Management of Psychosis and Agitation in Medical-Surgical Patients Who Have or Are at Risk for Prolonged QT Interval

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We review the literature on management of psychosis and agitation in medical-surgical patients who have or are at risk for prolonged QT interval, a risk factor for torsade de pointes (TdP), and we describe our protocols for treating these patients. We searched PubMed and PsycInfo for relevant studies and found few papers describing options for treating psychosis and agitation in these patients. Prolonged QTc interval has been more often associated with low-potency phenothiazines such as thioridazine; however, it may occur with high potency typical antipsychotics such as fluphenazine and haloperidol as well as with atypical antipsychotics such as quetiapine, risperidone, olanzapine, iloperidone, and particularly ziprasidone. Antipsychotics for which no association with prolonged QTc interval has been shown include lurasidone, clozapine, and aripiprazole. For patients who have risk factors for prolonged QTc interval but whose electrocardiograms do not show this, reasonable first choices include oral or intramuscular olanzapine or aripiprazole, followed by risperidone and quetiapine or oral or intramuscular haloperidol. For those who have prolonged QTc but that measures less than 500 ms, we limit the use of antipsychotics to aripiprazole, olanzapine, risperidone, or quetiapine. Finally, for patients who have a QTc of 500 ms or greater, we rely on aripiprazole, valproate, trazodone, and benzodiazepines. (*Journal of Psychiatric Practice* **2014;20:338–344**)

KEY WORDS: prolonged QT interval, psychosis, agitation, torsade de pointes, antipsychotic agents

At our hospital, the psychiatry consultation-liaison service receives requests to evaluate medical-surgical patients who are psychotic and agitated. Psychosis is associated with various conditions. Medical patients often have co-existing psychiatric disorders such as schizophrenia and bipolar disorder. Drug intoxication and withdrawal can also cause psychosis. Psychosis may also be seen in neurologic disorders such as dementia and encephalopathy. Medical conditions such as metabolic derangements and infections can lead to hallucinations. Intensive care settings are often disorienting and confusing to patients. In some cases, the correction of underlying medical issues is sufficient to reverse the psychosis, but more often than not, psychosis persists and worsens.

The choice of medications to decrease psychosis and agitation must be made carefully in these patients, who are medically unstable. Antipsychotics, mood stabilizers, and benzodiazepines that are used for this purpose have side effects that such patients may tolerate poorly. In particular, prolonged QT interval on electrocardiography makes it challenging to determine optimal management of psychotic agitation without compromising the patient's cardiac status. Here we review the recent and current literature on the use of antipsychotic medications in terms of their effects on QT interval and consider the options available for management of agitation and psychosis in patients seen on the consultation-liaison service. Factors unique to a consultation-liaison service include the fact that medical and surgical interventions often require urgent sedation, patients are sometimes not able to cooperate with a full cardiac work-up, and the underlying cause of psychosis may not be immediately apparent.

We searched both PubMed and PsycInfo for relevant studies. Much has been written on the treatment of agitation in medically ill patients. The literature regarding the association of antipsychotics and prolonged QT interval is also extensive. However, we found few papers describing options for

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treating psychosis and agitation in patients with prolonged QT interval. Furthermore, we found no literature that specifically addressed the role of the consultation-liaison psychiatrist in this matter. The dearth of studies may reflect the difficulties in conducting controlled studies of patients seen by a consultation-liaison service. Often, the patient already had a prolonged QT interval before receiving antipsychotic medication, the reason for which is not always understood. Also, it is often not possible to ascertain whether decreased agitation results from the antipsychotic agent or from improvement in the medical condition. Nor is it possible to track the effects of antipsychotic treatment on the QT interval for any set duration because once the agitation subsides and the medical or surgical condition is treated, the antipsychotic medication is discontinued, and the patient may be discharged within a few days.

ANTIPSYCHOTICS AND PROLONGED QT INTERVAL

QT interval is defined as the time from the onset of ventricular depolarization to the end of repolarization. It is outside the scope of this article to discuss the electrophysiology of the QT interval, which is more accurately measured as corrected QT (QTc), adjusted for heart rate, sex, and age. As a practical guideline, QTc prolongation is defined as longer than 460 ms for women and longer than 450 ms for men.[1] It is well established that QT prolongation can be associated with torsade de pointes (TdP), a pernicious ventricular arrhythmia that can lead to ventricular fibrillation and sudden death.

Common risk factors for prolonged QT interval include electrolyte abnormalities such as hypokalemia, hypocalcemia, and hypomagnesemia. Various medical conditions (renal dysfunction, diabetes, hypothyroidism, malnutrition, obesity) that can cause these electrolyte imbalances are also risk factors for prolonged QT interval. Female sex and older age may also predispose to this condition.[2,3] Experts concur that a QTc greater than 500 ms or an increase from baseline of more than 60 ms poses an increased risk for the development of TdP, although TdP can occur at QTc intervals less than 500 ms and with changes of less than 60 ms.[2]

QTc prolongation has been attributed to both typical and atypical antipsychotics. Among the typical group, prolonged QTc has been associated more with low-potency than high-potency antipsychotics.[4] Warner et al. found that TdP can occur with the low-potency phenothiazines, especially at higher doses (the equivalent of 2000 mg of chlorpromazine).[5] Thioridazine (a phenothiazine) has been clearly linked to TdP and to a significant number of sudden deaths.[6]

However, high-potency typical antipsychotics can also prolong the QTc. Chong et al. described QTc prolongation with fluphenazine, a phenothiazine.[7] Both QTc lengthening and TdP have been linked to haloperidol, a butyrophenone.[8–10] Pimozide is a potent dopamine blocker in the diphenylbutylpiperidine class of typical antipsychotics. Although pimozide is approved by the Food and Drug Administration (FDA) in the United States only for treatment of Gilles de la Tourette syndrome, it is used in Europe for psychosis due to chronic schizophrenia. It is used off-label in the United States by dermatologists and psychiatrists for delusional parasitosis and monosymptomatic hypochondriacal psychosis. In a study to assess the cardiovascular safety of pimozide, Gulisano et al. found a significant prolongation in mean QTc of 24.3 ± 15.9 ms.[11] Pimozide also decreased systolic and diastolic blood pressure significantly. Harrigan et al. studied both typical and atypical antipsychotics and found that ziprasidone caused QTc interval prolongation of 15.9 ms, followed by haloperidol (7.1 ms), quetiapine (5.7 ms), risperidone (3.6–3.9 ms), and olanzapine (1.7 ms).[9] These values were less than for thioridazine, which had the highest mean QTc interval prolongation (30.1 ms). A New Drug Application for sertindole reported an increase in the QTc of an average 22 ms at therapeutic doses.[4,12] Sertindole has not been approved for use in the United States. While Harrigan's study used 15 mg of haloperidol in oral form, studies using haloperidol in intramuscular form (7.5 mg) showed an increase in QT interval similar to that observed with the oral route in patients without underlying illness.[13,14] Iloperidone, a newer antipsychotic, has been shown in short-term trials to increase QTc by up to 11.4 ms.[15] Potkin et al. found that QTc increases with iloperidone (at 8- and 12-mg twice daily doses) were similar to those observed with ziprasidone, but higher than increases observed with quetiapine.[16]

Other antipsychotics have been found to have no significant association with QTc prolongation. No significant increases in QTc were observed in a study of lurasidone by Caccia et al.[17] However, this study

did not have a large group of women. Because female sex is a risk factor for prolonged QT interval, the authors acknowledged that further studies with a more inclusive population would be useful. A literature review by Warner and Hoffman[18] and a study by Grande et al.[19] indicated that clozapine (a dibenzodiazepine and atypical antipsychotic) did not cause prolonged QTc or TdP. Even in patients with coexisting medical conditions, aripiprazole has not been found to cause significant QTc prolongation.[20,21]

MANAGEMENT OF AGITATED PSYCHOSIS

Managing agitated and psychotic patients on the consultation-liaison service of a general hospital is challenging because of their medically compromised condition. At the same time, the fact that they are in a general hospital with access to cardiac monitoring enables treatment in a safe environment.

At our institution, we categorize patients into three groups when considering QTc: those who have risk factors for prolonged QTc but whose electrocardiograms do not show this; those who have prolonged QTc but measuring less than 500 ms; and those who have QTc of 500 ms or greater.

Patients with Risk Factors for Prolonged QTc but Normal Electrocardiograms

Glassman advised screening for "cardiac vulnerability" in the beginning and throughout treatment with antipsychotics for individuals with risk factors for prolonged QT intervals.[22] Beach et al. also emphasized this point and recommended obtaining a baseline QTc measurement for patients with risk factors for QT prolongation, with intermittent monitoring of QTc following antipsychotic initiation.[23] They suggested employing antipsychotics such as quetiapine and olanzapine, because the sedative properties of these agents may enable the use of lower doses and hence decrease the risk of QT prolongation.

Nielsen at al. noted the importance of avoiding antipsychotic polypharmacy and not combining an antipsychotic medication with other drugs that prolong QTc.[24] Obtaining an electrocardiogram and measuring serum electrolyte levels are standard precautions that his group recommends when there are concerns about cardiac risk.

Based on the results of Harrigan et al.,[9] we start with medications that are less likely to cause QT prolongation. Breier et al.[13] and Wright et al.[14] described the safety of olanzapine, and Muzyk et al.[20] and Belgamwar and El-Sayeh[21] reported on the safety of aripiprazole. Therefore, reasonable first choices include oral or intramuscular olanzapine or aripiprazole, followed by risperidone and quetiapine. Often, however, the patient's medical condition requires vigilant avoidance of a decrease in blood pressure. Because these atypical antipsychotics tend to lower blood pressure, we use haloperidol instead in such situations. Haloperidol is recommended at low doses in oral or intramuscular form, observing for possible extrapyramidal side effects; we do not recommend intravenous haloperidol. The FDA issued a warning in 2007 that haloperidol administered intravenously might pose an increased risk for QT prolongation and TdP compared with oral administration. The FDA currently recommends cardiac monitoring for all patients who are given intravenous haloperidol.[10]

Pimozide, for the reasons mentioned earlier, may be encountered on the consultation service. However, it is not used to treat psychosis on medical/surgical floors. If it is already being given for Tourette's syndrome or delusional disorder, we would recommend discontinuation if the QTc is already prolonged or careful monitoring if the patient is at risk for prolonged QTc.

In patients who have no QTc prolongation, latitude is greater in the use of antipsychotics. Therefore, we may also use fluphenazine and low doses of chlorpromazine. Ziprasidone has been associated with TdP in only a few case reports (all of which involved possible confounding factors).[23,25–28] However, as noted above, ziprasidone can cause greater QT prolongation than other antipsychotic agents.[9] Therefore, we concur with the view of Nielsen at al.[24] that "ziprasidone…should be avoided in those with known cardiovascular disease, prior myocardial infarction, cardiomyopathy, electrolyte disturbances or hypertension," and that it should not be combined with any other medication that can prolong the QTc interval.

Patients with Prolonged QTc < 500 Ms

For those with prolonged QTc that is less than 500 ms, we limit the use of antipsychotics to aripiprazole, olanzapine, risperidone, or quetiapine. Olanzapine and aripiprazole are administered either orally or intramuscularly. Blood pressures are monitored fre-

quently, as all four of these agents can cause hypotension. Electrocardiograms are repeated to monitor for lengthening of QTc. We work closely with electrophysiology specialists on the cardiac team; if antipsychotics must be continued, cardiac monitoring is implemented. If the patient is already taking haloperidol or ziprasidone, we advise discontinuation of these antipsychotics even if it is not clear whether these medications have induced the prolonged QTc.

Asenapine, a second-generation antipsychotic, was approved in 2010 by the FDA for the treatment of acute schizophrenia and for the treatment of mixed or manic phases of bipolar I disorder. Asenapine was found to have a mild effect on the QT interval similar to that of quetiapine.[29] A study of asenapine sublingual tablets in the treatment of acutely agitated patients in an emergency department setting has been completed. The efficacy of asenapine in decreasing agitation was measured using the Positive and Negative Syndrome Scale–Excited Component (PANSS-EC) from 0 to 120 minutes after administration of sublingual asenapine. The results of the completed study showed efficacy of sublingual asenapine 10 mg as early as 15 minutes after the medication was given. The medication was well-tolerated and no adverse events were reported during the 2 hours of evaluation. The number needed to treat for response to asenapine 10 mg versus placebo was found to be comparable to that for intramuscular ziprasidone (10 or 20 mg), intramuscular olanzapine (10 mg), intramuscular aripiprazole (9.75 mg), intramuscular haloperidol (6.5 or 7.5 mg), and intramuscular lorazepam (2 mg). The study concluded that asenapine 10 mg "appears to be a rapid, effective, and safe treatment option that may be more acceptable to some individuals with agitation than presently available parenterally administered medications."[30]

For patients with prolonged QTc of less than 500 ms, we also consider alternatives such as valproate (after ascertaining there is no hepatic compromise) and trazodone, which are not generally known to prolong QTc.[23,31–33] However, Tarantino et al. demonstrated that trazodone prolongs QTc in a dose-dependent manner, via inhibition of the repolarizing current mediated by the human ether-à-go-go-related gene (hERG) channel.[34] The results of their study are consistent with earlier descriptions of prolonged QTc by Burgess et al.,[35] who showed that trazodone caused prolonged QT, and with a study by Mazur et al.,[36] who reported a case of prolonged QTc and polymorphous ventricular tachycardia in a patient who was receiving a combination of trazodone and amiodarone. Based on their findings, Tarantino et al. stressed caution in using trazodone and being mindful of combining trazodone with other medications that could potentiate its sedative and hypotensive effects.[34] Patients with cardiac disease would be especially susceptible to such effects.

Data on valproate causing QT prolongation are limited. In a letter to the editor, Kazim et al. hypothesized that hypocalcemia may underlie QT prolongation seen in valproate toxicity.[37] While data on valproate causing QT prolongation are limited, Kurt et al. studied the possible "cardiac conduction stabilizing effect" of valproate through its activation of gamma aminobutyric acid pathways.[38] They found a lower QTcD in patients on valproate than in healthy control subjects. QTcD is defined as the difference between the longest QT and shortest QT, corrected by Bazett's formula. It is regarded as a predictor of dysrhythmias.[39]

The exigency may at times lie more with the agitation than the psychosis per se. In this case, achieving sedation may take priority over, for example, decreasing delusions. Benzodiazepines will not reverse psychosis, but they are not known to cause prolongation of the QT interval.[23,31] While they are sedating, they can increase confusion and lead to respiratory compromise. Infrequent, paradoxical reactions resulting in agitation have also been well documented in the literature. We recommend choosing short-acting benzodiazepines, such as alprazolam or lorazepam, to minimize the potential for prolonged side effects.

Patients with QTc ⩾ 500 Ms

Options for managing psychosis and agitation become very limited for patients with QTc of 500 ms or greater. Roden wrote that "the prolongation of the QT interval to longer than 500 msec during drug therapy should prompt a critical reevaluation of the risks and benefits of that therapy and consideration of therapeutic alternatives, in concert with a search for underlying predisposing factors such as hypokalemia or drug interactions."[40]

Unless these agents are medically contraindicated, we rely on aripiprazole, valproate, trazodone, and benzodiazepines while waiting to see whether the

QTc will normalize with measures such as repleting electrolytes and correcting underlying medical issues.

Our research for this article did not find literature specifically addressing QTc prolongation with oral loxapine, a first-generation typical antipsychotic in the dibenzoxazepine class. However, loxapine in inhalable form has received approval from the FDA for the short-term treatment of acute agitation in schizophrenia and bipolar disorder.[41] Previously in use in Europe, inhalable loxapine became available in the United States in the first half of 2014. The preparation is self-administered by patients using a hand-held delivery device.[41]

In a review of inhaled loxapine, Currier and Walsh stated that it appears to be beneficial for "mild to moderate agitation" in patients with schizophrenia or bipolar disorder.[42] Data are not available for efficacy in severe agitation. Inhalation of this medication confers its main advantage through rapid bioavailability; however, inhalation also raises concerns for pulmonary complications such as bronchospasm. The medication may be difficult to use with uncooperative patients who are unable to self-administer the medication via a hand-held device. The FDA required the product insert to include a boxed warning regarding pulmonary safety. In terms of effects on QTc, the prescribing information states under the heading "Thorough QTc study" that inhalable loxapine "did not prolong the QTc interval."[41]

Suzuki et al. reported that a switch to perospirone normalized prolonged QTc induced by zotepine in a Japanese patient.[43] Both perospirone and zotepine are atypical antipsychotics that are not available in the United States. The authors acknowledged that further studies are needed to determine the effects of perospirone on the QTc. However, if perospirone does become available for use in the United States and further studies show that it does not prolong QT interval, it may show promise for treating agitation and psychosis.

At our institution, we hold interdisciplinary conferences to address management of complicated cases. With the patient's permission, we also involve family members. If necessary, we obtain input from the ethics committee if the risk of harm to self or others from agitation outweighs the risk of prolonged QTc escalating to TdP.

We also use nonpharmacologic interventions such as encouraging family members to stay nearby to calm the patient. Another such intervention we use is music therapy. Music therapy is defined as "the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program."[44] Music therapy has been shown to improve physiologic indices and psychologic states associated with medical illness. Hospital staff have reported decreased agitation in medically ill patients who receive music therapy, without the necessity of sedative medication.[45] Pelletier published a meta-analysis showing a significant decrease in stress when music was used in various medical situations such as myocardial infarction and cardiac catheterization and during obstetrical labor.[46]

CONCLUSION

No set algorithm exists to guide the psychiatric consultant in how to manage agitated and psychotic patients who have or are at risk for prolonged QT interval. The consultant must consider many variables, such as co-existing medical conditions and multiple risk factors for prolonged QT interval. Patients are often taking several medications that can prolong QT interval. Prior to considering administration of any medication, a thorough cardiac assessment is essential, since prolonged QT interval is only one parameter in the overall cardiac status.

It is well established that ziprasidone prolongs the QT interval to a greater extent than do olanzapine, risperidone, or quetiapine. Aripiprazole does not appear to be associated with significant prolongation of QT interval. However, these alternatives to ziprasidone can lower the blood pressure and may cause other cardiac side effects. Risperidone and quetiapine are not available in injectable form for acute agitation. Haloperidol in oral or intramuscular form may be used, but intravenous administration is ill advised; if the intravenous form must be used, it should be administered with extreme caution and under continuous cardiac monitoring. Valproate and trazodone are also useful alternatives. Benzodiazepines are not known to prolong QTc but may increase confusion.

A QTc interval above 500 ms is associated with an increased risk of TdP; therefore, when monitoring for worsening of an already prolonged QT interval, it is prudent to keep the QT below 500 ms, although this is not a guarantee that the patient will not develop

TdP. Beyond general guidelines, the clinician must exercise keen judgment in weighing the risks and benefits of the medications he or she chooses in managing this challenging situation. There is a fine line between undermedicating and overmedicating. In 2005, Battaglia wrote that, in recent decades, typical antipsychotics and benzodiazepines were the preferred medications for treating acute agitation.[47] Of these, haloperidol and lorazepam were widely used safely and effectively in medical settings. He opined that intramuscular ziprasidone (keeping in mind its effect on QT) and olanzapine "may represent a historic advance in the treatment of acute agitation."[47] Indeed we now do have many more choices, but each choice still requires the clinician to have an educated understanding of its advantages and drawbacks. A longitudinal controlled study including a large cohort with prolonged QT interval will be necessary to derive a better understanding of the effectiveness and risks of antipsychotic medications used to manage agitation and psychosis by a psychiatry consultation-liaison service.

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