The Risk of QTc Interval Prolongation with Psychotropics

Christopher M. Celano, MD, FACLP
Associate Director, Cardiac Psychiatry Research Program
Massachusetts General Hospital
Assistant Professor of Psychiatry, Harvard Medical School

October 22, 2020
Disclosure: Christopher Celano, MD

<table>
<thead>
<tr>
<th>Company</th>
<th>Sunovion Pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Management</td>
<td></td>
</tr>
<tr>
<td>Independent Contractor</td>
<td></td>
</tr>
<tr>
<td>Consulting</td>
<td></td>
</tr>
<tr>
<td>Speaking &amp; Teaching</td>
<td>D</td>
</tr>
<tr>
<td>Board, Panel or Committee</td>
<td></td>
</tr>
<tr>
<td>Membership</td>
<td></td>
</tr>
</tbody>
</table>

D – Relationship is considered directly relevant to the presentation
I – Relationship is NOT considered directly relevant to the presentation
Topics for Discussion

- QTc interval and its measurement
- Risk factors for QTc prolongation
- Relationships between psychiatric medications and QTc prolongation
- QTc monitoring in clinical practice
What is the QT interval?

QRS Complex = ventricular depolarization

ST segment + T wave = ventricular repolarization
How to Measure QTc

• Pick an appropriate lead on the ECG.
  – Usually II, V2, or V3.

• Measure the QT interval.

• Measure the heart rate or RR interval.

• Calculate the QTc.
Measure the QT interval

9 boxes + 10 msec
QT = 370 msec
QT intervals are HR-dependent
Measure the RR interval

17 boxes + 10 msec
RR = 690 msec

QT = 370 msec
## Correction Formulae

<table>
<thead>
<tr>
<th>Method</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazett</td>
<td>$QT_c = QT/\sqrt{RR}$</td>
</tr>
<tr>
<td>Fridericia</td>
<td>$QT_c = QT/\sqrt[3]{RR}$</td>
</tr>
<tr>
<td>Framingham</td>
<td>$QT_c = QT + 0.154 \times (1000 - RR)$</td>
</tr>
<tr>
<td>Hodges</td>
<td>$QT_c = QT + 1.75(\text{HR} - 60)$</td>
</tr>
</tbody>
</table>
QTc Correction Methods

B

![Graph showing frequency distribution of QTc values with different correction methods](image)

- QTc Bazett
- QTc Fridericia
- QTc Framingham
- QTc Hodges

Patel 2016
### Normal Ranges

<table>
<thead>
<tr>
<th>Rating</th>
<th>Adult Men</th>
<th>Adult Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 430 msec</td>
<td>&lt; 450 msec</td>
</tr>
<tr>
<td>Borderline</td>
<td>431-450 msec</td>
<td>451-470 msec</td>
</tr>
<tr>
<td>Prolonged</td>
<td>&gt; 450 msec</td>
<td>&gt; 470 msec</td>
</tr>
</tbody>
</table>

However, we generally become more concerned if QTc > 500 msec.

Moss 2003
Why do we worry about QTc prolongation?

- Torsades de pointes (TdP)
  - “Twisting of the points”
  - May lead to sudden syncope or dizziness

Beach 2013
Risk Factors for QTc Prolongation

- Female gender
- Increased age
- Congenital Long QT Syndrome
- Structural Cardiovascular Disease
- Electrolyte abnormalities
- Hepatic dysfunction
- Other medications that prolong QTc
- Metabolic inhibitors

Beach 2013
Psychiatric Medications and QTc

• Antipsychotic Medications
  – First Generation
  – Second Generation
• Antidepressants
  – SSRIs
  – Tricyclic Antidepressants
  – Atypical Antidepressants
• Other psychiatric medications
Antipsychotic medications

• Nearly all antipsychotics prolong QTc, but the degree of prolongation differs substantially among agents.

• Haloperidol
  – In oral form, haloperidol leads to QT prolongation that is similar to aripiprazole, quetiapine, and asenapine.
  – Intravenous form may lead to higher risk of QTc prolongation, with some caveats.
  – FDA recommends cardiac monitoring for patients receiving intravenous haloperidol.

Antipsychotic Medications

- Second generation antipsychotics

Huhn 2019
Antipsychotic Medications

Huhn 2019
Antipsychotic Medications

• Second generation antipsychotics
  – Highest risk: ziprasidone and iloperidone
  – Lowest risk: aripiprazole and lurasidone
  – FDA warnings
    • Ziprasidone (black box)
    • Quetiapine
    • Intravenous haloperidol

  – There may be a dose-response relationship for antipsychotics and QTc, but evidence is mixed.
Antipsychotic Medications and Mortality

• Both first- and second-generation antipsychotics have been linked to ventricular arrhythmias or sudden cardiac death.
  – Case-crossover study (N=17,718)
    • OR=1.53
    • Haloperidol, prochlorperazine, thioridazine, quetiapine, and risperidone were associated with increased risk.

• FDA black box warning for second-generation antipsychotics in elderly patients with dementia.

Wu 2015, US FDA 2005
Antidepressants and QTc

• SSRIs
  – Initially thought to be quite safe
    • SADHART, ENRICH, CREATE
  – FDA warnings:
    • Initial
      – Citalopram should not be prescribed at doses greater than 40mg
      – Citalopram should not be used at doses >20mg in those with liver dysfunction or over age 60
    • Revision
      – Citalopram is not recommended at doses greater than 40mg
      – Citalopram should be discontinued in anyone with QTc>500 ms

# Citalopram and QTc

<table>
<thead>
<tr>
<th>Medication and dose</th>
<th>QT prolongation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram 20mg daily</td>
<td>8.5 (6.2, 10.8)</td>
</tr>
<tr>
<td>Citalopram 40mg daily</td>
<td>12.6 (10.9, 14.3)</td>
</tr>
<tr>
<td>Citalopram 60mg daily</td>
<td>18.5 (16.0, 21.0)</td>
</tr>
<tr>
<td>Moxifloxacin 400mg daily</td>
<td>13.4 (10.9, 15.9)</td>
</tr>
</tbody>
</table>

US FDA 2011
## Escitalopram and QTc

<table>
<thead>
<tr>
<th>Medication and dose</th>
<th>QT prolongation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram 10mg daily</td>
<td>4.5 (2.5, 6.4)</td>
</tr>
<tr>
<td>Escitalopram 20mg daily</td>
<td>6.6 (5.3, 7.9)</td>
</tr>
<tr>
<td>Escitalopram 30mg daily</td>
<td>10.7 (8.7, 12.7)</td>
</tr>
<tr>
<td>Moxifloxacin 400mg daily</td>
<td>9.0 (7.3, 10.8)</td>
</tr>
</tbody>
</table>

US FDA 2012
Effects of SSRIs on QTc

Castro 2013
## Effects of Antidepressants on QTc

<table>
<thead>
<tr>
<th>Medication</th>
<th>N</th>
<th>Difference in QTc (ms)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>696</td>
<td>10.58</td>
<td>.002</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>360</td>
<td>7.27</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>135</td>
<td>4.50</td>
<td>.32</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>27</td>
<td>-5.00</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1486</td>
<td>-1.04</td>
<td>.67</td>
</tr>
<tr>
<td>Sertraline</td>
<td>369</td>
<td>3.00</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SSRIs</td>
<td>3,079</td>
<td>6.10</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TCAs</td>
<td>1,587</td>
<td>10.01</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
SSRIs and Ventricular Arrhythmias

- Evidence is less clear
  - Danish case-time-control study

Weeke 2012
SSRIs and Ventricular Arrhythmias

• Tennessee Medicaid Cohort Study
  – Retrospective cohort study of 54,220 patients receiving high dose citalopram (>40mg daily) or escitalopram (>20mg daily) or equivalent doses of other SSRIs.
  – Neither citalopram nor escitalopram had higher risks of sudden unexpected death or all-cause mortality than other SSRIs.

• Patient-level meta-analysis for escitalopram
  – Escitalopram led to mild 3.5msec increases in QTc, compared to placebo.
  – Rates of cardiovascular side effects were similar between escitalopram and placebo.

Ray 2017, Thase 2013
Tricyclic Antidepressants and QTc

• Tricyclic antidepressants
  – Affect sodium, calcium, and potassium channels
  – Generally are considered to be higher risk for QTc prolongation than SSRIs
  – Have other cardiovascular side effects as well
Atypical Antidepressants and QTc

- **Venlafaxine**
  - Minimal risk at therapeutic doses (1 case report), low risk in overdose (1%).

- **Bupropion**
  - Associated with QTc prolongation in overdose; possibly confounded by tachycardia

- **Trazodone**
  - Associated with mild QTc prolongation in overdose

- **Mirtazapine**
  - No clear QTc prolongation risk, though it has been associated with a higher risk of SCD or ventricular arrhythmias than paroxetine in one study

- **Newest antidepressants (duloxetine, vilazodone, vortioxetine, levomilnacipran, desvenlafaxine, brexpiprazole)**
  - Not associated with clinically meaningful QT prolongation

Beach 2013, Jasiak 2014, Allen 2020
Other Psychiatric Medications and QTc

- Lithium
  - Can cause QTc prolongation at levels > 1.2 mmol/L
- Anticonvulsants
  - Not associated with QTc prolongation
- Stimulants
  - Not associated with QTc prolongation
- Benzodiazepines
  - Not associated with QTc prolongation

Beach 2013
Skills for QTc Monitoring in Practice

• Know how to calculate a QTc on an ECG.
  – Do not rely on the QTc measured by the machine.
  – Use the Fridericia or Hodge’s formula to correct for heart rate.

• Know the risk factors for QTc prolongation.

• Know which medications are higher-risk.
  – Antipsychotics: thioridazine, ziprasidone, possibly iloperidone
  – Antidepressants: citalopram, escitalopram, tricyclic antidepressants
When to monitor QTc

• Know when to monitor QTc.
  – For patients without significant risk factors and on lower-risk medications, no monitoring is needed.
  – For patients with significant risk factors or on a higher-risk medication, check QTc at baseline, then again at steady-state or when risk factors change (e.g., change in dose).
Association of Medicine and Psychiatry

Algorithm

Risk Factors (individual risk score in parentheses)

- Female (1)
- Age ≥65 years (1)
- Starvation, Alcohol use disorder, methamphetamine use disorder** (1)
- Potassium (K) <3.2 mmol/L (2)
- Magnesium (Mg) <1.4 mg/dL (2)
- Heart Rate <60 (2)
- Heart disease (coronary artery disease, congestive heart failure, structural heart disease) (2)
- Congenital or acquired Long QT Syndrome (3)
- History of sudden cardiac death in first-degree family member (3)
- Two or more QTc-prolonging agents (2)
- Methadone dose ≥ 120 mg daily (2)

Total Risk Score <2*

No baseline QTc needed

Total Risk Score ≥2

Xiong 2020
Association of Medicine and Psychiatry Algorithm

Check ECG prior to start of medication OR
Start lower risk medication (QTc <10-20 msec) if feasible, then check ECG in <3 months

Risk score <5: Obtain ECG in 2-4 weeks (if already on psychiatric medications)
Risk score ≥5: Consider urgent/emergent cardiology referral

**QTc <450 ms (M); QTc <470 ms (F)**
Start medication; repeat ECG in 2-4 weeks.
Repeat ECG when risk factors change or when increasing dose by >30-50%
Assess risk factors annually

**QTc >450 ms (M); QTc >470 ms (F)**
TdP risk is intermediate.
Ensure that chosen medication has greatest benefit:risk ratio.
Check K and Mg. Replace to goal of K=~4.0 and Mg=~2.0***
Repeat ECG in 2-4 weeks

**QTc >500 msec**
TdP risk is high
Check K and Mg. Replace to goal of K=~4.0 and Mg=~2.0***
Consider dose reduction or switch to alternate psychiatric medication with QTc prolongation <10-20 msec
Repeat ECG in 2-4 weeks
Consider cardiology referral

Xiong 2020
References


References


References

References

- Wu CS, Tsai YT, Tsai HJ. Antipsychotic Drugs and the Risk of Ventricular Arrhythmia and/or Sudden Cardiac Death: A Nation-wide Case-Crossover Study. J Am Heart Assoc. 2015;4(2).