Prolongation of QTC is an electrocardiographic finding indicating prolongation of cardiac repolarization, which increases the risk for torsades de pointes, a form of ventricular tachycardia that can lead to sudden cardiac death.

Sudden cardiac death in the setting of antipsychotic treatment was first described in the 1960s with thioridazine; since that time, many other psychotropic medications have been associated with QTC prolongation.

This article reviews the electrophysiology of the cardiac cycle and the mechanism of QTC prolongation. Each major class of psychotropic medications also is reviewed, focusing on its propensity to prolong QTC and association with torsades de pointes (TdP) and sudden cardiac death. Other risk factors for TdP are also discussed. Examination of the management and treatment of QTC prolongation and TdP aims to assist the
clinician with an approach to patients receiving psychotropic medications.

Assessing the association between psychotropic medications and adverse outcomes related to cardiac arrhythmia is challenging. One factor that has been identified, however, is the association of risk with lengthening of the cardiac depolarization-repolarization cycle, a period generally measured by the corrected QT interval (QTc). It should be kept in mind that other factors, including age and prescription of nonpsychotropic medications, can also prolong QTc. Moreover, while the presence of multiple risk factors appears to increase the chance of fatal cardiac arrhythmias, largely TdP, the degree to which these risk factors influence overall clinical outcome is unknown.

Another consideration is whether certain QTc-prolonging medications are more apt to predispose the patient to TdP than others. Ziprasidone, for example, is known to significantly increase the QTc, but has a relatively low risk for TdP, and has produced no reports of sudden cardiac death. This implies that there are other factors besides QTc prolongation that can affect risk for TdP and, hence, for sudden cardiac death.

**MECHANISM OF QTc PROLONGATION**

To understand the implications of a prolonged QT interval, a brief review of electrophysiology is warranted. The electrocardiogram (ECG) provides a surface measurement of the dynamic electrophysiology of the cardiac cycle. The P wave represents atrial depolarization and the PR interval corresponds to atrial repolarization. Similarly, the QRS complex represents ventricular depolarization and the T wave, ventricular repolarization. The QT interval (time between the start of the Q wave and the end of the T wave) therefore represents the period of ventricular depolarization and repolarization. This interval is partially determined by heart rate (ie, faster heart rate shortens the QT interval), and a rate-corrected QT interval (QTc) is therefore necessary to accurately assess the true length of the QT interval.¹

Several formulas exist to calculate QTc. The most well-known and accepted formula is Bazett’s formula (see Figure 1), which is calculated by dividing the QT interval by the square root of the R-R interval.² Some studies have suggested that Bazett’s formula overestimates QTc in drug-induced QTc prolongation, but it still remains the most common method of manual calculation.³ Normal QTc values are below 440 msec. Borderline values are between 440 and 460 in men, 440 and 470 in women;⁴ values outside of these ranges are considered prolonged. Modern ECG machines automatically calculate and provide the corrected QT interval, also frequently employing Bazett’s formula.

Cardiac depolarization is prompted by an influx of sodium ions, driving the membrane from resting level to the threshold of an action potential. Repolarization is triggered by an efflux of potassium and calcium ions (see Figure 2). The role of potassium is much greater than of calcium, largely dependent on the delayed-rectifier potassium channel (IKr). This transmembrane channel senses voltage changes in the cell and plays an important role in returning cardiac cells to a resting state after depolarization.

While several potassium voltage-gated channels exist, nearly all drugs that cause QTc prolongation block the IKr channel. Prolonged repolarization can in turn cause early afterdepolarizations (EAD) that result in depolarizing oscillations across the cell membrane. These oscillations allow the cell membrane to reach threshold more readily, which increases risk for TdP and ventricular fibrillation.⁵

**TORSADES DE POINTES**

“Torsades de pointes” is from the French for “twisting of the points” and is represented by an undulating (twisting) pattern of the QRS axis on ECG (see Figure 3). Symptoms of TdP include palpitations, syncope, and seizure-like activity. Most cases of TdP are self-limited, but can progress to ventricular fibrillation and sudden cardiac death.⁶
Reported Cases of TdP

The average QTc was 567 (versus 532 in the other 15). Of the TdP patients, with drug-induced QTc prolongation, 90% of cases had QTc intervals greater than 500 msec, history of congenital long QT syndrome or prior drug-induced TdP. Risk of developing TdP also increases with higher blood levels of offending medications.

Drugs that inhibit the cytochrome p450 system (particularly 3A4 inhibitors) in addition to blocking IK channels can increase the likelihood of QTc prolongation by decreasing the clearance of offending medications. Evidence also suggests that patients with decreased cardiac repolarization reserve (as seen in cardiac hypertrophy, heart failure, bradycardia, paroxysmal atrial fibrillation, hypertension) are at higher risk of developing QTc prolongation and subsequent TdP.

Other Risk Factors for Development of TdP

Not all patients with QTc prolongation will develop TdP, and some will get TdP with relatively mild prolongation. Risk factors include female gender, age older than 60 years, electrolyte abnormalities (hypokalemia, hypomagnesemia), prolonged baseline QTc (> 450 msec), history of congenital long QT syndrome or prior drug-induced TdP.

Risk for sudden cardiac death remains unclear. In a case-control study of 495 patients taking both typical and atypical antipsychotics, 8% developed QTc prolongation, with thioridazine and droperidol having the highest risk. Of note, these drugs are also the most potent IK blockers of the neuroleptics.

However, some drugs that do not substantially prolong QTc can still cause TdP. According to the FDA Reporting System, between 2004 and 2007, 35 drugs were reported to have been associated with TdP (for a partial list, see Table 1).

Of note, these reports do not review medical comorbidity, clinical status, doses of drug, or underlying conditions for which the medications were used, so the magnitude of risk associated with these drugs cannot be estimated fully from these reports.

In 2009, a retrospective cohort study of 46,089 users of single typical and atypical antipsychotics, matched to 186,600 comparison subjects, reported that users of typical and atypical antipsychotic drugs had higher rates of sudden cardiac death than nonusers, with adjusted odds ratios of 1.99 (95% confidence interval [CI], 1.68-2.34) and 2.26 (95% CI, 1.88-2.72), respectively. Risk for sudden cardiac death was directly dose-related with higher doses of both typical and atypical antipsychotics.

A major limitation of the study, how-

TABLE 1.
Cases of Torsades de Pointes Related to Psychotropic Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reported Cases of TdP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>28</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>17</td>
</tr>
<tr>
<td>Risperidone</td>
<td>17</td>
</tr>
<tr>
<td>Citalopram</td>
<td>12</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>12</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>11</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>10</td>
</tr>
</tbody>
</table>

Source: Poluzzi et al.

Dangerous QTc Prolongation

The QT interval is not a perfect measurement for predicting TdP, but there is a relationship between lengthening of QT interval and increasing risk for TdP; while a definitive “cut-off” QTc value has not been established, a duration greater than 500 msec is commonly associated with an increased risk. This consensus threshold is based on data from both case reports and placebo-controlled trials. In 1997, a review by the British Committee for Proprietary Medicinal Products (CPMP) found that a change in QTc of greater than 60 msec relative to drug-free baseline and absolute QTc value of 500 msec were both associated with increase in risk for ventricular arrhythmias.

There has been limited systematic study of the prevalence of QT prolongation and subsequent risk for TdP. In a review of 189 reported cases of TdP, a large report that included 133 cases of non-antiarrhythmic, drug-induced TdP found 90% of cases had QTc intervals in excess of 500 msec. An observational study of 21 hospitalized patients with drug-induced QTc prolongation, six developed TdP. Of the TdP patients, the average QTc was 567 (versus 532 in the other 15).

History of QTc and Psychotropic Drugs

In 1963, the first report of TdP associated with thioridazine appeared. Twenty-six additional case reports of TdP in patients receiving 1,500 to 3,600 mg per day of thioridazine soon followed.

In the 1970s, ventricular arrhythmias were reported in patients taking tricyclic antidepressants in the setting of overdose and in patients with previous conduction abnormalities; in some cases serum levels were barely above therapeutic levels.

As more attention was paid to this outcome, the US Food and Drug Administration (FDA) placed a black-box warning that risk of QT interval prolongation and ventricular tachycardia increased in a dose-dependent manner in patients prescribed thioridazine.

FDA warnings have also been issued for pimozide, haloperidol, and droperidol. This was followed in 2011 when a black box warning was given to the selective serotonin receptor inhibitor, citalopram, at doses greater than 40 mg and in patients with known cardiac disease due to the risk for QTc prolongation.

Specific Psychotropics and QTc Prolongation

Although a clear association exists between antipsychotics and QTc prolongation, the risk for TdP and sudden cardiac death remains unclear. In a case-control study of 495 patients taking both typical and atypical antipsychotics, 8% developed QTc prolongation, with thioridazine and droperidol having the highest risk. Of note, these drugs are also the most potent IK blockers of the neuroleptics.

However, some drugs that do not substantially prolong QTc can still cause TdP. According to the FDA Reporting System, between 2004 and 2007, 35 drugs were reported to have been associated with TdP (for a partial list, see Table 1).

Of note, these reports do not review medical comorbidity, clinical status, doses of drug, or underlying conditions for which the medications were used, so the magnitude of risk associated with these drugs cannot be estimated fully from these reports.

In 2009, a retrospective cohort study of 46,089 users of single typical and atypical antipsychotics, matched to 186,600 comparison subjects, reported that users of typical and atypical antipsychotic drugs had higher rates of sudden cardiac death than nonusers, with adjusted odds ratios of 1.99 (95% confidence interval [CI], 1.68-2.34) and 2.26 (95% CI, 1.88-2.72), respectively. Risk for sudden cardiac death was directly dose-related with higher doses of both typical and atypical antipsychotics.

A major limitation of the study, how-

60 | Healio.com/Psychiatry

PSYCHIATRIC ANNALS 43:2 | FEBRUARY 2013
ever, is that people with serious mental illness also have a higher risk of mortality from other factors, such as cardiovascular disease, concurrent use of other proarrhythmic medications, and possibly behavioral risk factors, including substance abuse, poor self-care, and smoking.15,16

First-Generation Antipsychotics

Haloperidol

There have been a number of case reports and case series of QTc prolongation, TdP, and sudden cardiac death in patients taking haloperidol (oral or intravenous) at therapeutic doses, even in the absence of known cardiac risk factors.17 Haloperidol is often used in the intensive care setting for patients with agitation because of its parenteral availability. Most patients in this setting are monitored with frequent ECGs or continuous telemetry monitoring, allowing some investigation of the phenomenon.

In one ICU study, eight of 223 (3.6%) of patients treated with intravenous haloperidol developed TdP.18 The FDA issued a warning in 2007 stating that TdP and QT prolongation have been observed in patients receiving haloperidol, especially when the drug is administered intravenously or in higher doses than recommended.19

Overall, the risk for TdP and sudden death is much lower for haloperidol than with thioridazine. In a Finnish autopsy study, 49 cases of sudden cardiac death over a 3-year period (1985-1988) were noted to have been associated with the use of antipsychotics or antidepressants. Of the deaths, 6/49 (13%) cases of sudden cardiac death were associated with haloperidol (as compared with 28/49 or 57% with thioridazine).20

In a randomized controlled trial comparing QTc prolongation between pimozide, haloperidol and placebo, haloperidol and placebo were not associated with QTc prolongation, though pimozide was.21

Thioridazine

Because of the abundance of data associating thioridazine with TdP and sudden death at therapeutic dose, it now only recommended for use in schizophrenia in the context of failure to reach adequate response with other antipsychotic drugs.10

Pimozide

In the UK and US, recommendations for pimozide include monitoring of baseline and intermittent ECGs during treatment. This recommendation is based on numerous case reports of sudden cardiac death and serious cardiac events in patients taking pimozide.21

Droperidol

In 2001, the FDA issued the following warning regarding droperidol: “Cases of QT prolongation and/or torsades de pointes have been reported in patients receiving droperidol at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal.”22

Droperidol is now only recommended for patients with schizophrenia who have failed to show adequate response to other trials of antipsychotics. Droperidol has also been used as an anesthetic, and showed dose-dependent QTc prolongation in these patients.17

Chlorpromazine

The relationship between chlorpromazine and QTc prolongation is less well established, though a small number of cases of TdP have been reported.23

Second-Generation Antipsychotics

Sertindole

Sertindole was never approved for use in the US due to post-marketing studies showing an average increase of QTc duration of 21 msec. Twelve cases of sudden death were reported with sertindole,24 and in a randomized control trial comparing sertindole with haloperidol, 8% of sertindole-treated patients were found to have a QTc > 500 msec compared with none in the haloperidol group.25 Although sertindole has never been used in the US, it has been used in research studies as a comparison due to its predictable, dose-dependent effects of QTc.

Ziprasidone

Ziprasidone affects cardiac repolarization in a non-dose-dependent manner. In short-term, double blinded, placebo-controlled trials submitted to the FDA for drug approval, ziprasidone was shown to prolong QTc more than haloperidol, olanzapine, quetiapine, or risperidone, but less than sertindole and thioridazine.17 In 2000, Pfizer conducted a study (study 054) to measure QTc at peak drug exposure levels.26 The study included ziprasidone, quetiapine, olanzapine, risperidone, thioridazine, and haloperidol. Baseline ECGs were performed when participants were drug-free, after which they were randomly assigned to receive medications at the highest recommended dose (with the exception of thioridazine, due to its known effects on QTc). The data showed that thioridazine was the most likely to increase the QTc duration, with haloperidol being the least (see Table 2).
Unfortunately, it is difficult to extend these data to estimate risk of developing TdP and sudden death. For example, haloperidol was associated with only minor increases in QTc, but is known to cause TdP and sudden death. In a case series of 10 ziprasidone overdoses, there were no cardiac deaths, though QTc prolongation and TdP were reported. The highest dose ingested was 3,240 mg, which was associated with QTc prolongation of 20 msec. In a patient ingesting 1,880 mg of ziprasidone, there was no change in QTc.27

The Ziprasidone Observational Study of Cardiac Outcomes, or ZODIAC study,28 was a large-scale observational study comparing mortality associated with ziprasidone and olanzapine. This open-label trial of 18,154 patients with schizophrenia in naturalistic practice randomly assigned patients to treatment with ziprasidone or olanzapine.

The study found that an odds ratio for nonsuicide mortality within 1 year of initiating pharmacotherapy of 0.91 for ziprasidone (n = 9,077) versus 0.90 for olanzapine (n = 9,077). The authors concluded that despite known risk for QTc prolongation with ziprasidone, the study failed to show that ziprasidone is associated with an elevated risk of nonsuicidal mortality relative to olanzapine in real-world use.28

### Clozapine

Early reports of clozapine and sudden death were reported at a rate of 0.71% (4/561) in an observational study. However, an autopsy was done on just one of the sudden deaths, and a pulmonary embolism was found. The exact cause for the other three deaths is unknown. Since that time, there have been reports of QTc prolongation in a dose-dependent manner in patients receiving clozapine, but this prolongation is rarely pathological.

A 2005 review of adverse cardiac events associated with clozapine, clozapine is associated with a low (0.015% to 0.188%) risk of potentially fatal myocarditis or cardiomyopathy. Clozapine was not shown to be independently associated with pathologic QTc prolongation.29 No significant prolongation was seen in a 2011 study of 82 patients on therapeutic doses of clozapine after 18 weeks of treatment as compared to baseline.30 In the FIN11 study, national registries in Finland were assessed between 1996 and 2006 to determine the all-cause mortality in 66,881 patients with schizophrenia taking antipsychotics. According to the data, clozapine was associated with substantially lower all-cause mortality, including cardiovascular, than other antipsychotics.31

### Risperidone

Risperidone has been associated with minor increases in QTc in both therapeutic doses and in overdose.32,33 and TdP has been reported in cases both in risperidone monotherapy and in combination with other drugs.32,34 There is one report of sudden cardiac death in a 34-year-old woman shortly after she started risperidone. However, although the death may have been induced by risperidone, it was not associated with TdP or ventricular fibrillation.35

### Other Second-Generation Antipsychotics

An analysis of four randomized controlled trials (n = 2,700) using olanzapine showed that the incidence of maximum QTc > 450 msec was approximately equal to the incidence of QTc > 450 msec at baseline. No patients had a QTc > 500 msec during treatment.36 Quetiapine has been associated with minor increases of QTc.17 In a case report of a quetiapine overdose in a 14-year-old-male in which 1,900 mg was ingested, ECG revealed an increase of QTc from 444 msec to 500 msec, but this was not associated with an arrhythmia.37 Quetiapine has also been associated with several cases of TdP.13

In a 2010 meta-analysis comparing amisulpride, aripiprazole, olanzapine, sertindole, ziprasidone, and risperidone, aripiprazole demonstrated both smaller mean change in QTc (and a lower risk of QTc prolongation).38 No reports of sudden cardiac death have been associated with any of these medications.

### Antidepressants

#### Tricyclic antidepressants (TCA)

As reviewed above, cardiac depolarization is caused by an influx of sodium ions through selective sodium channels. Tricyclic antidepressants (TCAs) block these selective sodium channels and slow the rate of depolarization, widening the QRS and indirectly prolonging the QTc. This mechanism is quite different than the mechanism of drugs that block the potassium delayed rectifier channels. This is clinically important because TCAs have not been associated with sudden cardiac death in otherwise healthy adults. Their propensity to cause cardiac dysrhythmias seems to be limited to extremely high doses, overdose, children, and patients with pre-existing cardiac disease.39

At their peak use in the 1970s, TCAs

<table>
<thead>
<tr>
<th>Citalopram Dose</th>
<th>Increase in QT Interval (msec)</th>
<th>90% Confidence Interval (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/day</td>
<td>8.5</td>
<td>6.2-10.8</td>
</tr>
<tr>
<td>40 mg/day</td>
<td>12.6</td>
<td>10.9-14.3</td>
</tr>
<tr>
<td>60 mg/day</td>
<td>18.5</td>
<td>16-21</td>
</tr>
</tbody>
</table>

Source: Dear Healthcare Professional Letter

### TABLE 3.

<table>
<thead>
<tr>
<th>Citalopram Dose</th>
<th>Increase in the Corrected QT Interval for Citalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/day</td>
<td>Increase in QT Interval (msec) 90% Confidence Interval (msec)</td>
</tr>
<tr>
<td>20 mg/day</td>
<td>8.5 6.2-10.8</td>
</tr>
<tr>
<td>40 mg/day</td>
<td>12.6 10.9-14.3</td>
</tr>
<tr>
<td>60 mg/day</td>
<td>18.5 16-21</td>
</tr>
</tbody>
</table>

Source: Dear Healthcare Professional Letter
were associated with more than 1,000 overdose deaths yearly. Due to these safety concerns, TCAs are no longer used as first-line agents to treat depression, but still have clinical uses in treatment-resistant depression and obsessive-compulsive disorder. The issue of sudden unexplained death in children is largely unresolved due to the lack of double blind, randomized control trials. Due to this fact, TCAs are not first-line in the treatment of childhood psychiatric disorders.

Selective Serotonin Reuptake Inhibitors

Citalopram

In 2007, case reports began to accumulate with QTc prolongation and TdP with use of citalopram. The first case report cited TdP in an elderly male with severe medical illness. The FDA then conducted a QT study assessing the effects of 20 mg and 60 mg doses of citalopram on the QT interval in adults. In this randomized, multicenter, double blind, placebo-controlled, crossover study, 119 participants received citalopram 20 mg per day, citalopram 60 mg per day, or placebo (see Table 3, page 62). Data from this study revealed a dose-dependent increase in QT intervals.

This evidence, in addition to the reported cases of TdP, led the FDA to place a black box warning on the drug in August 2011. To date, there are no confirmed cases of sudden death associated with citalopram. However, there is one case report in which a 24-year-old female died of ventricular fibrillation while taking citalopram. Blood levels revealed a toxic level of citalopram, but an atrioventricular (AV) node tumor was found on autopsy.

Escitalopram

To date, there is one case report in which an otherwise healthy female developed QTc prolongation after receiving escitalopram 5 mg for 2 days. QTc prolongation was also reported in a 34-year-old female who ingested approximately 300 mg to 400 mg in a suicide attempt. In addition to escitalopram, lithium was also ingested (see below). Maximum QTc was below 500 msec, despite the significant amount of the drug ingested.

Trazodone

Trazodone has been associated with both QTc prolongation and death in overdose. In a case report, QTc was increased to 631 msec in a 30-year-old female, but did not progress to TdP. In a fatal overdose, the patient died of multiorgan failure within 24 hours of ingestion, though it is unknown whether death was related to cardiac dysfunction.

Other Antidepressants

Other antidepressants are considered to be generally safe and carry no known risk for sudden cardiac death. A cohort study examining the association between exposure to antidepressants and emergency department or inpatient admission for sudden cardiac death and ventricular arrhythmia compared 11 antidepressants to paroxetine (due to its known cardiac safety profile), finding that only mirtazapine had a statistically significantly greater sudden death risk (hazard ratio [HR] = 1.26; 95% CI, 1.11-1.42). However, baseline differences between mirtazapine users suggest that this finding may be attributable to differences in clinical status at baseline.

Venlafaxine has not been associated with TdP or sudden cardiac death at therapeutic doses, but arrhythmias have been reported rarely in some cases of overdose. Cohort studies of duloxetine or bupropion have failed to show an association with adverse cardiac events or sudden cardiac death.

Mood Stabilizers

Lithium

The effect of lithium on QTc is not fully understood when compared with antipsychotics or certain antidepressants. ECG changes, including transient ST elevation and arrhythmias, have been described in patients with lithium toxicity and in overdose. At therapeutic levels, lithium has been associated with cardiac arrhythmia, hypotension, peripheral circulatory collapse, sinus node dysfunction with severe bradycardia, and an unmasking of Brugada-like syndrome. (Brugada syndrome is a rare, genetic, primary electrical disease, involving L-type calcium channels, which is associated with a risk of syncope and sudden cardiac death.) Most cases of cardiac arrhythmias and sudden cardiac death are thought to be secondary to a Brugada-like syndrome, rather than QTc prolongation and TdP secondary to delayed-potassium channel blockade.

Other Anticonvulsant Mood Stabilizers

Neither valproic acid, carbamazepine, nor lamotrigine appear to be associated with QTc prolongation, TdP, or sudden cardiac death. One case report exists in which a Brugada-like syndrome developed in a woman with lamotrigine toxicity. There has been some evidence that referred to possible connection between anti-epileptic drugs increasing risk for sudden death (especially carbamazepine) in children with epilepsy, but this evidence is tenuous with no confirmations that death were cardiac in origin.

MANAGING QTc RISK

To evaluate the risk for QTc prolongation and associated arrhythmias, both patient history and risk factors should be assessed. Age, gender, underlying psychiatric diagnosis, and prior treatment response are good starting points. For example, an elderly female patient with dementia being treated for agitation carries a very different risk profile compared with a young male with schizophrenia. History should focus on
comorbid medical illnesses (ie, cardiac disease, hepatic impairment), concomitant medications (especially diuretics and other drugs known to increase QT interval), personal history of congenital long QT syndrome (LQTS — a genetic defect in the Ikr channels), and family history of sudden death. If risk factors are present, it would be reasonable to obtain a baseline ECG prior to starting pharmacotherapy. If QTc is less than 440 msec, then intermittent monitoring (every 3 to 6 months) of QTc interval during therapy could be considered. If QTc is in the borderline range, a careful risk-benefit analysis and consideration of alternative treatments is necessary.

There are no absolute contraindications to starting a known QT interval-prolonging medication, but careful monitoring, informed consent and patient education of the signs and symptoms of TdP is necessary. If baseline QTc exceeds 500 msec, it would be prudent to refer the patient to a cardiologist for evaluation. The benefits of treatment may still outweigh the risks; certainly the risks of untreated or undertreated psychiatric illness must be taken in to consideration.

In the hospital setting, daily ECGs or continuous telemetry monitoring could be considered while on treatment of QTc prolonging medications (especially antipsychotics), but no data have yet shown that this promotes earlier detection of fatal arrhythmias. Modifiable risk factors can also be closely monitored and managed in the hospital setting (ie, correcting electrolyte abnormalities).

A careful investigation of patient’s medication regimen should also be performed and other QT-prolonging medications discontinued. Another strategy to decrease risk of developing TdP is to administer medications more frequently but at lower doses, because higher serum drug concentrations appear to be another risk factor. For example, in a medically compromised patient, giving haloperidol 0.5 mg four times a day may be preferable to haloperidol 2 mg once per day.

CONCLUSIONS

Many psychotropic medications have been associated with QTc prolongation, and it is important to understand the risk for each individual and the data behind risks linked to specific medications. The high morbidity and mortality resulting from untreated psychiatric illness is not reviewed in this article, but is an important consideration when determining risks and benefits and reviewing them with patients and families.

Overall, there are very limited data to suggest that QTc prolongation in patients with schizophrenia on neuroleptics represents a clinically significant risk in the absence of other risk factors. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, no adverse events were associated with the mild increase of QT intervals measured.59 However, off-label use of neuroleptic medications, especially in the elderly or demented patient population can be dangerous and careful risk versus benefit analyses must be undertaken, in close communication with patients and families and with appropriate monitoring.

REFERENCES

20. Mehtonen OP, Aranko K, Malkonen L, Vaapatalo H. A survey of sudden death associated with the use of antipsychotic or anti
49. Mansfield JK, Kennedy SH. Current use of venlafaxine not associated with excess risk of sudden cardiac death or near death compared with fluoxetine, citalopram or dosulepin. Evid Based Ment Health. 2010;13(3):89.