Safety of Psychotropics with Clarithromycin

Clarithromycin is among the most widely used macrolide antibiotics. It is metabolized via the cytochrome P450 pathway and may cause neurotoxicity when used with other drugs that are also metabolized via CYP450, including many psychotropic agents. A systematic review of the literature was undertaken to highlight the neurotoxic effects.

Cases of clarithromycin-associated neurotoxicity in adults (n=38) reported between 1994 and 2009 were reviewed. Mean patient age was 51 years, and 53% were female. The antibiotic had been prescribed for respiratory infection in most patients (58%). Eleven patients had received no concomitant drug therapy, while 13 (34%) had a comorbid psychiatric illness and had received fluoxetine; lithium; carbamazepine; paroxetine; diazepam; haloperidol; benzodiazepines; mirtazapine; or imipramine. After the addition of 500–2000 mg/day clarithromycin, delirium developed in 12 patients (32%), acute psychosis in 11 (29%), mania in 10 (26%), hallucinations in 3 (8%), and serotonin syndrome and a major depressive episode in 1 patient each (2%). Onset occurred a mean of 5 days after clarithromycin initiation. The interaction did not appear to be dose-related, as only 2 of the patients received high-dose clarithromycin (2000 mg/day). Outcomes appear to be good with early detection and prompt discontinuation of clarithromycin. All patients in this series recovered after stopping clarithromycin, most within 1–3 days.

Bandettini di Poggio M, Anfosso S, Audenino D, Primavera A: Clarithromycin-induced neurotoxicity in adults. Journal of Clinical Neuroscience 2011;18 (March):313–318. From the University of Genoa, Italy; and other institutions. Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.

Drug Trade Names: carbamazepine—Epitol, Tegretol; clarithromycin—Biaxin; fluoxetine—Prozac; haloperidol—Haldol; imipramine—Tofranil; mirtazapine—Remeron; paroxetine—Paxil

Serotonin Transporter Variants and Drug Response

The promoter region of the serotonin transporter gene contains 2 variants of the 5-HTTLPR sequence: a short form, and the functionally more active long form. It has been suggested that SSRIs may be more effective in persons homozygous for the long form. Previous studies of this question have had conflicting results. The controlled Genetic Predictors of Outcome in
Depression study was undertaken to clarify the effects of serotonin transporter gene polymorphisms on depression outcomes.

**Methods:** This multicenter British study enrolled 601 patients, aged 18–74 years, with unipolar depression (Beck Depression Inventory [BDI] score >14) who had been referred from primary care practices. Patients underwent genotyping and were randomly assigned to receive 20 mg/day citalopram or 4 mg b.i.d. reboxetine. Clinical outcomes were measured with the BDI at 6 weeks.

**Results:** Thirty-four percent of patients were homozygous for the long form of the gene, 48% were heterozygous, and 18% had only the short form. This gene frequency is comparable to patient samples in 2 other U.S. and European antidepressant studies.

There were no between-group differences in baseline BDI scores (mean, 33–34). Efficacy did not differ between the 2 drugs in any genotypic group. BDI scores at 6 weeks ranged from 18 to 20 points. Remission (BDI score <10) was achieved by similar percentages of patients in each treatment group and did not differ by genotype. (See table.) The investigators found no main effect of genotype on outcome, irrespective of drug treatment. Reboxetine was less well tolerated than citalopram, with 36% and 17% of patients, respectively, discontinuing treatment before 6 weeks.

**Discussion:** According to the authors, it is unlikely that future research will find a clinically important effect of the 5-HTTLPR genotype on antidepressant response. A previous meta-analysis that found an association may have failed to exclude the possibility of publication bias. An analysis of data from the STAR*D clinical trial also found no association.

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

<table>
<thead>
<tr>
<th>Remission Rates at 6 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
</tr>
<tr>
<td>Homozygous long form</td>
</tr>
<tr>
<td>Homo- or heterozygous short form</td>
</tr>
</tbody>
</table>

*See Reference Guide.

**Low-Dose Topiramate for Anger Control**

A series of 10 patients with anger-control issues treated with very-low-dose topiramate (Topamax) suggests that dosages as low as 6 mg/day may effectively control anger. A recent report described 3 cases that are representative of the 10 patients, none of whom appeared to experience adverse effects of topiramate treatment.¹

A 39-year-old female with a history of untreated postpartum depression received cognitive behavioral therapy (CBT) plus 6 mg/day topiramate for depression and daily anger attacks. Within 1 week she reported having much better anger control and the ability to suppress anger outbursts. Improvement was maintained at 2-month follow-up.

A 22-year-old female with probable borderline personality disorder and depressive and anxiety symptoms reported experiencing daily uncontrollable anger attacks. CBT produced some improvement, but anger attacks remained problematic. Within several weeks of starting...
12.5 mg/day topiramate she described better emotional stability and considerably fewer anger attacks. Topiramate was reduced to 6 mg/day, and more than a year later she continued to report no anger attacks.

A 55-year-old male with Tourette’s syndrome received 25 mg/day topiramate in addition to CBT to control daily anger attacks that occurred along with depressive and anxiety symptoms. Within 1 month he experienced a noticeable improvement in mood, and 6 months later topiramate was reduced to 12.5 mg/day. Anger attacks remained under control for an additional 18 months of follow-up.

**Discussion:** Previous research has shown that treatment with topiramate reduces anger in men with borderline personality disorder, and in women with recurrent major depression. In those studies, doses were on the low end of the topiramate dosing range at 200–250 mg/day. Serious adverse effects (e.g., metabolic acidosis, angle-closure glaucoma, hyperammonemia) may be dose-related and using lower dosages could reduce the risks. The present case series supports the use of very-low-dose topiramate to control anger.


### Antipsychotics May Reduce Brain Volume

Results of a longitudinal study in patients with first-episode schizophrenia suggest long-term antipsychotic medication may be associated with losses in brain volume. According to an editorial, the clinical interpretation of this finding is not straightforward, but it does indicate antipsychotics should be prescribed cautiously and their risks and benefits closely monitored, particularly in light of the growing use of antipsychotics for off-label indications and in children and the elderly.

**Methods:** Study subjects (n=211; mean age, 26 years at baseline; 152 males) underwent a brain MRI during their first episode of schizophrenia or schizoaffective disorder. Patients were followed every 6 months to determine illness severity, medication use, and substance abuse or misuse. MRI scans were repeated every 3 years. The mean number of scans was 3, and the mean follow-up was 7 years. Patients received antipsychotic treatment as usual in the community, consisting predominantly of conventional agents in the early years (study period, 1991–2009) and atypicals in later years. About 25% of patients received clozapine (*Clozaril*). Patients had adequate antipsychotic drug exposure, with a mean treatment duration of about 5 months.

**Results:** Higher antipsychotic doses during follow-up were associated with greater decreases in brain volume overall, in both white and gray matter, and in specific structures throughout the brain, as well as with increases in cerebrospinal fluid and putamen volume. The effect of antipsychotic dose on brain volume persisted after adjustment for illness severity and duration and substance misuse. Longer duration of illness also was predictive of loss of brain volume, while illness severity and substance misuse had few or no effects. Conventional antipsychotics, clozapine, and other atypicals had similar effects on brain volume.

**Discussion:** Although an association was found, it can not be assumed to be causal. The results of the present study are consistent with those of earlier MRI studies showing increased basal ganglia size in patients with schizophrenia and PET studies showing changes in regional blood flow in the affected areas. Experiments in animals also tend to support the present observations.
Editorial: It is not clear whether changes in brain volume are "bad" for patients or whether they are related to the drugs' beneficial effects on symptoms. It is possible that patients who had the greatest benefit from pharmacotherapy were the ones who continued treatment and therefore had the highest exposure. Symptom improvement and brain volume reductions may occur via unrelated mechanisms. The results highlight the need to carefully monitor treated patients and to prescribe the lowest possible dosages to achieve therapeutic goals.

1 Ho B-C, Andreasen N, Ziebell S, Pierson R, et al: Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Archives of General Psychiatry 2011;68 (February):128–137. From the University of Iowa Carver College of Medicine, Iowa City. Funded by the NIMH. Several study authors disclosed financial relationships with commercial interests.

2 Lewis D: Antipsychotic medications and brain volume: do we have cause for concern [editorial]? Archives of General Psychiatry 2011;68 (February):126–127. From the University of Pittsburgh, Penn. The author disclosed financial relationships with several commercial interests.

Trazodone Improved Nightmares

A 24-year-old male was hospitalized for a major depressive episode. Symptoms included depressed mood, fatigue, feelings of hopelessness, and insomnia with vivid nightmares. On admission his Hamilton Rating Scale for Depression (HAM-D) score was 16. Treatment was started with 10 mg/day escitalopram, and after 14 days his HAM-D score was 9. However, insomnia and nightmares continued. Because of its sedative properties, 50 mg trazodone was added at night. Sleep and nightmares improved, but he experienced dizziness, headaches, and nausea. The nightmares returned when trazodone was replaced with 10 mg zolpidem.

Trazodone is a serotonergic, histaminergic, and alpha-adrenergic receptor antagonist that has been shown to increase total sleep time. The alpha-adrenergic blocker prazosin has been shown to reduce nightmares in patients with PTSD, but its use is controversial. Nightmares have been suggested to be related to suicide, independently of depression. The present case suggests trazodone may be an effective treatment for nightmares, but further study is needed.


Drug Trade Names: escitalopram—Lexapro; prazosin—Minipress; trazodone—Oleptro, and others; zolpidem—Ambien

Aripiprazole Augmentation of Clozapine

In a small trial that received no industry funding, patients with residual symptoms of schizophrenia despite adequate clozapine treatment experienced improvement in overall psychopathology and some positive symptoms with aripiprazole augmentation. Negative symptoms and cognitive abilities were not affected.

Methods: Outpatients with persistent positive and negative symptoms despite treatment with clozapine at the highest tolerated dose for at least 1 year were included in the study. Participants, aged 25–38 years (n=40; 23 males), received double-blind randomized adjunctive treatment with either aripiprazole or placebo for 24 weeks. Antidepressant and anticonvulsant use was prohibited. To test the effects of different doses, aripiprazole was added at 10 mg/day for 12 weeks and then increased to 15 mg/day for the remaining 12 weeks of the study. Response was assessed with the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), the Scale for the Assessment of Positive Symptoms (SAPS), and the Calgary Depression Scale for Schizophrenia (CDSS), as well as various tests of neurocognitive function.

Results: Of 40 patients who began treatment, 31 completed the study (14 with aripiprazole, 17 with placebo) and were included in the analysis. No last observation carried forward analysis was conducted. At both the 12- and 24-week endpoints, patients who received
Aripiprazole experienced statistically significant decreases in total symptom scores on the SAPS (p<0.0001), with decreases in thought disorder at week 12 and bizarre behavior at week 24. Of the negative symptoms, only alogia was improved, and only at week 24 (p=0.002). Of the neurocognitive tests, semantic fluency worsened between weeks 12 and 24 in the patients who received aripiprazole. The drug combination was well tolerated and associated with only transient adverse effects.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aripiprazole</td>
<td>Placebo</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>SAPS Total</td>
<td>10</td>
<td>11.8</td>
<td>3.8</td>
</tr>
<tr>
<td>SANS Total</td>
<td>28.6</td>
<td>33.9</td>
<td>19.5</td>
</tr>
<tr>
<td>BPRS Total</td>
<td>33.4</td>
<td>35.8</td>
<td>28.3</td>
</tr>
<tr>
<td>CDSS Total</td>
<td>5.4</td>
<td>6.4</td>
<td>4.7</td>
</tr>
</tbody>
</table>

**Discussion:** The few previous studies of aripiprazole augmentation of clozapine were limited by weak designs and had inconsistent results. The present study was limited by small sample size and the use of low doses of aripiprazole. The results suggest aripiprazole may help reduce positive symptoms but, surprisingly, may not improve negative symptoms or cognitive function. It may be that because patients had only mild-to-moderate negative symptoms to begin with, there was little room for improvement.

Muscatello M, Bruno A, Pandolfo G, Mico U, et al: Effect of aripiprazole augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study. *Schizophrenia Research* 2011; doi 10.1016/j.schres.2010.12.01. From the University of Messina, Italy. This study was conducted with no external funding. The authors disclosed no commercial interests that pose a conflict of interest.

*Drug Trade Names: aripiprazole—Abilify; clozapine—Clozaril*

*See Reference Guide.*

**Guidelines for Generalized Anxiety Disorder**

Treatment of generalized anxiety disorder should be on a stepped-care basis, with low-intensity psychological interventions as first-line therapy, according to a partially updated British treatment guideline. Since the previous guidance in 2004, there is more evidence supporting the use of SSRI therapy.

The guidance, from the National Institute for Health and Clinical Excellence (NICE), suggests that education and active monitoring may improve less severe cases and that comorbid emotional disorders or substance misuse should be treated before addressing the generalized anxiety. First-line, low-intensity psychological interventions can include individual self-help programs and participation in psychoeducational groups. If symptoms are marked or have not improved after low-intensity work, patients may choose either higher-intensity psychological intervention such as CBT or applied relaxation or pharmacotherapy. If drug therapy is chosen, the guideline recommendations include the following:

- The first choice in medication should be an SSRI, particularly sertraline.
- If sertraline is ineffective, it can be followed by another SSRI or an SNRI, or with pregabalin if the patient cannot tolerate SSRIs/SNRIs or if they are ineffective.
- Antipsychotics and long-term benzodiazepine use should be avoided.
Effectiveness and side effects of medication should be reviewed every 2–4 weeks initially, and subsequently every 3 months.

Effective medication should be continued for at least 1 year, as relapse risk is high.

If the disorder is refractory and the patient has considerable functional impairment or risk of self-harm, combination treatments should be offered: psychological interventions combined with drugs, or antidepressant augmentation. However, evidence for the effectiveness of combination treatments is lacking.


Drug Trade Names: pregabalin—Lyrica; sertraline—Zoloft

Fatal Quetiapine Hepatotoxicity

Liver abnormalities are a recognized, but rare complication of quetiapine (Seroquel) therapy. There have been 2 previous reports of quetiapine-related hepatotoxicity in the literature. The present case appears to be the first fatal case associated with very-low-dose treatment.

The 77-year-old patient had received 12.5 mg quetiapine b.i.d. for agitation and severe insomnia. She had no history of liver disease, was receiving no concurrent medications, and results of recent liver-enzyme tests had been unremarkable. She was admitted with a 1-week history of fatigue, vomiting, and loss of appetite. Laboratory testing on admission showed markedly elevated liver enzyme levels. Aspartate aminotransferase (AST) was 1415 U/l (normal range, 10–35 U/l); alanine aminotransferase (ALT) was 1565 U/l (normal range, 10–35 U/l); alkaline phosphatase was 178 U/l (normal range, 38–155 U/l); gamma-glutamyl transferase was 95 U/l (normal range, 7–32 U/l); and bilirubin was 4.77 mg/dL (normal range, 0.1–1 mg/dl). Viral, autoimmune, and metabolic causes were ruled out, and abdominal ultrasound was unremarkable. Quetiapine was stopped, and over the subsequent 7 days liver function began to improve (AST, 942 U/l; ALT, 1020;U/l). However, despite supportive therapy, the patient died on day 8. According to the Naranjo Probability Scale,* the association between quetiapine and the liver abnormality was "probable."


*Risperidone Augmentation in MDD

A substantial portion of patients with major depressive disorder (MDD) do not experience adequate response despite appropriate antidepressant therapy, and the atypical antipsychotics aripiprazole and quetiapine are FDA approved for adjunctive treatment of MDD. After 2 case series suggested efficacy of risperidone augmentation in MDD, several clinical trials of augmentation were undertaken.

A comprehensive literature search identified 5 studies, and the findings were reviewed.1 (See table, next page, for individual study information.) All of the studies showed risperidone augmentation improved depressive symptoms as measured by standardized rating scales including the Montgomery-Asberg Depression Rating Scale (MADRS) and the Beck Scale for Suicide Ideation (BSSI). Treatment was generally well tolerated, with headache (9–12%), dry mouth (30%), and increased appetite and weight gain (8%) as the most commonly reported
adverse effects. Study durations were short, ranging from 4 to 24 weeks, and many of the patient populations were small.

### Studies of Risperidone Augmentation in MDD

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Risperidone Dosage</th>
<th>Patients</th>
<th>Antidepressant</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label augmentation followed by double-blind placebo-controlled continuation&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Mean, 1.1 mg/day</td>
<td>n=368 open-label, n=241 continuation</td>
<td>Citalopram</td>
<td>MADRS scores decreased from 28 to 13 during augmentation (p&lt;0.001) Risperidone prolonged time to relapse (102 vs 85 days; p=ns)</td>
</tr>
<tr>
<td>Double-blind placebo-controlled study&lt;sup&gt;3&lt;/sup&gt;</td>
<td>≤1 mg/day</td>
<td>n=274</td>
<td>SSRIs, SNRIs, trazodone, bupropion</td>
<td>Response and remission rates at 6 weeks risperidone/placebo Response: 46%/30% (p=0.004) Remission: 25%/11% (p=0.004)</td>
</tr>
<tr>
<td>Double-blind placebo-controlled study&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.25–2 mg/day</td>
<td>n=24</td>
<td>SSRIs, SNRIs, TCAs, nefazodone, bupropion</td>
<td>BSSI score reductions: Risperidone from 24 to 15; placebo from 25 to 19 (p=ns)</td>
</tr>
<tr>
<td>Open-label augmentation followed by double-blind placebo-controlled continuation&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Mean, 0.7–0.8 mg/day</td>
<td>n=93 open-label, n=63 continuation</td>
<td>Citalopram</td>
<td>MADRS scores decreased by 0.43 points/day during augmentation Risperidone prolonged time to relapse (105 vs 57 days; p=ns)</td>
</tr>
<tr>
<td>Double-blind placebo-controlled study&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.5–3 mg/day</td>
<td>n=97</td>
<td>SSRIs, SNRIs, trazodone, bupropion, nefazodone, mirtazapine</td>
<td>Response and remission rates risperidone/placebo Response: 55%/33% (p=0.049) Remission: 52%/24% (p=0.01)</td>
</tr>
</tbody>
</table>

**Discussion:** According to the limited clinical evidence, risperidone appears to be a safe and effective augmentation option for patients with MDD who do not adequately respond to antidepressant monotherapy. However, the long-term efficacy can not be determined by the current evidence.

<sup>1</sup>Owenby R, Brown L, Brown J: Use of risperidone as augmentation treatment for major depressive disorder. *Annals of Pharmacotherapy* 2011;45 (January):95–100. From Durham VA Medical Center, N.C.; and Campbell University, Buies Creek, N.C. The authors disclosed no conflicts of interest.


**Drug Trade Names:** aripiprazole—Abilify; bupropion—Wellbutrin; citalopram—Celexa; mirtazapine—Remeron; nefazodone—Serzone; quetiapine—Seroquel; risperidone—Risperdal; trazodone—Oleptro, and others
**Reference Guide**

**Last Observation Carried Forward:** A method of data analysis in which missing data for individual patients is replaced by the last observed value of that variable.

**Naranjo Probability Scale:** A 10-point scale used to determine the likelihood that an adverse reaction is caused by an implicated medication. Based on scores, associations are considered doubtful, possible, probable, or highly probable.

**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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- Release date: February 2011
- Exam must be returned by: June 30, 2012

**Target Audience**

This activity is intended for physicians and other healthcare providers who are involved with or have an interest in the management of psychiatric disorders.

**Learning Objectives**

- Recognize and implement new approaches to the treatment of psychiatric disorders.
- Determine appropriate treatment selection for psychiatric disorders.
- Identify and appropriately prescribe medications or other therapeutic interventions for various psychiatric disorders.
- Recognize, avoid, and manage drug side effects and drug interactions.

**Disclosure Declarations:** All members of the CME planning committee have no relevant financial relationships.

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