

Review Article

QTc Prolongation, Torsades de Pointes, and Psychotropic Medications

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Background: Prolongation of the corrected QT (QTc) interval is a key issue for patients who receive psychotropic medications. Such patients may have baseline clinical risk factors for QTc prolongation, and many psychotropic medications may further prolong this interval. This has great clinical relevance, as QTc prolongation is linked with dangerous arrhythmias, especially torsades de pointes (TdP). **Methods:** We summarize current literature regarding appropriate methods of calculating the QTc interval, the association of the QTc interval with TdP, and risk factors for QTc prolongation. We then review connections between psychiatric medications and QTc prolongation, with a specific focus on antidepressants and antipsychotics. **Results:** QTc interval prolongation is an established, though imperfect, risk marker for TdP. There are no well-controlled studies that assess the risk of TdP associated with psy-

chotropic agents. There are limited data that selective serotonin reuptake inhibitors (SSRIs) as a class are linked to QTc prolongation; citalopram appears more likely than others to induce this phenomenon. Among antipsychotics, thioridazine remains the agent most associated with QTc prolongation; intravenous haloperidol also appears to carry an increased risk. Of the atypical antipsychotics, ziprasidone appears most likely to prolong the QTc interval. **Conclusions:** The majority of patients in need of psychotropic medications display few risk factors for QTc prolongation and should be considered to be at low risk for TdP. The frequency of cardiac monitoring for patients receiving psychiatric medications should be individually determined, based on the prescribed agent(s) and additional risk factors for TdP.

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Prolongation of the electrocardiographic QT interval is an established risk factor for torsades de pointes (TdP),¹ a malignant ventricular arrhythmia, though the relationship between prolonged QT and TdP is complex.² Patients seen in medical or psychiatric settings may have multiple risk factors for QT prolongation and TdP, and, importantly, a variety of psychotropic medications have been linked to lengthening of this cardiac interval.¹ In this review, we will discuss the nature and measurement of the QT interval, describe TdP and its consequences, and outline non-pharmacologic risk factors for QT prolongation and TdP. We will then more comprehensively review the relationship between psychotropic medications and QT prolongation, with a specific focus on antidepressants and antipsychotics. To complete this non-

systematic review, articles were identified initially through PubMed using standard search terms (e.g., “QT prolongation,” “Torsades de pointes,” “antipsychotics”), with supplementation via search of reference lists from articles identified in the initial search.

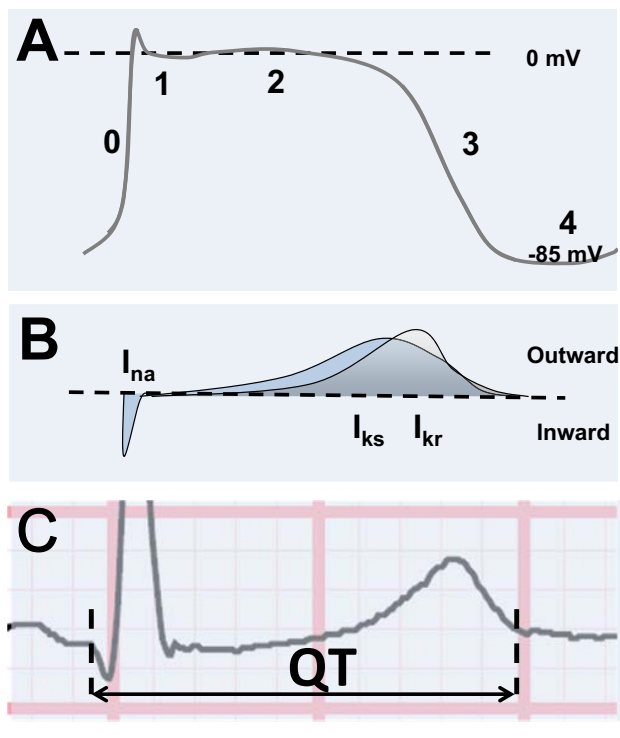
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THE QT INTERVAL

On the electrocardiogram (ECG), the QT interval (Figure 1) reflects the time from the onset of ventricular depolarization to the end of repolarization. Ventricular depolarization results from rapid influx of sodium ions into the cardiomyocytes. Subsequent repolarization of the ventricle results primarily from an outward flow of potassium through two delayed rectifying currents—rapid (I_{Kr}) and slow (I_{Ks}). Blockade of either current may prolong the action potential and thereby lengthen the QT interval.³

FIGURE 1. The Cardiac Action Potential (A) Occurs in Five Phases: Rapid depolarization (phase 0) caused by inward sodium currents; initial repolarization (phase 1) caused by inactivation of sodium currents; and onset of transient outward potassium currents, isoelectric plateau (phase 2) caused by a balance between inward calcium and outward potassium currents; rapid repolarization (phase 3) caused by inactivation of calcium currents while potassium channels remain open, and the resting membrane potential (phase 4). The main currents (B) responsible for the action potential are the rapid influx of sodium during depolarization and the outward flow of potassium through two delayed rectifying currents (Rapid/ I_{Kr} and Slow/ I_{Ks}) during repolarization. on the electrocardiogram (C); the QT interval is measured from the onset of ventricular depolarization (onset of QRS complex) to the end of ventricular repolarization (end of the T wave).



Production of I_{Kr} is regulated by the human ether-a-go-go-related gene (hERG), making hERG expression an important factor in QT prolongation.

The QT interval is measured on the ECG from the beginning of the QRS complex (initial deflection or Q wave) to the end of the T wave.³ A useful way to determine the end of the T wave (particularly if the T wave offset is indistinct) is to use the intersection of a tangent to the steepest slope of T wave and the baseline (usually using either lead II or V5).⁴ Since this interval is inversely proportional to heart rate, the QT interval is typically corrected for heart rate (QTc). The onset of ventricular depolarization (phase 0 of the action potential) is inscribed as the Q wave, the ST segment occurs during the isoelectric plateau phase (phase 2 of the action potential), and repolarization (phase 3 of the action potential) occurs during the T wave.⁵ The QT interval is typically manually measured in a single lead. However, because of the phenomenon of “QT dispersion” (the heterogeneity of repolarization across the myocardium), it should be measured in the lead with the longest QT interval; this is most often V2 or V3.⁶ Automated digital ECG machines often simultaneously analyze all leads and measure the QT interval from the earliest Q wave in any lead to the last T wave in any lead. As a result, the automated QT is often longer than the QT interval measured in any individual lead,⁷ and automated QT interval estimates should always be confirmed with manual measurements. To gain the most accurate assessment of pharmacologic QT prolongation, ECG readings should be made at or near the maximum daily blood level of medications affecting the QT interval.⁵

As noted, the QT interval shortens at faster heart rates.⁸ The most commonly used formula to correct the QT interval (including that made by most ECG machines) is Bazett’s square root formula ($[QTc] = QT/R-R \text{ interval}^{1/2}$).³ This correction results in significant error at the extremes of heart rate (i.e., at fast heart rates, the actual QTc is shorter than that estimated by Bazett’s formula, whereas the opposite is true for slower heart rates), and alternative methods, such as Hodges formula ($QTc = QT + 1.75[HR-60]$) may be preferable. Indeed, these alternative linear correction methods have been recommended by the American Heart Association guidelines for ECG interpretation,⁷ though these methods are not yet widely adopted.⁹ In clinical practice, if the QT interval appears to be greater than half of the RR interval (and heart rate is close to 60 bpm) an observer can easily and rapidly identify QTc prolongation. Large, prospective, population-based studies have linked QTc prolongation with increased mortality,

and a prolonged QTc interval at baseline has been shown to be a risk factor for drug-induced QT prolongation and life-threatening arrhythmia.^{8,9} However, no studies have been undertaken to determine whether any specific method of QT measurement does a better job of predicting sudden death.⁵

In addition to heart rate, age, and sex have a significant impact on the QT interval. In general, the QT interval is longer in young women. The gender difference develops during adolescence (perhaps due to the effects of testosterone) and diminishes in older adulthood.⁷ Detailed age- and sex-specific nomograms are available, but for simplicity, a normal QTc interval is generally defined as <460 ms for women and <450 ms for men.⁷ Though these “normal” cut-off values are often used, the QTc interval represents a continuous risk factor for adverse events.

TORSADES DE POINTES (TdP)

TdP, a form of polymorphic ventricular tachycardia occurring in the setting of a prolonged QTc interval, is a malignant arrhythmia, often asymptomatic but associated with syncope and sudden death. The term, meaning “twisting of the points,” refers to the pattern of polymorphic ventricular tachycardia seen on the ECG. ECG warning signs that precede TdP include marked QTc prolongation, premature ventricular contractions, and short-long intervals¹⁰ (Figure 2). An unstable rhythm typically unresponsive to common antiarrhythmic medications (many of which prolong the QTc interval or cause bradycardia), TdP may resolve with infusion of magnesium sulfate (even in patients with normal magnesium levels), overdrive pacing

or isoproterenol infusion to increase heart rate (and thus shorten the QTc), and removal of the offending agent.¹¹ If left untreated, TdP may recur, with deterioration to ventricular fibrillation and death.⁵ TdP has a very high risk of immediate recurrence.¹⁰

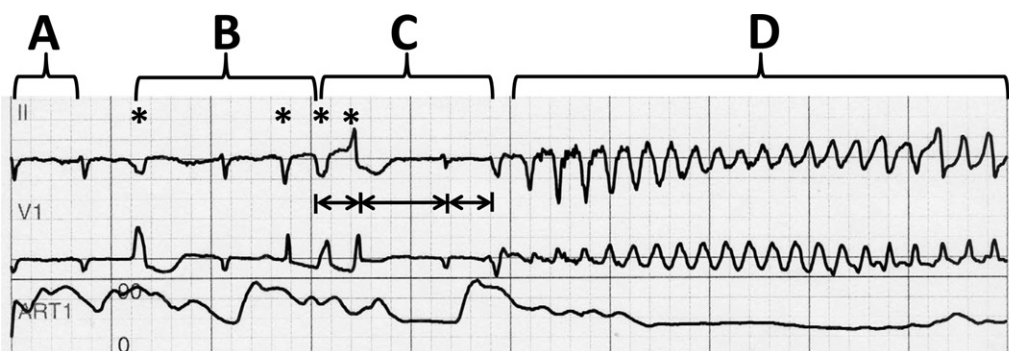
QTc interval prolongation has a graded relationship to the risk of cardiac mortality and sudden death (presumably related to TdP in many cases), although the risk of sudden death, at the individual level, remains low.^{2,12} It has been suggested that the hazard ratio for cardiac events linked to the QTc is 1.052,¹⁰ where “x” is 1 ms increase in QTc over 400 ms.⁶ Thus, a patient with a QTc of 500 ms would have a 1.66-fold greater risk of such a cardiac event than a patient with a QTc of 400 ms, whereas a patient with a QTc of 550 ms would have a 2.14-fold greater risk.

RISK FACTORS FOR PROLONGED QTc AND TdP

Long QT syndrome (LQTS), one of the most common genetic arrhythmia syndromes, can be caused by hundreds of mutations in 10 identified genes, though mutations in three genes account for the vast majority of cases.¹³ TdP is a hallmark of LQTS and is a frequent cause of death or syncope patients with this syndrome. The prevalence of mutations is 1 per 2000 individuals, though clinically manifest disease (syncope or resuscitated sudden cardiac death) is less common.¹⁴

The majority of LQTS patients, 88% in one study, have prolonged QTc at baseline.¹⁰ Importantly, 5%–10% of patients who develop drug-induced TdP are silent carriers of gene mutations related to LQTS, suggesting that a “second hit” (such as drug exposure) can uncover the LQTS pheno-

FIGURE 2. A Representative Telemetry Strip Illustrating the Typical Initiation Sequence for TdP. At baseline there is either acquired or congenital prolongation of the QT interval (A), which results in triggered electrical activity (early after depolarizations) and premature ventricular complexes (B, asterisks). These premature ventricular complexes create a stereotypic “Short-Long-Short” variation in the R-R intervals (C, arrows), which further prolongs repolarization (after the long R-R interval) and results in TdP (D). Of note, the arterial pulse is lost during TdP as illustrated by the arterial line tracing.



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TABLE 1. Risk Factors for Prolonged QT^{1-4,9}

Female
Increased age
Congenital LQTS
Electrolyte abnormalities
Hypokalemia
Hypocalcemia
Hypomagnesemia
Anorexia nervosa*
Diuretic use*
Heart conditions
Bradycardia
Left ventricular dysfunction
Heart failure
Mitral valve prolapse
Myocardial infarction
Other medical conditions
Renal dysfunction*
Hepatic dysfunction
Hypoglycemia*
Hypertension**
Diabetes*
Hypothyroidism*
Pituitary insufficiency*
CNS injury (stroke, trauma, tumor, infection)*
AIDS
Malnutrition*
Obesity (including acute weight gain)*

LQTS = Long QT syndrome.

* Causes QTc prolongation via effects on electrolytes.

** Causes QTc prolongation via diastolic dysfunction.

type despite a “normal” QTc in the unprovoked state. This concept has been termed “repolarization reserve.” Despite having a baseline QTc in the normal range, carriers of silent mutations are more susceptible to additional QT prolonging factors and are at elevated risk for arrhythmia.

Besides genetic mutations, several other risk factors for TdP have been identified, many of which are also risk factors for QTc prolongation; these are listed in Table 1. Diurnal variation of the QTc interval is substantial, up to 75–100 ms, and sleep is a risk factor for QTc prolongation.^{1,11}

Medications are another major cause of QTc prolongation. It is estimated that up to 3% of all prescriptions are for potentially QTc prolonging medications.¹⁰ In the past decade, the single most common cause of post-marketing withdrawal or restriction of drugs has been prolongation of the QTc interval.¹⁵ Some noncardiovascular drugs that have been withdrawn from the market cause an increase in the QTc interval of only 5–10 ms.¹⁵ Most medications that prolong the QTc interval block the I_{Kr} channel² and can induce TdP sudden death in previously healthy adults.

Several medications have been associated with pro-

longation of the QTc interval (Table 2). For some, such as Class I antiarrhythmic medications, the risk of TdP is correlated with the extent of QTc prolongation, but this is not necessarily true of other medications that prolong the QTc interval.¹¹ Amiodarone and ranolazine, for example, may prolong the QTc substantially but are not associated with TdP,¹⁵ whereas quinidine causes only modest QT prolongation but is clearly associated with TdP.⁵ The explanation for this may be related to the lower QT dispersion seen with the former agents and the greater dispersion seen with the latter, as agents that prolong the QT interval in a heterogeneous manner (affecting some regions of myocardium more than others) likely are more pro-arrhythmic.

The histamine blocker terfenadine and the esophageal prokinetic agent cisapride have been withdrawn from the market because of concerns for TdP. Though methadone is a known QTc-prolonging agent, other opiates are not thought to have this effect. Many other substances, includ-

TABLE 2. Nonpsychiatric Medications Associated with QTc Prolongation

Antiarrhythmics
Class I
Quinidine
Disopyramide
Procainamide
Class III
Sotalol
Amiodarone
Dofetilide
Antibiotics
Macrolides
Erythromycin
Clarithromycin
Azithromycin
Quinolones
Levofloxacin
Moxifloxacin
Antifungals
Fluconazole
Ketoconazole
Other Antibiotics
Pentamidine
Antimalarials
Chloroquine
Halofantrine
Other Medications
Tamoxifen
Vandetanib
Furosemide
Terfenadine (withdrawn due to TdP)
Cisapride (withdrawn due to TdP)
Methadone

ing alcohol, cocaine, and stimulants have also been shown to prolong the QTc interval.¹⁶

Drug interactions can lead to TdP either via a pharmacodynamic interaction in which the cumulative effect of two QTc-prolonging agents places the patient at risk, or via a pharmacokinetic interaction, usually mediated through inhibition of cytochrome P450 isoenzymes, in which a medication reduces the clearance of a second medication that has QTc-prolonging properties.^{17,18} Agents that are known to contribute to QTc prolongation via pharmacokinetic interactions include macrolide antibiotics, antifungal agents, the antiretroviral agent ritonavir, and grapefruit juice.¹¹ Decreased liver function may also lead to higher serum drug levels and elevate the risk for TdP.²

FUTURE DIRECTIONS IN TdP RISK ASSESSMENT

Given the limitations of correlating QTc interval with TdP risk, several investigators are exploring alternative markers for TdP. Some have advocated for the use of a QT nomogram, using QT-HR pairs, similar to the nomogram used to guide management of acetaminophen overdose.¹⁹ QT-HR pairs above the nomogram line were associated with an increased risk of TdP according to a systematic review of known cases of drug-induced TdP compared with a data set of control patients taking noncardiotoxic drugs (acetaminophen, diazepam, oxazepam, temazepam) in overdose. In a study using this metric, the QT nomogram gave an overall better prediction of TdP than did Bazett's formula with high sensitivity and specificity.¹⁹

Another potential marker involves morphology of the T or U waves. At least one study suggests that the height of pathologic U-waves may be a better predictor of drug-induced TdP than QTc prolongation.²⁰ Furthermore, there is some suggestion that abnormalities of the morphology of the T wave (such as inverted, biphasic, or notched T waves) may indicate abnormalities of repolarization and potential risk of arrhythmia.¹ Finally, measuring QT dispersion may provide more information regarding risk, compared to assessment of QTc.⁷

ANTIDEPRESSANTS AND THE QTc INTERVAL

Selective Serotonin Reuptake Inhibitors (SSRIs)

Since the introduction of fluoxetine in 1986, SSRIs have largely been considered to have a favorable cardiac safety profile, and have been consistently identified as preferable to tricyclic antidepressants (TCAs) for patients

with heart disease.^{21,22} Until recently, the International Registry for Drug-Induced Arrhythmias Arizona Classification listed fluoxetine, paroxetine, and sertraline in "group 4," considered unlikely to cause prolonged QTc or increase TdP risk when used at recommended doses in patients without other risk factors.²³ Over the years, case reports have appeared linking all of the SSRIs except paroxetine to QTc prolongation and, in some instances, to TdP.²⁴⁻²⁸ However, case reports by their nature are anecdotal and nonsystematic, and many of these specific reports have suffered from incomplete data, such as concomitant medical illness or method of QT measurement.

Emerging evidence over the past decade has suggested that some SSRIs, particularly citalopram, may have a predictable negative effect on the QTc interval. This evidence culminated in the recommendation by the Food and Drug Administration (FDA) in August 2011 to limit the maximum daily dose of citalopram to 40 mg (20 mg in patients with hepatic impairment or those older than 60 years) because of the increased risk of QTc prolongation at higher doses, and to declare its use contraindicated in patients with LQTS.²⁹ Less stringent recommendations in March 2012 included a revision of the statement from "citalopram should no longer be used at doses >40 mg per day" to "citalopram is not recommended for use at doses >40 mg per day," downgrading of citalopram from "contraindicated" to "not recommended" for patients with congenital LQTS and a recommendation to discontinue citalopram in any patient with a QTc interval greater than 500ms.³⁰ No QTc-related recommendations have been issued for other SSRIs.

These warnings regarding citalopram were based on a randomized, multi-center, double-blind, placebo-controlled, crossover study mandated by the FDA.²⁹ In this study, 119 subjects received three different 22-day treatments in random order, separated by at least 14 days. The first treatment consisted of citalopram 20 mg daily for 9 days, followed by citalopram 40 mg daily for 4 days, followed by citalopram 60 for 9 days. The second treatment involved 8 days of placebo, followed by a single dose of moxifloxacin 400 mg, followed by 12 days of placebo and an additional dose of moxifloxacin 400 mg. The final treatment involved 22 days of placebo. Maximum mean prolongations in the QTc intervals were 8.5 and 18.5 ms for 20 and 60 mg citalopram, respectively. For 40 mg citalopram, prolongation of the QTc interval was estimated to be 12.6 ms, based on serum concentrations. Though the absolute change in the QTc interval was modest, the FDA concluded that there was not sufficient

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evidence for a therapeutic benefit of 60 mg compared with 40 mg to warrant the risk of additional QTc prolongation at this higher dose.

Though four prior studies had shown prolongation of the QTc interval as an effect of citalopram overdose^{31–34} and 12 case reports highlighted prolongation of the QT interval as an adverse effect of citalopram (five of which occurred at therapeutic doses),^{3,24,35–44} this FDA study was the first prospective trial to show risk of prolonged QT with therapeutic doses of citalopram; notably two prior prospective studies found that citalopram 60 mg daily for 4 weeks had no effect on the QTc interval of healthy male volunteers, and an additional study determined that citalopram 40 mg daily for 12 weeks resulted in no QTc-prolongation in depressed patients with coronary artery disease.^{45–47} On the other hand, a recent study suggested that citalopram was associated with out-of-hospital cardiac arrest, though it did not examine the QTc interval specifically.⁴⁸

Despite the structural similarities between citalopram and escitalopram, the FDA recommendations have not been extended to escitalopram. Indeed, a thorough QT study of escitalopram ($n = 113$), essentially identical to that performed for citalopram, found dose-dependent but substantially less marked increases of QTc associated with escitalopram (4.5 and 10.7 ms for 10 and 30 mg, respectively).⁴⁹

Though case reports have linked other SSRIs with QTc prolongation, no prospective studies have shown such agents to have a statistically significant effect on the QTc interval. At least 13 studies designed to measure this effect, including five studies involving fluoxetine and five involving paroxetine, failed to show any association between these agents and QTc prolongation.^{21,22,50–60} Current evidence thus suggests that citalopram may be separate from other SSRIs in its propensity to prolong the QTc interval. Citalopram is known to inhibit hERG in animal models,⁶¹ and the development of citalopram was delayed due to QTc prolongation and arrhythmias in beagles, eventually attributed to a species-specific metabolite, didesmethyl-citalopram (DDCT).⁶² DDCT is thought to be a minor metabolite in humans, and some animal studies have suggested that hERG blockade occurs only with high concentrations of the metabolite. However, 2% of the United States population are cytochrome P450 2D6 ultrarapid metabolizers and, thus, could have higher concentrations.⁶³ This may help to explain why QTc prolongation appears more common with citalopram than with other SSRIs.^{12,64} Though fluoxetine is also noted to be a potent

inhibitor of hERG channels, additional calcium channel blocking properties may mitigate the effects of selective hERG blockade on QTc-prolongation.¹²

Despite the risk for prolonged QTc interval with citalopram, there is no consensus regarding the appropriate management of citalopram overdose. Some recommend continuous ECG monitoring for overdoses of greater than 600 mg,⁶⁵ others recommend a minimal observation period of 24 hours with continuous ECG monitoring following any citalopram overdose,²⁴ and some have further suggested administration of activated charcoal following citalopram overdose to reduce absorption and prevent QTc prolongation.^{66,67} In general, QTc prolongation rates may be relatively low with citalopram, even in overdose, as a study of 215 patients with a citalopram overdose found that 32% had a QTc over 440 ms and 2% had a QTc over 500 ms³⁴.

Other Antidepressants

All tricyclic antidepressants (TCAs) cause prolongation of the QTc interval through sodium channel blockade (leading to QRS widening) as well as calcium channel blockade, mechanisms distinct from that of SSRIs.⁶⁸ TCAs generally only pose a significant risk of ventricular arrhythmia to patients with preexisting cardiac disease, including intraventricular conduction disease or ischemic heart disease.⁶⁹ However, like other QTc-prolonging meds, TCAs also block I_{Kr} . A systematic review in 2004 highlighted 13 cases of TdP with TCAs, finding amitriptyline and maprotiline to be most commonly implicated,⁶⁸ whereas clomipramine appears to be associated with the least QTc prolongation.⁷⁰

A single case report has linked therapeutic doses of venlafaxine to QTc prolongation, but no systematic studies have shown an association.⁷¹ A study also examined venlafaxine in overdose and found QTc prolongation >440 ms in 18% and >500 ms in 1% of 223 patients, lower than the rates for citalopram.³⁴ In the same study, among 103 patients ingesting mirtazapine in overdose, 16% had prolongation of the QTc >440 ms, with none >500 ms³⁴.

Among other agents, duloxetine has not been associated with prolongation of the QTc interval.⁵⁶ Some have reported prolongation of the QT interval in the setting of bupropion overdose, though this finding may be confounded by tachycardia.⁷² No studies have linked therapeutic doses of bupropion to QTc prolongation.

ANTIPSYCHOTICS AND QTc PROLONGATION

Antipsychotic medications have long been known to have the potential to cause QTc interval prolongation and TdP. Retrospective and cohort studies have linked antipsychotic use with sudden cardiac death, and most antipsychotic medications have been shown to cause some degree of QT prolongation.^{73–75} As with citalopram, the mechanism by which this occurs is thought to involve blockade of I_{Kr} channels.

Typical Antipsychotics

Thioridazine was the first antipsychotic medication associated with QTc prolongation and TdP,⁷⁶ and it continues to present the greatest risk among neuroleptics. In a randomized, prospective study evaluating the effects of QTc on medically healthy individuals with psychotic disorders, thioridazine (at a moderate dose of 300 mg/d) showed the greatest prolongation of the QTc (30 ms) compared with ziprasidone (160 mg/d), risperidone (up to 16 mg/d), olanzapine (20 mg/d), quetiapine (750 mg/d), or haloperidol (15 mg/d).⁷⁷ Phenothiazines in general—and thioridazine in particular—also are over-represented in cases of sudden death compared to antidepressants or other types of antipsychotics (e.g., butyrophenones, thioxanthenes), suggesting that the QTc prolongation seen with phenothiazines may be arrhythmogenic, especially in patients with concomitant risk factors.^{11,77,78}

Although thioridazine may be most commonly associated with QTc prolongation, other typical antipsychotics also have been implicated. Fluphenazine, a high-potency antipsychotic, has been associated with QTc prolongation in patients with schizophrenia.⁷⁹ Pimozide and droperidol prolong the QTc and have been clearly associated with TdP.⁵ Chlorpromazine, a low-potency phenothiazine like thioridazine, has been shown to block the I_{Kr} channel, has been associated with QTc prolongation, and may cause TdP at high doses.^{79,80} In general, low potency typical antipsychotics are thought to carry a greater risk than high-potency agents, and this risk is thought to be dose-related.⁵

Haloperidol, despite being a high-potency agent, has also been linked in case reports to QTc prolongation and TdP, though the frequency and magnitude of QTc prolongation is thought to be substantially less than with thioridazine and similar to that with many atypical antipsychotics.^{77,81} Given the widespread use of haloperidol in the management of delirium of patients in the intensive care

unit setting, this modest effect on QTc may nonetheless take on special importance.

In one of the few randomized studies of its effects on QTc, haloperidol (15 mg by mouth daily) led to an average increase in QTc of 7.1 ms, which was less than the prolongation caused by thioridazine or ziprasidone but greater than that caused by olanzapine, risperidone, or quetiapine.⁷⁷ In a nearly identical study of the same medications, oral haloperidol 15 mg daily led to an average QTc increase of 4.7 ms, which was less than ziprasidone, olanzapine, risperidone, quetiapine or thioridazine.⁸¹ The intramuscular (IM) form of haloperidol similarly has a relatively mild QTc-prolonging effect of up to 8 ms (following a 7.5 mg IM injection) in patients without significant medical illness.^{82,83} Despite the relatively mild QTc prolongation associated with the oral and IM forms of haloperidol, this medication has clearly been linked to TdP. A post-marketing analysis of the adverse effects of haloperidol in 2007 identified 229 cases of prolonged QTc interval, including 73 cases of TdP, although the incidence of TdP cannot be accurately determined. While the investigators noted that many of these reports were confounded by other QT-prolonging medications and medical illnesses, the sheer quantity of case reports and the knowledge of haloperidol's propensity to prolong QTc suggest that haloperidol may well have played a role in the development of TdP in some of these cases.⁸⁴

The intravenous (IV) form of haloperidol may carry a higher risk of QTc prolongation and TdP than the oral form. In a cross-sectional study of 1017 medically healthy patients with schizophrenia, IV—but not oral—haloperidol was associated with QTc prolongation.⁸⁵ Furthermore, in post-marketing analyses, of 11 cases of fatal TdP, eight (73%) occurred with IV haloperidol.⁸⁴ As noted, this may be explained in part by the fact that IV haloperidol is used relatively frequently in medically ill individuals (who most likely would be at higher risk for QTc prolongation and TdP), whereas the oral formulation may be used more frequently in healthier individuals with chronic psychotic illnesses. The FDA recommends cardiac monitoring for all patients receiving IV haloperidol.⁸⁴

Atypical Antipsychotics

Atypical antipsychotics also appear to have a risk of QTc interval prolongation, though these agents have only been implicated in the development of TdP in rare case reports and FDA adverse event reports.^{86,87} As noted above, in healthy

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volunteers, ziprasidone causes the greatest mean QTc prolongation compared with olanzapine, risperidone, and quetiapine.^{77,81} Ziprasidone's modest but definite effect on repolarization does not appear to be dose-dependent.^{77,81,88} In clinical trials of patients taking therapeutic doses of ziprasidone (i.e., not in overdose), the incidence of QTc prolongation exceeding 500 ms has been estimated at less than 0.06%.⁸⁹ Consistent with these rates is the finding that ziprasidone has been associated with TdP in only two case reports.^{90,91}

In two randomized, open-label studies, olanzapine, risperidone, and quetiapine were found to have less QTc prolongation than thioridazine and comparable effects to oral haloperidol.^{77,81} While these medications all are associated with QTc prolongation, their associations with TdP are less clear. In one large case-control study, atypical antipsychotics were associated with an increased risk of sudden death after controlling for cardiac risk factors, hypokalemia, renal disease, and SSRI use.²³ However, the risk appeared greatest for those patients who were prescribed the medications for the first time within the past 30 days, suggesting that these medications may in some cases have been used for delirium or management of agitation in the setting of medical illness. In a separate, retrospective, population-based cohort study, both typical and atypical antipsychotics were associated with an approximately 2-fold increased risk of sudden cardiac death; similar risk increases were found among all agents examined individually (thioridazine, haloperidol, olanzapine, quetiapine, risperidone, and clozapine).⁹² Notably, while clozapine was associated with an increased risk of sudden cardiac death in this study, it has only been associated with QTc prolongation in rare case reports, suggesting that another mechanism may be mediating its relationship with sudden cardiac death.^{87,93,94} Finally, in elderly patients with dementia, atypical antipsychotics have been associated with mortality related to cardiac events (some of which may represent episodes of ventricular arrhythmia such as TdP); this has led to an FDA black box warning for these medications and highlights the caution needed when prescribing these medications in certain populations.⁹⁵

There are less data available about the newest atypical antipsychotics, including aripiprazole, asenapine, paliperidone, and iloperidone; nearly all of the available data are derived from studies referenced in package inserts. Of these, iloperidone and paliperidone seem to have the highest risk for QTc prolongation, particularly in the presence of 2D6 and 3A4 inhibitors.⁹⁶⁻¹⁰⁴ However, there do not appear to be any reported cases of TdP with any of these new medications.⁶⁸ Aripiprazole has not been associated

TABLE 3. QTc-Prolongation Risk Stratification for Commonly Used Antipsychotic Medications*

	Association with QTc Prolongation	Association with Torsades de Pointes
High risk		
Thioridazine	+++	+++
Haloperidol (IV)	+++	+++
Ziprasidone	+++	+
Moderate risk		
Fluphenazine	++	-
Haloperidol (PO/IM)	++	++
Iloperidone	++	-
Paliperidone	++	-
Risperidone	+	+
Low risk		
Asenapine	+	-
Lurasidone	+	-
Olanzapine	+	+
Quetiapine	+	+
Minimal risk		
Aripiprazole	-	-

IV = intravenous; PO = orally; IM = intramuscularly.

* The relative risks for QTc prolongation may vary depending on dose, concomitant medications, and other medical illnesses.

with significant QTc prolongation, even in the setting of significant medical comorbidity.^{105,106}

Based on the above information, it is possible to stratify antipsychotic medications based on their propensity to prolong the QTc (Table 3). Stratification may help guide treatment decisions in those patients at higher risk for QTc prolongation and its associated arrhythmias.

Other Psychiatric Medications

Other psychiatric medications have been associated with QTc-prolongation. Lithium in concentrations above 1.2 mmol/L can prolong the QTc interval, though no cases of TdP have been reported.¹⁰⁷ Anticonvulsant mood stabilizing agents, including valproate, lamotrigine, carbamazepine, or oxcarbazepine, have not been found to cause QTc prolongation. Among sleep aids, trazodone has been associated with mild QTc prolongation, mainly in the setting of overdose.⁷⁰ Though stimulants may have other cardiac effects, such as tachycardia, there is no strong evidence to suggest that methylphenidate or amphetamines cause clinically significant increases in QTc,¹⁰⁸ while the effects of atomoxetine on QTc remain uncertain. Finally, there is no evidence to suggest that benzodiazepines cause QTc prolongation.

 CONCLUSION

Clinicians should be aware of the myriad risk factors for QTc prolongation in their patients and should be mindful of these when prescribing psychotropic medications. Unfortunately, although a link exists between QTc and TdP, this link is neither linear nor straightforward. Most experts do agree that a QTc above 500 ms represents a risk factor for TdP.

With respect to antidepressants, extant data—though limited—suggest that SSRIs are generally safe in patients with risk factors for prolonged QTc. However, citalopram use in at-risk patients might increase the propensity for QTc prolongation in a dose-dependent manner. The International Registry for Drug-Induced Arrhythmias Arizona Classification now lists citalopram on its “Torsades List,” escitalopram on its “Possible Torsades List,” and paroxetine, fluoxetine and sertraline on its “Conditional Torsades List.”¹⁰⁹ Resources such as this serve as a useful reference guide to clinicians, though they do not account for the risk–benefit analysis involved in complex psychiatric decision-making such as managing a patient with serious depression and heart disease.

Clinically, one reasonable approach may be to use sertraline for patients with cardiac disease and/or risk factors for QTc prolongation, given that this agent has few drug–drug interactions, has not been consistently linked to QTc prolongation, and has been the most studied agent in cardiac patients.^{59,110} Other SSRIs can be used in this population, especially if patients have current or prior good response to a specific agent; indeed, even citalopram use is reasonable in patients who have responded well or have few other options, as long as QTc is monitored at baseline and intermittently post-initiation and found to be <500 ms.

At this stage, there is no clear rationale for routinely obtaining electrolytes, other labs, or an ECG prior to initiation of an antidepressant. We would recommend obtaining an ECG, potassium, and magnesium before starting a patient with substantial risk factors for TdP (e.g., significant structural heart disease [such as prior myocardial infarction], history of non-TdP ventricular arrhythmia) on citalopram, and before starting any patient with prior TdP on any antidepressant. For patients with substantially prolonged QTc (e.g., over 550 ms), or when considering initiating citalopram in patients with multiple or substan-

tial risk factors for TdP, consultation with a cardiologist may be warranted.

Regarding antipsychotics, low-potency typicals, IV haloperidol, and ziprasidone may carry the highest risk, though there is limited evidence for actual adverse QTc-related outcomes with ziprasidone. Though limited evidence suggests that some atypical antipsychotics (i.e., olanzapine) may be less likely to prolong the QTc interval, this has not been rigorously studied. For patients with risk factors for QTc prolongation, QTc should be assessed at baseline and intermittently post-initiation when prescribing any antipsychotic.

For patients receiving parenteral haloperidol in the hospital for agitation or psychosis, it is prudent to monitor QTc at baseline, and then at least daily, and sometimes more frequently depending on the risk. If the QTc extends beyond 500 ms, potassium/magnesium should be repleted and the patient’s medication regimen should be examined for other potential QTc-prolonging agents, with consideration given to holding haloperidol until the QTc has dropped below 500 ms. Other options to manage acute agitation should be considered, including valproate, trazodone, and alternative antipsychotic agents, with the caveat that none of the antipsychotics typically used to treat agitation in the hospital have zero risk of QTc prolongation. When an alternative antipsychotic medication is used, it often is helpful to choose one which is more sedating (e.g., quetiapine or olanzapine) so that a lower overall dose can be used; this may reduce the risk of QTc prolongation. In some situations, however, the risk of self-injury or harm to others because of severe agitation may outweigh the risk of arrhythmia, suggesting an indication for continuation of IV haloperidol with ongoing close monitoring.

In all cases, the decision on starting (and continuing) a psychotropic medication in a patient with increased risk for prolonged QTc should involve a careful risk–benefit analysis, taking into account indications for the medication, necessity for immediate treatment, and potential alternative strategies.

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