66 (95% CI, 1.02-2.68) and for all drugs across all indications was 1.95 (95% CI, 1.28-2.98). The overall risk difference for all drugs across all indications was 0.02 (95% CI, 0.01-0.03). CONCLUSION: Use of antidepressant drugs in pediatric patients is associated with a modestly increased risk of suicidality.

37. Hartford, J., S. Kornstein, et al. (2007). "Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial." *Int Clin Psychopharmacol* 22(3): 167-74.

This study examined the efficacy and tolerability of duloxetine 60-120 mg/day for the treatment of patients with generalized anxiety disorder. This was a multicenter, randomized, double-blind, flexible-dose, placebo and active-controlled (venlafaxine extended-release 75-225 mg/day) trial designed to assess duloxetine 60-120 mg/day during 10 weeks of treatment in adults with Diagnostic and statistical manual of mental disorders-IV-defined generalized anxiety disorder. The primary efficacy outcome measure was mean change from baseline to endpoint in the Hamilton Anxiety Rating Scale total score assessed using analysis of covariance. A total of 487 patients were randomly assigned to duloxetine (n=162), venlafaxine XR (n=164), or placebo (n=161). Significantly greater improvement on the Hamilton Anxiety Rating Scale total score occurred in the duloxetine (P=0.007) and venlafaxine XR (P<0.001) groups compared with the placebo group. Overall discontinuation rates did not differ among the three groups, but adverse event-related discontinuation was significantly higher in the duloxetine (14.2%, P<0.001) and venlafaxine XR (11.0%, P=0.001) groups than in the placebo group (1.9%). During the 2-week drug-tapering phase, discontinuation-emergent adverse events were significantly greater in the venlafaxine XR group (26.9%, P=0.04), but not in the duloxetine group (19.4%, P=0.448) compared with placebo (15.8%). Duloxetine 60-120 mg/day and venlafaxine XR 75-225 mg/day were each efficacious treatments for patients with generalized anxiety disorder.

38. Herran, A., M. L. Ramirez, et al. (2006). "Panic disorder, treatment with selective serotonin reuptake inhibitors, and cholesterol levels." *J Clin Psychopharmacol* 26(5): 538-40.

39. Jensen, P. S. (2006). "After TADS, can we measure up, catch up, and ante up?" *J Am Acad Child Adolesc Psychiatry* 45(12): 1456-60.

40. Kasper, S., O. M. Lemming, et al. (2006). "Escitalopram in the long-term treatment of major depressive disorder in elderly patients." *Neuropsychobiology* 54(3): 152-9.
AIM: The primary aim was to investigate the long-term safety and tolerability of escitalopram (10 or 20 mg/day) treatment of elderly patients suffering from major depressive disorder. The secondary aim was to examine response to treatment, as measured by change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from study entry to each visit, using observed cases. METHOD: This extension trial included 225 patients who had completed an 8-week, double blind, placebo-controlled lead-in study, which was performed in outpatients in primary care and in specialist clinics. The intent-to-treat population comprised 223 patients. RESULTS: The overall withdrawal rate was 24%. The most common reason for withdrawal was adverse events (9%). The 5 most common adverse

events were accidental injury, rhinitis, weight increase, arthralgia and coughing, with an incidence ranging from 8 to 13%. No new types of adverse events were reported in this extension study compared to the 8-week lead-in study. The mean weight increased from 69.7 kg at study entry to 70.3 kg at endpoint. The percentage of patients in remission (MADRS total score \leq 12) increased from 48% at study entry to 72% by week 52.

CONCLUSION: Escitalopram demonstrated a favourable tolerability profile during 52 weeks of open-label treatment of elderly patients, with further improvement in depressive symptoms.

41. Kennard, B., S. Silva, et al. (2006). "Remission and residual symptoms after short-term treatment in the Treatment of Adolescents with Depression Study (TADS)." *J Am Acad Child Adolesc Psychiatry* 45(12): 1404-11.

OBJECTIVE: To ascertain remission rates in depressed youth participating in the Treatment for Adolescents With Depression Study (TADS), a multisite clinical trial that randomized 439 adolescents with major depressive disorder (MDD) to a 12-week treatment of fluoxetine (FLX), cognitive-behavioral therapy (CBT), their combination (COMB), or clinical management with pill placebo (PBO). METHOD: Using an end-of-treatment Children's Depression Rating Scale-Revised (CDRS-R) total score of 28 or below as the criterion for remission, rates of remission were examined with logistic regression, controlling for site. Loss of MDD diagnosis and residual symptoms in responders (defined as Clinical Global Impressions-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved) were also examined across treatment groups. RESULTS: After 12 weeks of treatment, 102 (23%) of 439 youths had reached remission. The remission rate was significantly higher in the COMB group (37%) relative to the other treatment groups (FLX, 23%; CBT, 16%; PBO, 17%), with odds ratios of 2.1 for COMB versus FLX, 3.3 for COMB versus CBT, and 3.0 for COMB versus PBO. In addition, 71% of subjects across treatment groups no longer met criteria for MDD at the end of acute treatment. Fifty percent of the youths who responded by CGI-I criteria continued to have residual symptoms, such as sleep or mood disturbances, fatigue, and poor concentration. CONCLUSIONS: The combination of FLX and CBT was superior to both monotherapy and PBO in terms of remission rates, but overall rates of remission remain low and residual symptoms are common at the end of 12 weeks of treatment.

42. Kennedy, S. H., K. A. Fulton, et al. (2006). "Sexual function during bupropion or paroxetine treatment of major depressive disorder." *Can J Psychiatry* 51(4): 234-42.

OBJECTIVE: The primary objective was to evaluate sexual function (SF) separately in men and women with major depressive disorder (MDD) before and during treatment with bupropion sustained release (SR) or paroxetine. The secondary objectives involved a comparative evaluation of the Sex Effects Scale (Sex FX) and the Investigator-Rated Sexual Desire and Functioning Scale (IRSD-F), as well as a comparison of antidepressant outcomes and an examination of the relation between level of depression and SF over time. METHOD: There were 141 patients (68 women and 73 men) who met DSM-IV criteria for a current major depressive episode. They were randomly assigned to receive bupropion SR (150 to 300 mg daily) or paroxetine (20 to 40 mg daily) under double-blind trial conditions. Patients were assessed at baseline and at 2, 4, 6, and 8 weeks with the 17-item Hamilton Depression Rating

Scale (HDRS17), Sex FX, and IRSD-F. RESULTS: Prior to treatment, women reported significantly lower SF on both the Sex FX and IRSD-F scales, compared with men. During treatment, there were no significant drug differences on measures of SF over time for women; however, men who were treated with paroxetine reported a worsening of SF, whereas bupropion SR did not significantly alter SF. Both bupropion SR and paroxetine produced clinically and statistically significant reductions in HDRS17 scores as well as comparable rates of response and remission. There was a statistically significant correlation between the 2 measures of SF at all visits. There was also a significant inverse relation between depression and SF in women, but not in men, irrespective of drug. CONCLUSION: According to the Sex FX scale, a significant difference in antidepressant-related sexual dysfunction was detected in men, but not women, during treatment with bupropion SR or paroxetine.

43. Kim, T. S., C. U. Pae, et al. (2006). "Comparison of venlafaxine extended release versus paroxetine for treatment of patients with generalized anxiety disorder." *Psychiatry Clin Neurosci* 60(3): 347-51.

This trial was to evaluate the efficacy and tolerability of venlafaxine extended release (XR) and paroxetine for treatment of patients with generalized anxiety disorder (GAD). Sixty patients who met DSM-IV criteria for GAD were randomly assigned to either venlafaxine XR or paroxetine for 8 weeks. Efficacy was assessed with the Hamilton Rating Scale for Anxiety (HAM-A) and Clinical Global Impression-Severity of Illness (CGI-S) scale at the baseline, week 1, week 4, and week 8. The side-effects were collected with reported adverse events and laboratory tests throughout the study period. Repeated measures analysis of variance (ANOVA) on the HAM-A and CGI-S scores showed a significant decrease over time in both treatment groups without significant group difference or time x group interaction effect. There were no serious adverse events in both groups. This open trial demonstrated that either venlafaxine XR or paroxetine would be effective and tolerable for the treatment of patients with GAD. Double blind, placebo-controlled head-to-head comparison studies are needed to draw a definite conclusion.

44. Kornstein, S. G., A. Bose, et al. (2006). "Escitalopram maintenance treatment for prevention of recurrent depression: a randomized, placebo-controlled trial." *J Clin Psychiatry* 67(11): 1767-75.

BACKGROUND: Major depressive disorder is a recurrent illness that often requires maintenance antidepressant treatment. Escitalopram is a selective serotonin reuptake inhibitor (SSRI) that has shown efficacy in both acute and continuation treatment of major depressive disorder. The current trial examined the efficacy of maintenance escitalopram treatment in preventing depression recurrence in patients who responded to acute SSRI therapy. METHOD: Patients with recurrent DSM-IV-defined major depressive disorder (≥ 2 previous episodes; baseline Montgomery-Asberg Depression Rating Scale [MADRS] score ≥ 22) who had responded (MADRS score ≤ 12) to acute open-label treatment (8 weeks) with 1 of 4 SSRIs (fluoxetine, sertraline, paroxetine, or citalopram) received open-label, flexible-dose continuation treatment (16 weeks) with escitalopram (10-20 mg/day). At the end of continuation treatment, patients maintaining response criteria were randomly assigned to 52 weeks of double-blind, fixed-dose maintenance treatment with escitalopram

(10 or 20 mg/day) or placebo. Recurrence was defined as a MADRS score ≥ 22 or insufficient therapeutic response during the double-blind phase. The study was conducted between October 16, 2000, and February 4, 2003. RESULTS: A total of 234 patients who responded to acute open-label treatment with 1 of 4 SSRIs received at least 1 dose of open-label escitalopram continuation treatment. Of 164 patients who completed escitalopram continuation treatment, 139 were randomly assigned to double-blind maintenance treatment with escitalopram (N = 73) or placebo (N = 66). Mean baseline MADRS scores at the start of the maintenance phase were < 5 for both the placebo- and escitalopram-treatment groups. Time to recurrence was significantly longer in patients who received maintenance treatment with escitalopram compared with patients switched to placebo (hazard ratio = 0.26, 95% CI = 0.13 to 0.52, $p < .001$). Long-term escitalopram treatment was well tolerated. CONCLUSION: Maintenance treatment with escitalopram was well tolerated and significantly reduced the risk for recurrence of depression. Patients with few residual symptoms following continuation treatment with escitalopram experienced a high rate of depression recurrence when switched to placebo, demonstrating the need for maintenance therapy of recurrent major depressive disorder beyond 4 to 6 months of initial symptom resolution even if few residual symptoms are present.

45. Kornstein, S. G., T. B. Pearlstein, et al. (2006). "Low-dose sertraline in the treatment of moderate-to-severe premenstrual syndrome: efficacy of 3 dosing strategies." *J Clin Psychiatry* 67(10): 1624-32.

OBJECTIVE: Many studies have demonstrated the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of premenstrual dysphoric disorder, but few studies have investigated the efficacy of SSRIs in the treatment of premenstrual syndrome (PMS). The objective of this study was to evaluate the safety and efficacy of sertraline in the treatment of moderate-to-severe PMS using 3 different dosing strategies: luteal phase (2 cycles), followed by continuous dosing throughout the month (1 cycle), followed by dosing begun at the first onset of PMS symptoms, or "symptom-onset" dosing (1 cycle). METHOD: 314 women with PMS from 22 U.S. sites were randomly assigned to fixed-dose treatment with sertraline (25 or 50 mg/day) or placebo for 4 menstrual cycles after a single-blind, placebo lead-in cycle. Assessments included the Daily Symptom Report (DSR), the Clinical Global Impressions-Severity of Illness and -Improvement scales, the Patient Global Evaluation scale, the Quality of Life Enjoyment and Satisfaction Questionnaire, and the Social Adjustment Scale-Self Report. RESULTS: Intermittent luteal-phase dosing with low doses of sertraline (25 and 50 mg/day) produced significant improvement across 2 menstrual cycles, based on total DSR scores, compared with placebo. Continuous and symptom-onset dosing were also effective in treating PMS symptoms, particularly at the lower dose of 25 mg/day. CONCLUSIONS: The results of the current study suggest that low doses of sertraline may be a safe, effective, and well-tolerated treatment for moderate-to-severe PMS.

46. Kratochvil, C., G. Emslie, et al. (2006). "Acute time to response in the Treatment for Adolescents with Depression Study (TADS)." *J Am Acad Child Adolesc Psychiatry* 45(12): 1412-8.

OBJECTIVE: To examine the time to response for both pharmacotherapy and psychotherapy in the Treatment for Adolescents with Depression Study (TADS). METHOD: Adolescents

(N = 439, ages 12 to 17 years) with major depressive disorder were randomized to fluoxetine (FLX), cognitive-behavioral therapy (CBT), their combination (COMB), or pill placebo (PBO). Defining response as very much improved or much improved on the Clinical Global Impression-Improvement Scale (CGI-I), survival analyses using Cox proportional hazards models, and Kaplan-Meier curves were conducted to evaluate time to first response and time to stable response for subjects receiving pharmacotherapy (COMB, FLX, PBO) as well as for subjects receiving CBT (COMB, CBT). Direct comparisons between pharmacotherapy and CBT were not made because of differences in visit schedules. **RESULTS:** Based on pharmacist CGI-I scores, COMB and FLX showed faster onset of benefit than PBO on time to response and time to stable response ($p < .001$), and COMB was faster than FLX on time to stable response ($p = .034$). The probability of sustained early response was approximately threefold greater for COMB than PBO, twofold greater for FLX than PBO, and 1.5-fold greater for COMB than FLX. On the psychotherapist CGI-I scores, both first response and stable response occurred faster in COMB than CBT ($p < .001$), with a probability of sustained early response approximately threefold greater for COMB than CBT. **CONCLUSIONS:** In the acute treatment of depressed adolescents, FLX and COMB accelerate response relative to PBO, and COMB accelerates response relative to CBT alone.

47. Lam, R. W. and H. F. Andersen (2006). "The influence of baseline severity on efficacy of escitalopram and citalopram in the treatment of major depressive disorder: an extended analysis." *Pharmacopsychiatry* 39(5): 180-4.

OBJECTIVE: To determine the differences between escitalopram and citalopram in the treatment of patients with major depressive disorder across a range of baseline severity of depression using trend analysis. **METHODS:** Data from the three placebo-controlled studies comparing escitalopram to citalopram were analyzed. The pre-specified primary outcome variable was MADRS total score; secondary outcomes included Clinical Global Impression-Severity (CGI-S) and -Improvement (CGI-I) scores. All analyses were based on an intent-to-treat (ITT) population and all direct comparisons were done by ANCOVA adjusting for baseline value and centre. **RESULTS:** Analyses of the pooled data (N=1203) show that, while the difference between citalopram and placebo was approximately constant across the range of baseline severity, the difference between escitalopram and placebo ($p=0.0010$ for no trend) and between escitalopram and citalopram ($p=0.0012$ for no trend) became greater, the more severely depressed the patients were at baseline. A similar pattern was apparent with the CGI-S and CGI-I results. There was a significant superiority of escitalopram over citalopram in response rate (defined as $> \text{ or } = 50\%$ decrease in MADRS total score), and this difference increased with increasing baseline severity. **CONCLUSION:** These trend analyses thus indicate that the superiority of escitalopram over citalopram is more apparent as the baseline severity of depression increases.

48. Lam, R. W., A. J. Levitt, et al. (2006). "The Can-SAD study: a randomized controlled trial of the effectiveness of light therapy and fluoxetine in patients with winter seasonal affective disorder." *Am J Psychiatry* 163(5): 805-12.

OBJECTIVE: Light therapy and antidepressants have shown comparable efficacy in separate studies of seasonal affective disorder treatment, but few studies have directly compared the two treatments. This study compared the effectiveness of light therapy and an antidepressant

within a single trial. **METHOD:** This double-blind, randomized, controlled trial was conducted in four Canadian centers over three winter seasons. Patients met DSM-IV criteria for major depressive disorder with a seasonal (winter) pattern and had scores ≥ 23 on the 24-item Hamilton Depression Rating Scale. After a baseline observation week, eligible patients were randomly assigned to 8 weeks of double-blind treatment with either 1) 10,000-lux light treatment and a placebo capsule, or 2) 100-lux light treatment (placebo light) and fluoxetine, 20 mg/day. Light treatment was applied for 30 minutes/day in the morning with a fluorescent white-light box; placebo light boxes used neutral density filters. **RESULTS:** A total of 96 patients were randomly assigned to a treatment condition. Intent-to-treat analysis showed overall improvement with time, with no differences between treatments. There were also no differences between the light and fluoxetine treatment groups in clinical response rates (67% for each group) or remission rates (50% and 54%, respectively). Post hoc testing found that light-treated patients had greater improvement at 1 week but not at other time points. Fluoxetine was associated with greater treatment-emergent adverse events (agitation, sleep disturbance, palpitations), but both treatments were generally well-tolerated with no differences in overall number of adverse effects. **CONCLUSIONS:** Light treatment showed earlier response onset and lower rate of some adverse events relative to fluoxetine, but there were no other significant differences in outcome between light therapy and antidepressant medication. Although limited by lack of a double-placebo condition, this study supports the effectiveness and tolerability of both treatments for seasonal affective disorder and suggests that other clinical factors, including patient preference, should guide selection of first-line treatment.

49. Landen, M., H. Nissbrandt, et al. (2007). "Placebo-controlled trial comparing intermittent and continuous paroxetine in premenstrual dysphoric disorder." *Neuropsychopharmacology* 32(1): 153-61.

Serotonin reuptake inhibitors (SRIs) do not have to be administered continuously to be effective for premenstrual dysphoric disorder (PMDD), but can be given during luteal phases only. This is of practical importance, but also of theoretical interest since it suggests that the onset of action of SRIs is shorter in PMDD than in, for example depression. In this study, both continuous and intermittent SRI administration was compared with placebo, with the special purpose of analyzing if different PMDD symptoms respond differently depending on the treatment regimen. To this end, women meeting slightly modified DSM-IV criteria for PMDD (mean \pm -SD age, 37 \pm -6.3 years) were treated for three menstrual cycles with paroxetine continuously, paroxetine during the luteal phase only, or placebo, the population completing at least one treatment cycle comprising 55-56 subjects per group. Continuous treatment with paroxetine reduced premenstrual symptoms effectively with a response rate of 85%. The effect size was highest for irritability (1.4) and lowest for lack of energy (0.5). Intermittent treatment was as effective as continuous treatment in reducing irritability, affect lability, and mood swings, but had a somewhat weaker effect on depressed mood and somatic symptoms. The study indicates that the response rate when treating PMDD with SRIs is high, and that irritability is a key target symptom. Symptoms such as irritability, affect lability, and mood swings appear to be more inclined to respond rapidly to SRIs, enabling intermittent treatment, than are, for example, the somatic symptoms.

50. Lee, P., L. Shu, et al. (2007). "Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil." *Psychiatry Clin Neurosci* 61(3): 295-307.

The aim of the present paper was to compare the efficacy and safety of duloxetine with paroxetine in the acute treatment of major depressive disorder (MDD). In a randomized, double-blind trial of 8 weeks active treatment, patients with non-psychotic MDD were randomized to duloxetine 60 mg (n = 238) or paroxetine 20 mg (n = 240) once daily. Efficacy was primarily measured on change in the 17-item Hamilton Rating Scale for Depression (HAMD(17)) using a non-inferiority test with a margin of 2.2. Secondary efficacy measures included the HAMD(17) subscales, Hamilton Rating Scale for Anxiety, Clinical Global Impressions-Severity, Patient Global Impressions-Improvement, Somatic Symptoms Inventory and Visual Analog Scales (VAS) for pain. Safety measures included treatment-emergent adverse events (TEAE), vital signs, weight, laboratory analyses and electrocardiograms. Non-inferiority of duloxetine to paroxetine was demonstrated because the upper bound of the confidence interval for mean difference in HAMD(17) change (0.71) was less than the non-inferiority margin. Secondary efficacy end-points did not differ significantly between treatments with the exception of VAS back pain, where the pooled mean was lower in the duloxetine group (17.1) compared with the paroxetine group (20.3, P = 0.048). No significant differences were observed in the number of early discontinuations and overall TEAE. However, significantly greater proportions of patients in the duloxetine group experienced nausea and palpitations. No clinically relevant changes in laboratory values, vital signs, weight or electrocardiograms were observed with either treatment. The present study verifies the utility of duloxetine as an efficacious and safe treatment for both emotional and physical symptoms of MDD in this predominantly Asian patient sample.

51. Lesperance, F., N. Frasure-Smith, et al. (2007). "Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial." *Jama* 297(4): 367-79.

CONTEXT: Few randomized controlled trials have evaluated the efficacy of treatments for major depression in patients with coronary artery disease (CAD). None have simultaneously evaluated an antidepressant and short-term psychotherapy. **OBJECTIVE:** To document the short-term efficacy of a selective serotonin reuptake inhibitor (citalopram) and interpersonal psychotherapy (IPT) in reducing depressive symptoms in patients with CAD and major depression. **DESIGN, SETTING, AND PARTICIPANTS:** The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy, a randomized, controlled, 12-week, parallel-group, 2 x 2 factorial trial conducted May 1, 2002, to March 20, 2006, among 284 patients with CAD from 9 Canadian academic centers. All patients met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for diagnosis of major depression of 4 weeks' duration or longer and had baseline 24-item Hamilton Depression Rating Scale (HAM-D) scores of 20 or higher. **INTERVENTIONS:** Participants underwent 2 separate randomizations: (1) to receive 12 weekly sessions of IPT plus clinical management (n = 142) or clinical management only (n = 142) and (2) to receive 12 weeks of citalopram, 20 to 40 mg/d (n = 142), or matching placebo (n = 142). **MAIN OUTCOME**

MEASURES: The primary outcome measure was change between baseline and 12 weeks on the 24-item HAM-D, administered blindly during centralized telephone interviews (tested at $\alpha = .033$); the secondary outcome measure was self-reported Beck Depression Inventory II (BDI-II) score (tested at $\alpha = .017$). **RESULTS:** Citalopram was superior to placebo in reducing 12-week HAM-D scores (mean difference, 3.3 points; 96.7% confidence interval [CI], 0.80-5.85; $P = .005$), with a small to medium effect size of 0.33. Mean HAM-D response (52.8% vs 40.1%; $P = .03$) and remission rates (35.9% vs 22.5%; $P = .01$) and the reduction in BDI-II scores (difference, 3.6 points; 98.3% CI, 0.58-6.64; $P = .005$; effect size = 0.33) also favored citalopram. There was no evidence of a benefit of IPT over clinical management, with the mean HAM-D difference favoring clinical management (-2.26 points; 96.7% CI, -4.78 to 0.27; $P = .06$; effect size, 0.23). The difference on the BDI-II did not favor clinical management (1.13 points; 98.3% CI, -1.90 to 4.16; $P = .37$; effect size = 0.11). **CONCLUSIONS:** This trial documents the efficacy of citalopram administered in conjunction with weekly clinical management for major depression among patients with CAD and found no evidence of added value of IPT over clinical management. Based on these results and those of previous trials, citalopram or sertraline plus clinical management should be considered as a first-step treatment for patients with CAD and major depression. **TRIAL REGISTRATION:** isrctn.org Identifier: ISRCTN15858091.

52. Lustman, P. J., R. E. Clouse, et al. (2006). "Sertraline for prevention of depression recurrence in diabetes mellitus: a randomized, double-blind, placebo-controlled trial." *Arch Gen Psychiatry* 63(5): 521-9.

CONTEXT: In patients with diabetes mellitus, depression is a prevalent and recurrent problem that adversely affects the medical prognosis. **OBJECTIVE:** To determine whether maintenance therapy with sertraline hydrochloride prevents recurrence of major depression in patients with diabetes. **DESIGN:** A randomized, double-blind, placebo-controlled, maintenance treatment trial. Patients who recovered from depression during open-label sertraline treatment continued to receive sertraline ($n = 79$) or placebo ($n = 73$) and were followed up for up to 52 weeks or until depression recurred. **SETTING:** Outpatient clinics at Washington University, St Louis, MO, the University of Washington, Seattle, and the University of Arizona, Tucson. **PATIENTS:** One hundred fifty-two patients with diabetes (mean age, 52.8 years; 59.9% female; 82.9% with type 2 diabetes) who recovered from major depression (43.3% of those initially assigned) during 16 weeks of open-label treatment with sertraline (mean dose, 117.9 mg/d). **INTERVENTION:** Sertraline continued at recovery dose or identical-appearing placebo. **MAIN OUTCOME MEASURES:** The primary outcome was length of time (measured as the number of days after randomization) to recurrence of major depression as defined in DSM-IV. The secondary outcome was glycemic control, which was assessed via serial determinations of glycosylated hemoglobin levels. **RESULTS:** Sertraline conferred significantly greater prophylaxis against depression recurrence than did placebo (hazard ratio = 0.51; 95% confidence interval, 0.31-0.85; $P = .02$). Elapsed time before major depression recurred in one third of the patients increased from 57 days in patients who received placebo to 226 days in patients treated with sertraline. Glycosylated hemoglobin levels decreased during the open treatment phase (mean \pm SD glycosylated hemoglobin level reduction, -0.4% \pm 1.4%; $P = .002$). Glycosylated hemoglobin levels remained significantly lower than baseline during depression-free maintenance ($P = .002$) and did not

differ between treatment groups ($P = .90$). **CONCLUSIONS:** In patients with diabetes, maintenance therapy with sertraline prolongs the depression-free interval following recovery from major depression. Depression recovery with sertraline as well as sustained remission with or without treatment are associated with improvements in glycosylated hemoglobin levels for at least 1 year.

53. March, J., S. Silva, et al. (2006). "The Treatment for Adolescents with Depression Study (TADS): methods and message at 12 weeks." *J Am Acad Child Adolesc Psychiatry* 45(12): 1393-403.

Funded by the National Institute of Mental Health, the Treatment for Adolescents With Depression Study (TADS) is intended to evaluate the short-term (12 weeks) and longer-term (36 weeks) effectiveness of four treatments for adolescents with DSM-IV major depressive disorder: clinical management with fluoxetine (FLX), cognitive-behavioral therapy (CBT), FLX and CBT combined (COMB), and clinical management with placebo (PBO). We previously reported that COMB and FLX were more effective in reducing depression than CBT or PBO after 12 weeks of acute treatment. In this special section of the Journal, separate articles extend these findings to the impact of TADS treatments on remission, speed of response, function and quality of life, predictors of outcome, and safety during the first 12 weeks of treatment. To set the stage for the special section, we briefly review the rationale, design, and methods of the TADS; describe the TADS sample to which the TADS findings generalize; using all of the currently available data, summarize the intent-to-treat outcomes across multiple endpoints at 12 weeks; and consider the public health value of the TADS findings in the context of design decisions and methodological limitations of the TADS, including some that may have advantaged the combined treatment condition. Reflecting the ordering of effect sizes at week 12--COMB (0.98) > FLX (0.68) > CBT (-0.03)--combined treatment proved superior to PBO on 15 of 16 endpoints, to CBT on 14 of 16 endpoints, and to FLX on 8 of 16 endpoints, whereas FLX was superior to CBT on 8 of 14 and to PBO on 7 of 16 measures. CBT did not differ from PBO on any measure. Despite the fact that suicidality improved markedly across all of the treatment conditions, suicidal events were twice as common in patients treated with FLX alone than with COMB or CBT alone, perhaps indicating that CBT protects against suicidal events. Thus, combined treatment appears to accelerate recovery relative to CBT and, for some outcomes, FLX alone, while minimizing the risk of suicidality relative to FLX alone. Taking benefit and risk into account, we conclude that the combination of FLX and CBT appears superior to either monotherapy as a treatment for moderate to severe major depressive disorder in adolescents.

54. Marchesi, C., A. Cantoni, et al. (2006). "Predictors of symptom resolution in panic disorder after one year of pharmacological treatment: a naturalistic study." *Pharmacopsychiatry* 39(2): 60-5.

OBJECTIVE: In this naturalistic and prospective study, patients with panic disorder (PD) were treated for one year 1) to verify the rate of patients achieving the resolution of full-symptom attacks, limited-symptom attacks, anticipatory anxiety, phobic avoidance and depression; and 2) to identify the predictors of symptom resolution for each domain.

METHOD: One hundred patients with PD, according to DSM-IV criteria, participated in the study. In all patients, a baseline and a follow-up with monthly evaluations of SCL-90, Ham-

A, Ham-D and panic diaries were carried out over a one-year period. All patients were treated with paroxetine or citalopram. RESULTS: Seventy-one patients completed the study, whereas the remaining 29 dropped out. Among completers, remission of full- and limited-symptom panic attacks was observed in 76 % of patients, whereas complete remission (resolution of panic attacks, anticipatory anxiety, phobic anxiety, and depression) was achieved by only 46 % of patients. Predictors of absence of symptom remissions were obsessive-compulsive disorder (OCD) and recurrent major depression (MD) comorbidity (for panic attacks), pre-treatment severity of anxious symptoms (for anticipatory anxiety), phobic anxiety (for phobic avoidance), and depressive symptoms (for depression). CONCLUSION: This naturalistic study shows that the high comorbidity of OCD and MD and the greater pre-treatment severity of anxious, phobic and depressive symptoms reduced the likelihood of achieving complete remission of symptoms in PD patients who completed the protocol, even though they were adequately treated with SSRI medication.

55. Marchesi, C., C. De Panfilis, et al. (2006). "Personality disorders and response to medication treatment in panic disorder: a 1-year naturalistic study." *Prog Neuropsychopharmacol Biol Psychiatry* 30(7): 1240-5.

OBJECTIVE: In this naturalistic and prospective study, personality was assessed in patients with panic disorder (PD), in order to evaluate whether personality features negatively influence the outcome of pharmacological treatment. METHOD: Before drug treatment, PD was diagnosed with the Structured Clinical Interview for DSM-IV disorders and personality was assessed with the Structured Interview for DSM-IV Personality Disorders. Moreover, all patients were evaluated with the SCL-90, the Ham-A and Ham-D. Then, patients were randomly treated with paroxetine (33.5+/-13.3 mg/day) or citalopram (34.7+/-15.2 mg/day) and were followed at monthly intervals for 1 year. Absence of full and limited-symptom attacks, anticipatory anxiety, phobic avoidance and depression for 3 months was used to establish remission. The effect of personality traits on each symptom domain was evaluated. RESULTS: Seventy-one patients completed the study. Remission rate was 76% for panic attacks and 46% for complete remission. When the effects of age, gender, age of onset and duration of PD, baseline SCL-90 phobic anxiety, Ham-A and Ham-D scores, Axis I comorbidity and the SIDP traits on remission were analyzed in a logistic regression, only borderline traits negatively influenced remission of panic attacks (OR=0.69; 95% CI=0.49-0.96; p=0.03), whereas the number of traits of each personality Cluster and the total number of SIDP traits did not affect the outcome of treatment. CONCLUSIONS: This study suggests that in PD patients, borderline features may negatively influence the response to monotherapy with SSRI drugs; therefore, other treatment strategies (i.e., combination of SSRI with psychotherapy) are needed to obtain remission in these patients.

56. Marshall, R. D., R. Lewis-Fernandez, et al. (2007). "A controlled trial of paroxetine for chronic PTSD, dissociation, and interpersonal problems in mostly minority adults." *Depress Anxiety* 24(2): 77-84.

This study evaluated the efficacy of paroxetine for symptoms and associated features of chronic posttraumatic stress disorder (PTSD), interpersonal problems, and dissociative symptoms in an urban population of mostly minority adults. Adult outpatients with a primary DSM-IV diagnosis of chronic PTSD received 1 week of single-blind placebo (N = 70). Those

not rated as significantly improved were then randomly assigned to placebo (N = 27) or paroxetine (N = 25) for 10 weeks, with a flexible dosage design (maximum 60 mg by week 7). Significantly more patients treated with paroxetine were rated as responders (14/21, 66.7%) on the Clinical Global Impression-Improvement Scale (CGI-I) compared to patients treated with placebo (6/22, 27.3%). Mixed effects models showed greater reductions on the Clinician-Administered PTSD Scale (CAPS) total score (primary plus associated features of PTSD) in the paroxetine versus placebo groups. Paroxetine was also superior to placebo on reduction of dissociative symptoms [Dissociative Experiences Scale (DES) score] and reduction in self-reported interpersonal problems [Inventory of Interpersonal Problems (IIP) score]. In a 12-week maintenance phase, paroxetine response continued to improve, but placebo response did not. Paroxetine was well tolerated and superior to placebo in ameliorating the symptoms of chronic PTSD, associated features of PTSD, dissociative symptoms, and interpersonal problems in the first trial conducted primarily in minority adults.

57. Martenyi, F., E. B. Brown, et al. (2007). "Failed efficacy of fluoxetine in the treatment of posttraumatic stress disorder: results of a fixed-dose, placebo-controlled study." *J Clin Psychopharmacol* 27(2): 166-70.

A multicenter, double-blind, 12-week, placebo-controlled trial of 411 randomized patients, predominantly women diagnosed with posttraumatic stress disorder, failed to show a difference between either dose of fluoxetine treatment and placebo. The mean changes from baseline (SD) measured by the Clinician-Administered PTSD Scale scores were -42.9 (23.1), -42.8 (27.9), and -36.6 (25.7) in the 20-mg fluoxetine, 40-mg fluoxetine, and placebo arms, respectively. Placebo response rate was substantially higher in this study than in a previously published fluoxetine trial of posttraumatic stress disorder.

58. Mayes, T. L., R. Tao, et al. (2007). "Do children and adolescents have differential response rates in placebo-controlled trials of fluoxetine?" *CNS Spectr* 12(2): 147-54.

OBJECTIVE: Recent acute efficacy trials of antidepressants in youth have suggested that high placebo-response rates in children (< 12 years of age) indicate that children may be more responsive to non-specific treatment interventions. Yet, these studies generally have not presented age-specific outcome data. The objective of this study was to compare the efficacy outcomes for children (< 12 years of age) and adolescents (> or = 12 years of age) using the combined data from two previously published double-blind, placebo-controlled trials of fluoxetine. **METHODS:** Children (< 12 years of age) and adolescents (> or = 12 years of age) with major depressive disorder were randomized to fluoxetine or placebo for 8-9 weeks of treatment. Outcome was assessed using the Children's Depression Rating Scale-Revised (CDRS-R) and Clinical Global Impressions scale. **RESULTS:** Random regression of the CDRS-R showed a treatment group by age group interaction ($F(1,338)=4.10, P=.044$), indicating that the treatment effect was significantly more pronounced in children than adolescents. Within children, response at exit to fluoxetine was significantly better than placebo (56.9% vs 33.3%; $P=.009$). Adolescent response rates at exit were not significantly different between the groups (51.1% vs 38.6%; $P=.128$). Remission rates were low for both groups. **CONCLUSION:** In the combined fluoxetine trials, drug-placebo difference was

greater in children compared with adolescents. Contrary to expectations, the placebo-response rate was lower in the children than the adolescents.

59. McGrath, P. J., J. W. Stewart, et al. (2006). "Predictors of relapse in a prospective study of fluoxetine treatment of major depression." *Am J Psychiatry* 163(9): 1542-8.

OBJECTIVE: Loss of response to a previously effective antidepressant is a common clinical problem. Retrospective analyses have shown that the pattern of response during antidepressant treatment (late onset and persistent versus other patterns) can be used to predict relapse during continuation and maintenance treatment and possibly to identify placebo responses to treatment. This study was designed to test the predictive value of response pattern prospectively and to examine the data for other predictors of relapse.

METHOD: Five hundred seventy persons with major depressive disorder were treated with fluoxetine for 12 weeks and their pattern of response was determined. Those who responded (N=292) underwent random assignment, under double-blind conditions, to continue taking fluoxetine or to switch to placebo for 52 weeks or until relapse. Survival analysis was used to examine the effect of covariates on relapse. **RESULTS:** Although fluoxetine was significantly more effective than placebo during maintenance treatment, this chronically ill group had a high rate of relapse. Contrary to previous findings, a pattern of acute response was not predictive of relapse. Chronicity, symptom severity, a neurovegetative symptom pattern, and female gender were all associated with a significantly greater risk of relapse, with no difference observed between fluoxetine and placebo. **CONCLUSIONS:** The pattern of response to acute treatment appears to be inconsistently predictive of relapse. There is a high rate of relapse with both active medication and placebo in patients with chronic depression. Illness characteristics predict loss of response both to fluoxetine and to placebo. No variable examined was predictive of differential relapse rates between fluoxetine and placebo.

60. Melvin, G. A., B. J. Tonge, et al. (2006). "A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression." *J Am Acad Child Adolesc Psychiatry* 45(10): 1151-61.

OBJECTIVE: To evaluate cognitive-behavioral therapy, antidepressant medication alone, and combined CBT and antidepressant medication in the treatment of depressive disorders in adolescents. **METHOD:** Seventy-three adolescents (ages 12-18 years) with a primary diagnosis of DSM-IV major depressive disorder, dysthymic disorder, or depressive disorder not otherwise specified were randomly allocated to one of three treatments. Treatment outcome measures were administered before and after acute treatment, and at a 6-month follow-up. Depression diagnosis was the primary outcome measure; secondary measures were self- and other report and clinician rating of global functioning. The trial was conducted at three community-based clinics between July 2000 and December 2002. Data analyses used an intent-to-treat strategy. **RESULTS:** Following acute treatment, all treatment groups demonstrated statistically significant improvement on outcome measures (depressive diagnosis, Reynolds Adolescent Depression Scale, Revised Children's Manifest Anxiety Scale, Suicidal Ideation Questionnaire), and improvement was maintained at follow-up. Combined cognitive-behavioral therapy and antidepressant medication was not found to be superior to either treatment alone. Compared with antidepressant medication alone,

participants receiving cognitive-behavioral therapy alone demonstrated a superior acute treatment response (odds ratio = 6.86; 95% confidence interval 1.12-41.82). Although cognitive-behavioral therapy was found to be superior to antidepressant medication alone for the acute treatment of mild to moderate depression among youth, this may have stemmed from the relatively low dose of sertraline used. **CONCLUSIONS:** All treatments led to a reduction in depression, but the advantages of a combined approach were not evident.

61. Miranda, J., B. L. Green, et al. (2006). "One-year outcomes of a randomized clinical trial treating depression in low-income minority women." *J Consult Clin Psychol* 74(1): 99-111. This study examines 1-year depressive symptom and functional outcomes of 267 predominantly low income, young minority women randomly assigned to antidepressant medication, group or individual cognitive-behavioral therapy (CBT), or community referral. Seventy-six percent assigned to medications received 9 or more weeks of guideline-concordant doses of medications; 36% assigned to psychotherapy received 6 or more CBT sessions. Intent-to-treat, repeated measures analyses revealed that medication ($p=.001$) and CBT ($p=.02$) were superior to community referral in lowering depressive symptoms across 1-year follow-up. At Month 12, 50.9% assigned to antidepressants, 56.9% assigned to CBT, and 37.1% assigned to community referral were no longer clinically depressed. These findings suggest that both antidepressant medications and CBT result in clinically significant decreases in depression for low-income minority women.

62. Mohamed, S., K. Osatuke, et al. (2006). "Escitalopram for comorbid depression and anxiety in elderly patients: A 12-week, open-label, flexible-dose, pilot trial." *Am J Geriatr Pharmacother* 4(3): 201-9.

BACKGROUND: Comorbid depression and anxiety may result in greater symptom severity and poorer treatment response than either condition alone. Selective serotonin reuptake inhibitors have been found to be effective in treating both depression and anxiety; however, pharmacodynamic and pharmacokinetic changes associated with aging warrant special attention in medication trials in older patients. **OBJECTIVE:** The objective of this study was to assess the efficacy and tolerability of short-term (12-week) administration of escitalopram oxalate 10 to 20 mg/d for moderate to marked comorbid depression and anxiety in elderly patients. **METHODS:** This open-label, flexible-dose (10-20 mg/d), pilot trial was conducted at the Psychiatry Service, Veterans Affairs Medical Center, Cincinnati, Ohio. Outpatients aged ≥ 65 years were included if they met the criteria for comorbid major depressive disorder (MDD) and generalized anxiety disorder (GAD), as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, for ≥ 4 weeks and had a baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 22 and a Hamilton Rating Scale for Anxiety (HAM-A) score of ≥ 18 . All patients received escitalopram 10 to 20 mg/d. The primary efficacy variables were the mean changes from baseline in total MADRS and HAM-A scores at 12 weeks (last observation carried forward). The secondary efficacy end point was the change from baseline in Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) 8 subscale scores. Adverse events were assessed at each visit (treatment weeks 1, 2, 3, 4, 6, 8, 10, and 12) with the use of open-ended questioning. **RESULTS:** Twenty patients were enrolled (mean [SD] age, 73.0 [4.8] years; 6 [30%] women; race: 17 [85%] white, 2 [10%] black, and 1 [5%] "other"). Seventeen (85%)

of 20 patients completed the study; 3 (15%) withdrew: 1 (5%) due to lack of efficacy and 2 (10%) due to adverse events (dizziness and somnolence [1 (5%) patient each]). Statistically significant improvements from baseline to end point were found with escitalopram treatment (MADRS: $t_{19} = 7.38$, $P < 0.001$, effect size = 2.93; HAM-A: $t_{19} = 4.19$, $P < 0.001$, effect size = 1.83). Significant changes from baseline in scores on 4 (Social Functioning, Role Functioning-Emotional, Mental Health, and Energy/Fatigue) of the 8 subscales of the SF-36 were also found (all, $P < 0.01$). CONCLUSION: In this small study in elderly patients with comorbid MDD and GAD, treatment with escitalopram 10 to 20 mg/d for 12 weeks was associated with significant improvements in symptoms of depression and anxiety.

63. Montgomery, S. A. and H. F. Andersen (2006). "Escitalopram versus venlafaxine XR in the treatment of depression." *Int Clin Psychopharmacol* 21(5): 297-309.

This article reanalyses and reviews data from the two published randomized clinical trials comparing escitalopram and venlafaxine XR in the treatment of patients with major depressive disorder. The aim was to further compare the efficacy and tolerability of escitalopram and venlafaxine XR and to assess the impact of the two treatments on the patient's quality of life, as well as the benefit/risk of treatment. A total of 243 escitalopram-treated patients and 240 venlafaxine XR-treated patients were included in this analysis. Comparable treatment efficacy was achieved with respect to the prospectively defined primary efficacy endpoint (mean change from baseline in Montgomery Asberg Depression Rating Scale (MADRS) total score at week 8). An analysis of the outcome at the end of study by baseline severity showed that the treatment difference became greater the more severely depressed the patients were at baseline. At the highest permitted doses, in the subgroup of patients who were severely depressed (baseline MADRS ≥ 30), patients treated with escitalopram had a statistically significantly greater improvement ($P < 0.05$) in mean MADRS total scores than patients treated with venlafaxine XR at endpoint. For these patients, treatment with 20 mg/day escitalopram resulted in a statistically significantly ($P < 0.05$) higher remission rate at week 8 (47%) than treatment with venlafaxine XR (29%). This difference was confirmed by the analysis of the pooled data, which showed that patients in the escitalopram group had a significantly ($P < 0.05$) higher mean number of depression-free days (30.4 days) than those in the venlafaxine XR group (26.2 days) over the 8-week period. The relative benefit of escitalopram versus venlafaxine XR was 1.46, indicating that a patient was more likely to benefit from treatment with escitalopram. The proportions of patients who withdrew owing to adverse events were 7.5% in the escitalopram group and 11.2% in the venlafaxine XR group. The mean number of discontinuation emergent signs and symptoms in the venlafaxine XR group (mean: 5.0) was significantly ($P < 0.001$) higher than for the escitalopram group (mean: 2.4).

64. Musselman, D. L., W. I. Somerset, et al. (2006). "A double-blind, multicenter, parallel-group study of paroxetine, desipramine, or placebo in breast cancer patients (stages I, II, III, and IV) with major depression." *J Clin Psychiatry* 67(2): 288-96.

OBJECTIVE: This study compared the efficacy and safety of paroxetine and desipramine with those of placebo in the treatment of depressive disorders in adult women with breast cancer, stages I-IV. METHOD: In a double-blind, placebo-controlled study, 35 female outpatients with breast cancer and DSM-III-R major depression or adjustment disorder with

depressed mood were randomly assigned to treatment with paroxetine (N=13), desipramine (N=11), or placebo (N=11) for 6 weeks. Primary efficacy was assessed by change from baseline in score on the 21-item Hamilton Rating Scale for Depression (HAM-D), and the secondary outcome measure was change from baseline in the Clinical Global Impressions-Severity of Illness scale (CGI-S) score. RESULTS: Mean changes in the total HAM-D and CGI-S scores from baseline to 6-week endpoint for the paroxetine and desipramine groups were not significantly different than those for the placebo-treated group. An unusually high rate of response (defined as $\geq 50\%$ improvement in the HAM-D score) in the placebo group was observed (55% [N=6]); adverse events precipitated patient discontinuation in the active treatment groups (9% [N=1] for desipramine, 15% [N=2] for paroxetine) similar to that in the placebo-treated patients (18% [N=2]). Improvement on symptom dimensions within the HAM-D and Hamilton Rating Scale for Anxiety (depressive, anxiety, cognitive, neurovegetative, or somatic) was also similar between groups. CONCLUSION: The small number of women in this study most likely contributed to the lack of observed differences in efficacy observed during the 6 weeks of treatment. Randomized, placebo-controlled trials of adequate power seeking to determine efficacy of antidepressants in the United States for the treatment of women with breast cancer and comorbid depression remain of paramount importance.

65. Nelson, J. C., S. B. Hollander, et al. (2006). "Mirtazapine orally disintegrating tablets in depressed nursing home residents 85 years of age and older." *Int J Geriatr Psychiatry* 21(9): 898-901.

INTRODUCTION: Treatment studies of depression in the very oldest patients are infrequent. For these reasons, this study of mirtazapine orally disintegrating tablets was carried out in nursing home residents ≥ 85 years old with physician-diagnosed depression. The naturalistic conditions of the study allowed us to include patients with cognitive impairment, concomitant medications and comorbid illness. METHODS: This was a subgroup analysis of nursing home residents ≥ 85 years old who took part in a larger 12-week open-label trial. Patients were eligible if they had physician-diagnosed depression, and a Mini-Mental State Exam score ≥ 10 . The physician or nurse coordinator obtained data from healthcare professionals in daily contact with the patient to complete the Clinical Global Impression (CGI) scale, a modified 16-item Hamilton Depression Scale (HAM-D), and the Cornell Scale for Depression in Dementia (CSDD). Treatment-emergent adverse events were recorded. RESULTS: Of the 50 patients enrolled at 23 sites, 72% completed the 12-week trial. The mean age of the participants was 89.3 years. The mean HAM-D score declined from 16.9 at baseline to 7.3 at endpoint (ITT, LOCF analysis) For the CSDD, the mean score declined from 15.1 to 7.1. The percentage of responders on the CGI-Improvement (CGI-I) scale increased at each assessment reaching 55% at endpoint. Only 10% of the patients discontinued treatment because of adverse events. There was a mean increase in weight of 1.32 lbs (0.6 kg) at day 84. CONCLUSION: Although lacking a placebo control, this naturalistic study suggests that mirtazapine orally disintegrating tablets were effective and well tolerated in this sample of depressed nursing home residents ≥ 85 years of age.

66. Nierenberg, A. A., J. H. Greist, et al. (2007). "Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study." *Curr Med Res Opin* 23(2): 401-16.

OBJECTIVE: The goal of a non-inferiority study is to test whether a new treatment has at least as much efficacy as an established treatment. The purpose of this non-inferiority study was to compare the speed of onset of antidepressant efficacy for duloxetine (a dual serotonin and norepinephrine reuptake inhibitor) and escitalopram (a selective serotonin reuptake inhibitor). **RESEARCH DESIGN AND METHODS:** This was a randomized, double-blind, placebo- and active comparator-controlled study, in which patients (> or = 18 years) meeting DSM-IV criteria for Major Depressive Disorder (MDD) received duloxetine 60 mg once daily (QD; N = 273), escitalopram 10 mg QD (N = 274), or placebo (N = 137) for 8 weeks. The primary objective was to compare the onset of antidepressant efficacy, by testing the hypothesis that the percentage of duloxetine-treated patients achieving onset criteria at Week 2 was not inferior to that in the escitalopram group. **MAIN OUTCOME MEASURES:** Onset of efficacy was defined as a 20% decrease from baseline on the 17-item Hamilton Rating Scale for Depression (HAM-D(17)) Maier subscale that was maintained or exceeded at all subsequent visits. **RESULTS:** Probabilities of meeting onset criteria at Week 2 for duloxetine- and escitalopram-treated patients were 42.6% versus 35.2%, respectively (treatment difference = 7.4%; 95% confidence interval, -1.3% to 16.2%; p = 0.097). Both drugs showed significant improvement compared with placebo (p < or = 0.05) on the primary efficacy measure (Maier subscale) at Week 1 and endpoint (Week 8). No differences were found between duloxetine, escitalopram, and placebo rates of remission or response at 8 weeks. Adverse events that occurred significantly more frequently among duloxetine-treated patients when compared with those receiving escitalopram were nausea, dry mouth, vomiting, yawning, and irritability. The rate of discontinuation due to adverse events did not differ significantly between treatment groups. **LIMITATIONS:** Given the difficulties in constructing appropriate dose comparisons, the results of this study should be interpreted specific to the doses tested and not extrapolated to the drug as a whole. This study employed a fixed-dose design; flexible-dose designs are more likely to find a difference between antidepressants and placebo. **CONCLUSION:** In this study, both duloxetine and escitalopram showed significantly greater improvement on the primary efficacy measure than placebo over the 8-week acute treatment period, while no differences were observed between drugs or between drugs and placebo on response and remission rates at 8 weeks. Escitalopram at a starting dose of 10 mg QD was better tolerated than duloxetine at a starting dose of 60 mg QD. This study met its pre-defined primary objective of assessing if duloxetine was non-inferior to escitalopram in antidepressant onset efficacy, and the results show that duloxetine is at least as fast as (non-inferior to) escitalopram.

67. Papakostas, G. I., D. J. Nutt, et al. (2006). "Resolution of sleepiness and fatigue in major depressive disorder: A comparison of bupropion and the selective serotonin reuptake inhibitors." *Biol Psychiatry* 60(12): 1350-5.

BACKGROUND: The purpose of this study was to examine whether the treatment of major depressive disorder (MDD) with the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion results in a greater resolution of sleepiness and fatigue than with the selective serotonin reuptake inhibitors (SSRIs). **METHODS:** Six double-blind, randomized clinical

trials comparing bupropion (n = 662) with an SSRI (n = 655) for the treatment of MDD were pooled. Hypersomnia scores were defined as the sum of scores of the Hamilton Depression Rating Scale (HDRS) items #22, 23, and 24. Fatigue scores were defined as the score of HDRS item #13. RESULTS: There was a greater improvement in hypersomnia scores among bupropion-treated than SSRI-treated ($p < .0001$) or placebo-treated patients ($p = .0008$). There was also a greater improvement in fatigue scores among bupropion-treated ($p < .0001$) and SSRI-treated ($p = .0005$) than placebo-treated patients as well as a greater improvement in fatigue scores among bupropion-treated than SSRI-treated patients ($p = .0078$). Fewer bupropion-remitters than SSRI-remitters experienced residual hypersomnia (20.5% vs. 32.1%; $p = .0014$) or residual fatigue (19.5% vs. 30.2%; $p = .0020$). CONCLUSION: Treatment of MDD with the NDRI bupropion resulted in a greater resolution of sleepiness and fatigue than SSRIs treatment. Although preliminary, these results warrant prospectively designed studies examining potential differences between bupropion and the SSRIs on these specific depressive symptoms.

68. Perahia, D. G., F. Wang, et al. (2006). "Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial." *Eur Psychiatry* 21(6): 367-78.
- OBJECTIVE: Duloxetine doses of 80 and 120 mg/day were assessed for efficacy and safety in the treatment of major depressive disorder (MDD). METHODS: In this randomized, double-blind trial, patients age ≥ 18 meeting DSM-IV criteria for MDD were randomized to placebo (N=99), duloxetine 80 mg/day (N=93), duloxetine 120 mg/day (N=103), or paroxetine 20 mg/day (N=97). The primary outcome measure was mean change from baseline in the 17-item Hamilton rating scale for depression (HAMD(17)) total score after 8 weeks of treatment; a number of secondary efficacy measures also were assessed. Safety and tolerability were assessed via collection and analysis of treatment-emergent adverse events (TEAEs), vital signs, and weight. The Arizona sexual experiences scale was used to assess sexual functioning. Patients who had a $\geq 30\%$ reduction from baseline in the HAMD(17) total score at the end of the acute phase entered a 6-month continuation phase where they remained on the same treatment as they had taken during the acute phase; efficacy and safety/tolerability outcomes were assessed during continuation treatment. RESULTS: More than 87% of patients completed the acute phase in each treatment group. Duloxetine-treated patients (both doses) showed significantly greater improvement ($P < 0.05$) in the HAMD(17) total score at week 8 compared with placebo. Paroxetine was not significantly different from placebo ($P = 0.089$) on mean change on the HAMD(17). Duloxetine 120 mg/day also showed significant improvement on most secondary efficacy measures (six of nine) compared with placebo while duloxetine 80 mg/day (three of nine) and paroxetine (three of nine) were significantly superior to placebo on fewer secondary measures. HAMD(17) mean change data from this study and an identical sister study were pooled as defined a priori for the purposes of performing a non-inferiority test versus paroxetine. Both duloxetine doses met statistical criteria for non-inferiority to paroxetine. TEAE reporting rates were low in all treatment groups and no deaths occurred in the acute or continuation phases.
- CONCLUSIONS: The efficacy of duloxetine at doses of 80 and 120 mg/day in the treatment of MDD was demonstrated. Tolerability, as measured by TEAEs, and safety were similar to paroxetine 20 mg/day and consistent with previous published data on duloxetine in the treatment of MDD.

69. Perlis, R. H., C. M. Beasley, Jr., et al. (2007). "Treatment-associated suicidal ideation and adverse effects in an open, multicenter trial of fluoxetine for major depressive episodes." *Psychother Psychosom* 76(1): 40-6.

BACKGROUND: Some reports suggest that a subset of depressed patients may experience suicidality - that is increase or emergence of suicidal ideation (SI) or behavior--after initiation of an antidepressant. The time course and clinical correlates of this phenomenon have not been characterized in detail. **METHOD:** We conducted a secondary analysis of a multicenter, prospective, open, 12-week trial of fluoxetine 20 mg in outpatients with nonpsychotic major depressive episodes. Adverse effects and other clinical features associated with the emergence of suicidality, defined using item 3 of the Hamilton Depression Rating Scale, were examined using Cox regression models. **RESULTS:** Among 414 subjects without SI at baseline, 59 (14.3%) reported SI on at least 1 postbaseline visit. In a Cox regression, emergence of activation and worsening of depression severity were independently associated with emergence of SI, along with female gender, younger age and having thoughts that life was not worth living prior to treatment. Treatment response and remission were significantly less likely among subjects who developed SI. **CONCLUSIONS:** New SI was relatively common in this trial of fluoxetine and associated with the emergence of activation and overall symptomatic worsening. Whether prophylaxis against or aggressive treatment of adverse events can decrease emergence of SI merits further study.

70. Poling, J., R. Pruzinsky, et al. (2007). "Clinical efficacy of citalopram alone or augmented with bupropion in methadone-stabilized patients." *Am J Addict* 16(3): 187-94.

Despite the success of opiate-agonist therapies such as methadone for the treatment of opiate addiction, treatment response is not complete. This study evaluates the efficacy of citalopram augmented with bupropion in the treatment of illicit opiate use in a methadone-stabilized population. We conducted a 12-week randomized, double-blind, outpatient clinical trial in which 60 subjects were randomized into one of three treatment groups: placebo, citalopram (40 mg/day) plus placebo, or citalopram (40 mg/day) plus bupropion (50 mg/day). The results indicate that neither citalopram nor citalopram augmented with bupropion were more effective than placebo in the treatment of opioid abuse.

71. Pollack, M. H., U. Lepola, et al. (2007). "A double-blind study of the efficacy of venlafaxine extended-release, paroxetine, and placebo in the treatment of panic disorder." *Depress Anxiety* 24(1): 1-14.

To date, no large-scale, controlled trial comparing a serotonin-norepinephrine reuptake inhibitor and selective serotonin reuptake inhibitor with placebo for the treatment of panic disorder has been reported. This double-blind study compares the efficacy of venlafaxine extended-release (ER) and paroxetine with placebo. A total of 664 nondepressed adult outpatients who met DSM-IV criteria for panic disorder (with or without agoraphobia) were randomly assigned to 12 weeks of treatment with placebo or fixed-dose venlafaxine ER (75 mg/day or 150 mg/day), or paroxetine 40 mg/day. The primary measure was the percentage of patients free from full-symptom panic attacks, assessed with the Panic and Anticipatory Anxiety Scale (PAAS). Secondary measures included the Panic Disorder Severity Scale, Clinical Global Impressions--Severity (CGI-S) and--Improvement (CGI-I) scales; response

(CGI-I rating of very much improved or much improved), remission (CGI-S rating of not at all ill or borderline ill and no PAAS full-symptom panic attacks); and measures of depression, anxiety, phobic fear and avoidance, anticipatory anxiety, functioning, and quality of life. Intent-to-treat, last observation carried forward analysis showed that mean improvement on most measures was greater with venlafaxine ER or paroxetine than with placebo. No significant differences were observed between active treatment groups. Panic-free rates at end point with active treatment ranged from 54% to 61%, compared with 35% for placebo. Approximately 75% of patients given active treatment were responders, and nearly 45% achieved remission. The placebo response rate was slightly above 55%, with remission near 25%. Adverse events were mild or moderate and similar between active treatment groups. Venlafaxine ER and paroxetine were effective and well tolerated in the treatment of panic disorder.

72. Reynolds, C. F., 3rd, M. A. Dew, et al. (2006). "Maintenance treatment of major depression in old age." *N Engl J Med* 354(11): 1130-8.

BACKGROUND: Elderly patients with major depression, including those having a first episode, are at high risk for recurrence of depression, disability, and death. **METHODS:** We tested the efficacy of maintenance paroxetine and monthly interpersonal psychotherapy in patients 70 years of age or older who had depression (55 percent of whom were having a first episode) in a 2-by-2, randomized, double-blind, placebo-controlled trial. Among patients with a response to treatment with paroxetine and psychotherapy, 116 were randomly assigned to one of four maintenance-treatment programs (either paroxetine or placebo combined with either monthly psychotherapy or clinical-management sessions) for two years or until the recurrence of major depression. Clinical-management sessions, conducted by the same nurses, social workers, and psychologists who provided psychotherapy, involved discussion of symptoms. **RESULTS:** Major depression recurred within two years in 35 percent of the patients receiving paroxetine and psychotherapy, 37 percent of those receiving paroxetine and clinical-management sessions, 68 percent of those receiving placebo and psychotherapy, and 58 percent of those receiving placebo and clinical-management sessions ($P=0.02$). After adjustment for the effect of psychotherapy, the relative risk of recurrence among those receiving placebo was 2.4 times (95 percent confidence interval, 1.4 to 4.2) that among those receiving paroxetine. The number of patients needed to be treated with paroxetine to prevent one recurrence was 4 (95 percent confidence interval, 2.3 to 10.9). Patients with fewer and less severe coexisting medical conditions (such as hypertension or cardiac disease) received greater benefit from paroxetine ($P=0.03$ for the interaction between treatment with paroxetine and baseline severity of medical illness). **CONCLUSIONS:** Patients 70 years of age or older with major depression who had a response to initial treatment with paroxetine and psychotherapy were less likely to have recurrent depression if they received two years of maintenance therapy with paroxetine. Monthly maintenance psychotherapy did not prevent recurrent depression. (ClinicalTrials.gov number, NCT00178100.).

73. Rush, A. J., M. H. Trivedi, et al. (2006). "Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression." *N Engl J Med* 354(12): 1231-42.

BACKGROUND: After unsuccessful treatment for depression with a selective serotonin-reuptake inhibitor (SSRI), it is not known whether switching to one antidepressant is more effective than switching to another. **METHODS:** We randomly assigned 727 adult outpatients with a nonpsychotic major depressive disorder who had no remission of symptoms or could not tolerate the SSRI citalopram to receive one of the following drugs for up to 14 weeks: sustained-release bupropion (239 patients) at a maximal daily dose of 400 mg, sertraline (238 patients) at a maximal daily dose of 200 mg, or extended-release venlafaxine (250 patients) at a maximal daily dose of 375 mg. The study was conducted in 18 primary and 23 psychiatric care settings. The primary outcome was symptom remission, defined by a total score of 7 or less on the 17-item Hamilton Rating Scale for Depression (HRSD-17) at the end of the study. Scores on the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR-16), obtained at treatment visits, determined secondary outcomes, including remission (a score of 5 or less at exit) and response (a reduction of 50 percent or more on baseline scores). **RESULTS:** Remission rates as assessed by the HRSD-17 and the QIDS-SR-16, respectively, were 21.3 percent and 25.5 percent for sustained-release bupropion, 17.6 percent and 26.6 percent for sertraline, and 24.8 percent and 25.0 percent for extended-release venlafaxine. QIDS-SR-16 response rates were 26.1 percent for sustained-release bupropion, 26.7 percent for sertraline, and 28.2 percent for extended-release venlafaxine. These treatments did not differ significantly with respect to outcomes, tolerability, or adverse events. **CONCLUSIONS:** After unsuccessful treatment with an SSRI, approximately one in four patients had a remission of symptoms after switching to another antidepressant. Any one of the medications in the study provided a reasonable second-step choice for patients with depression. (ClinicalTrials.gov number, NCT00021528.).

74. Rynn, M., K. D. Wagner, et al. (2006). "Long-term sertraline treatment of children and adolescents with major depressive disorder." *J Child Adolesc Psychopharmacol* 16(1-2): 103-16.

OBJECTIVE: The aim of this study was to assess the long-term safety, tolerability, and efficacy of sertraline 50-200 mg once-daily in children (6-11 year olds) and adolescents (12-18 year olds) with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosis of major depressive disorder (MDD). **METHODS:** This study consisted of a 24-week open-label observational study of children and adolescents who had completed either of two 10-week double-blind, placebo-controlled trials. The Children's Depression Rating Scale-Revised (CDRS-R) was the primary measure of efficacy. **RESULTS:** Two hundred ninety nine (299) patients completed the acute studies and were eligible for the extension study. Of these, 226 enrolled, but 5 did not receive treatment. Of 221 patients (107 children and 114 adolescents), 62.4% completed the study. The endpoint mean daily dose was 109.9 mg/day. The mean decrease in CDRS-R score from double-blind baseline was 34.8 points ($p < 0.001$), with patients showing continued improvement in CDRS-R scores regardless of which treatment they received in the double-blind studies. At endpoint, 86% of patients met CDRS-R responder and 58% CDRS-R remitter criteria. **CONCLUSIONS:** Sertraline appears to be well tolerated and safe over 24 weeks of treatment in children and adolescents with MDD. Children and adolescents treated with sertraline appear to have

increased improvement over that seen in the first 10 weeks of treatment. These findings need confirmation in placebo-controlled studies.

75. Schatzberg, A. and S. Roose (2006). "A double-blind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depression." *Am J Geriatr Psychiatry* 14(4): 361-70.

BACKGROUND: Despite the high prevalence of depression in elderly patients, few well-designed, placebo-controlled studies of antidepressants have been conducted in this population. This masked, placebo-controlled trial assessed the efficacy and safety of venlafaxine and fluoxetine in depressed patients older than 65 years. **METHOD:** Three hundred patients were randomly assigned to treatment with venlafaxine immediate release ([IR]; N = 104), fluoxetine (N = 100), or placebo (N = 96) in an eight-week trial. Venlafaxine doses were titrated from 37.5 to 225 mg per day and fluoxetine doses were titrated from 20 to 60 mg per day, as necessary, over 29 days. Efficacy variables included the 21-item Hamilton Depression Rating Scale (HAM-D21) total score, HAM-D21 depressed mood item score, scores on the Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impression-Severity of Illness (CGI-S) and Improvement (CGI-I) scales, and rates of response (based on change from baseline HAM-D or MADRS score or CGI-I score) and remission (HAM-D17 < or =7). For the purposes of this report, efficacy analyses are focused on the HAM-D21 total score. Safety assessments included monitoring of adverse events (AEs), physical examinations, vital signs assessments, laboratory determinations, and electrocardiograms. **RESULTS:** In all three of the treatment groups, there was a significant reduction at week 8 compared with the baseline HAM-D21 total score. However, there were no significant differences among the three treatment groups on the change in HAM-D21, MADRS, or CGI scores from baseline to week 8. There was no statistically significant difference in the proportion of remitters at the last on-therapy visit. The incidence of individual AEs was higher in the venlafaxine group (27%) compared with patients taking fluoxetine (19%) or placebo (9%). **CONCLUSION:** In this study, there was no significant difference in efficacy among placebo, venlafaxine, and fluoxetine for the treatment of depression.

76. Shelton, R. C., K. L. Haman, et al. (2006). "A randomized, double-blind, active-control study of sertraline versus venlafaxine XR in major depressive disorder." *J Clin Psychiatry* 67(11): 1674-81.

OBJECTIVE: Sertraline may produce dual neurotransmitter effects similar to the serotonin-norepinephrine reuptake inhibitors (SNRIs); however, it has been tested against an SNRI in only 1 previous study, and never at an optimal dose. The objective of the current multisite study was to compare relatively higher doses of sertraline (i.e., 150 mg/day) and venlafaxine extended release (XR) (225 mg/day) in outpatients with major depressive disorder.

METHOD: Subjects with DSM-IV major depressive disorder were randomly assigned to 8 weeks of double-blind treatment with sertraline (N = 82) or venlafaxine XR (N = 78). The study ran from January 2002 through January 2003. The primary outcome measure was the Quality of Life Enjoyment and Satisfaction Questionnaire; secondary outcome variables included the 17-item Hamilton Rating Scale for Depression. **RESULTS:** Both treatments led to significant improvement in depressive symptoms and quality-of-life measures. No

significant differences were noted between treatment groups for final scores on the primary or secondary measures. The treatment groups did not differ significantly in the percentage of responders (sertraline = 55%, venlafaxine XR = 65%; intent-to-treat [ITT] sample) or remitters (sertraline = 38%, venlafaxine XR = 49%; ITT sample), although the proportions are similar to those found in earlier selective serotonin reuptake inhibitor (SSRI) vs. venlafaxine meta-analyses. In patients who achieved the maximum dose of drug and maintained it for 3 weeks, response rates were similar to those found at lower doses (sertraline = 59%, venlafaxine XR = 70%); however, remission rates for this sample were comparable for both drug groups (sertraline = 48%, venlafaxine XR = 50%).

CONCLUSIONS: The efficacies of sertraline and venlafaxine XR were comparable. Although response and remission rates did not differ statistically, the rates were analogous to those reported in previous meta-analyses. However, at clinically relevant higher doses, the remission rates were very similar. **CLINICAL TRIALS REGISTRATION:** ClinicalTrials.gov identifier NCT00179283.

77. Simis, S. and R. Nitrini (2006). "Cognitive improvement after treatment of depressive symptoms in the acute phase of stroke." *Arq Neuropsiquiatr* 64(2B): 412-7.

The outcome of antidepressant treatment for depressive symptoms and cognitive impairment at the acute phase of stroke is controversial. We investigated 93 patients, treating with citalopram 36 with severe depressive symptoms (HAM-D: Hamilton Depression Rating Scale >18), whilst 19 patients with mild depressive symptoms, and 38 non-depressed patients, remained untreated. At baseline (two weeks after stroke), patients with severe depressive symptoms had lower scores in total Dementia Rating Scale (DRS) and in the attention and memory DRS subscales, than the non-depressed patients ($p < 0.001$). At the end of the three-month follow-up period, these differences had disappeared, but patients initially with mild depressive symptoms had higher HAM-D scores than the non-depressed patients ($p = 0.015$), and lower scores in DRS attention and memory subscales ($p < 0.01$), than the patients treated with citalopram. Treatment was associated with improved mood, memory and attention, and a placebo-controlled study on the treatment of mild depressive symptoms is warranted.

78. Simon, N. M., A. K. Zalta, et al. (2006). "Preliminary support for gender differences in response to fluoxetine for generalized anxiety disorder." *Depress Anxiety* 23(6): 373-6. Women have a higher prevalence of generalized anxiety disorder (GAD) than do men, but few studies have assessed gender differences in response to pharmacotherapy. In this study we examined gender as a correlate of response to 6 weeks of open, prospective fluoxetine treatment in 23 men and 22 women with a primary diagnosis of GAD. There was no difference by gender in age or prevalence of mood and anxiety comorbidity; however, GAD onset occurred at a significantly younger age in women compared with men. Despite a lack of difference in baseline severity measures, women had a significantly poorer response to fluoxetine as measured by both the Hamilton Anxiety Rating Scale (HAM-A) and Clinician Global Impression-Severity Scale (CGI-S). In multivariate analyses, there was a significant interaction between age of onset and gender: men with younger age of onset and women with older age of onset exhibited poorer response on the HAM-A. These data, though limited in sample size and by the post hoc nature of our analyses, offer preliminary support that women

with GAD, particularly those with a later age of onset, may have a poorer response to the selective serotonin reuptake inhibitor (SSRI) fluoxetine. Larger placebo-controlled trials are needed to more definitively examine gender and treatment response in anxiety disorders.

79. Stein, D. J., E. W. Andersen, et al. (2007). "Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study." *Curr Med Res Opin* 23(4): 701-11.

OBJECTIVE: A randomized, placebo controlled fixed-dose trial was undertaken to determine the efficacy and tolerability of escitalopram in obsessive-compulsive disorder (OCD), using paroxetine as the active reference. **RESEARCH DESIGN AND METHODS:** A total of 466 adults with OCD from specialized clinical centres, psychiatric hospital departments, psychiatric practices, or general practice were randomized to one of four treatment groups: escitalopram 10 mg/day (n = 116), escitalopram 20 mg/day (n = 116), paroxetine 40 mg/day (n = 119), or placebo (n = 115) for 24 weeks. The primary efficacy endpoint was the mean change in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score from baseline to week 12. Secondary efficacy endpoints included remission (defined as Y-BOCS total score < or =10), NIMH-OCS, and CGI-S and CGI-I scores at weeks 12 and 24. Tolerability was based on the incidence of adverse events, and on changes in vital signs (blood pressure and pulse). **Main outcome measures; Results:** Escitalopram 20 mg/day was superior to placebo on the primary and all secondary outcome endpoints, including remission. Escitalopram 10 mg/day and paroxetine 40 mg/day were also effective on the primary scale as well as some other outcome measures. In the escitalopram 20 mg/day group, the improvement in Y-BOCS total score was significantly better than in the placebo group as early as week 6. The most common AEs in the active treatment groups were nausea (19-27%), headache (17-22%), and fatigue (12-19%). More paroxetine-treated patients withdrew due to adverse events than escitalopram- or placebo-treated patients. **CONCLUSION:** Given that escitalopram 20 mg/day was associated with an earlier onset, higher response and remission rates, improved functioning, and better tolerability than the reference drug, escitalopram deserves to be considered as one of the first-line agents in the pharmacotherapy of OCD for longer-term treatment periods.

80. Stein, D. J., B. A. van der Kolk, et al. (2006). "Efficacy of sertraline in posttraumatic stress disorder secondary to interpersonal trauma or childhood abuse." *Ann Clin Psychiatry* 18(4): 243-9.

BACKGROUND: In posttraumatic stress disorder (PTSD), the nature of the trauma and the age of occurrence may have substantial effects on psychobiological sequelae and treatment response. Interpersonal trauma (physical/sexual assault) and childhood abuse are both prevalent and associated with later PTSD. This analysis was conducted to specifically assess the efficacy of sertraline in the treatment of PTSD secondary to interpersonal trauma or childhood abuse. **METHODS:** 395 adult patients with PTSD were randomized to 12-weeks double-blind treatment with flexible dose sertraline (50-200 mg/d) or placebo. Patients with different index traumas were compared in terms of baseline demographic and clinical characteristics, as well as treatment response. Primary efficacy variables included part 2 of the Clinician Administered PTSD Scale (CAPS-2). **RESULTS:** Interpersonal trauma and childhood abuse were both more common in females than males, and were associated with

early age at time of index trauma and longer duration of PTSD, but not with PTSD symptom severity. Sertraline was significantly more effective than placebo on most primary efficacy variables, irrespective of whether patients had experienced interpersonal trauma or childhood abuse. **CONCLUSIONS:** These data demonstrate that sertraline is valuable for the treatment of PTSD, irrespective of whether the precipitating trauma involves interpersonal trauma in general, or childhood abuse in particular.

81. Van Ameringen, M., C. Mancini, et al. (2007). "Nefazodone in the treatment of generalized social phobia: a randomized, placebo-controlled trial." *J Clin Psychiatry* 68(2): 288-95. **OBJECTIVE:** Numerous studies have demonstrated the efficacy of serotonergic antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), in the treatment of social phobia. We evaluated the efficacy, safety, and tolerability of nefazodone, a 5-HT₂ antagonist, in patients with generalized social phobia (GSP). **METHOD:** One hundred five patients with GSP (confirmed using the Structured Clinical Interview for DSM-IV) from 4 Canadian outpatient anxiety clinics were assigned randomly to nefazodone (300-600 mg/day, flexible dose) or placebo for 14 weeks of double-blind treatment. Data were collected from October 12, 1999, through December 8, 2001. Primary efficacy outcomes were the Clinical Global Impressions-Improvement scale (CGI-I) score and the Liebowitz Social Anxiety Scale score. **RESULTS:** In the intent-to-treat sample, 16 (31.4%) of 51 subjects taking nefazodone and 12 (23.5%) of 51 subjects taking placebo were rated as much or very much improved on the CGI-I at endpoint ($\chi^2 = 0.79$, $p = .38$). With the exception of the Social Phobia Scale, no significant differences were found in measures of social phobia when comparing the nefazodone and placebo groups. **CONCLUSION:** These findings suggest that nefazodone is not an effective agent in the treatment of GSP. These data parallel some recent findings with the use of the SSRI fluoxetine in GSP. The lack of efficacy of 2 serotonergic antidepressants in GSP suggests that serotonin reuptake inhibition may not be the only mechanism of action required for efficacy to occur in the treatment of GSP.
82. Ventura, D., E. P. Armstrong, et al. (2007). "Escitalopram versus sertraline in the treatment of major depressive disorder: a randomized clinical trial." *Curr Med Res Opin* 23(2): 245-50. **OBJECTIVE:** This trial was conducted to compare the efficacy and tolerability of a fixed dose of escitalopram 10 mg/day with sertraline optimally dosed within its recommended dose range (50-200 mg/day) for the treatment of major depressive disorder. **METHODS:** In this multicenter trial, depressed patients (DSM-IV defined; baseline Montgomery-Asberg Depression Rating Scale [MADRS] ≥ 22) aged 18-80 years were randomly assigned to 8 weeks of double-blind treatment with escitalopram (10 mg/day) or sertraline (50-200 mg/day) following a 1-week single-blind placebo lead-in period. There was no placebo comparison arm. Sertraline was initiated at 50 mg/day, and could be increased by 50 mg/day at weekly intervals based on clinical need and tolerability at the lower dose level. The blind was maintained with matching double-blind placebo capsules for the escitalopram group. Change from baseline to endpoint in MADRS total score (last observation carried forward) was the primary efficacy measure. **RESULTS:** A total of 212 patients received double-blind medication. At week 8, the mean sertraline dosage was 144 mg/day (median = 150 mg/day). Mean changes from baseline to endpoint in MADRS scores were -19.1 and -18.4 for the

escitalopram and sertraline groups, respectively. At endpoint, 75% and 70% of escitalopram- and sertraline-treated patients, respectively, were responders (> or =50% improvement from baseline in mean MADRS scores). Both treatments were generally well tolerated; only 2% and 4% of patients prematurely discontinued escitalopram and sertraline treatment, respectively, due to adverse events. CONCLUSION: No differences in efficacy were observed for fixed-dose escitalopram 10 mg/day and sertraline flexibly dosed from 50-200 mg/day. At these doses, both escitalopram and sertraline were generally well tolerated.

83. Vitiello, B., P. Rohde, et al. (2006). "Functioning and quality of life in the Treatment for Adolescents with Depression Study (TADS)." *J Am Acad Child Adolesc Psychiatry* 45(12): 1419-26.

OBJECTIVE: To test whether 12-week treatment of major depression improved the level of functioning, global health, and quality of life of adolescents. METHOD: The Treatment for Adolescents With Depression Study was a multisite, randomized clinical trial of fluoxetine, cognitive-behavioral therapy (CBT), their combination (COMB), or clinical management with placebo in 439 adolescents with major depression. Functioning was measured with the Children's Global Assessment Scale (CGAS), global health with the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA), and quality of life with the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q). Random-effects regression models were applied to the data. RESULTS: Compared with placebo, COMB was effective on the CGAS ($p < .0001$), HoNOSCA ($p < .05$), and PQ-LES-Q ($p < .001$), whereas fluoxetine was superior to placebo on the CGAS only ($p < .05$). COMB was superior to fluoxetine on the CGAS ($p < .05$) and PQ-LES-Q ($p = .001$). Fluoxetine was superior to CBT on the CGAS ($p < .01$). CBT monotherapy was not statistically different from the placebo group on any of the measures assessed. Treatment effects were mediated by improvement in depressive symptoms measured on the Child Depression Rating Scale-Revised. CONCLUSIONS: The combination of fluoxetine and CBT was effective in improving functioning, global health, and quality of life in depressed adolescents. Fluoxetine monotherapy improved functioning.

84. von Knorring, A. L., G. I. Olsson, et al. (2006). "A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder." *J Clin Psychopharmacol* 26(3): 311-5.

In a European, multicenter, double-blind study, 244 adolescents, 13 to 18 years old, with major depression were randomized to treatment with citalopram ($n = 124$) or placebo ($n = 120$). One third of the patients in both groups withdrew from the study. No significant differences in improvement of scores from baseline to week 12 between citalopram and placebo were found. The response rate was 59% to 61% in both groups according to the Schedule for Affective Disorders and Schizophrenia for school-aged children-Present episode version (Kiddie-SADS-P) (depression and anhedonia scores $< \text{or} = 2$) and Montgomery Asberg Depression Rating Scale (MADRS) ($> \text{or} = 50\%$ reduction). Remission (MADRS score $< \text{or} = 12$) was achieved by 51% of patients with citalopram and 53% with placebo. A post hoc analysis revealed that more than two thirds of all patients received psychotherapy during this study. For those patients not receiving psychotherapy, there was a higher percentage of Kiddie-SADS-P responders with citalopram (41%) versus placebo

(25%) and a significantly higher percentage of MADRS responders and remitters with citalopram (52% and 45%, respectively) versus placebo (22% and 19%, respectively). Mild to moderate treatment-emergent adverse events were reported in 75% citalopram and 71% of placebo patients, most commonly headache, nausea, and insomnia. Serious adverse events occurred in 14% to 15% in both groups. Suicide attempts, including suicidal thoughts and tendencies, were reported by 5 patients in the placebo group and by 14 patients in the citalopram group (not significant) with no pattern with respect to duration of treatment, time of onset, or dosage. In contrast, the suicidal ideation (Kiddie-SADS-P) single item showed worsening more frequently in the placebo (18%) than in the citalopram group (8%).

85. Wade, A., N. Despiegel, et al. (2006). "Escitalopram in the long-term treatment of major depressive disorder." *Ann Clin Psychiatry* 18(2): 83-9.

BACKGROUND: Escitalopram has been proven safe and efficacious in the treatment of major depressive disorder (MDD) in short-term studies. The long-term clinical tolerability and response to treatment are presented from a 12-month open-label study with a total exposure time to escitalopram of 486 patient years. **METHODS:** Patients (n = 590) with MDD entered the study after completing one of two 8-week, double-blind, placebo-controlled, lead-in studies in primary care. Escitalopram was administered at doses of 10 or 20 mg/day (dose based on physician's clinical judgement) with an average exposure to escitalopram of 315 days. The primary efficacy parameter was the Montgomery Asberg Depression Rating Scale (MADRS) total score. **RESULTS:** The overall withdrawal rate was 26%; and the withdrawal rate due to adverse events was 9%. The most common adverse events were headache, back pain, upper respiratory tract infection, rhinitis and nausea, with an incidence ranging from 11% to 17%. No new types of adverse events were seen after the acute period of 8 weeks, and the incidence declined with time. At baseline (entry into the 12-month study), patients had a mean MADRS total score of 14.2, which decreased to 10.5 after 8 weeks and 7.2 after 52 weeks (LOCF). The percentage of patients in remission (MADRS total score \leq 12) increased from 46% at baseline to 65% by Week 8 and 86% by Week 52. **CONCLUSIONS:** Escitalopram (10 to 20 mg/day) demonstrated a favorable safety and tolerability profile over 12-months treatment, with further improvement in patient response.

86. Wagner, K. D., J. Jonas, et al. (2006). "A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression." *J Am Acad Child Adolesc Psychiatry* 45(3): 280-8.

OBJECTIVE: Escitalopram is a selective serotonin reuptake inhibitor antidepressant indicated for use in adults. This trial examined the efficacy and safety of escitalopram in pediatric depression. **METHOD:** Patients (6-17 years old) with major depressive disorder were randomized to receive 8 weeks of double-blind flexibly dosed treatment with escitalopram (10-20 mg/day; n = 131) or placebo (n = 133). Randomization was not stratified by age. The primary efficacy measure was the mean change from baseline to endpoint in Children's Depression Rating Scale-Revised (CDRS-R) scores, using the last observation carried forward approach. **RESULTS:** A total of 82% of patients completed treatment. Escitalopram did not significantly improve CDRS-R scores compared to placebo at endpoint (least squares mean difference = -1.7, p = .31; last observation carried forward). In a post hoc analysis of adolescent (ages 12-17 years) completers, escitalopram significantly improved

CDRS-R scores compared with placebo (least squares mean difference = -4.6, $p = .047$). Headache and abdominal pain were the only adverse events in >10% of patients in the escitalopram group. Discontinuation rates caused by adverse events were 1.5% for both groups. Potential suicide-related events were observed in one escitalopram- and two placebo-treated patients. There were no completed suicides. **CONCLUSIONS:** Although there were no significant differences between escitalopram and placebo in the total population, the data suggest that escitalopram may have beneficial effects in adolescent patients. Escitalopram appeared to be well tolerated.

87. Wan, G. J., H. F. Zhang, et al. (2006). "Estimation of symptom-free days in generalized anxiety disorder." *Curr Med Res Opin* 22(3): 587-91.

OBJECTIVE: The efficacy of treatments for generalized anxiety disorder has usually been measured in terms of response or remission of symptoms. These endpoints, however, may not adequately capture the transient periods of symptom abatement and relapse characteristic of chronic psychiatric disorders. Here, we evaluate the measurement of treatment effectiveness in terms of the number of symptom-free days (SFDs). **RESEARCH DESIGN AND METHODS:** A pooled analysis was performed of data from five manufacturer-initiated trials of venlafaxine extended-release (XR) in patients with generalized anxiety disorder without co-morbid major depressive disorder. The trials were randomized, double-blind, placebo-controlled and of 8 weeks duration (total intent-to-treat population 1295 venlafaxine XR, 544 placebo). Two of the studies had extensions up to 6 months (intent-to-treat population 514 venlafaxine XR, 253 placebo). The patients were ≥ 18 years of age with a Hamilton Rating Scale for Anxiety (HAM-A) score of ≥ 18 . **MAIN OUTCOME MEASURES:** SFDs were estimated using weekly scores on the HAM-A. Values of 7 and 0 SFDs, respectively, were assigned to each week the patient had a HAM-A score of ≤ 7 (the remission threshold) and ≥ 18 (the minimum threshold for anxiety). Fractional SFD values were assigned proportionately to weekly HAM-A scores between 7 and 18. **RESULTS:** The median (inter-quartile range) SFDs were 19 (2-36) for venlafaxine XR and 10 (0-27) for placebo in the 8-week studies ($p < 0.0001$). In the 6-month extension studies the SFDs were 102 (27-139) for venlafaxine XR and 36 (0-94) for placebo ($p < 0.0001$). **CONCLUSIONS:** SFDs differentiate between active treatment and placebo in clinical trials and may be an appropriate measure of treatment effectiveness.

88. Winkler, D., E. Pjrek, et al. (2007). "Escitalopram in a working population: results from an observational study of 2378 outpatients in Austria." *Hum Psychopharmacol* 22(4): 245-51.

OBJECTIVE: The aim of this observational study was to evaluate the effectiveness of escitalopram in a naturalistic sample of employed people with mood and anxiety disorders. **METHOD:** Days on sick leave 3 months prior and 3 months during treatment with escitalopram were recorded and compared (mirror study design) in 2378 patients (949 men and 1376 women). A further clinical examination including the clinical global impression of severity (CGI-S) and improvement (CGI-I) scales and assessments of tolerability were used to evaluate treatment effects in a subgroup of 807 study subjects. **RESULTS:** Escitalopram treatment (mean final daily dosage: 12.4 \pm 5.0 mg) led to a significant reduction (baseline versus end of study) of sick leave (11.0 \pm 12.8 days versus 5.4 \pm 11.0 days; $p < 0.001$). CGI-S scores decreased from 4.7 \pm 0.9 at baseline to 2.4 \pm 1.1 after 3 months ($p < 0.001$), the CGI-I

after 3 months was 1.9+/-0.9. The incidence of adverse events after initiation of treatment with escitalopram was 13.1%, with only 1.3% of patients experiencing severe adverse events interfering with patient functioning. CONCLUSION: Our results suggest that escitalopram is an efficacious and overall well-tolerated treatment in a naturalistic sample of working patients. A decrease in the days on sick leave is indicative of indirect cost-effectiveness of this treatment.

89. Yonkers, K. A., G. A. Holthausen, et al. (2006). "Symptom-onset treatment for women with premenstrual dysphoric disorder." *J Clin Psychopharmacol* 26(2): 198-202. Symptoms of premenstrual dysphoric disorder (PMDD) respond to serotonin reuptake inhibitors when treatment is limited to 14 days of the menstrual cycle. Many women have less than a week of symptoms, and shorter treatment intervals would further reduce medication exposure and costs. METHODS: Twenty women with PMDD were randomly assigned to either paroxetine CR or placebo for 1 cycle and crossed over to the other condition for a second cycle. Subjects initiated treatment when premenstrual symptoms began and stopped within 3 days of beginning menses. RESULTS: Women took capsules for an average of 9 days (range, 3-15 days), including the first few days of menses. Moderate "PMDD level" symptoms occurred in 1 subject (6%) for 2 days and 4 subjects (24%) for 1 day before starting paroxetine or placebo. Daily Record of Severity of Problems scores were lower in the paroxetine group compared with the placebo group, although the differences were not statistically significant. However, the mean on-treatment Inventory of Depressive Symptomatology (clinician-rated) score for the paroxetine group was 17.9 +/- 8.3 compared with 31.5 +/- 11.2 in the placebo group (adjusted mean difference = 13.6, P = 0.009). Response (Clinical Global Impressions Scale score of 1 or 2) occurred in 70% of subjects randomized to paroxetine CR and 10% of those assigned to placebo ($\chi^2(1) = 7.5$, P = 0.006). Discontinuation symptoms did not differ in the groups. CONCLUSION: These data suggest the need to further evaluate symptom-onset treatment in a larger randomized clinical trial.
90. Yoon, S. J., C. U. Pae, et al. (2006). "Mirtazapine for patients with alcohol dependence and comorbid depressive disorders: a multicentre, open label study." *Prog Neuropsychopharmacol Biol Psychiatry* 30(7): 1196-201. Major depressive disorder and alcohol dependence are common and serious mental illnesses. There is a great interest in discovering useful treatments for both mood symptoms and alcohol abuse in those patients with depressive disorders and comorbid alcohol dependence. The primary purpose of this study was to evaluate the effectiveness and tolerability of mirtazapine for the treatment of patients with alcohol dependence comorbid with a depressive disorder in an open label, naturalistic multicentre treatment setting. The 17-item Hamilton Depression Rating Scale (HDRS), the Hamilton Anxiety Rating Scale (HARS) and the Clinical Global Impression-Severity (CGI-S) scale were measured at baseline and at weeks 4 and 8 for the assessment of treatment effectiveness. Alcohol craving was measured using the Obsessive Compulsive Drinking Scale (OCDS) and the Visual Analog Scale for Craving (VAS). This study showed a statistically significant reduction of the scores on the HDRS (13.9+/-7.3, $p < 0.0001$), HARS (10.8+/-7.2, $p < 0.0001$) and the CGI-S (1.7+/-1.0, $p < 0.0001$) from baseline to the endpoint (week 8). The OCDS and VAS scores were also

decreased significantly by 42.3% and 53.2% (9.0 ± 10.0 , $p < 0.0001$; 2.5 ± 2.4 , $p < 0.0001$, respectively). The number of patients with a 50% reduction or more in the HDRS and HARS scores was 103 (72.0%) and 106 (74.1%) at the endpoint, respectively. Adverse events related to mirtazapine were observed in 10% or more of the patients in this study. In conclusion, the results from this naturalistic study suggest that the use of mirtazapine for the patients with alcohol dependence comorbid with depressive disorder is accompanied by clinical improvement in their mood and alcohol craving.