

# Psychotropics and Sudden Cardiac Death

TUAN ANH DINH; JESSICA L. GÖREN, PHARMD, BCPP

## ABSTRACT

Over the past two decades there has been a large increase in the number of patients prescribed psychotropic medications. Many of these agents are associated with QTc prolongation which is considered a marker for increased risk of sudden cardiac death due to malignant arrhythmias such as Torsades de pointes (TdP). Psychotropics rarely lead to sudden death in healthy individuals on a single QTc prolonging medication. However, factors such as polypharmacy, recent initiation of a QTc prolonging medication, bradycardia, electrolyte abnormalities and preexisting arrhythmias increase the likelihood of psychotropic-induced sudden cardiac death. Therefore, clinicians must recognize which psychotropics and risk factors are associated with increased risk in order to minimize the risks of psychotropic QTc prolongation.

**KEYWORDS:** psychotropic, side effect, cardiac, QTc, Torsades, arrhythmia

## INTRODUCTION

There has been increasing concern regarding the cardiac side effects of psychotropics. Some psychotropic medications increase the risk of sudden cardiac death. However, these drugs are important for many patients. Therefore, it is important to assess cardiac risks associated with psychotropics. This article will summarize these effects and provide recommendations on cardiac risk assessment for patients treated with psychotropic medications.

### The QT interval and Torsades de pointes

The QT interval is the measure of cardiac conduction speed that starts from the beginning of a QRS wave and ends with the T wave on an electrocardiogram (ECG). Usually the length of the QT wave decreases as heart rate increases, so a corrected value (QTc) is used to assess cardiac conduction. QTc is measured in milliseconds and the average QTc is between 430 and 450 milliseconds. (Table 1) Females usually have a slower cardiac conduction rhythm than males and thus a longer QTc.<sup>1-3</sup> The QTc varies by up to 10 milliseconds during the course of a day with maximal intervals during the first few hours of awakening.<sup>4</sup>

Prolonged QTc intervals can lead to ventricular tachyarrhythmia and TdP. While the true incidence of TdP is unknown, the number of reported cases is low. Over a period of 15 years only 761 cases were reported to the World Health Organization.<sup>5</sup> Therefore, prolonged QTc has become a surrogate marker for TdP.<sup>1,5</sup>

It is important to note that drug induced QTc prolongation alone rarely leads to TdP. A review of population studies reported prolonged QTc was associated with TdP in patients with preexisting cardiovascular disease, but not with healthy patients.<sup>6</sup> Rather TdP is most likely to occur when prolonged QTc is combined with at least two risk factors such as electrolyte abnormalities, bradycardia or congenital cardiac abnormalities. The most important risk factors appear to be preexisting heart disease, age >65 years, and female sex.<sup>6,7</sup> Torsades de pointes may be increased in hospitalized patients because hospitalized patients are more likely to have risk factors such as heart disease, advanced age, bradycardia or electrolyte disturbances than outpatients.<sup>8</sup>

QTc prolongation is often dose dependent but the maximal effect of many drugs is limited.<sup>6</sup> Therefore, massive drug overdoses of QTc prolonging medications do not necessarily result in severe QTc prolongation or TdP.

### Psychotropics and QTc

Psychotropics, such as antidepressants and antipsychotics, affect the heart by blocking certain potassium channels. This leads to a blockade of type  $I_{Kr}$  (a fast potassium channel in the heart), causing a delay in repolarization and thus QTc prolongation.<sup>1,2</sup> This is accomplished via either HERG (Human ether-a-go-go Related Gene) blockade or abnormal protein trafficking for HERG. Almost all drugs which can induce TdP block HERG, while a few indirectly affect HERG function.<sup>1,2</sup> Drugs which prolong the QTc by alternate means are less likely to result in TdP.

Table 1. Average QTc<sup>1-3</sup>

	MEN	WOMEN
NORMAL	<430	<450
BORDERLINE	431-450	451-470
PROLONGED	>450	>470

Population-based studies indicate there is a two- to three-fold increased risk of sudden cardiac death in patients taking non-cardiac QTc prolonging medications.<sup>6,7</sup> Antidepressants are the psychotropic class most commonly associated with TdP (9%).<sup>7,9,10</sup> For antipsychotics, it is estimated there are 10-15 sudden cardiac deaths/10,000 years of observation, and only a small proportion of these deaths are likely attributable to TdP.<sup>11</sup> Risk of QTc prolongation with other psychotropics such as benzodiazepines and anticonvulsants is low.

Risk of sudden cardiac death is highest in the first 90 days of initiating, increasing the dose or adding an interacting medication. Female sex, polypharmacy, congenital long QT syndrome, electrolyte abnormalities, increasing age and higher doses of QTc prolonging medication all increase the likelihood of experiencing drug induced QTc prolongation.<sup>10,11</sup>

While studies have reported psychotropics increase patients' average QTc, the QTc interval typically remains less than 500 milliseconds, considered a clinically relevant indicator of TdP risk.<sup>4,10,11</sup> In patients with schizophrenia a reported history of arrhythmia and other metabolic factors had greater influence on the prolongation of QTc interval than use of psychotropics alone.<sup>9</sup> Therefore, it seems likely psychotropic induced QTc prolongation is unlikely to lead to TdP in the absence of other risk factors.

#### Antipsychotics and QTc

Although large epidemiologic studies have reported first- and second-generation antipsychotics are associated with increased risk of sudden cardiac death, the absolute risk of death remains quite low.<sup>1,3,6,7,9-14</sup> In addition, while numerous antipsychotics have been shown to prolong the QTc (Table 2), relatively few antipsychotics have been associated with TdP.<sup>1,3,13,14</sup> Thioridazine, pimozide and ziprasidone are known to cause the greatest QTc prolongation while quetiapine, risperidone and clozapine are associated with lower risk.<sup>1,12-14</sup> Significant evidence of antipsychotic induced TdP is only associated with mesoridazine, thioridazine and haloperidol.<sup>1,15</sup> While haloperidol has been linked to TdP, risk is much lower than with thioridazine.<sup>1,13,14</sup> Aripiprazole appears to have a lower risk of QTc prolongation, although there is one well documented case report of QTc prolongation with low dose monotherapy aripiprazole.<sup>13-16</sup>

#### Antidepressants and QTc

Large epidemiologic trials have demonstrated an elevated risk of sudden cardiac death with tricyclic antidepressants (TCAs). TCAs have been shown to prolong the QTc 10-25 ms and cases of TdP have been reported with most, although not all, TCAs.<sup>13-15</sup> Newer antidepressants have less risk of QTc prolongation and sudden cardiac death compared with TCAs although QTc prolongation of 5-12 ms and cases of TdP have been reported for citalopram, fluoxetine and paroxetine.<sup>13-15</sup> Reports of QTc prolongation are mixed with the serotonin norepinephrine reuptake inhibitors (SNRIs). However, for both SSRIs and SNRIs, risk appears to be greatest in patients

with preexisting risk factors or those with elevated blood concentrations due to over dose, high doses or drug interactions. Bupropion, mirtazapine and trazodone all appear to have minimal risk of QTc prolongation at typical doses.<sup>15</sup>

**Table 2.** Mean QTc prolongation and psychotropics<sup>12-15</sup>

DRUG	MEAN QTc (msec)
<b>ANTIDEPRESSANTS</b>	
TCAs	>16
Mirtazapine	5-8
Trazodone	5-8
Venlafaxine	4.7
Duloxetine	0
Fluoxetine	9-16
Citalopram	8-10
Escitalopram	4.5
Paroxetine	1 – 4
Fluvoxamine	0-2
Sertraline	0
Bupropion	0
<b>ANTIPSYCHOTICS</b>	
Thioridazine	25-30
Ziprasidone	5-22
Pimozide	13
Clozapine	8-10
lloperidone	9
Haloperidol	7
Quetiapine	6
Risperidone	0-5
Olanzapine	2
Asenapine	2-5
Aripiprazole	0

### Psychotropic Polypharmacy and QTc

The risk of QTc prolongation with antipsychotics and antidepressants is typically dose related.<sup>1,4,5,10</sup> Therefore any combination of medications which results in elevated concentrations of antidepressants or antipsychotics increases the likelihood of QTc prolongation. Conversely, any psychotropic that increases the concentration of non-psychotropic QTc prolonging medications increases the risk of drug induced arrhythmia. Additionally, the risk of sudden cardiac death is increased in patients on multiple QTc prolonging medications, whether the psychotropics are combined with other QTc prolonging psychotropic or non-psychotropic medications. Thus careful consideration should be given to utilization of psychotropic polypharmacy and combinations of psychotropics and non-psychotropic medications.

### Monitoring

Psychotropic drugs are known to affect the QTc interval and should be utilized with caution in patients with risk factors such as age >65, female gender, congenital long QTc syndrome, electrolyte abnormalities, polypharmacy and pre-existing cardiac disease.<sup>1,13-15</sup> For relatively healthy patients without preexisting risk factors, routine ECG monitoring should be considered for those with episodes of blackouts, fainting, seizures, or with unexplained lightheadedness, palpitations or dizziness.<sup>15</sup> A baseline ECG should be considered in patients who are on multiple QTc prolonging medications or on high risk medications such as thioridazine. An ECG recording should be obtained for patients with any risk factors before treatment with a QTc prolonging psychotropic is started and once the medications are at steady state. If the QTc is mildly elevated consider lowering the dose or utilizing another agent with less potential for QTc prolongation. In patient whose QTc exceeds 500 milliseconds or whose QTc increases >60 milliseconds when starting a new psychotropic consider discontinuation of QTc prolonging psychotropics or switching to agents with a lower propensity for QTc prolongation. Electrolytes should be monitored in patients taking diuretics or those with severe diarrhea, vomiting or other risk factors for electrolyte imbalances.<sup>1,13-14</sup>

### TREATMENT RECOMMENDATIONS

The risk of TdP is low in patients who are relatively healthy without cardiac disease. Therefore, for patients who do not have other risk factors, it is reasonable to use psychotropic medications that may prolong the QTc. For patients with prolonged QTc of <500 milliseconds at baseline, psychotropic medications are a reasonable treatment with ECG monitoring.

Since the risk is highest during the first 90 days after starting a medication, healthy patients on a stable regimen with a prolonged QTc of < 500 milliseconds can be continued on their current medication regimen. If the patient develops other risk factors, ECG is a useful tool for reevaluating the medication regimen. If the dose of a QTc prolonging

medication is increased, a pre- and post-baseline ECG will be useful in determining risk of the dose increase.

For patients with a prolonged QTc of  $\geq 500$  milliseconds, consider discontinuing any QTc prolonging medications and/or substituting with medications less likely to prolong the QTc. Also, consider consulting a cardiologist.

### SUMMARY

Since psychotropic-induced QTc prolongation is typically dose related, patients should be maintained on the lowest effective doses of psychotropics. Additionally, careful review for drug interactions should be conducted prior to adding any medications to ongoing psychotropic treatment. The risk of psychotropic-induced QTc prolongation is highest when a medication is started, reaches steady state or after dose increases. Therefore, patients successfully treated for >90 days are less likely to experience psychotropic induced arrhythmias unless there are changes in medication treatment or new risk factors. Sudden cardiac death is unlikely in patients without preexisting risk factors and is a rare outcome for those with risk factors. Even for patients with risk factors who may have a prolonged QTc that is < 500 milliseconds, treatment with a psychotropic may be reasonable with appropriate monitoring. Physicians should not be discouraged from psychotropic use unless patients have a contraindication, such as a cardiac arrhythmia or congenital long QT syndrome.

### References

- Huffman JC, Stern TA. QTc Prolongation and the Use of Antipsychotics: A Case Discussion. *Prim Care Companion J Clin Psychiatry*. 2003;5(6):278-281.
- Ponte ML, Keller GA, Di Girolama G. Mechanism of Drug Induced QT Interval Prolongation. *Current Drug Safety*. 2010;5:44-53.
- Yap YG, Cramm AJ. Drug Induced QT Prolongation and torsades de pointes. *Heart*. 2003;89(11):1363-1372.
- Nielsen J, Graff C, Kanters JK, Toft E, Taylor D, Meyer JM. Assessing the QT interval prolongation and its associated risks with antipsychotics. *CNS Drugs*. 2011;25(6):473-490.
- Darpo B. Spectrum of drugs prolonging QT interval and the incidence of torsades de pointes. *Eur Heart J (Suppl K)*. 2001;3:K70-K80.
- Montanez A, Ruskin JN, Herbert PR, et al. Prolonged QTc interval and risk of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. *Arch Int Med*. 2004;164(9):943-948.
- Astrom-Lilja C, Odeberg JM, Ekman E, Hagg S. Drug-induced torsades de pointes: a review of the Swedish pharmacovigilance database. *Pharmacoepidemiol Drug Saf*. 2008;17:587-592.
- Tisdale JE, Wroblewski HA, Overholser BR, Kingery JR, Trujillo TN, Kovacs RJ. Prevalence of QT interval prolongation in patients admitted to cardiac care units and frequency of subsequent administration of QT interval prolonging drugs. *Drug Saf*. 2012;35(6):459-470.
- De Bruin ML, Langendijk PN, Koopmans RP, et al. In-hospital cardiac arrest is associated with use of non-antiarrhythmic QTc-prolonging Drugs. *Br J Clin Pharmacol*. 2007;63:216-223.

10. Strauss S, Sturkenboom M, Bleumink G, et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. *Eur Heart J*. October 2005;26(19):2007-2012.
11. Nielsen J. The safety of atypical antipsychotics: does QTc provide all the answers? *Exp Opin*. 2011;10(3):341-344.
12. Harrigan EP, Micelli JJ, Anziano R, et al. A Randomized Evaluation of the Effects of Six Antipsychotic Agents on QTc, in the Absence and Presence of Metabolic Inhibition. *J Clin Psychopharmacol*. 2004;24:62-69.
13. Wenzel-Seifert K, Wittmann M, Haen E. QTc prolongation by psychotropic drugs and the risk of Torsades de Pointes. *Deutsches Arzteblatt*. 2011;108(41):667-697.
14. Alvarez PA, Pahissa J. QT alterations in psychopharmacology: proven candidates and suspects. *Curr Drug Saf*. 2010;5(1):97-104.
15. <http://www.torsades.org> accessed August 27, 2012
16. Nelson S, Leung JG. Torsades de Pointes after administration of low dose aripiprazole. *Ann Pharmacother*. 2013 [Epub ahead of print, Jan 29]

### Authors

\*Jessica L. Gören, PharmD, BCPP is Associate Professor, Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island; Instructor in Psychiatry, Harvard Medical School, Boston, MA; Senior Pharmacist Specialist, Cambridge Health Alliance, Cambridge, MA

Tuan Anh Dinh is a Doctor of Pharmacy Student, College of Pharmacy, University of Rhode Island. He is a candidate for graduation in 2014.

### Correspondence

Jessica L. Gören, PharmD, BCPP  
 University of Rhode Island  
 7 Greenhouse Road  
 Kingston RI 02881  
 617-806-8514  
[jgoren@uri.edu](mailto:jgoren@uri.edu)