Citalopram-Associated QT Prolongation

A 40-year-old woman with a long history of depression but no other medical conditions was hospitalized following the occurrence of 2 syncopal episodes. In the emergency department, electrocardiography showed a prolonged QT interval of 535 milliseconds, and she experienced multiple episodes of torsades de pointes, most of which were asymptomatic. Results of laboratory evaluations were unremarkable, and she reported no citalopram overdose or ingestion of illicit drugs. Echocardiogram showed normal left ventricular thickness and function, and there were no apparent structural defects. Because of increasing depression, her treatment had been switched from fluoxetine to 40 mg citalopram b.i.d. 4 weeks before the syncopal episodes occurred. Citalopram was stopped, and the QT interval normalized. The patient was started on nadolol for presumed concealed long QT syndrome (LQTS), and the citalopram was replaced with 15 mg/day mirtazapine. The regimen was well tolerated, and at 6-month follow-up the QT interval was in the normal range and she reported no further syncope.

The cardiac safety profile of citalopram is better than that of the TCAs. However, there have been reports of cardiac arrhythmias and death associated with citalopram overdose and with combined use with other antidepressants or antiarrhythmics. Torsades de pointes has also been reported with citalopram but only in patients with end-stage renal disease or electrolyte imbalance. The absence of these features, along with the improvement when citalopram was discontinued in the present case, suggests a diagnosis of LQTS that was unmasked by citalopram treatment. The authors recommend thorough screening of family history for sudden deaths before prescribing citalopram and avoidance of the drug for patients with LQTS.

Deshmuk A, Ulveling K, Alla V, Abuissa H, et al: Prolonged QTc interval and torsades de pointes induced by citalopram. Texas Heart Institute Journal 2012;39 (1):68–70. From the Cardiac Center of Creighton University, Omaha, Neb. The authors did not include disclosure of potential conflicts of interest.

Drug Trade Names: citalopram—Celexa; fluoxetine—Prozac; mirtazapine—Remeron; nadolol—Corgard
Citalopram Dosing Clarification

In 2011, the FDA issued a Drug Safety Communication indicating that citalopram should not be used in dosages >40 mg/day because of the risk of QT prolongation. However, because it may be necessary for some patients already at risk of QT prolongation to use the drug, the label has been revised to clarify dosing recommendations and warnings. According to the updated label, citalopram:

- Is not recommended at doses >40 mg/day because increased dosages confer no additional benefit and may have too large an effect on the QT interval.
- Is not recommended at doses >20 mg/day for patients with hepatic impairment, those aged >60 years, patients who are CYP2C19 poor metabolizers, or patients who are taking a concomitant CYP2C19 inhibitor (e.g., cimetidine), because these factors lead to increased blood levels of citalopram, which in turn increase the risk of QT prolongation and torsades de pointes.
- Is not recommended for patients with congenital long QT syndrome, bradycardia, hypokalemia, hypomagnesemia, recent MI, uncompensated heart failure, or those taking other drugs that prolong the QT interval.

When patients for whom citalopram is not recommended require low-dose treatment with the agent because they have no other viable options, electrolyte and/or electrocardiographic monitoring is recommended. Citalopram should be discontinued in patients with persistent QTc measurements >500 ms.


Drug Trade Names: cimetidine—Tagamet; citalopram—Celexa

Long-Term Lithium and Renal Failure

Lithium treatment of bipolar affective disorder should not be withheld out of fear of renal impairment, nor should it be discontinued in patients with long-term renal adverse effects, according to a decision analysis. Fear of adverse renal effects, one of several causes of the declining use of lithium, may be outweighed by the mental-health benefits of the drug.

Methods: Decision analysis is a type of mathematical model that simulates a decision process based on known risks and benefits of treatment and on numerical scores reflecting the desirability or undesirability of the possible outcomes. For the present study, 2 models of the lithium decision process were developed in which the greatest expected benefit (i.e., prevention of bipolar relapse or suicide) was balanced against the most undesirable side effect (i.e., end-stage renal disease). One model involved treatment initiation, and the other treatment discontinuation after many years of therapy in patients showing signs of kidney disease. Probability estimates for different outcomes given different treatment choices were based on a systematic literature review.

Results: At the start of treatment, the model identified lithium as the treatment of choice. Concern about stabilizing bipolar disorder was the predominant factor driving the choice, suicide risk played a more minor role in the model, and concerns about kidney failure were negligible. Twenty years into treatment, when patients would be more likely to incur kidney disease, the model still favored continuation of lithium over a switch to anticonvulsants. Concern about end-stage renal disease became more significant than earlier in treatment but still did not outweigh the clinical benefits in this model. Although concern about relapse carried less weight than it had at the start of treatment, it was still the predominating factor.
in the decision to continue lithium. The contribution of suicide to the model was also relatively minor at the latter time point because it is a far less common outcome than relapse.

**Discussion:** Intuitively, it may seem that patients with kidney disease who continue lithium have a greater risk of renal failure, but this has never been shown, and lithium discontinuation may not prevent renal failure. Nephrologist consultation should include discussion of the expected consequences of switching from lithium to another drug, and the focus might be better placed on managing the risks of continued lithium therapy, rather than on deciding whether it should be discontinued.

The study authors caution that these results should be viewed only as a first attempt to quantify this decision process. They do not account for many nuances, including the high rate of lithium nonadherence in this patient population and non-renal side effects of lithium and other drugs.

Werneke U, Ott M, Salander Renberg E, Taylor D, et al: A decision analysis of long-term lithium treatment and the risk of renal failure. *Acta Psychiatrica Scandinavica*; published online ahead of print; doi 10.1111/j.1600-0447.2012-01847.x. From Umeå University, Sweden; and other institutions. **Funded by the Research and Development Fund of Norrbotten County, Sweden; and Sunderby Hospital, Lulea, Sweden.** One study author disclosed relationships with commercial sources; the other 4 authors declared no conflicts of interest.

### Drug Interactions in Anxiety

Pharmacokinetic interactions include 3 types: those mediated by drug-induced changes in hepatic metabolism; those involving drug transporters like P-gp, which limits drug absorption from the gut and penetration to the brain; and those involving competition between drugs for protein binding. Pharmacokinetic interactions can be easily confirmed by a change in plasma drug concentrations. In contrast, pharmacodynamic interactions, which occur when 2 drugs share the same site of action, result in additive, synergistic, or antagonistic effects without alterations in plasma concentrations.

Because most drugs used to treat anxiety disorders have the potential for clinically relevant interactions with psychotropic and other agents, an updated literature review was conducted of all clinically relevant drug interactions with first-line anxiolytics: SSRIs, SNRIs, benzodiazepines, and the calcium-channel modulator pregabalin.

Most medications used to treat anxiety disorders are metabolized by the major hepatic enzyme system, CYP, and are prone to pharmacokinetic interactions; however, because these drugs have a wide margin of safety and multiple metabolic pathways, the interactions may not be clinically relevant. The SSRIs have a high potential to inhibit CYP activity, and some may also inhibit P-gp. Among these agents, citalopram and escitalopram have the most favorable drug-interaction profile. Duloxetine is a moderate inhibitor of CYP, but other SNRIs, benzodiazepines, and pregabalin generally do not cause significant pharmacokinetic interactions. The major risk of pharmacodynamic interactions results from the combination of SSRIs, SNRIs, or buspirone with other serotonergic drugs, which can lead to serotonin syndrome.

The combined use of different anxiolytic drugs is common, and antipsychotics may be coadministered with anxiolytic drugs in patients with psychosis. Combinations of drugs with serotonergic effects confer the greatest risk. If concomitant use of SSRIs and a TCA is necessary, it is best to avoid those with greater interaction potential, such as fluvoxamine, fluoxetine, or paroxetine. Fluoxetine and paroxetine can each inhibit the metabolism of risperidone, necessitating a dose reduction of the antipsychotic. Fluoxetine and fluvoxamine can each increase levels of clozapine. Pharmacokinetic interactions with second-generation antipsychotics are less likely with sertraline, citalopram/escitalopram, and venlafaxine. Pregabalin has minimal potential for interactions with antipsychotics. (See table, next page, for interactions judged to be clinically relevant.)
Data on interactions of SSRIs with antiepileptic mood stabilizers are conflicting. Risks differ for different cholinesterase inhibitors used to treat dementia. Interactions can also occur with non-CNS drugs, including anti-inflammatories, cardiovascular agents, and chemotherapy drugs. Risks may be reduced by avoiding polypharmacy if possible, anticipating and reducing risks from known interacting drug combinations, and individualizing the dose, guided by clinical response and possibly by monitoring plasma drug concentrations.

Muscatoello M, Spina E, Bandelow B, Baldwin D: Clinically relevant drug interactions in anxiety disorders. *Human Psychopharmacology and Clinical Experience* 2012; published online ahead of print; doi 10.1002/hup.2217. From the University of Messina, Italy; and other institutions. **Source of funding not stated. Three of the 4 authors declared relationships with commercial sources.**

**Drug Trade Names:** buspirone—Buspar; citalopram—Celexa; clozapine—Clozaril; duloxetine—Cymbalta; escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox; metoprolol—Toprol XL; olanzapine—Zyprexa; paroxetine—Paxil; pregabalin—Lyrica; propranolol—Inderal, InnoPran; quetiapine—Seroquel; risperidone—Risperdal; sertraline—Zoloft; tamoxifen—Nolvadex; venlafaxine—Effexor

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Quetiapine vs Psychotherapy in Bipolar Depression

In a small randomized pilot study, patients with bipolar II depression responded equally well to both a disorder-specific psychotherapy and pharmacotherapy with quetiapine (*Seroquel*).

**Background:** Interpersonal and Social Rhythm Therapy (IPSRT) was developed specifically for bipolar disorder and focuses on interpersonal relationships, psychoeducation, and modification of social rhythms. The treatment is based on the theory that circadian biology is abnormal in bipolar disorder and that patients can improve by developing more regular routines and social patterns. Patients track the regularity of their social routines weekly using a standardized assessment and try to modify their social interactions to promote mood stability.

**Methods:** Study subjects (n=25) were patients with bipolar II disorder currently experiencing depression. All had a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥15 and a Young Mania Rating Scale (YMRS) score of ≤10. Following a washout of any psychotropic medications (6 patients), participants were randomly assigned to 12 weeks of treatment with either quetiapine flexibly-dosed to a maximum of 300 mg/day (mean dosage, 244 mg/day; range, 25–300 mg/day) or IPSRT.

**Results:** Two patients in each treatment group did not complete the 12-week study; all were included in the intent-to-treat analysis. Both treatment groups experienced significant improvement in depression over the course of treatment. Mean HAM-D scores decreased from 20 to 13 with IPSRT and from 18 to 9 with quetiapine. Rates of response (i.e., ≥50% reduction in 25-item HAM-D and a YMRS score of ≤10) were similar in patients who underwent IPSRT (29%) and those who received quetiapine (27%).

At enrollment, patients had been surveyed about treatment preference. Outcomes did not differ between those who preferred psychotherapy, those who preferred medication, and those with no preference. Patients in both groups gained weight.

**Discussion:** The rate of response to quetiapine in this study was lower than rates previously reported for bipolar II depression. The authors suggested that future research should examine factors that may predict differential responses to medication and psychotherapy.

**Study Rating*—15 (88%):** This study met most criteria for a randomized controlled trial. Because of the nature of the interventions, patients could not be blinded to treatment assignment. Although clinicians who rated patient improvement were uninvolved in their treatment, it is not clear from the study report if they were blinded to treatment assignment.

Swartz H, Frank E, Cheng Y: A randomized pilot study of psychotherapy and quetiapine for the acute treatment of bipolar II depression. *Bipolar Disorders* 2012;14:211–216. From the University of Pittsburgh School of Medicine, Pa. Funded by the National Alliance for Research in Schizophrenia and Affective Disorders (NARSAD); and the NIMH. Two authors disclosed relationships with commercial sources.

*See Reference Guide.

SRIs and Pulmonary Hemodynamics

Ongoing treatment with a serotonin reuptake inhibitor was not associated with pulmonary hemodynamics in adults scheduled for coronary bypass surgery.

**Background:** Elevated levels of serotonin have been associated with pulmonary arterial hypertension. In animal models and human adults, SSRIs seem to protect against pulmonary hypertension by blocking the function of the serotonin transporter. In newborns exposed in utero, SSRIs have the opposite effect. The effect is believed to be mediated by serotonin receptor gene polymorphisms.
Methods: An observational study was carried out in 16 adults with stable angina scheduled to undergo coronary artery bypass graft surgery. Eight patients had been receiving SRI therapy (5 with citalopram, 2 escitalopram, and 1 venlafaxine) for ≥6 weeks (mean duration, 41 months; range, 2–120 months), and 8 had no history of SRI therapy. Patients receiving SRIs and controls were matched for gender and approximate age. Before surgery, hemodynamics, serum SRI concentrations, and 5-HT2A receptor binding were measured and genotyping of the serotonin-transporter-linked polymorphic region (5HTTLPR) and the 2A receptor were carried out. Pulmonary hemodynamics were measured directly with a pulmonary artery catheter, in contrast to previous studies that used less sensitive measurement.

Results: There were no significant differences between the groups in age, gender distribution, myocardial infarction history, or other medical conditions including heart failure, hypertension, and diabetes. The SRI-treated patients did not differ from the comparison group in any hemodynamic measurement or in receptor binding. No patient had pulmonary arterial hypertension. Mean pulmonary arterial pressure differed by 0.5 mmHg between the groups, a difference not considered clinically significant. Pulmonary artery pressure was not correlated with the SRI dose, duration of treatment, or serum concentration. No variant alleles were found in the group receiving SRI therapy, but 3 patients in the comparison group had variant alleles. These were not associated with hemodynamic differences.

Discussion: Because all SRIs and SNRIs have the same effect on the serotonin transporter, it is likely that these results extend to all drugs in these classes. The frequency of the variant alleles for 5HTR2A was so low that it would have been unlikely to find an effect in such a small patient sample, but it may also be that this receptor has little importance in regulating pulmonary arterial pressure in humans.


Drug Trade Names: citalopram—Celexa; escitalopram—Lexapro; venlafaxine—Effexor

Publication Bias in Antipsychotic Studies

A comparison of published and unpublished clinical trials of second-generation antipsychotics in schizophrenia found mixed evidence of publication bias. While studies with negative results were more likely than positive trials to remain unpublished, inclusion of the unpublished trials in a meta-analysis only modestly affected the overall effect size estimates for this class of drugs.

Methods: The investigators identified 24 phase 2 and 3 placebo-controlled clinical trials of 8 atypical antipsychotics (i.e., aripiprazole; iloperidone; olanzapine; paliperidone; quetiapine; risperidone; risperidone long-acting injection; ziprasidone) that were registered with the FDA and conducted between December 1993 and May 2005. The literature was searched for journal articles matching each clinical trial and published before May 2010.

Results: Of the 24 trials registered with the FDA, 20 were published; results of 15 of these were considered positive and 5 were negative or questionable. Of the 4 unpublished trials (2 aripiprazole, 2 ziprasidone), results of 3 were negative or questionable. One of these aripiprazole studies was disqualified because of research misconduct. In the second unpublished study, aripiprazole did not differ from placebo but the active comparator, haloperidol, did. Results of 1 unpublished ziprasidone trial found it inferior to haloperidol, and although the other found ziprasidone superior to placebo, it raised safety concerns about QT prolongation.

In a pooled analysis, the overall effect size* for the atypical antipsychotics in schizophrenia was 0.47 in the published trials and 0.23 in the unpublished trials (p=0.027). However, combining the published and unpublished trials resulted in a modest, statistically insignificant decrease in the overall effect size, to 0.44. Among the published trials, some outcome reporting bias was
detected, particularly in the iloperidone trials. Overall effect size estimates for some drugs were higher in analysis of journal publications, compared with all FDA submissions—20% higher for ziprasidone, 15% for risperidone, 12% for aripiprazole, and 8% for olanzapine.

**Discussion:** Selective publication of research findings can undermine the integrity of the evidence base used for making treatment decisions. This does not appear to be the case for second-generation antipsychotics. However, the authors caution that the present study evaluated only efficacy and not safety, which is an important part of real-world effectiveness.

Turner E, Knoepflmacher D, Shapley L: Publication bias in antipsychotic trials: an analysis of efficacy comparing the published literature to the US Food and Drug Administration database. *PLoS Medicine* 2012;9 (March):e1001189; doi 10.1371/journal.pmed.1001189. From Oregon Health & Science University, Portland; and other institutions. Funded by the Stanley Medical Research Institute. Two study authors disclosed financial relationships with commercial sources.

**Drug Trade Names:** aripiprazole—Abilify; iloperidone—Fanapt; olanzapine—Zyprexa; paliperidone—Invega; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

*See Reference Guide.

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**Social Anxiety Disorder: Evidence-Based Treatment**

SSRIs and venlafaxine should be considered first-line treatment for social anxiety disorder, according to a review of research articles, meta-analyses, and guidelines published between 1980 and 2010.

**First-Line Treatment.** Medications appear to be superior to psychotherapy as acute treatment for social anxiety disorder, according to a meta-analysis and several individual trials. Among the effective agents, SSRIs have a moderate effect size, are the most extensively studied drug class, are relatively well tolerated, and may also improve comorbid conditions, such as major depressive disorder and other anxiety disorders. Fluoxetine appears to be less effective than other SSRIs. Venlafaxine has similar efficacy and safety to the SSRIs.

**Second-Line Options.** As a class, benzodiazepines appear to have the largest effect size in social anxiety disorder, but this conclusion is based on a small number of trials that had inconsistent results. Phenelzine and other irreversible MAOIs have been shown to be as effective as SSRIs, but their efficacy is supported by less clinical trial evidence, and these drugs require special precautions. Gabapentin and pregabalin, as well as benzodiazepines, may be considered as alternatives if SSRI therapy fails.

**Treatment Resistance.** Little evidence is available concerning treatment of resistant social anxiety disorder. Results of a single trial suggest it may be necessary to continue the first-line agent for as long as 12 weeks to achieve response. At that point, a new medication should be considered if the patient has had no response; or a second agent, such as a benzodiazepine or gabapentin, may be added to a partially effective SSRI. No study has systematically investigated either of these strategies. Reasons for treatment resistance should also be investigated. These may include medication noncompliance, a comorbid psychiatric or medical disorder, a drug interaction, or individual pharmacokinetic characteristics (e.g., rapid drug metabolism). Adjunctive cognitive-behavioral therapy should also be considered in treatment-resistant disease.

**Duration of Treatment.** Evidence on the optimal duration of therapy is also limited. Study results suggest relapse rates are high after SSRI discontinuation. The authors recommend continuing treatment for at least 3–6 months after the patient has responded, with longer periods considered in individual cases.

Blanco C, Bragdon L, Schneier F, Liebowitz M: The evidence-based pharmacotherapy of social anxiety disorder. *International Journal of Neuropsychopharmacology* 2012; published online ahead of print; doi 10.1017/S1461145712000119. From Columbia College of Physicians and Surgeons and New York State Psychiatric Institute, New York, N.Y. Funded by the NIH; and the New York State Psychiatric Institute. Two study authors disclosed financial relationships with commercial sources.

**Drug Trade Names:** fluoxetine—Prozac; gabapentin—Neurontin; phenelzine—Nardil; pregabalin—Lyrica; venlafaxine—Effexor
**Review: Antipsychotics in Tourette Syndrome**

Expert guidelines and clinical practice favor the use of second-generation antipsychotics in the treatment of Tourette Syndrome (TS). However, only haloperidol and pimozide (both first-generation agents) are currently FDA approved to treat TS. Because their approval was based on older trials, an updated literature review was undertaken to re-evaluate their efficacy and to assess the efficacy of newer antipsychotic agents. A total of 43 articles published between 2001 and May 2011 were reviewed.

Risperidone has been found effective in multiple studies with high methodologic standards. In addition to helping control tics, risperidone may be useful in treating comorbidities like obsessive-compulsive and aggressive symptoms. Its high discontinuation rate, due to side effects like somnolence and weight gain, is a disadvantage. According to the review authors, risperidone is the preferred first-line therapy for tics and TS.

Pimozide should be considered in patients who have not responded to risperidone. Its cardiac risk profile and the lack of recent data suggest it should be the second- rather than first-choice medication. Haloperidol and fluphenazine are effective and well tolerated, but given haloperidol’s adverse-effect profile and the lack of recent data for both, the authors suggest they be used as reserve medications.

Based on clinical trial evidence of efficacy in TS and its usefulness for some comorbid symptoms, olanzapine can be recommended as early-stage therapy for TS, but metabolic effects can be problematic. Aripiprazole has only observational evidence of efficacy, but it can be recommended as second-line therapy because of its unique mechanism of action and relatively harmless adverse-effect profile. Quetiapine and ziprasidone appear to be promising, but evidence is preliminary and the agents cannot be recommended because of a lack of high-level evidence. Clozapine may exacerbate tics and is not recommended.

Huys D, Hardenacke K, Poppe P, Bartsch C, et al: Update on the role of antipsychotics in the treatment of Tourette syndrome. *Neuropsychiatric Disease and Treatment* 2012;8:95–104. From the University of Cologne, Germany. **Funded by the Deutsche Forschungsgemeinschaft.** Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors disclosed no competing interests.

**Drug Trade Names:** aripiprazole—*Abilify*; clozapine—*Clozaril*; fluphenazine—*Prolixin*; haloperidol—*Haldol*; olanzapine—*Zyprexa*; pimozide—*Orap*; quetiapine—*Seroquel*; risperidone—*Risperdal*; ziprasidone—*Geodon*

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**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.