Antipsychotic Risk in Elderly: Gender Differences

In a population-based study, older patients with dementia had a high incidence of serious adverse events in the 30 days after starting atypical antipsychotic drug therapy. The risk was nearly 50% higher in men than in women.

Methods: Using administrative data, a retrospective cohort study was carried out in residents of Ontario, Canada, who were aged ≥66 years, had a diagnosis of dementia, and received a new prescription for an atypical antipsychotic drug between April 2007 and March 2010. Patients with serious psychiatric illness were excluded. Serious adverse events were defined as those that resulted in hospitalization or death within 30 days of initiating treatment.

Results: The investigators identified 21,526 patients newly prescribed an atypical agent for dementia. The median age of the cohort was 84 years, and 64% were women. Of the 3 atypicals available on the Ontario formulary during the study period, risperidone was prescribed in 47.5% of patients, quetiapine in 37%, and olanzapine in 15.5%. About 4% of patients were given prescriptions for high-dose therapy.

A serious adverse event occurred within 30 days of starting antipsychotic therapy in 8% of women and 11% of men. In the overall cohort, 7% had a hospital admission and 3% died. After adjustment for age, setting of care, dementia type, comorbidity, and other factors, men had a nearly 50% greater risk of a serious event than women (adjusted odds ratio,* 1.47).

In both genders, risk increased with medium-dose and particularly with high-dose therapy. Men who received high-dose therapy had the highest risk of all; nearly 20% had a serious adverse event. Risk was not associated with age, was lower in patients living in a long-term care facility rather than the community, and was greater in those with higher medical comorbidity.

Discussion: The general medical literature shows that risks of medication side effects are greater in women than men. The results of this study suggest the pattern may differ in the elderly.
Numerically more women than men experience serious adverse events following atypical antipsychotic therapy, but women represent a larger proportion of the elderly population and are more likely than men to have dementia. However, men appear to be at much greater risk of serious adverse events.


*Drug Trade Names:* olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal

*See Reference Guide.*

**Aripiprazole-Associated Torsades de Pointes**

Several available antipsychotic agents have been associated with prolongation of the corrected QT (QTc) interval and resultant torsades de pointes. Aripiprazole has not previously been shown to induce QTc interval prolongation or torsades de pointes, and some data suggest it may shorten the QTc interval. However, the present case suggests that even at low dosages, aripiprazole may have the potential to cause both QTc interval prolongation and torsades de pointes.

A 42-year-old man with schizophrenia was admitted to a medical intensive care unit for treatment of severe sepsis. On admission, treatment with 400 mg/day quetiapine was discontinued but then restarted 1 week later. After 1 quetiapine dose, the patient’s QTc interval was found to be 644 ms (normal range for men, $\leq 450$ ms) and quetiapine was stopped. Following resolution of the patient’s acute medical illness nearly 1 month later, the QTc interval was 414 ms. Aripiprazole was started because it was believed to have minimal QT effects. After 5 days of treatment with 2.5 mg/day aripiprazole, the patient experienced cardiac arrest due to torsades de pointes; electrocardiograph recorded his QTc interval at 624 ms. Sinus rhythm was restored, and cardiac catheterization showed no significant disease. Aripiprazole was stopped, and QTc values were 537 ms on day 1, 472 ms on day 5, and 450 ms on day 14. According to the Naranjo probability scale,* the relationship between torsades de pointes and aripiprazole was “probable”. The patient’s only other risk factor was treatment with IV famotidine, which has been reported to rarely prolong the QT interval in patients with renal impairment. However, famotidine treatment preceded the aripiprazole, and QTc measurements had been in the normal range.

This appears to be the first reported case of torsades de pointes with aripiprazole. Prescribers should be aware that despite its presumed safety, even at low dosages it appears that the agent may produce significant QT prolongation in patients with minimal risk factors.


*Drug Trade Names:* aripiprazole—Abilify; quetiapine—Seroquel

*See Reference Guide.*

**Augmentation Strategies in OCD**

The limited efficacy of SSRIs as first-line therapy for obsessive-compulsive disorder has made augmentation strategies part of standard treatment of this disorder. Augmentation with antipsychotics is the approach best supported by evidence, according to a literature review.

When treating OCD, if the first SSRI is ineffective, evidence supports switching to a second SSRI and, if the response continues to be unsatisfactory, switching to clomipramine. Augmentation strategies may be useful in 3 types of patients with OCD: partial responders to SSRIs (with
25–35% reduction in Yale-Brown Obsessive-Compulsive Scale [Y-BOCS] scores); patients who have shown a response but have not achieved remission (>35% Y-BOCS reduction but with a score of ≥16); and those who have not experienced response with adequate trials of 2 SSRIs.

The evidence for augmentation with antipsychotics consists of 13 randomized controlled trials with varying methods and most with small sample sizes. In a meta-analysis, the number needed to treat\(^*\) (NNT) with antipsychotic augmentation to achieve 1 response was nearly 6, which is reasonable considering the few other options. Risperidone is the only antipsychotic consistently shown in multiple studies to be effective as augmentation in OCD. Limited evidence also supports aripiprazole and haloperidol. Olanzapine and quetiapine have not shown reliable efficacy and require further study. If used in OCD, antipsychotics should be prescribed at their minimum effective doses. Full effects may not be apparent for 4–8 weeks.

The evidence concerning other drug augmentation strategies is less clear. Drugs that act on the serotonin system have been investigated as augmenting agents of SSRIs. Among these, the antiemetic agent ondansetron was found to be effective in placebo-controlled trials and has the additional benefit of reducing the gastrointestinal side effects of SSRIs. Clomipramine has been used to augment SSRIs and is often combined with citalopram, likely because of the reduced potential for pharmacokinetic interaction. Other categories of drugs, including glutamatergic agents and anticonvulsants, show promise but require further investigation. If augmentation with an antipsychotic is unsuccessful, a trial of cognitive behavioral therapy (if not already utilized) appears to be warranted before embarking on a series of augmentation trials with drugs of questionable efficacy.


Drug Trade Names: aripiprazole—Abilify; citalopram—Celexa; clomipramine—Anafranil; haloperidol—Haldol; olanzapine—Zyprexa; ondansetron—Zofran; quetiapine—Seroquel; risperidone—Risperdal

*See Reference Guide

### Adjunctive Granisetron for Negative Symptoms

The antiemetic granisetron, added to risperidone, produced significant reductions in negative symptoms in a group of patients with stable schizophrenia.\(^1\)

**Background:** Negative symptoms of schizophrenia are particularly difficult to treat and have been associated with poor outcomes and disability. The serotonergic system has been implicated in the pathogenesis of negative symptoms, and the 5-HT3 antagonist ondansetron has been shown to improve negative symptoms.\(^2\) Granisetron may have longer duration of action than other 5-HT3 antagonists, may be less likely to alter cytochrome P-450 activity and cause drug interactions, and have better tolerability than ondansetron. The present study was undertaken to determine whether granisetron would improve negative symptoms.

**Methods:** Study subjects were 40 outpatients, aged 18–50 years (mean age, 37 years; 43% women), who met diagnostic criteria for schizophrenia with a duration of ≥2 years and had been receiving a stable dose of risperidone for ≥8 weeks before randomization. Patients were required to be clinically stable, with no more than a 20% change in weekly consecutive Positive and Negative Syndrome Scale (PANSS) score for ≥4 weeks. In addition to risperidone (mean dosage, 4.3 mg/day), participants were randomly assigned to receive 1 mg of double-blind granisetron or placebo every 12 hours for 8 weeks. The primary outcome measure was change from baseline in PANSS negative symptom score.
**Results:** One patient in each group did not complete treatment. Mean PANSS total scores decreased in both groups over the 8 weeks of treatment, but improvement was significantly greater in the granisetron group. (See table.) The between-group difference was driven by a significantly greater improvement in negative symptoms in the granisetron group. Changes in positive and general psychopathology scores did not differ between the groups. Mean negative symptom scores decreased from 11.7 at baseline to 8.8 with granisetron and from 12 to 11.9 with placebo (p<0.001; effect size,*1.9). Common adverse events, affecting 18–23% of patients included: drowsiness; constipation; dizziness; appetite changes; nausea; agitation; pruritis; fatigue; and diarrhea. Frequency did not differ between the treatment groups.

**Discussion:** Although this study had some limitations, including short duration and small sample size, the results suggest granisetron warrants further research as a safe and effective treatment for negative symptoms of schizophrenia.

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


**Drug Trade Names:** granisetron—Kytril; ondansetron—Zofran; risperidone—Risperdal

*See Reference Guide.

### SNRIs and Bone Resorption in Elderly

Serotonergic antidepressants are believed to increase bone turnover, but TCAs, which block the norepinephrine transporter, appear to have no such effects. The potential of serotonin-norepinephrine reuptake inhibitors (SNRIs) to adversely affect bone health was evaluated in a group of older patients with depression.

**Methods:** Study subjects were 76 patients, aged ≥60 years (mean age, 69 years; 64% women), who participated in a larger uncontrolled study of extended-release venlafaxine (*Effexor XR*) for late-life depression. Previous antidepressants, used by 30 patients, were discontinued a minimum of 2 weeks before study entry. All patients were started on venlafaxine, titrated to 150 mg/day over 2 weeks, with a dosage increase of up to 300 mg/day if remission (i.e., Montgomery-Asberg Depression Rating Scale score of ≤10) did not occur within 6 weeks. Bone turnover markers—beta-isomerized C-terminal cross-linking telopeptide of type 1 collagen (B-CTX), a marker of bone resorption, and N-terminal propeptide of type 1 procollagen (PINP), a marker of bone formation—were assayed in 76 study participants who completed treatment and had both pre- and post-treatment serum collected.
Results: At 12 weeks, venlafaxine treatment was associated with a significant increase in the marker for bone resorption: the mean β-CTX level increased from 390 pg/mL to 422 pg/mL (p=0.02), along with a numerically lower but non-significant change in the marker for bone formation (p=0.12). Increases in bone resorption were confined to the 29 patients (38%) whose depression did not remit during venlafaxine treatment.

Concurrent medications that could potentially affect turnover included vitamin D supplements in 26% of patients, bisphosphonates in 5%, and estrogen in another 5%. There were no differences in the skeletal effects of venlafaxine between patients taking these agents and those who were not. There were also no differences by gender or by venlafaxine dosage or blood level.

Discussion: Of several serotonin receptor subtypes identified on bone cells, blocking of the serotonin transporter (5-HTT) receptor is believed to adversely affect bone health. Although venlafaxine is less potent than SSRIs at the 5-HTT receptor, it is still much more selective for 5-HTT than for norepinephrine, which may underlie its negative skeletal effects. However, remission of depression appears to offset the negative effect of venlafaxine, perhaps by increasing physical activity or reducing the negative biological effects of depression.

Shea M, Garfield L, Teitelbaum S, Civitelli R, et al: Serotonin–norepinephrine reuptake inhibitor therapy in late-life depression is associated with increased marker of bone resorption. Osteoporosis International 2013; doi 10.1007/s00198-012-2170-z. From Washington University School of Medicine, St. Louis, MO; and other institutions. Funded by the NIMH. Several study authors disclosed financial relationships with commercial sources.

Adjunctive Agomelatine for Bipolar II Depression

In a pilot study, the melatonergic antidepressant agomelatine was effective as an adjunct to mood-stabilizing drugs in acute treatment of bipolar II depression.1

Background: Agomelatine acts as both a melatonin receptor agonist and a 5-HT2C/2B serotonin receptor antagonist. The drug has shown promising results in the treatment of bipolar I disorder,2 as well as major depression and several anxiety disorders (see Psychiatry Drug Alerts September 2010, September 2012, and February 2013 issues), but it is not available in the U.S.

Methods: The 28 study subjects (mean age, 41 years) met DSM-IV criteria for type II bipolar disorder and were currently experiencing depression, despite having therapeutic blood levels of lithium or valproate for ≥6 months. In addition to the mood stabilizer, all patients received 25 mg/day open-label agomelatine at bedtime for 6 weeks, with an optional 30-week extension. Response, the primary efficacy outcome, was defined as a >50% decrease in score on the 17-item Hamilton Rating Scale for Depression (HAM-D) at 6 weeks. Secondary outcomes were measured with the Young Mania Rating Scale and the Pittsburgh Sleep Quality Index (PSQI).

Results: At week 6, mean HAM-D scores had decreased from 26 at baseline to 10 in the valproate group and to 11.5 in the lithium group. Response occurred by week 6 in 12 of the 17 patients who were taking valproate and in 6 of the 11 lithium-treated patients (71% and 55%, respectively). At the end of 36 weeks, 14 patients in the valproate group (82%) and 10 in the lithium group (91%) experienced response. PSQI scores showed statistically significant improvement, and patients lost a small but statistically significant amount of weight. The effects of agomelatine on depression, mania, sleep, and body mass did not differ depending on whether it was added to valproate or lithium.

Four patients dropped out of the study by week 6 because of adverse events, which included 1 case each of mania and hypomania. Two additional patients discontinued treatment at week 36 because of hypomania. An additional 4 patients experienced insomnia, which was managed by switching administration from bedtime to early morning.
Discussion: This study was conducted in Italy where many medications are available free of charge from the National Health System. Agomelatine is not currently among the medications supplied at no cost. This could have contributed to a selection bias that favored recruitment of patients with more financial stability and/or stronger motivation for treatment. Nevertheless, future studies of agomelatine in bipolar II depression appear to be warranted.


Drug Trade Names: agomelatine—Valdoxan; valproate—Depakene, Depakote

Antipsychotic-Associated Parotitis

Parotitis—swelling and inflammation of 1 or both of the parotid salivary glands—is a rare complication of drug therapy. According to a literature review, evidence clearly supports the association of this complication with clozapine (Clozaril).

Using a 1993 analysis of drug-induced parotitis and a literature search for all subsequent case reports published through mid-2012, 84 cases of possible drug-induced parotitis involving 40 different drugs were identified. Studies of iodine-containing drugs (e.g., contrast media), which are well known to cause parotitis, were not included. The study authors attributed causality based on the occurrence of ≥5 cases reported by ≥3 investigators. At least 1 case was required to meet causality criteria of the Naranjo probability scale,* a 10-item scoring system for adverse drug effects.

Clozapine-related parotitis was found to have been reported in 13 patients. Hypersalivation was reported in 9 of the 13 cases. Unlike many other antipsychotics, clozapine is known to cause excessive salivation, which can lead to inflammation of the salivary glands and subsequent calculus formation. The agonist activity of clozapine at M4 muscarinic receptors may account for this effect. Parotitis has also been linked tentatively to many phenothiazine antipsychotics. Reported mechanisms have included allergic reactions leading to parotid swelling and xerostomia predisposing patients to parotid gland infections.

Drug-induced parotitis is usually bilateral, but unilateral cases have been reported. Parotitis usually resolves with discontinuation of the causal agent.


*See Reference Guide.

ECG Effects of Antidepressants Compared

A pharmacovigilance study confirmed the association of citalopram with QT interval prolongation, showed that risk was dose-related, and found similar risks for several other antidepressants. The results also suggest that bupropion has a protective effect against QT interval prolongation.

Methods: Electronic health records from a large New England healthcare system were reviewed to identify patients who had undergone an electrocardiogram (ECG) between 14 and 90 days after they received an antidepressant prescription. The delay was to allow for patients to fill the prescription and for the drug to reach steady state. The analysis included all commonly used antidepressants, with methadone, a known contributor to QT prolongation, as an active control. Standard thresholds of corrected QT (QTc) interval prolongation were used to categorize results
as normal, borderline, abnormal, or high (see table), based on their likelihood of predicting risk of arrhythmia. Patients also receiving an antipsychotic or who had in the previous year used another agent known to prolong the QT interval were excluded.

**Results:** More than 38,000 patients received an antidepressant followed by an ECG during the study period (February 1990–August 2011). About 20% of the patient population overall was characterized as having abnormal or high QTc values. QTc prolongation was associated with use of citalopram, escitalopram, amitriptyline, and, as expected, methadone. Bupropion was associated with decreases in the QTc interval.

A subset of patients (n=470) had ECG data available for >1 medication dose. For these patients, mean change in QTc interval between doses was also evaluated. When specific daily doses were compared, risk of QTc prolongation was significantly increased as doses of citalopram, escitalopram, and amitriptyline increased. QTc decreased in patients who had a bupropion dose increase.

**Discussion:** QTc prolongation is often used as a marker, albeit an imperfect one, for increased risk of torsades de pointes, a rare ventricular arrhythmia. Reports of QTc prolongation led the FDA to warn against use of high-dose citalopram, leaving many clinicians uncertain about next-step strategies for this widely used antidepressant. The QTc interval increases shown in the present study were small in magnitude, and the FDA warning was issued despite epidemiologic studies showing no difference among antidepressants in risk for arrhythmia. Whether patients should receive a routine ECG before or after starting antidepressants remains an open question. Agents with less risk than citalopram might be preferable for patients with known arrhythmia risk factors. For patients treated with citalopram, adding bupropion to low-dose treatment may be preferable to increasing the citalopram dose in those with partial response.

<table>
<thead>
<tr>
<th>Category</th>
<th>QTc Value</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>≤430 ms for men ≤450 ms for women</td>
</tr>
<tr>
<td>Borderline</td>
<td>431–450 ms for men 451–470 ms for women</td>
</tr>
<tr>
<td>Abnormal</td>
<td>451–500 ms for men 471–500 ms for women</td>
</tr>
<tr>
<td>High</td>
<td>&gt;500 ms for both men and women</td>
</tr>
</tbody>
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**Drug Trade Names:** amitriptyline—Elavil, Endep, Enovil; bupropion—Wellbutrin; citalopram—Celexa; escitalopram—Lexapro

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**Progestin for Hypersexuality**

High-dose oral medroxyprogesterone acetate (MPA) appears to be an effective third-line treatment for inappropriate hypersexuality in elderly men with dementia, according to a retrospective review.

**Background:** Inappropriate hypersexuality should be treated nonpharmacologically whenever possible. SSRIs are considered first-line drug treatment. Conventional and atypical antipsychotics are second-line therapy, although these carry an FDA black box warning about increased mortality in elderly patients with dementia-related psychosis. Hormones are selected when these approaches have failed or cannot be tolerated. MPA is a progestin that decreases testosterone production and lacks the feminizing actions of estrogen. Previous reports have described the successful use of oral, intramuscular, or subcutaneous injection of MPA to control inappropriate hypersexuality.

**Methods:** For the present study, electronic charts were reviewed for 10 male patients, aged ≥65 years (median age, 80 years), who had been admitted to the inpatient unit because of sexual
behavior that caused serious safety concerns in their previous care environment. All patients had received other pharmacologic treatments before starting oral MPA. The typical starting dosage of MPA was 100 mg/day (a dose that is not commercially available but that can be compounded in capsule form). Treatment success was defined as discharge to patients’ pre-admission living arrangements.

**Results:** After treatment with oral MPA, 7 of the patients had documented symptom resolution or improvement and were able to return to their prior living arrangement (mean time to discharge, 22 days). Two others required more advanced care for deteriorating function and unstable comorbid medical conditions, and 1 man was not readmitted to his previous facility because of concerns about his extreme sexual behavior. The oral MPA dosage that achieved a dramatic reduction in hypersexual behavior ranged from 100 to 400 mg/day (mean, 300 mg/day). No adverse effects of MPA were documented during inpatient treatment.