Increased awareness about the condition and its treatment among mental health physicians will assist with the early detection and institution of appropriate evidence-based treatments of RLS among psychiatry patients. Prospective studies involving larger samples will enhance our understanding of the prevalence, etiology, impact, and treatment of RLS among patients with severe mental illness.

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Aripiprazole-Associated QTc Prolongation in a Geriatric Patient

To the Editors:

Second-generation antipsychotics (SGAs) are used in the treatment of geriatric patients (aged 65 years or older) with different psychiatric conditions (eg, delirium, dementia, schizophrenia, psychotic mood disorders).[1] Second-generation antipsychotics are generally associated with various degrees of QTc interval prolongation (Table 1).[2–5] QTc is a heart rate–corrected value that represents the time between the onset of electrical depolarization of the ventricles and the end of repolarization.[6] QTc prolongation (defined as QTc values above 450 milliseconds [men] or 470 milliseconds [women]) usually results from delayed or prolonged repolarization, which may arise as a consequence of a reduction in function of the delayed rectifier potassium channel (Ikr).[3,7] Prolonged QTc is a proarrhythmic risk for torsades de pointes (TdP) and cardiac arrest. Although TdP can occur with lower QTc values or changes, a critical risk of developing TdP occurs with QTc greater than 500 milliseconds or greater than 60 milliseconds above the baseline.[6] Unlike other SGAs, aripiprazole is believed to cause a decrease in the QTc interval.[2,8] This makes it a desirable option particularly in geriatric patients who may have multiple risk factors for QTc prolongation. However, a single case report of a 42-year-old intensive care patient with delirium described the occurrence of QTc prolongation and resulting TdP and cardiac arrest while receiving 5 days of aripiprazole 2.5 mg by mouth daily.[9] Although generally studied in younger patients, there are comparatively limited data on its effects on electrocardiographic measures in the elderly. This is of particular concern in the older psychiatric patients who are more likely to have preexisting systemic medical conditions, including cardiovascular disease. Notably, a QTc greater than 450 milliseconds is associated with a higher risk of all-cause mortality in the geriatric patients,[10] whereas QTc greater than 500 milliseconds is associated with higher mortality in all ages.[11] We herein report a case focusing on the potential role of aripiprazole to extend the QTc interval in a geriatric patient.

CASE

A 69-year-old Indian female was treated in an outpatient clinic for bipolar I disorder, most recent episode manic, severe, with psychotic features. She had no history of illicit drug, alcohol, or tobacco use. She lived with her children, and they dispensed her medications for monitoring adherence. Medical history included hypertension, dyslipidemia, and type 2 diabetes mellitus. She had no previous occurrences of medication-mediated QT interval prolongation and no family history of congenital long QT syndrome or sudden death. Past psychiatric treatments with lithium, risperidone, and olanzapine were ineffective. Subsequent monotherapy with quetiapine 200 mg at bedtime led to significant improvement of her mood and psychotic symptoms. Concurrent medications included atenolol 100 mg daily, amlodipine 5 mg daily, telmisartan 80 mg daily, metformin 1000 mg twice daily, and gliclazide MR 60 mg daily. A 12-lead electrocardiography (ECG) QTc revealed 433 milliseconds; there was no ECG performed before starting quetiapine trial.

After 9 months, she remained psychiatrically stable but complained of progressive dizziness noted since beginning

TABLE 1. Effects of Select SGAs on QTc Interval[2–5]

SGA Drug	QTc Prolongation and Clinical Relevance*	Mean QTc Prolongation Compared With Baseline in Milliseconds
Aripiprazole	Ø	−4.1
Paliperidone	Ø	+3.7
Asenapine	Ø	+5.0
Lurasidone	Ø	+5.1
Olanzapine	+	+6.4
Risperidone	++	+10.0
Clozapine	++	+10.0
Quetiapine	++	+14.5
Ziprasidone	+++	+20.6
Sertindole	+++	+30.1

*US Food and Drug Administration categorizes clinically meaningful increases in risk for arrhythmias associated with mean QTc prolongation from baseline as follows: ≤5 milliseconds, probably no concern (Ø); 6–20 milliseconds, inconclusive concern, although some have been associated with proarrhythmic risk (+, ++); and ≥20 milliseconds, definite concern (+++).

quetiapine therapy. Subsequent ECG revealed a QTc of 448 milliseconds. There was no evidence of orthostatic hypotension. Because of concerns that her dizziness was related to quetiapine, she was switched to aripiprazole, which was titrated to 7 mg daily. However, 2 months later, she continued to complain of dizziness. QTc had increased to 482 milliseconds. Laboratory tests showed serum sodium of 142 mEq/L (135–145 mEq/L), potassium of 4.7 mEq/L (3.5–5.5 mEq/L), and albumin of 40 g/L (35–50 g/L). There was no hepatic or renal impairment. Because of the increase of the QTc interval, aripiprazole was decreased to 2 mg daily. Eleven days later, ECG showed a normal sinus rhythm and a QTc of 492 milliseconds, which was 59 milliseconds above the baseline. Subsequently, aripiprazole was completely discontinued, and no further psychotropic agents were used. She no longer complained of dizziness. A 48-hour Holter monitoring performed 13 days later showed a normal sinus rhythm, QT interval of 403 milliseconds, and heart rate of 71 beats per minute (resulting in a QTc of 438 milliseconds, which was a return to her previous ECG baseline). Divalproex was further proposed as maintenance treatment for her bipolar disorder.

DISCUSSION

Female sex, older age, slow metabolizer status, pharmacodynamic and pharmacokinetic interactions, congenital long QT syndromes, heart failure, bradycardia, and electrolyte imbalance are all risk factors for QTc prolongation and/or TdP.[6] No aripiprazole dose adjustments are currently recommended for patients with hepatic or renal impairment.[12] In our case, excessive increases of the QTc interval in a female geriatric patient on treatment with aripiprazole was compelling in the context of no history of bradycardia, prolonged baseline QT interval, electrolyte disturbances, high dosing of medication, and/or known genetic risk factors. Resolution of her QTc prolongation followed only after discontinuation of aripiprazole. The Naranjo score of 6 suggests that aripiprazole was probably the causative agent.[13] As this case illustrates a plausible contribution of aripiprazole on the QTc interval prolongation, a few possible explanations are further entertained.

The degree of QTc prolongation with antipsychotics has been reported as dose dependent.[6] Both aripiprazole and its active metabolite dehydro-aripiprazole are greater than 99% protein bound (primarily to albumin) (Bristol-Myers Squibb Canada, Abilify Prescribing Information, Available at: http://www.bmscanada.ca/static/products/en/pm_pdf/ABILIFY_EN_PM.pdf. Accessed February 23, 2014). Notably, serum albumin concentrations decrease with age, and values less than 38 g/L have been associated with increased morbidity, mortality, and disability in the elderly.[14] In addition, combining aripiprazole with other agents, which are also highly protein bound (eg, amlodipine, telmisartan, and gliclazide), can increase the free fraction of aripiprazole that may lead to clinically relevant adverse effects, and thus, a dose adjustment is warranted on this basis. As aripiprazole is eliminated by the cytochrome P450 (CYP) 3A4 and 2D6 isoenzymes, dosage adjustment is also necessary when there is a known genetic polymorphism of CYP2D6 (Bristol-Myers Squibb Canada, Abilify Prescribing Information). Notably, approximately 5% of Indians are poor metabolizers, with a decreased ability to metabolize CYP2D6 substrates.[15]

Moreover, our patient displayed excessive increases in the QTc values despite decreasing the dosage of aripiprazole. This may be at least partly explained by the long elimination half-life of aripiprazole of approximately 75 hours (for CYP2D6 extensive metabolizers) or 146 hours (for CYP2D6 poor metabolizers), with a risk of cumulative effects, particularly in the elderly.[16] Therefore, steady state serum concentrations can be reached in approximately 2 weeks but can be doubled in CYP2D6 poor metabolizers, resulting in a 60% higher exposure to aripiprazole (Bristol-Myers Squibb Canada, Abilify Prescribing Information). Therefore, it is prudent to obtain baseline and subsequent ECGs when initiating aripiprazole in elderly patients, particularly when administering concurrent therapy (due to the risk of QTc prolongation associated with concurrent medications and/or due to the effects of other medications on protein binding that can increase the unbound fraction of aripiprazole). Using the lowest effective dose of antipsychotic even in those with no personal or family history of congenital long QT syndrome or cardiovascular disease is advised. Time to steady state needs to be considered when assessing appropriate dose titrations of aripiprazole.

This case illustrates that despite its previous association with QT interval shortening, aripiprazole may in some cases have a proarrhythmic potential as reflected by a significant increase in the QTc. Psychiatrists should screen ECGs for changes associated with QTc prolongation pretreatment and during treatment with aripiprazole. A prompt referral to cardiology is advisable if evidence of QTc prolongation is noted. In such a case, aripiprazole should be stopped immediately, and treatment with a psychotropic medication not associated with increased QTc should be initiated.

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Acute Lurasidone Overdose

To the Editors:

Lurasidone is a benzoisothiazol derivative that was approved for the treatment of schizophrenia by the Food and Drug Administration (FDA) in 2010.[1] Since that time, it has also been approved for the treatment of bipolar depression.[2] The maximum approved dose in the United States is 160 mg once daily.[3] It should be taken with food to increase the absorption of lurasidone.[1] A study by Preskorn et al[4] found that lurasidone exposure increased between "2- to 3-fold" when taken with meals of at least 1465 kJ. Absorption of lurasidone was not influenced by the fat content of the meal.[4] It is absorbed rapidly after oral administration, and it reaches its maximum concentration between 1 and 3 hours after ingestion. The bioavailability of lurasidone ranges from between 9% and 19%, and it is 99.8% protein bound.[1,5] A study of patients with schizophrenia found that single doses of lurasidone (between 120 mg and 160 mg) had a mean half-life of between 28.8 and 37.4 hours.[5] Elimination is primarily through the liver, and approximately 0.1% of lurasidone is excreted unchanged in the urine.[5]

Because lurasidone is primarily metabolized via the cytochrome P450 3A4 (CYP3A4) isoenzyme, its concentration would likely be affected when used concurrently with a CYP3A4 inhibitor or inducer.[1,6] In fact, a number of interactions between lurasidone and both moderate and strong CYP3A4 inducers and inhibitors have been observed.[1,6] Therefore, it has been recommended that lurasidone should not be used with strong CYP3A4 inhibitors or inducers.[1,6] It has also been recommended that, when lurasidone is coadministered with a moderate CYP3A4 inhibitor (such as diltiazem), the lurasidone dose should not exceed 40 mg/d.[6,7] The United States FDA definitions of moderate and strong inducers/inhibitors are listed in Table 1.[8] Lurasidone is metabolized into 2 active and 2 inactive metabolites.[1] It acts as a D_2 and $5HT_{2A}$ receptor antagonist.[1,9] It also has antagonistic effects at the α_{2C} and α_{2A} noradrenergic receptors.[1,10] It blocks the $5HT_7$ receptor and acts as a partial agonist of the $5HT_{1A}$ receptor.[1,11] Lurasidone has little, if any, affinity for histamine H_1 and acetylcholine M_1 receptors.[10]

The adverse events associated with lurasidone treatment are similar to those seen with the other atypical antipsychotic agents. Commonly seen adverse effects include akathisia, agitation, Parkinsonism, anxiety, somnolence, and dystonia.[6] As with other antipsychotic agents, there are rare reports of leukopenia or neutropenia. The lurasidone clinical trials found it effective for both positive and negative symptoms of schizophrenia and that the most common adverse events were movement abnormalities, akathisia, nausea, and drowsiness.[9] A later study by Citrome et al[10] examined more than 400 patients who were treated with lurasidone for 12 months. The lurasidone doses ranged from 40 mg to 120 mg daily. In this study, the most frequent adverse effects were nausea (16.7%), insomnia (15.8%), and sedation (14.6%).[10] Studies have found that there is no significant QTc prolongation associated with lurasidone use.[5] In fact, 1 study found that high-dose lurasidone (up to 600 mg daily) was associated with minimal QTc interval increases of between 4.4 and 6.4 milliseconds.[5] Overall, the authors felt that lurasidone was "safe and well tolerated" with minimal effect on prolactin levels, weight, or metabolic variables.[10] Lurasidone has been classified as pregnancy category B by the FDA.[1] It has been recommended that mothers do not breast feed while taking lurasidone.[1]

There are minimal data regarding overdose on lurasidone. In fact, a literature search was unable to find any case reports of overdose in the literature to date. The only mention of lurasidone overdose was the brief description of a single case in the package insert.[12] That patient ingested an estimated 560 mg of lurasidone and recovered without sequelae. We now report the case of a 31-year-old man who overdosed on a large amount of lurasidone in an attempt to commit suicide.

CASE REPORT

The patient was a 31-year-old man with a history of schizophrenia who was brought to the emergency department 90 minutes after an intentional overdose on seventeen 80-mg lurasidone tablets and five 1-mg clonazepam tablets in an attempt to end his life. The ingestion occurred immediately after lunch and was witnessed by his caregiver. His caregiver was able to confirm the number of pills ingested. His history was negative for tobacco, alcohol, or illicit drug use. His medical history was significant for hypertension and obesity as well as negative for any respiratory or endocrine disorder. Twenty-two days before this overdose, the patient weighed 131.8 kg and had a body mass index of 39.4. The patient's medication regimen consisted of lurasidone (160 mg nightly), trazodone (150 mg nightly), and clonazepam (1 mg every 8 hours as needed).

Upon presentation to the emergency department, the patient was noted to be cooperative, alert, and oriented in all