Fetal Safety of Methylphenidate

Growing use of methylphenidate to treat adult ADHD in women raises concerns about use during pregnancy and risks to the fetus. Because little data exists on use during pregnancy, fetal risk cannot be ruled out and methylphenidate is labeled as Pregnancy Category C.* According to a review of the limited available literature, first-trimester exposure to methylphenidate does not appear to substantially increase risk of congenital malformations.

Methods: Investigators identified studies of pregnancy outcomes after first trimester in-utero exposure to methylphenidate in the published literature and in population-based databases from Michigan, Sweden, and Denmark.

Results: Two isolated case reports of congenital malformations appeared in 1962 and 1975. In addition, 4 observational studies were identified, with sample sizes ranging from 11 to 104 and a total of 180 exposed fetuses. Of these, 4 exposed newborns (2.2%) had a congenital malformation, lower than the expected rate of spontaneous malformation of 3.5% (relative risk,* 0.6). Two infants had ventricular septal defects, 1 had a univentricular heart, and 1 had an unspecified cardiovascular defect.

Discussion: Results of studies in animals suggest that methylphenidate is not teratogenic except at very high doses. Although the conclusions are based on a small amount of relatively low-quality evidence (i.e., no randomized controlled trials), the authors comment that the apparent low rate of malformations with first-trimester exposure is reassuring. The widespread use of methylphenidate to treat adult ADHD in the past decade should provide better data to assess fetal safety in the near future.

*See Reference Guide.
Tolerability of Clonidine in Tourette Syndrome

Clonidine (Catapres) is often used as first-line treatment for Tourette syndrome, despite somewhat less efficacy than other agents, because of its benign side-effect profile. However, many studies of the drug’s side effects have been based on child samples and results have been inconsistent. The present retrospective review found that in adults with Tourette syndrome, clonidine was associated with frequent but generally mild side effects. Risk of adverse effects was increased with polypharmacy and a high starting dosage.

Of 177 adults with Tourette syndrome treated at a single specialty clinic between 2005 and 2009, 36 patients (mean age, 25 years; 27 men) were identified who had been given a prescription for clonidine. The median clonidine starting dosage was 25 mcg/day, and the median maintenance dosage was 50 mcg/day. Half of the clonidine-treated patients were receiving additional psychotropic medications; 9 patients had a comorbid diagnosis of obsessive-compulsive disorder, and 12 had ADHD.

Seventeen of the study subjects (47%) reported adverse effects: 2 reported psychiatric effects, and 15 reported somatic effects. The most common negative effects were sedation (n=9; 25%), headache (n=5; 14%), and dizziness (n=4; 11%). The majority of patients who experienced side effects (n=12; 71%) were taking other medications, in most cases an antipsychotic or antidepressant.

Five patients asked to discontinue clonidine because of intolerable effects (sedation in 4 cases, suicidal ideation in 1). An additional 4 patients withdrew because of lack of efficacy and 2 for reduced efficacy over time. In a multivariate analysis, side effect risk was not associated with demographic or clinical variables such as age, gender, tic severity, or comorbidity. Patients who had adverse effects were more likely to have started with a higher dosage of clonidine (50 vs. 25 mcg/day; p=0.036) and to be taking additional psychotropic drugs (p=0.019).


TCAs and Fracture Risk

Use of tricyclic antidepressants is associated with increased risk of fracture, according to results of a meta-analysis. The increase appears to be related to falls rather than to TCA effects on bone mineral density (BMD).

**Background:** Epidemiologic studies have assessed a possible association between TCAs and fracture; however, results have been inconsistent and outcomes depended in part on dose, duration, and timing of exposure. The present meta-analysis was undertaken to clarify the association.

**Methods:** All available longitudinal studies comparing fractures or BMD between patients exposed to TCAs and those not taking any antidepressants were identified by literature search. For inclusion in the analysis, studies needed only to have a design other than cross-sectional study (case-control and cohort studies were included), to be conducted in humans with TCA exposure, and to use fracture or BMD as an outcome. A total of 12 studies met these criteria: 5 cohort studies and 7 case-control studies. No randomized clinical trials were identified.

**Results:** All but 1 of the cohort studies were carried out in individuals aged ≥65 years, and 2 of these studies were carried out in women only. Follow-up ranged from 4 to 10 years. The case-control studies were conducted in mixed-age and gender groups. Overall, the relative risk* for
fracture with TCA use was 1.45 (p<0.001). Risks varied only slightly when the analysis was limited to studies whose results were adjusted for osteoporosis risk factors, studies conducted exclusively in older persons, and studies of higher methodologic quality.

Risk varied by exposure duration. Exposure of <6 weeks was associated with an excess risk of 2.4 (p<0.001), compared with longer exposure (relative risk, 1.13; p=0.04). Relative risks related to TCAs were higher for hip/femur fracture than fracture at other sites, higher for men than women, and higher for studies in which the analysis was adjusted for depression and BMD.

The analysis suggested some under-publication of negative results, but the effect of this publication bias was estimated to be small. Adjustment for possible publication bias reduced the overall relative risk to 1.36 (p<0.001).

Discussion: The mechanisms by which TCAs are associated with fractures remains speculative. Antidepressants as a class are associated with increased risk of falls in the elderly. In the early stages of treatment, TCAs are associated with decreased blood pressure and orthostatic hypotension, which may increase fall risk. They may also lead, via decreased blood flow to the CNS, to confusion and delirium, and they may increase body sway. These plausible mechanisms, coupled with the findings that adjustment for BMD did not affect the risk estimates and that past use did not increase risk, suggest that the fracture risk is not associated with the effect of TCAs on bone. The authors suggest that patients taking TCAs should be monitored for fracture risk, especially during initial treatment.

Study Rating*—16 (89%): This study met most criteria for a meta-analysis, but the source of funding was not stated.


*See Reference Guide.

Antidepressant Augmentation with Scopolamine

Oral scopolamine was an effective adjunct to antidepressant treatment in a placebo-controlled trial.

Methods: Study subjects were 40 adults, aged 18–55 years, with moderate-to-severe major depressive disorder and a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥22. At the start of study treatment, subjects had not received drug therapy in the previous 4 weeks. All participants received 40 mg/day citalopram and were randomly assigned to receive either 0.5 mg oral scopolamine hydrobromide b.i.d. or placebo for 6 weeks. The primary study outcome was improvement in the HAM-D score at the end of 6 weeks. Early improvement, a secondary outcome, was defined as a ≥20% reduction in the HAM-D score at weeks 1 and 2. Response was defined as a ≥50% improvement, and remission as a final score of ≤7.

Results: The mean baseline HAM-D score was 24 in each of the study groups, and patients had experienced a mean of 4 previous depressive episodes. By week 6, patients who were given adjunctive scopolamine had a mean HAM-D reduction of 18 points (74%), compared with 15 points (59%) in the placebo group (p=0.001; effect size,* 0.9). HAM-D improvements with scopolamine were statistically superior to placebo at 4 days and at 4 and 6 weeks.

More patients in the scopolamine group showed early improvement at week 1 (14 vs. 7 patients; relative risk,* 0.487; p=0.027). At week 2, nearly all patients in both groups met criteria for early improvement. By week 4, 13 scopolamine-treated patients and 6 in the placebo group met response criteria; all scopolamine-treated patients and nearly all placebo patients (about 85%)

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responded by week 6. Remission occurred by week 6 in 13 patients who received scopolamine and 4 in the placebo group (65% vs. 20%; relative risk, 0.338; p=0.004).

The primary adverse effects associated with scopolamine were dry mouth, dizziness, and blurred vision. These occurred in 40–50% of scopolamine-treated patients, compared with 15–20% of the placebo group (p=0.04 for dry mouth). There were no serious adverse events.

**Discussion:** The cholinergic pathway is under investigation as a possible therapeutic target for adjunctive drugs in depression, and results of some studies have supported the potential antidepressant action of scopolamine, including several studies using IV administration. The present study appears to be the first controlled trial of oral scopolamine.

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


**Drug Trade Names**: citalopram—Celexa; scopolamine, oral—Scopace

*See Reference Guide.

### Orlistat for Clozapine-Induced Constipation

In a randomized trial, the weight-loss drug orlistat was effective in relieving clozapine-induced constipation.1

**Background:** Constipation is a common adverse effect of clozapine, affecting up to 60% of treated patients, which can have serious consequences including death. According to a recent study, clozapine mortality associated with constipation is 3 times more likely than agranulocytosis mortality.2 There are no established guidelines for treatment of clozapine-associated constipation, and laxatives may have limited efficacy. Loose stools are often an unwanted effect of orlistat; however, this laxative effect has benefitted patients with opioid-associated constipation. In addition, orlistat appears to be the only weight-loss medication with no CNS effects, making it a good option for patients with serious mental illness.

**Methods:** Subjects were 54 patients with schizophrenia or schizoaffective disorder who were participants in a 16-week controlled trial of orlistat vs. placebo for antipsychotic-induced weight gain. The present analysis considered patients who were overweight or obese, were receiving clozapine, and were randomly assigned 120 mg orlistat t.i.d. or placebo. The mean clozapine dosage was 481 mg/day (range, 250–900 mg/day). During 5 weeks of the study (i.e., baseline and weeks 1, 4, 8, and 16), patients kept a record of bowel movements using the Bristol Stool Form Scale (BSFS), a 7-point scale based on stool texture and appearance. Constipation was defined as BSFS type 1 or 2 or as a lack of defecation during either 2 consecutive days or on both the first and last days of the assessment week. Diarrhea was defined as BSFS type 6 or 7 at least once during the assessment week.

**Results:** Of the 54 clozapine-treated participants, 40 completed the trial; 4 patients in the orlistat group and 1 in the placebo group withdrew because of diarrhea. Five patients did not provide data, and 4 withdrew for other reasons. Analysis of treatment completers found that during treatment, the prevalence of constipation decreased from 50% to 20% in the orlistat group (p=0.039) and decreased from 45% to 40% in the placebo group. Rates of diarrhea decreased from 30% to 15% with orlistat and increased from 15% to 35% with placebo. At end of study, 65% of the orlistat group and 25% of the placebo group had normal bowel movements. There was a trend for changes in constipation to be associated with weight loss in the orlistat group (p=0.056).
**Discussion:** The authors note several important limitations to this study. The patients were not selected on the basis of constipation, concomitant laxative use was not controlled for, and dietary fat intake was not examined. Nevertheless, the positive effects of orlistat on constipation, for which few other options are available, warrant further study. In addition, the weak association of weight loss with bowel function in these patients suggests that orlistat may have a true, although modest, weight loss effect as well as a bowel-clearing effect.

1Chukhin E, Takala P, Hakko H, Raidma M, et al: In a randomized placebo-controlled add-on study orlistat significantly reduced clozapine-induced constipation. *International Clinical Psychopharmacology* 2012; doi 10.1097/YIC.0b013e32835b08d2. From Helsinki University Central Hospital, Finland. **Funded by the Stanley Medical Research Institute; and Oy Eli Lilly Finland Ab. The authors reported no conflicts of interest.**


**Drug Trade Names:** clozapine—Clozaril; orlistat—Xenical

### Dosing Atypicals in Special Populations

Candidates for atypical antipsychotics have illnesses, such as schizophrenia, bipolar disorder, and major depression, that carry an increased risk of alcohol or drug abuse and of medical conditions (e.g., obesity, hypertension, diabetes, atherosclerosis) that cause renal or hepatic impairment. Such impairments should be an important factor in antipsychotic drug selection and dosage. Clinicians should assess patients using the FDA's standard definitions of these conditions. Renal impairment is classified on the basis of creatinine clearance, and hepatic impairment is rated according to the Child-Pugh score (CPS), which is based on 3-point ratings of 5 measures: total bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy. (See table.)

<table>
<thead>
<tr>
<th>Standard definitions of degrees of renal and hepatic impairment</th>
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<tr>
<td><strong>Degree of impairment</strong></td>
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In patients with renal impairment, dosage adjustments do not appear to be necessary for aripiprazole; asenapine; iloperidone; olanzapine; quetiapine; or ziprasidone. In those with liver disease, adjustments do not appear necessary for aripiprazole, olanzapine, paliperidone, or ziprasidone. While oral ziprasidone exposure and half-life are increased in patients with hepatic disease, the magnitude of the changes make dosing adjustments unnecessary.

Considering the dire need for treatments for resistant schizophrenia, renal and hepatic impairment studies were not performed and likely not required for clozapine approval. Clozapine is, however, known to be extensively metabolized by the liver into numerous metabolites, and the labeling recommends caution for its use in patients with renal or hepatic impairment.

Dose reductions and cautious titration are recommended for risperidone in both groups. Of note, in patients with moderate-to-severe renal impairment, risperidone clearance has been shown to be reduced by 60% and monitoring may be necessary. Lurasidone should be dosed cautiously, with a starting dosage of 20 mg/day and a maximum dosage of 80 mg/day in patients with moderate or severe renal or moderate hepatic impairment and with a maximum of 40 mg/day in those with severe hepatic impairment. Paliperidone dosing...
should be individualized according to patients’ renal function; exposure can be increased 1.5 to nearly 5-fold. Initial dosages should be 1.5 mg/day in moderate-to-severe renal impairment and 3 mg/day in mild renal impairment. Maximums should not exceed 6 mg/day and 3 mg/day, respectively. Quetiapine also requires individualization according to hepatic function. Asenapine and iloperidone are not recommended for patients with hepatic impairment.


Drug Trade Names: aripiprazole—Abilify; asenapine—Saphris; clozapine—Clozaril; iloperidone—Fanapt; lurasidone—Latuda; olanzapine—Zyprexa; paliperidone—Invega; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

Anticonvulsants for Compulsive Sexual Behavior

Two patients with compulsive sexual behavior experienced response to treatment with anticonvulsants.

A 25-year-old man presented for treatment with a 7-year history of exhibitionism, with frequent urges that occasionally resulted in exhibitionistic acts. He also had obsessive-compulsive disorder (OCD) and hypomanic traits. Treatment with 20 mg/day fluoxetine resulted in increased exhibitionism, and it was stopped. Topiramate was started and titrated to 50 mg/day, which resulted in decreased libido and no change in symptoms. When the topiramate dosage was increased to 100 mg/day and escitalopram was added, the patient’s OCD symptoms improved, the exhibitionistic urges stopped, and he reported a loss of interest in pornography as well as the ability to talk with women without wanting immediate physical gratification. However, both medications were stopped because of amotivation and sedation. Only topiramate was restarted, and it remained the mainstay of his treatment for the next 4 years. He stopped taking the drug on several occasions because of side effects, each time resulting in a return of compulsive sexual behavior.

A 26-year-old married man sought treatment after an arrest for soliciting prostitution. He reported using pornography 4 hours/day by the 7th grade and also had OCD and ADHD. Topiramate at 50 mg/day brought about a decrease in inappropriate sexual urges, but the patient experienced intolerable cognitive side effects. The addition of mixed amphetamine salts brought no cognitive benefit. The topiramate was switched to 250 mg levetiracetam b.i.d., and the patient reported cessation of pornography and reduced involvement with strip clubs. When he discontinued both mixed amphetamine salts and levetiracetam because of side effects (sedation and sexual dysfunction), his OCD and compulsive sexual behaviors returned and he stopped attending 12-step meetings. After the patient resumed taking the medications, he reported continued improvement in his sexual compulsions.

Topiramate was chosen as the initial anticonvulsant in these patients because of its reported efficacy for compulsive and addictive behaviors. Other treatments for compulsive sexual behavior include psychotherapy and 12-step programs. Evidence from case reports and open-label trials also support the use of lithium, various antidepressants, antipsychotics, and naltrexone. Use of topiramate is limited by its significant adverse cognitive effects, which levetiracetam lacks.


Drug Trade Names: escitalopram—Lexapro; fluoxetine—Prozac; levetiracetam—Keppra; mixed amphetamine salts—Adderall; naltrexone—Revia; topiramate—Topamax
**Antidepressants and Arterial Stiffness**

In a randomized trial, duloxetine, but not escitalopram, significantly increased arterial stiffness in a group of elderly patients with depression.

**Background:** Arterial stiffness is an easily measurable sign of arterial aging and a risk factor for cardiovascular disease. Carotid-femoral pulse wave velocity (PWV) is a noninvasive measurement of arterial stiffness that can predict cardiovascular endpoints. Depression has been associated with greater cardiovascular morbidity and mortality, but studies have not assessed whether depression treatment in older patients is associated with reduced cardiovascular risk.

**Methods:** At baseline, study participants, aged ≥70 years (mean age, 77 years; 71% women), underwent PWV measurement and were assessed for depression using DSM criteria. Patients with a history of antidepressant use and those with a recent cardiovascular event (e.g., stroke, myocardial infarction, angioplasty) or with moderate-to-severe heart failure were excluded. Of the 75 eligible study subjects, 48 had newly-diagnosed depression (Hamilton Rating Scale for Depression score of >12) and 27 had no depression. Patients with depression were randomly assigned to treatment with either 60 mg/day duloxetine or 10 mg/day escitalopram and were followed for 12 months. Arterial stiffness was reassessed with PWV at 12 months.

**Results:** At study entry, PWV was similar in adults with and without depression. After 1 year, treatment with duloxetine resulted in a significant increase in PWV, indicating increased arterial stiffness. Patients taking duloxetine experienced an 18% increase in blood pressure (BP)-normalized PWV, compared with a modest, nonsignificant increase in BP-normalized PWV in the escitalopram group and a small decrease in the nondepressed controls. Use of both antidepressants was associated with similar but small adverse changes in cardiovascular risk factors such as systolic BP, pulse pressure, and LDL cholesterol. Duloxetine was also associated with an 8.3% increase in heart rate.

**Discussion:** The present observations suggest that measuring PWV may be a simple, noninvasive way to assess older patients for cardiovascular risk before prescribing an antidepressant. The results also suggest that arterial aging is not immutable, but rather a modifiable risk factor for vascular events.


**Drug Trade Names:**
- duloxetine—*Cymbalta*
- escitalopram—*Lexapro*

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**Experimental NMDA-Blocking Antidepressant**

Demonstration of the rapid antidepressant efficacy of the N-methyl-D-aspartate antagonist ketamine (*Ketalar*) has pointed to a new direction in antidepressant drug development. Other drugs active at the NMDA receptor are now under investigation as possibly safer alternatives to ketamine. One such agent, AZD6765, had rapid but relatively modest antidepressant effects in a controlled, crossover study in a group of patients with treatment-resistant depression.

**Background:** AZD6765 is an intravenously administered NMDA receptor channel blocker with moderate receptor affinity and a low trapping effect. Trapping channel blockers such as ketamine, so called because they permit closure of the receptor channel, are more likely to produce psychotomimetic side effects than partially trapping agents.

**Methods:** The effects of a single infusion of AZD6765 on depression and psychotomimetic side effects were evaluated in a crossover study in 22 inpatients (45% women; mean age, 52 years)
with major depressive disorder. Other inclusion criteria were a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥20, a lifetime history of ≥2 failed antidepressant drug courses, and no psychotic features. After a 2-week drug-free period, patients received double-blind infusions of 150 mg AZD6765 and placebo, 1 week apart and in random order. The MADRS was the primary outcome measure, with response was defined as a ≥50% decrease in score.

**Results:** MADRS scores were significantly lower after infusion of AZD6765 than placebo (p<0.01 at 80 minutes, p<0.05 at 110 minutes; effect size,* 0.40). This effect did not persist after 110 minutes. A larger proportion of patients were responders after treatment with the active drug; 32% vs. 15% for placebo. Response was first assessed 60 minutes after drug administration, at which time all but 1 of the responses were evident; the remaining patient achieved response 1 day after receiving the active drug. Differences in response rates did not achieve statistical significance at any time point. No serious adverse events were observed in the study.

**Discussion:** Clinical improvements with AZD6765 were evident within minutes of the infusion. The results are noteworthy because patients had an average of 7 previously failed treatment trials, and nearly half had not responded to ECT. The effects of AZD6765 were not as robust or sustained as those observed with ketamine in refractory major depression. Further studies of AZD6765 appear to be warranted, particularly with higher or repeated doses.

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

Zarate C, Mathews D, Ibrahim L, Chaves J, et al: A randomized trial of a low-trapping nonselective N-methyl-D-aspartate channel blocker in major depression. *Biological Psychiatry* 2012; doi 10.1016/j.biopsych.2012.10.019. From the NIMH; and the Department of Health and Human Services, Bethesda, MD; and AstraZeneca Pharmaceuticals, Wilmington, DE. Funded by NIMH; AstraZeneca Pharmaceuticals; and other sources. Two study authors disclosed financial relationships with commercial sources associated with ketamine and AZD6765; the remaining 10 authors declared no conflicts of interest.

*See Reference Guide.

### 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.

**Pregnancy Category C:** If animal studies have shown adverse fetal effects, or if there are no adequate and well-controlled studies in humans and the benefits of the drug in pregnant women may outweigh the potential risks, the agent is classified as Category C. According to the FDA, these drugs should be used during pregnancy only when clearly needed if the potential benefit justifies the potential risk to the fetus.

**Relative Risk:** The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

**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.

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