PSYCHOTROPIC MEDICATION CARDIAC SIDE EFFECTS:
Focus on QT Prolongation and Torsades de Pointes

Justin Schreiber, DO, MPH, and Lee Berman, MD

Case Presentation: *During a busy clinic day, you see a 16 year old female for a first visit for depression. The patient and her family are interested in starting a medication. When asking about family medical history, his mother states that a cousin died suddenly at age 12. The family was told that the cousin had a genetic condition called long QT syndrome (LQTS). The patient has recently had an ear infection and is currently on amoxicillin/clavulanic acid. She is otherwise healthy and has never had an electrocardiogram (EKG) before. When getting her pulse, her heart rate is 60 - although on the lower side, she mentions she is an avid runner. Her mother had read that citalopram in high doses could cause heart problems and wondered if that was true. What would you tell her? Should you get an EKG? Does the teen need to be cleared by a primary care doctor or cardiologist before she can start a medication?*

Multiple decisions go into weighing the risks and benefits of starting a medication with a child, and one of the questions is how the medication will affect QT length. Most of the time it is not something we have to worry about because the medication is being prescribed to a medically healthy child with no significant family history. In such lower risk cases, QT prolongation may occur, but the amount is usually not considered dangerous.

The problem develops when there are existing risk factors for prolonging the QT interval, such as family history of sudden death or cardiac illness, using multiple medications that may affect cardiac conduction, or a history of long QT syndrome (LQTS). LQTS is rare, but may lead to torsades de pointes, a potentially fatal arrhythmia.

In this article we discuss why QT length matters to us, how psychiatric medications can prolong QT length, how to calculate the corrected QT (QTc), the risk factors that can cause a patient to have a baseline prolonged QT length, and when you need to do more, such as get an EKG or refer to a specialist.

Understanding the QT and QTc

We worry about the QT length because of its strong association with torsades de pointes, often referred to clinically as "torsades." Torsades is seen on an EKG as "twisting of the points" (see Figure 1), and it is associated with syncope and sudden death. For adults, the overall mortality rate is 10-17%.[1] Due to the strong association between torsades and QT length, the FDA has withdrawn or denied drug licenses based on QT prolongation more than any other reason in the last 10 years.[1]

"QT" is measured on an EKG from the initial deflection, reflecting the beginning of the QRS complex to the end of the T wave. The QT interval represents the onset of ventricular depolarization to repolarization, beginning with the rapid influx of sodium ions into the cardiomyocytes, associated with the outflow of potassium ions through the rapid and slow potassium channels.[2] The problem with looking at only the QT length is that it shortens as the heart rate increases, and the length needs corrected before clinical interpretation can begin.

There are standard methods used to deal with the dynamic nature of the QT interval and adjusting for the heart rate, allowing determination of a corrected QT interval, abbreviated "QTc". QTc is the standard measure when assessing the risk of QT prolongation.

Calculating the QTc is an important skill for prescribers. When approaching an EKG, it may be tempting to rely on the automated interpretation when available, but this can be inaccurate, particularly in special populations like children, or given variations in the beat-to-beat interval, such as with sinus arrythmia.[1] The general steps for reviewing the QT on an EKG are outlined below.

The first step is to measure the QT from the beginning of the QRS complex to the end of the T wave (see Figure 2).[4,13] The standard lead utilized is Lead II, as long as the T wave is clearly defined in this lead. Although there are different formulas, by far the most common approach is to calculate the QTc by using the Bazett's formula[1], which requires measuring the R-to-R interval of the beat before

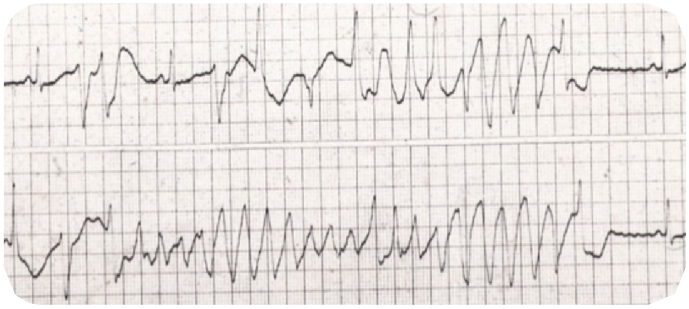

Figure 1. Torsades de Pointes on an EKG.

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the one used for QT assessment, and then dividing the QT by the square root of the R-to-R, measured in seconds ($QTc = QT/(R\text{-to-}R)^{1/2}$. To improve reliability, it is good to average multiple intervals. The upper limit of normal of the QTc does not vary with age and is 450ms for females and 440 for males.

Risk Factors for Torsades de Pointes

Though there is an association between QTc and torsades, it is thought that there are many other factors that could increase the risk of developing torsades. Table 1 reviews risk factors for torsades that are associated with common medical conditions. Some of these risk factors are acute and need to be taken into consideration when someone is sick or in the hospital. For example, certain electrolyte disturbances including hypokalemia, hypocalcaemia, and hypomagnesemia can influence the way the heart depolarizes and repolarizes, which will influence the length of the QT.[3]

Two of the most significant risk factors that increase the risk for QT prolongation and torsades when starting a medication are 1) another QT-prolonging medication, and 2) known history of LQTS.[4] Nearly 3% of all medications are found to prolong the QT in some way, so it is common for a patient to be placed on medications that prolong the QT (Table 2).

Most of the medications that influence QT block one of the repolarizing potassium channels, thus prolonging the repolarization phase. The exact relationship between degree of QT prolongation and risk of torsades not always known. For some medications the relationship is straightforward and the risk of torsades is directly associated with how much the QT is prolonged. For other medications, the risk of torsades can be high even with relatively small QT prolongation.[2] Thus, simply knowing the relative increase in QT is not enough to know a specific medication's risk for inducing torsades.

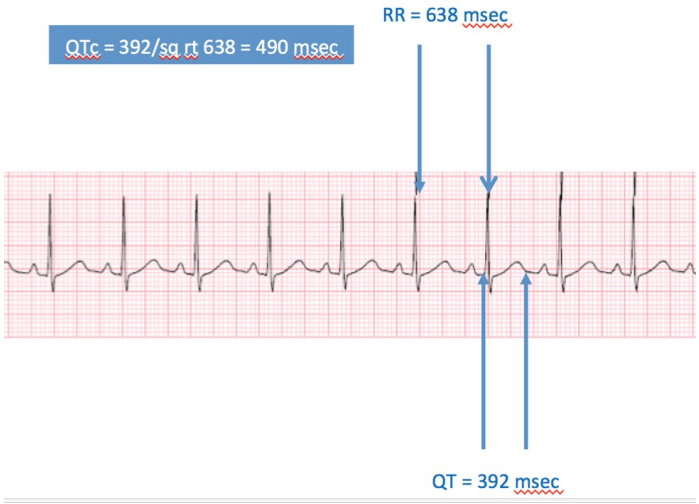

Figure 2. Calculating the corrected QT interval (QTc).

Medical history of QT prolongation is a risk of future QT prolongation. The extent to which it is a risk may vary depending on the individual. There is considerable individual variability. For example, a healthy child who was started on a medication known to prolong the QT may have a significant change, and another child with a history of LQTS who may have only a small change in QT.[5] As such, it is difficult to judge the relative importance of family history and prior QT prolongation history when prescribing. Nonetheless, identifying the influence of heritable factors, mostly through family history, is considered essential in determining associated risk of torsades. Clinicians must carefully record and consider family history, particularly a history of sudden death or unexplained syncope in young individuals under 40 years of age.

Additional information in labeling of medications that increase risk for torsades based on their prolongation of the QT is available, but there is little evidence that these labels alter prescribing practices.[5] To help people identify some of these medications, there are multiple websites, such as www.crediblemeds.org.[5]

Table 1: Risk Factors for Prolonged QT and Their Associated Conditions[1,3]

Risk Factor	Association
Electrolyte disturbances	Acute hypokalemia, chronic hypocalcemia, chronic hypokalemia, chronic hypomagnesemia
Medical history (endocrine)	Hyper/hypothyroidism, pheochromocytoma
Medical history (cardiac)	Congestive heart failure, myocarditis, complete atrioventricular block, severe bradycardia, sick sinus syndrome
Medical history (neurologic)	Stroke, head trauma, encephalitis, subarachnoid hemorrhage
Medical history (nutritional)	Alcoholism, liquid protein diet, starvation
Medical history (psychiatric)	Anorexia nervosa
Family history	Unexplained fainting spells or sudden death, epilepsy, sudden infant death syndrome (SIDS), unexplained auto accidents and drowning, Jervell Lange-Nielsen syndrome (autosomal recessive, rare), Romano-Ward syndrome (autosomal dominant, more common)

Table 2: Non-Psychiatric Medications That Prolong QT[1,2]

Type of Medication	Medication
Antibiotics/ antifungals	Macrolides, quinolones, pentamidine, chloroquine, halofantrine, fluconazole, ketoconazole, voriconazole
Antiarrhythmic agents	Quinidine, procainamide, disopyramide, sotalol, amiodarone, dofetilide
Diuretic	Furosemide
Estrogen antagonist	Tamoxifen
Opioid antagonist	Methadone

LQTS: A Heritable Risk

The heritable forms of LQTS can be due to mutations on several genes. LQTS type 1 (LQTS1) is due to a KCNQ1 (potassium voltage-gated channel) mutation and is the most common type of inherited LQTS. LQTS1 has two phenotypic presentations: Romano-Ward and Jervell Lange-Nielsen syndromes. Romano-Ward is by far the most common LQTS1 and is a heterozygous condition associated with one of the 13 genes and over 500 mutations that have been identified to cause this abnormality of repolarization. The Jervell Lange-Nielsen Syndrome is very rare and is the homozygous form, associated with sensorineural hearing loss and a much more severe clinical course, including high rates of death if left untreated.[7]

LQTS1 is the most common type of inherited LQTS. It responds well to beta blockers, and if those who have this diagnosis avoid all QT prolonging medications, their risk of sudden death is very small.[5] As with other individuals who have long QT, individuals with KCNQ1 mutation may be at increased risk for torsades when starting a QT prolonging medication.

Table 3: Antidepressant Medications:[6,10,11] Risks for QT Prolongation and Torsades de Pointes

Medication	Risk of Prolonged QT	Risk
Tricyclic antidepressants	Longest prolongation	Conditional risk
Citalopram	Longest prolongation	Known risk[a]
Escitalopram	Longest prolongation	Known risk
Mirtazapine	Moderate prolongation[b]	Possible risk[b]
Venlafaxine	Moderate prolongation	Possible risk
Sertraline	Least prolongation	Conditional risk
Fluoxetine	Least prolongation	Conditional risk
Paroxetine	Least prolongation	Conditional risk

Note: [a]Black box warning for doses >40mg; [b]Specifically seen in elderly

Psychiatric Medications and QT

Not all psychiatric medications are the same in their effect on QT prolongation. Citalopram, escitalopram, tricyclic antidepressants, and mirtazapine are associated with prolonged QT[8] and the influence is often related to dosage and/or method of administration. For example with citalopram, the greatest risk is thought to occur above 40 mg/day, and with haloperidol, there is an increased risk when given intravenously.

The data unfortunately are not always consistent, and controversy exists around the Food and Drug Administration (FDA) black box warning related to prolonged QT for citalopram doses greater then 40mg. The FDA advised not using citalopram above 40 mg based on a study showing an increase in the QT interval by 18.5 ms.[9] Subsequent studies have shown mixed results, reproducing or failing to reproduce the association.[9, 10, 11] However, most studies seem to support citalopram and escitalopram increasing the QT in a dose-related fashion. On the other hand, most studies on fluvoxamine, fluoxetine, paroxetine, and sertraline have shown very small or no increase in the QT or an association with torsades (Table 3).[11]

For antipsychotics, there has been a more consistent, significant association with QT prolongation and torsades (Table 4). Phenothiazines and other low-potency typical antipsychotics, such as thioridazine, pose the greatest risk

Table 4: Antipsychotic Medications[1, 6] and Risks for QT Prolongation and Torsades de Pointes

Medication	Risk of Prolonged QT	Torsades Risk
Haloperidol (IV)	Longest prolongation	Known risk
Haloperidol (PO/IM)	Medium prolongation	Known risk
Thioridazine (phenothiazines)	Longest prolongation	Known risk
Pimozide	Longest prolongation	Known risk
Ziprasidone[a]	Longest prolongation	Possible risk
Risperidone	Least prolongation	Possible risk
Olanzapine	Least prolongation	Possible risk
Quetiapine	Least prolongation	Possible risk
Paliperidone	Least prolongation	Possible risk
Iloperidone	Medium prolongation	Possible risk
Aripiprazole	Least prolongation	Possible risk

Note: IM = intramuscular; IV = intravenous; PO = oral
[a]Risk of torsades not found to be dose dependent

for QT prolongation and torsades.[2] As mentioned above, haloperidol has a higher risk when given intravenously, compared to orally or intramuscularly. Ziprasidone has an effect on repolarization, though this is not considered to be dose dependent.[2]

Putting It Together: Assessing Risk for Long QT

The American Heart Association provides recommendations for evaluating the risk of prolonged QT and what steps to take when considering a medication that may prolong the QT (Table 5). Other organizations also have similar recommendations, such as when to request a consultation (Table 5).

Table 5: Recommendations for Monitoring for Prolonged QT[1,12]

	American Heart Association Recommendations	McNally P, et al. Recommendations
Before starting a medication	Evaluate for family hx of LQTS or sudden unexplained deaths. Medical hx of palpitations, syncope, or near syncope. Medication history. Tell family about P450 affecting medications	Evaluate for family hx of sudden death, unexplained syncope or seizures, congenital heart disease, deafness, or electrolyte imbalances. Medication history. Tell families about P450 affecting medications.
If something on first evaluation is concerning	Refer to a pediatric cardiologist before starting medication	Baseline EKG and if abnormal refer to a pediatric cardiologist
Follow-up visit	Evaluate for new meds and physical exam of HR and BP	Repeat EKG if got one before, otherwise no repeat EKG, evaluate for new meds
When to get an EKG	If starting a TCA or phenothiazine and when at steady state	If abnormal history/risk factors and repeat when returning after starting the medication

Note: Hx = history; LQTS = long QT syndrome

The guidelines emphasize that one of the most important parts of an assessment is a thorough past personal and family medical history, including current and past medications. One should find out about any known previous EKGs showing prolonged QT, history of unexplained syncopal or light-headed events, and any other current or past medical concerns, such as symptoms suggesting electrolyte problems or eating disorders.[1,3,12]

When asking about family history, it is important to ask about LQTS, or syndromes known to have associated long QT, such as Jervell Lange-Nielsen Syndrome or Romano-Ward Syndrome, also anyone known to have had syncope, epilepsy, sudden infant death syndrome (SIDS), sudden death, unexplained accidents, such as fatal car accidents or drowning,[1,3,12]

It is also essential to ask about other medications that can prolong the QT (as mentioned above) or can either inhibit or activate the cytochrome P450 enzymes, thus influencing risk (Table 5). Medications known to influence cytochrome P450 enzymes may slow down the metabolism of the medication being prescribed, leading to a larger amount of active medication in the system, and a higher rate of side effects, including prolonging the QT.

It is also important to do a physical exam and assess for abnormalities, such as tachycardia or irregular heart rhythm. If abnormalities are present, the recommendation is either to get an EKG or refer to a cardiologist for an evaluation and EKG.[1,12]

Referral to Cardiology

Obtaining history from a primary care physician is indicated, especially if any cardiac risk factors are noted. This will allow the prescriber to understand the history better and may facilitate coordination of care with specialists. In addition, there are many common medications that influence the QT or the cytochrome P450 or other important enzymes, and communication with other providers is important. The primary care doctor should be able to help with medical history or other concerns that could influence making the decision to start a medication and could help with coordinating care with the pediatric cardiologist.

A referral to a cardiologist prior to initiation of medication is indicated with the QTc>460 ms.[1,3,12] Certainly, cardiology consultation should be recommended if the child has a known congenital heart defect or other factors suggesting heart disease (especially because this may affect how the EKG will be read). It is also important to monitor the patient closely, including follow-up EKGs and referrals once steady state of the drug is reached and with each change in dosing.[1,12]

Conclusion

Going back to the 16 year old with depression, there are clear risk factors that influence the decision to start a medication and what type of medication. Based on her family history and medications, discuss the risks and benefits of pharmacotherapy as well as alternatives. Next, if you decide a medication is warranted, she needs an EKG, and it would be advisable for the prescriber to consult with the pediatrician to confirm the history and discuss treatment. If the EKG or the history are concerning, then a referral to a cardiologist before starting the medication is indicated. In this case, with a relative with known LQTS, cardiology consultation is advised.

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