SSRI Safety in Pregnancy

In 2006 the FDA issued a public health advisory about the risk of persistent pulmonary hypertension of the newborn (PPHN) when mothers received SSRIs during pregnancy. PPHN is a condition that occurs when newborns do not adapt to breathing outside of the womb. The warning was based on a single study, and results of subsequent studies have been inconsistent. After review of the newer evidence, the FDA has decided that no conclusion can be reached at this time about the possible link between SSRI use in pregnancy and PPHN. Newborns with PPHN may require intensive care and mechanical ventilation. Severe PPHN can lead to organ damage, brain damage, and death. The FDA recommends that clinicians not change their current practices for treating depression during pregnancy.


ADHD Medications: Cardiovascular Safety in Adults

Stimulant medications and atomoxetine can increase blood pressure and heart rate, which could in turn increase risk of myocardial infarction (MI), stroke, and sudden cardiac death. However, a large cohort study of young and middle-aged adults found ADHD medications were not associated with increases in cardiovascular events.

Methods: The study, funded by several federal government agencies, examined ADHD medication use and serious cardiovascular events in persons aged 25–64 years. (A parallel study was conducted in younger patients, aged 2–24 years.) Participants were >150,000 patients who were continuously enrolled in health plans with pharmacy coverage, who received ADHD medication between 1986 and 2005, and were free of diseases likely to be fatal in the near term. Medication use was defined as filling a prescription, regardless of indication, for a stimulant (i.e., methylphenidate, amphetamines, or pemoline) or atomoxetine.
Each patient was matched for age, gender, and other factors with 2 stimulant nonusers from the same institutions. Study endpoints were MI, sudden cardiac death, and stroke.

**Results:** During the follow-up period (median, 1.3 years per patient), 1357 MIs, 296 sudden cardiac deaths, and 575 strokes occurred. Crude incidence rates ranged from 0.3 to 1.34 per 1000 patient-years. After adjustment for confounding factors (e.g., age, gender, smoking, concurrent medications), rates of cardiovascular events did not differ between users and nonusers of ADHD drugs. Results were similar for all medications, for all individual study endpoints including hemorrhagic and ischemic stroke, and regardless of diagnosis, patient age, and history of cardiovascular disease. New users of the medications were not at increased risk compared with nonusers. There was no association of cardiovascular risk with increasing duration of current use or with use during any window of time. Even in worst-case scenarios that assumed risks were at the upper end of the confidence intervals, elevations were small. The parallel study in young patients had similar results.

**Discussion:** More than 1.5 million U.S. adults were treated with stimulants in 2005, the end date of the study, and in recent years, use of these medications has increased more rapidly in adults than in children. Adverse event reports have called into question the cardiac safety of ADHD medications, and although epidemiologic studies did not support those reports, concern persisted. Although the limitations inherent to population-based cohort studies make it impossible to completely rule out a modest increase in risk, the present results support the cardiac safety of ADHD medications. However, treated adults should continue to be monitored for other possible adverse effects such as weight loss and insomnia.

Habel L, Cooper W, Sox C, Chan K, et al: ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA* 2011;306 (December 28):2673–2683. From Kaiser Permanente Northern California, Oakland; and other institutions. Funded by the Agency for Healthcare Research and Quality; and other sources. Several study authors disclosed financial relationships with commercial sources.

**Drug Trade Names:** atomoxetine—Strattera; methylphenidate—Ritalin; pemoline—Cylert

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**Atomoxetine Efficacy in Adult ADHD**

A manufacturer-sponsored randomized controlled trial has confirmed previous reports that atomoxetine is effective in adults with ADHD. In addition to improving ADHD core symptoms, atomoxetine also reduced emotional symptoms and improved self-esteem and quality of life.

**Methods:** Study subjects were adults, aged 18–50 years, with a chronic course of ADHD from childhood to adulthood; no patient was receiving stimulant treatment at entry. Following a 4-week washout of antidepressant therapy in 9 patients, all participants were randomly assigned to 12 weeks of either atomoxetine (maximum dosage, 80 mg/day) or a wait-list control. The main efficacy outcome, ADHD symptom severity, was measured with the observer-rated Conners’ Adult ADHD Rating Scale (CAARS). Treatment response, a secondary outcome, was defined as a decrease of ≥30% in the CAARS score. Other rating instruments included the Wender-Reimherr Adult Attention Deficit Disorder Scale, which measures emotional symptoms of ADHD, and the Quality of Life Enjoyment and Satisfaction Questionnaire. Although the nature of the control did not allow for patients to be blinded to treatment assignment, rating scales were administered by blinded clinicians.

**Results:** Sixty-four patients were randomly assigned to treatment with atomoxetine (n=27) or the waiting list (n=37). Participants were an average age of 35 years, and 58% were women. Fifteen patients were withdrawn from the control group for various reasons, and 5 patients in the atomoxetine group withdrew because of adverse events, most commonly irritability (n=4) and fatigue (n=2).
At the study endpoint, participants who received atomoxetine had significantly greater reductions than controls in the CAARS total score and in inattention and hyperactivity/impulsivity subscales (effect size* for observer-rated total score, 1.8; p<0.005). Treatment response occurred in 53% of the atomoxetine group, compared with 5% of the control group. Atomoxetine was also associated with statistically significant declines in hot temper, emotional lability, and over-reactivity. Scores on the CAARS self-concept domain showed somewhat greater improvement in self-esteem in the atomoxetine group. The atomoxetine group also had greater improvements in general quality of life; 54% of this group and 37% of controls were rated as treatment responders on the quality-of-life scale.

**Discussion:** Positive effects of atomoxetine on core ADHD symptoms, emotional symptoms, and quality of life have been reported in other studies, but this may be the first report of positive effects of atomoxetine on self-esteem in adults with ADHD. Several reports indicate short-term methylphenidate treatment improved self-concept in adults. The evidence suggests even short-term drug treatment of ADHD may improve self-image in this patient population.

**Study Rating**—17 (100%): This study met all criteria for a randomized controlled trial.


*Drug Trade Names:* atomoxetine—Strattera; methylphenidate—Ritalin and others

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**Escitalopram for Geriatric Depression**

In a clinical trial, escitalopram (Lexapro) produced significant clinical improvement in depression with no serious adverse effects in a group of elderly Chinese patients.

**Background:** Escitalopram is the most selective of the SSRIs and has little effect on other neurotransmitters. Because it has fewer CYP450 effects, it is less prone than other SSRIs to interact with other drugs. These factors may make it an attractive option for elderly patients with depression.

**Methods:** Study participants were 55 patients (34 females) aged ≥65 years with primary DSM-IV unipolar major depression and a minimum score of 20 on the Geriatric Depression Scale (GDS). Patients were randomly assigned to 8 weeks of treatment with either 10 mg/day escitalopram or placebo. The primary outcome measure was change in the GDS score from baseline to week 8. Personality was evaluated with the Eysenck Personality Questionnaire (EPQ), symptoms with the Symptom Checklist-90 (SCL-90), and illness severity with the Clinical Global Impressions-Severity (CGI-S) scale.

**Results:** Patients ranged in age from 65 to 79 years (mean, 69 years), and mean baseline CGI-I scores indicated the group was markedly ill. Patients had a wide range of depressive symptoms, including sleep disturbance and somatic problems such as headache, dizziness, and other nervous system complaints. A total of 23 patients (42%) had suicidal ideation, and 8 (14%) had made a suicide attempt.

All but 4 patients (2 in each group) completed the trial. Those who received escitalopram had significantly lower average GDS scores than the placebo group at the 4- and 8-week evaluations (p<0.05 at both time points). By week 8, patients receiving active medication had a 54% reduction in GDS scores, compared with a 12% decline with placebo. (See table, next page.) At 8 weeks, 11 of 27 escitalopram patients (41%) were considered clinically cured with a ≥75% decrease in GDS score, 6 patients (22%) were considerably improved (i.e., 51–75% GDS
reduction), and 11 patients (41%) were judged to be improved (i.e., 26–50% GDS reduction). In the placebo group, 4 of 24 patients (17%) were improved but no patient was considered greatly improved or cured.

### Comparison of GDS Scores

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Relative Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>23.4</td>
<td>14.5</td>
<td>10.7</td>
<td>54%</td>
</tr>
<tr>
<td>Placebo</td>
<td>24.0</td>
<td>22.4</td>
<td>21.1</td>
<td>12%</td>
</tr>
</tbody>
</table>

A total of 6 escitalopram-treated patients had mild, transient adverse events (including dizziness, dry mouth, and nausea) in the first 2-4 weeks of treatment. No serious events occurred, and there were no clinically important changes in laboratory measures.

**Study Rating**—**13 (76%)**: This study met most criteria for a randomized controlled trial; however, it was not clear from the report if patients or clinicians were blinded to treatment assignment, and the source of funding was not stated.

Chen Y-M, Huang X-M, Thompson R, Zhao Y-B: Clinical features and efficacy of escitalopram treatment for geriatric depression. *Journal of International Medical Research* 2011;39:1946–1953. From Shanghai Jiao Tong University, Shanghai, China; and Sanford-Burnham Medical Research Institute, La Jolla, Calif. Source of funding not stated. The authors disclosed no competing interests.

*See Reference Guide.*

### In-Office Clozapine Monitoring

Clozapine is often the drug of choice for resistant schizophrenia, but the required hematological monitoring can lead to noncompliance and forced discontinuation or to a reluctance to start treatment. A portable point-of-care device, the Chempaq XBC, was developed for use in primary care and oncology practices to measure white blood cells and granulocytes using capillary blood. A clinical study was undertaken to evaluate the tolerability of this point-of-care testing in psychiatric offices.

**Methods**: Study participants were 85 outpatients with schizophrenia (60% males) who had been receiving clozapine treatment for a mean of 9 years. In random order, participants underwent traditional venous blood sampling in a hospital laboratory and point-of-care capillary sampling in their psychiatrist’s office. Using a visual analog scale, patients rated both the painfulness and inconvenience of each procedure.

**Results**: Of the 85 patients enrolled, 8 were lost to follow-up. Among the 77 patients who underwent both types of blood sampling, 10 patients (12%) preferred the traditional procedure, 54 patients (63%) preferred the capillary sampling, and 22 patients (26%) had no preference. With the in-office capillary measurement, patients reported satisfaction with not waiting at the laboratory, getting test results faster, less pain, and less blood loss. In the majority of cases (87%), the treating psychiatrists felt the Chempaq monitoring system was more convenient for their patients.

**Discussion**: Current requirements for clozapine hematological monitoring include measures of white blood cells, granulocytes, and neutrophils. The Chempaq device does not measure neutrophils. However, as neutrophils have been shown to comprise 90% of granulocytes, the authors suggest it may be feasible to estimate absolute neutrophil counts. The present study
was not designed to evaluate the validity of the capillary measurements. If further research establishes the reliability of the device measures, point-of-care monitoring of clozapine may increase compliance.

Nielsen J, Thode D, Stenager E, Andersen K, et al: Hematological clozapine monitoring with a point-of-care device: a randomized cross-over trial. *European Neuropsychopharmacology* 2011; doi 10.1016/j.euroneuro.2011.10.001. From Aarhus University Hospital, Denmark; and other institutions. Funded by the manufacturer of the Chempaq WBC device. Several study authors disclosed financial relationships with commercial sources.

**Implications of Anxiety when Starting SSRIs**

In patients starting SSRI therapy for depression, early worsening of already high baseline levels of anxiety were predictive of greater depression severity and poorer treatment response.

**Methods:** This study, a secondary analysis of clinical trial data, was designed to assess the effects of SSRI therapy on anxiety and the implications for antidepressant treatment outcome in a representative sample of outpatients with depression. The primary study was an NIH-funded trial conducted in 6 primary care and 9 psychiatric treatment sites across the U.S. Patients received 8 weeks of treatment with an SSRI chosen by their physician. Anxiety was measured at biweekly clinic visits using the Beck Anxiety Inventory. Depression was measured using the 16-item Quick Inventory of Depressive Symptomatology—Clinician Rated (QIDS-C16).

**Results:** The sample consisted of 200 patients, two-thirds of whom were experiencing a recurrent depressive episode. More than half received citalopram (*Lexapro*). Over the 8-week study period, >80% of patients had significant improvement in depressive symptoms. In 48% of the patients, initial anxiety improved during the first 2 weeks of SSRI therapy. Anxiety severity was unchanged or minimally changed in 37% and worsened in 15%. There was a modest correlation (r=0.10) between changes in anxiety symptoms in the first 2 weeks and depressive-symptom outcomes after 8 weeks of treatment. Changes in anxiety symptoms were not associated with the likelihood of remission. However, when patients with anxious depression, defined as a score of ≥7 on the Hamilton Rating Scale for Depression Anxiety/Somatization factor, at baseline were considered separately, worsening of anxiety during initial SSRI treatment was associated with greater baseline depression severity and a less robust response to antidepressant therapy.

**Discussion:** These results suggest that in patients with depression and high or low levels of anxiety, depressive symptoms follow 2 different trajectories after initiation of SSRI therapy. Early worsening of anxiety in patients who already show high anxiety at baseline may be a marker for more severe depression. Clinicians may use this marker as an early indicator to determine whether it is worthwhile to continue with SSRIs.

Gollan J, Fava M, Kurian B, Wisniewski S, et al: What are the clinical implications of new onset or worsening anxiety during the first two weeks of SSRI treatment for depression? *Depression and Anxiety* 2011; doi 10.1002/da.20917. From Northwestern University, Chicago, Ill.; and other institutions. Funded by the NIMH; and other sources. All of the study authors disclosed relationships with commercial sources.

**Recommendations for Schizophrenia Maintenance Therapy**

Guidelines for maintenance-phase treatment of schizophrenia are diverse and not well-defined, in part because the evidence base for maintenance treatment is smaller than that for acute treatment.

A literature review was undertaken to identify all English-language guidelines and algorithms for maintenance treatment of schizophrenia published or revised since 2000. The 14 guidelines—published by agencies and/or projects such as the APA; the British Association for Psychopharmacology; the Canadian Psychiatric Association; the International Psychopharmacology Algorithm Project; the National Institute for Health and Clinical Excellence; the Texas Medication Algorithm...
Project; and others—were then evaluated for how they defined the maintenance phase and for their recommendations regarding antipsychotic dose reduction, discontinuation, and intermittent pharmacotherapy.

**Defining the Maintenance Phase.** Only 5 of the guidelines explicitly defined the maintenance phase, although others used various terms to describe sequential illness stages. The 5 explicit guidelines agreed on 3 phases: acute, stabilization, and stable. Only 2 guidelines provided typical durations: up to 6 months for the acute and stabilization phases combined, followed by months to years of stable illness.

**Antipsychotic Discontinuation.** Ten of the guidelines did not recommend discontinuation of antipsychotic therapy within 5 years. For first-episode schizophrenia, 6 guidelines recommended consideration of antipsychotic discontinuation after 1–2 years, and 2 did not recommend discontinuation. Drug discontinuation in patients with multi-episode schizophrenia was either not mentioned or not recommended in all guidelines.

**Intermittent Treatment.** Intermittent or targeted therapy—i.e., using antipsychotics only during periods of impending relapse or symptom exacerbation—was not endorsed by any of the 9 guidelines that mentioned this strategy. The guidelines did not discuss the new “extended but regular dosing” strategy, in which patients take their antipsychotic intermittently (e.g., every other day). Some evidence suggests this approach may be useful in clinical practice, reducing adverse effects without worsening the psychosis.

**Dosage Reductions.** Dosage reductions of conventional antipsychotics are recommended, although sometimes with reservations, in the 6 guidelines that discuss the strategy. Reductions in doses of atypical agents are recommended by only 2 of the guidelines, probably because the evidence is very limited and because of the atypicals’ relative lack of adverse motor effects. However, the guidelines may not take into account the serious metabolic side effects of the atypicals, many of which are dose-dependent. The guidelines do not address whether it is better to switch medications or reduce the dose of the current drug to control adverse effects or whether drug dosage should be guided by plasma concentrations.

<table>
<thead>
<tr>
<th>Overview of Antipsychotic Maintenance Recommendations</th>
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<tbody>
<tr>
<td><strong>Discontinuation in 5 years</strong></td>
</tr>
<tr>
<td>• Not recommended for schizophrenia in general</td>
</tr>
<tr>
<td>• Either not recommended or not considered for first-episode patients in 8 of the 14 guidelines; 6 do recommend discontinuation after 1 or 2 years</td>
</tr>
<tr>
<td>• Not recommended in the 6 guidelines that specifically address multiple-episode schizophrenia</td>
</tr>
<tr>
<td><strong>Intermittent therapy</strong></td>
</tr>
<tr>
<td>• Not recommended in any of the 9 guidelines that address this option</td>
</tr>
<tr>
<td><strong>Dosage reduction</strong></td>
</tr>
<tr>
<td>• For antipsychotic therapy overall, dosage reduction is recommended in 1 guideline; not recommended in 2 guidelines; partially recommended in 4 depending on adverse effects and first or multiple episodes; very high or very low dosages not recommended</td>
</tr>
<tr>
<td>• For conventional antipsychotics, 2 of the guidelines recommend dosage reduction; 4 offer a partial recommendation based on illness variables; and 8 do not address the option</td>
</tr>
<tr>
<td>• Possibility of atypical antipsychotic dosage reduction is not addressed in 8 of the guidelines; 4 do not recommend the practice; and 2 offer a partial recommendation depending on individual agents and patient characteristics</td>
</tr>
</tbody>
</table>
Although it is used commonly in clinical practice, the guidelines also do not provide much guidance for polypharmacy, other than generally recommending against it. In addition, except in terms of adherence, no guideline addressed whether oral or depot therapy is superior.

**Discussion:** According to the authors, the existing evidence base for maintenance treatment of schizophrenia is not sufficient to derive treatment recommendations. However, the existing evidence does not generally endorse antipsychotic discontinuation or intermittent therapy. There is some controversy regarding antipsychotic dose reduction in the maintenance phase depending on the type of antipsychotic, but many guidelines and algorithms have not commented on the issue. Further evidence is needed to guide optimal antipsychotic therapy for the maintenance phase of schizophrenia.

Takeuchi H, Suzuki T, Uchida H, Watanabe K, et al: Antipsychotic treatment for schizophrenia in the maintenance phase: a systematic review of the guidelines and algorithms. Schizophrenia Research 2011; doi 10.1016/j.schres.2011.11.021. From Keio University School of Medicine, Tokyo, Japan; and the Geriatric Mental Health Program, Toronto, Ont., Canada. This review was not funded. All study authors disclosed financial relationships with commercial sources.

### Comparative Benefits and Harms of Newer Antidepressants

Second-generation antidepressants (SGAs) are similar in efficacy but have differences in dosing, onset of action, and adverse effects that might influence treatment decisions, according to a meta-analysis.¹

**Background:** Two recent comparative effectiveness reviews of SGAs had conflicting results: 1 showed no difference among the drugs,² while the other concluded that escitalopram and sertraline had a superior combination of efficacy and tolerability.³ The present analysis, carried out by the Agency for Healthcare Research and Quality, attempted to resolve the question.

**Methods:** A comprehensive literature search was conducted to identify all English-language publications of randomized clinical trials of SGAs (see figure for included agents) in adults. Randomized trials were required to be ≥6 weeks in duration and included head-to-head comparisons as well as placebo-controlled trials. The analysis of harms was based on clinical trials and observational studies with ≥12 weeks of follow-up in ≥1000 participants. Studies of poor methodologic quality were excluded.

**Results:** The investigators identified 234 studies of good or fair quality, of which 118 were head-to-head comparisons. Pharmaceutical companies supported 77% of the studies. There was no evidence of publication bias.

Comparative effectiveness and efficacy of the SGAs did not differ from one another to any clinically meaningful extent. The drugs' beneficial effects were similar in acute, continuation, and maintenance treatment. Their efficacy did not differ in subgroups defined by age, gender, ethnicity, or comorbid conditions. Overall, 63% of patients responded to 6–12 weeks of treatment with their first-line antidepressant, and 47% achieved remission. About 1 in 4 patients who switched medications subsequently became symptom-free. Mirtazapine was shown to have a faster onset of action than SSRIs.

The investigators identified studies addressing 7 different symptom clusters accompanying depression: anxiety; insomnia; low energy; pain; psychomotor change; melancholia; and soma-
The antidepressants did not differ in their efficacy in patient groups with different symptom clusters, although for some clusters the number of studies was small and the strength of the evidence was low.

SGAs’ comparative risk for harm was investigated in 93 head-to-head clinical trials and in 48 additional studies. The general side effect profiles of the drugs were similar, although the incidence of some effects varied: for example, venlafaxine has a higher rate of nausea and vomiting than some other agents, sertraline has a higher incidence of diarrhea, and mirtazapine a higher rate of weight gain. Results of several trials indicate that bupropion has a lower liability for sexual side effects than several of the SSRIs. Most trials were too small and their durations too short to examine risks for rare but serious side effects such as suicidality, cardiovascular events, or serotonin syndrome.

Discussion: These observations suggest that while the SGAs are similar in efficacy, they should not be considered identical drugs. Differences with regard to onset of action, adverse events, and some measures of health-related quality of life may be considered in the choice of medication for a specific patient.

Study Rating—18 (100%): This study met all criteria for a systematic review and meta-analysis.


Drug Trade Names: bupropion—Wellbutrin; citalopram—Celexa; desvenlafaxine—Pristiq; duloxetine—Cymbalta; escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox; mirtazapine—Remeron; nefazodone—Serzone, and others; paroxetine—Paxil; sertraline—Zoloft; trazodone—Desyrel, Oleptro; venlafaxine—Effexor

Reference Guide

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance and large effect sizes do not ensure treatment efficacy.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.