ACLP How To Guide: QT Prolongation

How to Evaluate and Manage Risk of QTc Prolongation

Learning Objectives:

1) Learn to stratify risk of QTc prolongation and torsade de pointes associated with psychotropic medications
2) Learn to monitor patients when QTc prolongation is present

Step 1: Understand the QT interval

- Represents ventricular activation and depolarization until the end of ventricular repolarization
- Depolarization mediated by sodium channels
- Repolarization mediated by sodium, calcium and potassium channels, but delayed potassium rectified current (Ik_r) is most important

Step 2: Measure the QT interval

- Measure from the initial deflection (R wave up or Q wave down) to the end of the T wave (where the downward deflection meets isoelectric line).
- Tips:
    - The QT interval measured by ECG machines may be inaccurate due to artifact or in cases of irregular rhythm; confirm with manual measure
    - QT interval is generally longest in V2 or V3; best to measure QT interval in these leads
    - QT interval shortens with faster heart rates (HR); when the QT interval is corrected for heart rate it is known as the QTc and is a more accurate measure of the interval
    - Calculating the QTc in patients with atrial fibrillation may be difficult and most methods involve taking averages of multiple QTc measurements
    - For ECGs with widened QRS (paced rhythm, BBB), the QTc calculated can overestimate the risk of TdP without appropriate corrections. There is a lack of consensus in the literature as to which correction is most accurate for estimating TdP risk.
        - Correcting for the wide QRS using a Linear correction [wide QRS adjustment: QTc (wide QRS adjusted) = QTc – [QRS−100]
        - The other approach is to use the JT interval, more commonly used for estimating risk in patients with BBB. This formula is JT = QT duration– QRS duration, and the JT interval = JT(HR+100)/518. For the JTI, a value of 112 or greater indicates repolarization prolongation and therefore increased risk for TdP
        - The Bogossian correction, tested in patients with LBBB, reduces the wide QRS by a factor of 0.485 (simplified to 0.50*QRS) and subtracts it from the QT interval: QTm = QT – 0.5*QRS

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Box 1: Calculating the QTc

Bazett formula: $QT_C = QT / \sqrt{RR}$.
Fridericia formula: $QT_C = QT / RR.^{1/3}$
Framingham formula: $QT_C = QT + 0.154 (1 – RR)$
Hodges formula: $QT_C = QT + 1.75$ (heart rate – 60)

*Bazett's Formula is the default on ECG machines. It is inaccurate at rates that differ significantly from 60 bpm.
** Linear correction formulas are recommended by the American Heart Association and are more accurate for heart rates differing significantly from 60 bpm.
Prolonged QTc is defined by QTc in men >450 milliseconds(ms), in women >460ms
Online calculators can be used for various different types of QTc formulas.

Step 3: Understand relative risk: QTc prolongation and cardiac morbidity

- QTc > 500 ms carries a 1.66 X increase in adverse cardiac events vs QTc = 400 (1)
- QTc > 550 ms carries a 2.14 X increase risk vs QTc = 400

Table 1: Risk Factors for Prolonged QT (2)

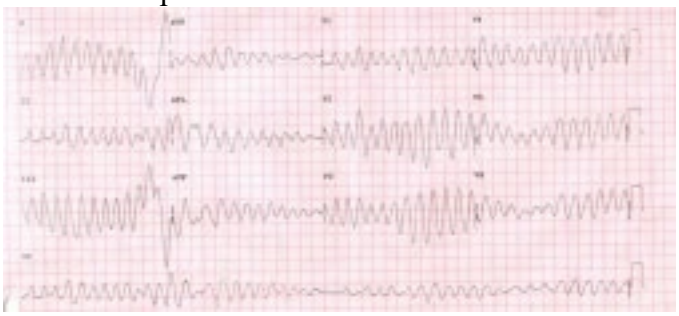
Categories of risk factors	Risk factors for prolonged QT
Sex	Female sex
Age	Increased age
Genetic	Long QT syndrome: caused by hundreds of mutations in at least 10 different genes
Electrolyte abnormalities	Hypokalemia Hypocalcemia Hypomagnesemia
Cardiac conditions	Prior arrhythmias Left ventricular dysfunction Mitral valve prolapse Congestive heart failure Myocardial infarction
State conditions	Bradycardia Sleep
Specific medications	See Table 2

Step 4: Understand torsades de pointe (TdP)

- Torsade de pointes (TdP) (illustrated in Figure 1) is a polymorphic ventricular tachycardia that can occur in the setting of a prolonged QTc interval. It is a "malignant" arrhythmia - often asymptomatic but also associated with syncope and sudden death.
- ECG warnings that might precede TdP

- Marked QT prolongation (> 500 ms)
- Premature ventricular contractions (PVCs)
- Short-long intervals (variation in R-R intervals)

Figure 1: Torsade de pointes



Step 5: Recognize mechanisms of medication-associated QTc prolongation

- Most meds block the IKr channel (rapid current-rectifying K channel).
- Drugs can lead to QT prolongation by cumulative effect of two QT prolonging agents.
- Drugs can increase risk by inhibition of CYP450 system, reducing clearance of QT-prolonging drugs.

Step 6: Become familiar with risk of QTc prolongation associated with specific medications

- Antidepressants and QTc prolongation
  - TCAs prolong the QRS interval via sodium channel blockade, and generally pose a risk of TdP only in overdose or in patients with pre-existing cardiac disease.
  - SSRIs as a class, are more studied and considered safer in patients with heart disease
  - All SSRIs, except paroxetine, have been associated in case reports with QT prolongation and/or TdP.
  - Citalopram carries FDA warning regarding QT prolongation and the risk for TdP
    - According to the current warning, citalopram is not recommended at doses > 40mg in healthy individuals, or doses > 20mg in those over age 60 or with hepatic impairment.
    - The risk is dose-dependent, with 60mg of citalopram causing an average prolongation of 18ms.
    - Citalopram separates out from other SSRIs in most studies.
    - Citalopram has not been demonstrated to be more associated with TdP or sudden cardiac death (SCD) than other SSRIs.
    - Reflexively reducing the dose of citalopram to 40mg or less may result in increased psychiatric morbidity and increased use of sedative/anxiolytics, without reducing risk of cardiac mortality.
  - Escitalopram also causes dose-dependent QT prolongation but to a lesser degree that is not felt to be clinically significant.
  - Among SSRIs, sertraline is the most studied in patients with cardiac disease, and is not thought to meaningfully prolong the QT

interval (2).
    - Bupropion has been associated with QT prolongation in overdose, but this is likely confounded by tachycardia.
    - Venlafaxine has been associated with mild QT prolongation but no greater rates of TdP.
    - There is no data to suggest that other antidepressants, including mirtazapine and duloxetine, are more or less risky in terms of QT prolongation than other antidepressants.
- Antipsychotics and QTc prolongation
    - Antipsychotic medications may prolong the QT via blockade of I_{Kr}.
    - Low-potency phenothiazines (chlorpromazine, thioridazine, mesoridazine) are the class most associated with QT prolongation and TdP.
    - Though haloperidol has been associated with QT prolongation, oral haloperidol has been shown to cause less QT prolongation than most other antipsychotics in head-to-head trials.
    - Intravenous (IV) haloperidol has an FDA warning related to QT prolongation and TdP
        - Based on 70 reports, with nearly all involving patients with other risk factors.
        - No head-to-head study has ever been conducted comparing IV and oral haloperidol.
    - Among atypical antipsychotics, ziprasidone and iloperidone have been associated with the greatest QT prolongation (3).
    - Quetiapine carries an increased warning related to QT prolongation, but does not clearly separate out from most other atypical agents.
    - Aripiprazole and lurasidone are associated with the least QT prolongation.
    - It is impossible to risk-stratify most antipsychotics with regards to QT prolongation and TdP.
- Other psychiatric medications and QT prolongation
    - Lithium in concentrations above 1.2 mmol/L can prolong the QTc, but no cases of TdP reported.
    - Valproate, carbamazepine, and oxcarbazepine are not associated with QTc prolongation.
    - Lamotrigine is associated with increased risk of QRS widening.
    - Stimulants are not associated with QT prolongation.
    - Benzodiazepines are not associated with QT prolongation.
- Certain non-psychiatric drugs are associated with QT prolongation. They are listed in Table 2

Table 2: Non-psychiatric drugs associated with QT prolongation

CLASSES	DRUGS
Class I Antiarrhythmics	Quinidine Disopyramide Procainamide

Class III Antiarrhythmics	Sotalol Amiodarone Dofetilide
Macrolide Antibiotics	Erythromycin Clarithromycin Azithromycin
Quinolone Antibiotics	Levofloxacin Moxifloxacin
Antifungals	Fluconazole Ketoconazole
Other Antibiotics	Petamidine
Antimalarials	Chloroquine Halofantrine
Other Meds	Tamoxifen Vandetanib Furosemide Methadone

Step 7: Choose the appropriate agent

- Guidelines for using antidepressants
    - Compelling case can be made for using higher doses (>40mg) of citalopram in specific patients, but needs to be done judiciously and with ECG monitoring (4).
    - No indication for baseline ECG with all antidepressant initiation (5).
    - Consider baseline ECG for patients being started on citalopram with no risk factors or for patients with significant risk factors being started on non-citalopram antidepressant.
    - Consider a cardiology consult when starting citalopram in a patient with significant risk factors.
- Guidelines for using antipsychotics
    - Using antipsychotics in outpatient setting
        - No monitoring for patients without risk factors unless prescribing thioridazine, ziprasidone or iloperidone.
        - For patients with multiple risk factors receiving any medication or patients with no risk factors taking a high-risk agent, obtain ECG at baseline and again at steady-state.
        - For patients with multiple risk factors receiving a high-risk medication, consider cardiology consultation.
    - Using intravenous haloperidol in the inpatient setting
        - Check baseline ECG and at least one follow-up.
        - No clear evidence for daily ECG.
        - Ensure repletion of electrolytes and minimize other risk factors.
        - For QTc > 500 ms, consider adjunctive agents

References:

1) Viskin S, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by noncardiac drugs. Prog Cardiovasc Dis. 2003;45(5):415-27.
2) Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC. QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics. 2013;54(1):1-13.
3) Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951-62.
4) Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, et al. QT Prolongation, Torsades de Pointes, and Psychotropic Medications: A 5-Year Update. Psychosomatics. 2018;59(2):105-22.
5) Funk MC, Beach SR, Bostwick JR, Celano C, Hasnain M, Pandurangi A, et al. QTc Prolongation and Psychotropic Medications. Am J Psychiatry. 2020;177(3):273-4.
6) Bogossian H, Frommeyer G, Ninios I, Hasan F, Nguyen QS, Karosiene Z, et al. New formula for evaluation of the QT interval in patients with left bundle branch block. Heart Rhythm. 2014 Dec;11(12):2273–7.