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 (I_kr) 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
  - ECG machines are often inaccurate; 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

Box 1: Measuring the QTc

(Bazett’s Formula*) \( QTc = (QT / R-R \text{ Interval})^{1/2} \)

(Hodges Formula**) \( QTc = QT + 1.75 \cdot [HR-60] \)

*Used by most ECG machines. Inaccurate at heart 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 in men > 460 milliseconds (ms), in women > 470 ms

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)

<table>
<thead>
<tr>
<th>Categories of risk factors</th>
<th>Risk factors for prolonged QT</th>
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<tbody>
<tr>
<td>Sex</td>
<td>Female sex</td>
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<tr>
<td>Age</td>
<td>Increased age</td>
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<tr>
<td>Genetic</td>
<td>Long QT syndrome: caused by hundreds of mutations in at least 10 different genes</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>Hypokalemia</td>
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<td></td>
<td>Hypocalcemia</td>
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<td>Hypomagnesemia</td>
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Academy of Consultation Liaison Psychiatry How To Guide: QTc Prolongation

<table>
<thead>
<tr>
<th>Cardiac conditions</th>
<th>Prior arrhythmias</th>
<th>Left ventricular dysfunction</th>
<th>Mitral valve prolapse</th>
<th>Congestive heart failure</th>
<th>Myocardial infarction</th>
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<tbody>
<tr>
<td>State conditions</td>
<td>Bradycardia</td>
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<tr>
<td>Specific medications</td>
<td>See Table 2</td>
<td></td>
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</tbody>
</table>

**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](image)

**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 are well studied and considered safe 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.
  - Other antidepressants, including mirtazapine and duloxetine, have not been associated with clinically significant QT prolongation.

- Antipsychotics and QTc prolongation
  - Antipsychotic medications may prolong the QT via blockade of Ik_r.
  - Low-potency phenothiazines (chlorpromazine, thioridazine, mesoridazine) are the class most associated with QT prolongation and TdP.
  - Among typical antipsychotics, pimozide is also associated with QT prolongation.
  - 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.
  - 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, lamotrigine, carbamazepine, and oxcarbazepine are not associated with QTc prolongation.
  - 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

<table>
<thead>
<tr>
<th>Classes</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Class I Antiarrhythmics</td>
<td>Quinidine, Disopyramide, Procainamide</td>
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<tr>
<td>Class III Antiarrhythmics</td>
<td>Sotalol, Amiodarone, Dofetilide</td>
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<tr>
<td>Macrolide Antibiotics</td>
<td>Erythromycin, Clarithromycin</td>
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</table>
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 patient being started on citalopram with no risk factors or for patient with significant risk factors being started on non-citalopram antidepressant.
  - Consider 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.

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<tr>
<th>Quinolone Antibiotics</th>
<th>Azithromycin</th>
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<tbody>
<tr>
<td>Levofoxacin</td>
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<td>Moxifloxacin</td>
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<td>Antifungals</td>
<td>Fluconazole</td>
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<td>Ketoconazole</td>
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<td>Other Antibiotics</td>
<td>Petamidine</td>
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<tr>
<td>Antimalarials</td>
<td>Chloroquine</td>
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<td></td>
<td>Halofantrine</td>
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<tr>
<td>Other Meds</td>
<td>Tamoxifen</td>
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<td></td>
<td>Vandetanib</td>
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<td></td>
<td>Furosemide</td>
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<td>Methadone</td>
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References:


