A focus on QTc monitoring in patients receiving psychotropics, especially when multiple medications are prescribed.

**Premiere Date:** March 20, 2016  
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This activity offers CE credits for:  
1. Physicians (CME)  
2. Other

**ACTIVITY GOAL**  
This article focuses on the importance of QTc monitoring in patients receiving psychotropics, especially when multiple medications are prescribed.

**LEARNING OBJECTIVES**  
At the end of this CE activity, participants should be able to:  
- Explain the need for QTc monitoring  
- Identify the medications that are most likely to increase the risk of QT prolongation  
- Define the patient characteristics that increase the risk of QT prolongation  
- Describe the lifestyle factors that exacerbate the risk of QT prolongation and cardiovascular effects

**TARGET AUDIENCE**  
This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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- Megan B. McCorkle, BA, has no disclosures to report.
- Nicole B. Washington, DO, has no disclosures to report.
- Nancy C. Brahm, PharmD, MS, BCPP, CGP, has no disclosures to report.
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Psychotropic medications, such as antipsychotics and antidepressants, prolong ventricular repolarization in varying severity. Patients with psychiatric disorders frequently have coexisting medical conditions and substance use disorders and may require multiple medications. In addition, they may exhibit multiple independent risk factors for cardiac disturbances.\textsuperscript{1} QT prolongation during medication exposure is of particular importance because it is a marker for disruption in cardiac conduction. The QT interval represents the amount of time for ventricular depolarization and repolarization and is measured from the start of the QRS wave complex to the end of the T wave. The QT interval varies secondary to heart rate. For this reason, the corrected QT interval (QTc) is used for heart rates that exceed 60 beats per minute. The QT interval time is approximately equal for men and women (< 420 msec vs < 430 msec).\textsuperscript{2,3}

**CASE VIGNETTE**

MF is a 52-year-old white woman who has bipolar I disorder with mania. She receives community-based integrated multidisciplinary services for medication management and adherence as well as social and psychiatric support. MF smokes a pack of cigarettes daily and has a history of alcohol abuse. She has no history of medication allergies or cardiac conduction abnormalities. During a recent inpatient psychiatric admission, a baseline electrocardiogram (ECG) showed a QTc interval of 507 msec. MF’s medication regimen includes haloperidol decanoate 200 mg intramuscular injection every 3 weeks, divalproex sodium extended-release 500 mg tablet once daily, fluvoxamine 50 mg tablet once daily, hydroxyzine 50 mg tablet once daily, tramadol 50 mg tablet 4 times daily, and zolpidem 10 mg once nightly at bedtime.

MF represents a typical patient seen in the psychiatric inpatient setting. She exhibits multiple independent risk factors for QTc prolongation: female gender, history of alcohol dependence, and current tobacco use. Individually, the medications prescribed for MF are not significant for lengthening the QT interval\textsuperscript{1,2}; however, the combination of these psychotropic medications predisposes MF to life-threatening cardiac disturbances. Her baseline QT interval of 507 msec represents a risk factor for arrhythmia. Although all medications were continued to achieve psychiatric stabilization, increased cardiac monitoring was used during the hospitalization because of MF’s baseline QT interval.

**QTc/JT interval**

The JT interval is more representative of cellular conditions of the heart that result in repolarization.\textsuperscript{4} Medications that prolong QTc also increase cardiac repolarization, which may heighten the risk of re-entrant arrhythmias, such as torsades de pointes (Tdp), and which could be observed on the JT interval. Current data do not report the JT intervals; however, future studies that include this value would help inform practitioners about the risk of Tdp.\textsuperscript{4,5}

The QT interval remains a reliable measure for cardiac action potentials and is easily assessed by ECG. QTc is useful to clinicians because variability in action potential duration is a key predictor of cardiac disturbances; a faster heart rate is associated with shorter QT intervals.\textsuperscript{1,2} QTc prolongation above 500 msec is a risk factor for Tdp (polymorphic ventricular tachycardia), a life-threatening ventricular arrhythmia that requires immediate intervention. (The Figure shows the cardiac action potential.)

**Pharmacological variables**

The mechanism of action of psychotropic medications primarily leads to lengthening of the QT interval via inhibition of potassium channels.\textsuperscript{1} In combination, psychotropic medications can predispose patients to arrhythmias due to excessive potassium channel inhibition that affects repolarization.

The hERG gene is accountable for the expression of potassium channels involved in myocyte repolarization.
repolarization. Genomic studies have identified genome variants that predispose patients to medication-induced QTc prolongation. These rare mutations increase a patient’s risk of TdP secondary to medication therapy. Studies have shown that patient-specific genetic factors alter drug metabolism. Consequently, genetic screening may provide information that will help with successful medication selection. Because of the extensive interplay between patient-specific considerations and medication-specific properties, careful selection of psychotropic medication should be determined on a case-by-case basis.

Medications known to produce QTc prolongation include antidepressants and antipsychotics. Prescribers should evaluate the appropriateness of treatment and the need for additional cardiovascular monitoring when these medications are used. Patient-specific factors should be assessed in each case. Independent risk factors for the development of QTc prolongation include, but are not limited to, age older than 65 years, female gender, existing cardiac condition or abnormality, electrolyte disturbances, concurrent psychiatric disorders, and excessive plasma concentrations of the medication in question. Comorbidities, such as substance use (including alcohol) disorders, have synergistic, rather than additive, effects on QT interval lengthening, which probably results from increased cardiotoxic activity. The Table provides a complete list of risk factors for QTc prolongation.

**Antidepressants**

**TCAs**

TCAs cause QTc prolongation via QRS widening. TCAs block sodium, chloride, and potassium channels. Amitriptyline, doxepin, imipramine, desipramine, and nortriptyline all prolong the QT interval. Maprotiline is associated with the highest QTc prolongation, lengthening the QTc interval by 17 msec. Clomipramine exhibits the least QTc prolongation. All of these agents have been implicated in TdP. TCAs should not be used in patients with cardiovascular complications or abnormalities because of the potential for adverse cardiac events.

**SSRIs**

SSRIs are more frequently used than TCAs. SSRIs have been implicated in dose-dependent QTc prolongation when administered at supratherapeutic doses. Citalopram is the most controversial because of its degradation into the active metabolite, desmethylicitalopram, which appears to have a toxic effect on cytochrome P-450 (CYP450) 2D6 ultrarapid metabolizers. Current FDA recommendations limit citalopram to a total daily dose of 40 mg, although these dosing parameters may err on the conservative side. The data conflict regarding whether citalopram alone is the causative factor of QTc prolongation. The mechanism of action of psychotropic medications primarily leads to lengthening of the QT interval via inhibition of potassium channels.

The FDA dosing restriction of citalopram has not been extended to escitalopram. Escitalopram and sertraline lengthen the QT interval by 7 msec and 3 msec, respectively. Fluoxetine poses a higher risk in the presence of independent risk factors; however, QTc prolongation has not been observed with fluoxetine. Paroxetine has not been implicated in QTc prolongation. Interestingly, fluvoxamine demonstrated QTc shortening at a measured -5 msec.

**Other agents**

Vilazodone is a serotonin agonist/antagonist. It has not been implicated in ECG abnormalities; however, strong CYP P450 inhibitors can increase serum concentrations to supratherapeutic levels. Desvenlafaxine has not been found to cause significant QT prolongation. Because of limited data, further studies are required to confirm the safety and efficacy of these agents when combined with other psychotropic medications.

Duloxetine and venlafaxine are serotonin and norepinephrine reuptake inhibitors. Duloxetine has not been implicated in QTc prolongation. Venlafaxine should be avoided in patients with cardiovascular disease because of potential cardiotoxicity. Newer agents such as levomilnacipran and milnacipran have not exhibited significant effects on cardiac repolarization. However, data are limited on these agents, and further research is required.

Bupropion, a norepinephrine reuptake inhibitor, has not been implicated in QTc prolongation. Mirtazapine increased QTc prolongation by roughly 3 msec, although it is significantly higher in cases of overdose. Trazodone has shown mild QTc prolongation, most notable in cases of overdose.

**Antipsychotics**

**Typical antipsychotics**

Phenothiazines have the potential to be arrhythmogenic and are more likely to result in TdP than other psychotropic medications; the highest risk of producing QT prolongation was seen with thioridazine. Caution should be exercised when prescribing these medications to patients with
existing risk factors. Low-potency antipsychotics, such as chlorpromazine, lengthen the QT interval in a dose-dependent manner (chlorpromazine caused TdP only at high doses). Additional monitoring of the QT interval is recommended with thioridazine or chlorpromazine. Haloperidol, a high-potency antipsychotic, increases the risk of QTc prolongation—the intravenous formulation poses the highest risk. Geriatric patients are at increased risk for QTc prolongation with any formulation; thus, additional monitoring of QT interval lengthening in this population is warranted.

Other high-potency antipsychotics and agents with related structures, such as pimozide and fluphenazine, have been implicated in significant QTc prolongation. Droperidol, a butyrophenone, has also been seen to prolong the QTc interval. Droperidol is of highest concern when used in combination with other known QTc-prolonging medications. Pimozide and droperidol can cause TdP.

Atypical antipsychotics
As a class, atypical antipsychotics are associated with less QTc prolongation potential; however, there is no indication that they pose less risk of TdP. Ziprasidone causes significant QTc prolongation. Long-term use of this agent is associated with the most significant QTc prolongation: 20 msec. Ziprasidone extends the duration of repolarization in a dose-independent manner. Minor QTc prolongation has been reported with olanzapine and risperidone, when either is used as a single agent or at low daily doses (ie, < 20 mg olanzapine; < 4 mg risperidone). The QTc prolongation potential of lurasidone is similar to that of olanzapine. However, the trials were small, and further research is needed. Available data suggest that lurasidone has better patient adherence because of once-daily dosing.

Olanzapine exhibited QTc prolongation and resultant TdP. Asenapine monotherapy did not exhibit QTc prolongation above 500 msec but did exhibit QT prolongation comparable to that of quetiapine. Olanzapine, risperidone, and quetiapine showed less QTc prolongation potential than did thioridazine.

Iloperidone and paliperidone have exhibited the highest risk of QT interval lengthening in observed data. QTc prolongation of roughly 9 msec in therapeutic trials of iloperidone has been reported; however, in the presence of concurrent paroxetine treatment, these values extended to 15.4 msec. Strong CYP2D6 and 3A4 inhibitors, such as paroxetine and ketoconazole, added to iloperidone or paliperidone therapy will significantly raise antipsychotic blood levels and may result in an increased QT interval.

Clozapine is frequently reserved for treatment resistance because of the potential for adverse cardiac effects of myocarditis and cardiomyopathy. Clozapine is typically reserved for last-line therapy because it prolongs the QT interval in a dose-dependent manner and is associated with an increased incidence of TdP.

Lifestyle variables
Substance use disorders
Concurrent use of cocaine and alcohol results in cocaethylene, which has a synergistic cardiotoxic potential compared with individual alcohol or cocaine exposure. Clinicians should recognize these risk factors when they prescribe medications that can exacerbate existing cardiovascular risk. Chronic ingestion of alcohol has been observed to result in cardiac insult. The destruction of the autonomic nervous system is due to acetaldehyde, which is the toxic substance that causes QT interval lengthening. QTc lengthening predisposes alcohol-dependent patients to cardiac arrhythmia independent of electrolyte disturbance. Furthermore, a pharmacodynamic interaction occurs with acute alcohol ingestion that inhibits the metabolism of TCAs. When TCAs are not cleared, increased serum concentrations can potentially result in medication overdose.

Decreased liver function poses additional risk for adverse events due to decreased metabolic activity. Consider the influence of alcohol, in combination with psychotropic agents, on QTc prolongation.

Tobacco use
Tobacco use, particularly smoking, is common among psychiatric patients. It is important to encourage patients and inform them of resources available for tobacco cessation. Components of tobacco smoke enhance cardiovascular risk as an independent risk factor for QTc prolongation. Nicotine has the potential to alter CYP450 metabolism and further lengthen QT intervals (although these data are not conclusive in human models).

Conclusion
Patients who receive psychotrophic treatment are at increased risk for QTc prolongation, and multiple medications further increase risk. The synergistic effect of QT-prolonging agents in combination with
patient-specific factors highlights the importance of discretion in therapeutic management. Identifying potential risk factors will aid providers in selecting the most appropriate drug therapy.

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Table – Risk factors for QTc prolongation

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<th>Risk Factors for QTc Prolongation</th>
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<tr>
<td>Age over 65 years</td>
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<td>Preexisting cardiovascular disease</td>
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<tr>
<td>Obesity</td>
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<td>Aortic valve disease</td>
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Figure. Observed cardiac action potential from ECG

Table – Risk factors for QTc prolongation

Evaluating a Patient With QTc Interval Prolongation Risk

Disclosures:
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