Shocking the Heart with Psychotropic Medications

Christie Hart, PharmD, MBA
Iowa City Veterans Affairs PGY1 Pharmacy Resident

QTc prolongation is the most common reason medications are withdrawn from the market after they have been approved

Pharmacist Objectives

• Identify the location of the QT interval on ECG and recall 2 cardiac outcomes related to QTc prolongation
• Explain the mechanism by which QTc prolongation arises
• Given a patient case determine the significant drug-drug and drug-disease interactions
• Recommend appropriate monitoring for patients on antipsychotic and antidepressant medications
• Apply knowledge of cardiac safety to create effective patient care plans for patients on psychotropic medications
Pharmacy Technician Objectives

- Identify the incidence of antipsychotic and antidepressant use among different age groups
- Recognize the risks associated with QTc prolongation
- Discuss what factors contribute to increasing the QTc interval
- From a list, select which patients are the highest risk for developing QTc prolongation from psychotropic medications
- Recall 3 psychotropic medications that pose the highest risk for QTc prolongation

Statistics

- 1 in 5 American adults took ≥1 psychiatric medication in 2010
  - Use increased by 22% from 2001 to 2010
- From 1988 to 2008 the rate of antidepressant use in the US increased nearly 400%
  - 3rd most common prescription drug taken by Americans of all ages from 2005-2008
- In 2008, 16 million prescriptions for atypical antipsychotics were filled

Background

- Patients with mental illness are at increased risk for cardiovascular events
  - Lifestyle
  - Physiological
  - Medications
- Psychotropic medications are associated with QTc prolongation
  - QTc prolongation is associated with
    - Torsade de Pointes (TdP)
    - Ventricular fibrillation
    - Sudden cardiac death

Pratt. CDC 2011.
Smith. APA 2012.
De Hert. Nature Reviews Endocrinology 2012
McIntyre. APA Guidelines 2004
QT Prolongation

**Congenital long QT syndromes**

- **Type 1**: Reduced repolarizing current $I_{Kr}$
- **Type 2**: Reduced repolarizing current $I_{Ks}$
- **Type 3**: Delayed inactivation of the $I_{Na}$

**Acquired prolongation of QT interval**

- Electrolytes
- Medications
- Disorders
- Nutritional

---

**ECG Background**

Atrial depolarization → Ventricular depolarization → Ventricular repolarization

- Phase 0 (Depolarization) Sodium current ($I_{Na}$)
- Phase 1 (Repolarization) Potassium current ($I_{K1}$)
- Phase 2 (Plateau) Calcium current ($I_{Ca}$)
- Phase 3 (Repolarization) Potassium currents ($I_{K1}$, $I_{Ks}$)

---

**QTc Prolongation Definition**

QTc > 500 ms proarrhythmic marker for both congenital (OR 2-3) and drug-induced (OR 1.2) LQTS

<table>
<thead>
<tr>
<th>QTc (ms)</th>
<th>Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>360</td>
<td>Normal Post-pubertal Males</td>
</tr>
<tr>
<td>440</td>
<td>Normal Post-pubertal Females</td>
</tr>
<tr>
<td>470</td>
<td>Long QT Syndrome</td>
</tr>
<tr>
<td>480</td>
<td>Borderline Zone</td>
</tr>
<tr>
<td>520</td>
<td></td>
</tr>
<tr>
<td>600</td>
<td></td>
</tr>
<tr>
<td>680</td>
<td></td>
</tr>
<tr>
<td>760</td>
<td></td>
</tr>
</tbody>
</table>

Male | Female
---|---
Prolonged | ≥470 msec | ≥480 msec
QT Interval

- Start of the Q wave to the end of the T wave
- Time taken for ventricular depolarization & repolarization
- Inversely proportional to heart rate (HR)
- Corrected QT interval (QTc) estimates the QT interval at a heart rate of 60 bpm

QTc Calculation

- \[ RR = \frac{60}{\text{heart rate}} \]
- Bazett’s
  - \[ \frac{QT}{\sqrt{RR}} \]
  - Most common
  - Over corrects at HR >100 bpm
  - Under corrects at HR <60 bpm
- Fredericia
  - \[ \frac{QT}{(RR)^{1/3}} \]
  - Use for HR outside of 60-100 bpm
- Framingham
  - \[ QT + 0.154(1 – RR) \]
  - Use for HR outside of 60-100 bpm

Let’s Visualize

- TF is a 57 year old male starting azithromycin for community acquired pneumonia
  - QT = 411 msec
  - HR = 79 bpm
- Bazett
  - \[ \frac{411}{\sqrt{79}} = 472 \text{ msec} \]
- Fredericia
  - \[ \frac{411}{\sqrt[3]{79}} = 450 \text{ msec} \]
- TF is a 57 year old male starting azithromycin for community acquired pneumonia
  - QT = 411 msec
  - HR = 48 bpm
- Bazett
  - \[ \frac{411}{\sqrt{48}} = 367 \text{ msec} \]
- Fredericia
  - \[ \frac{411}{\sqrt[3]{48}} = 382 \text{ msec} \]
Let's Visualize

- TF is a 57 year old male starting azithromycin for community acquired pneumonia
  - QT = 411 msec
  - HR = 79 bpm
- Bazett
  - \(\frac{411}{79} = 472\) msec
- Fredericia
  - \(\frac{411}{\sqrt{79}} = 450\) msec

- Bazett
  - \(\frac{411}{112} = 561\) msec
- Fredericia
  - \(\frac{411}{\sqrt{112}} = 506\) msec

Torsade de Pointes

- Uncommon, polymorphic ventricular tachycardia
  - Exact occurrence is unknown
  - 300,000 sudden cardiac deaths in US per year
    - TdP possibly accounting for 5%
- Prolonged QTc ≠ TdP
  - QTc ≥ 550 msec
  - The mean QTc interval prior to onset of TdP was 580 msec

Risk Factors

- Cardiac dysfunction
- Female
- Electrolyte dysfunction
  - Hypokalemia, hypocalcemia, or hypomagnesemia
- Malnutrition
- Elderly
- Renal/hepatic dysfunction
- DDI with CYP2D6 or CYP3A4
### Medications

<table>
<thead>
<tr>
<th>Antiarrhythmic</th>
<th>Antibiotic</th>
<th>Antifungal</th>
<th>Antimalarial</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IA</td>
<td>Macrolides</td>
<td>Fluconazole</td>
<td>Chloroquine</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Erythromycin</td>
<td>Ketoconazole</td>
<td>Halofantrine</td>
<td>Vandetanib</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td>Furosemide</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Azithromycin</td>
<td></td>
<td></td>
<td>Methadone</td>
</tr>
<tr>
<td>Class III</td>
<td>Quinolones</td>
<td></td>
<td></td>
<td>Digoxin</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Levofloxacin</td>
<td></td>
<td></td>
<td>Ondansetron</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Moxifloxacin</td>
<td></td>
<td></td>
<td>Droperidol</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Pentamidine</td>
<td></td>
<td></td>
<td>Domperidone</td>
</tr>
</tbody>
</table>

Which of the following is NOT a risk factor for prolonging QTc?

A. Heart failure  
B. Hypokalemia  
C. Hypomagnesemia  
D. Furosemide  
E. Male sex  
F. None of the above

Pathophysiology

- Blockade of rapid rectifier potassium channel (IKr)
  - Decreased potassium efflux
    - Increases time for repolarization
    - Allows for development of spontaneous depolarization
Clinical Picture

Presentation

• Bradycardia
• Palpitations
• Orthostatic hypotension
• Syncope

Diagnosis

• ECG
  - Relative increase in QTc of at least 60 msec from baseline
  - QTc >500 msec

De Hert. Nature Reviews Endocrinology 2012
Beach. Psychosomatics 2013.

Monitoring

• No rationale for routinely ordering an electrocardiograph (ECG) in patients
  - Exception: pimozide and thioridazine
• Follow-up ECG if
  - Structural heart disease worsens or bradyarrhythmia occurs
  - Increase in dose
  - Adding another QTc prolonging agent
  - Electrolyte abnormalities
• Monitoring electrolytes has shown benefit in some clinical trials

De Hert. Nature Reviews Endocrinology 2012
Beach. Psychosomatics 2013.
LaPointe. CPNP.

Patient Case - JP

JP is 57 year old male being seen by a psychiatrist for the first time regarding recent changes in mood. His psychiatrist diagnoses JP with major depressive disorder (MDD) and would like to start JP on fluoxetine

• PMH: HTN, heart failure, chronic pain, and DM
• Current medications
  - Lisinopril, metoprolol succinate, furosemide, metformin, and methadone
• Baseline QTc = 424 msec
Patient Case - JP

• What risk factors does JP have for QTc prolongation?

• What monitoring would you recommend for JP?

Psychotropic Medications

Antidepressant Overview

SSRI

• Generally safe in cardiovascular disease
• Only SSRIs with confirmed QTc prolongation is citalopram and escitalopram

TCA

• All TCA’s have been associated with QTc prolongation
• Several TCAs are metabolized by CYP2D6
SADHART

- Objective
  - Evaluate the safety and efficacy of sertraline for treatment of MDD in patients hospitalized for acute MI or UA

- Intervention
  - 369 patients to receive either sertraline or placebo for 24 weeks

- Outcome

<table>
<thead>
<tr>
<th></th>
<th>Placebo Baseline</th>
<th>Sertraline Baseline</th>
<th>Placebo Week 16</th>
<th>Sertraline Week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>424 msec</td>
<td>420 msec</td>
<td>419 msec</td>
<td>428 msec</td>
</tr>
<tr>
<td>QTc &gt;450 msec</td>
<td>30 (19%)</td>
<td>30 (19%)</td>
<td>21 (13%)</td>
<td>19 (12%)</td>
</tr>
</tbody>
</table>


SSRI

- Citalopram

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Prolongation (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>8.5</td>
</tr>
<tr>
<td>40</td>
<td>12.6</td>
</tr>
<tr>
<td>60</td>
<td>18.5</td>
</tr>
</tbody>
</table>

- Escitalopram

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Prolongation (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>4.5</td>
</tr>
<tr>
<td>20</td>
<td>6.6</td>
</tr>
<tr>
<td>30</td>
<td>10.7</td>
</tr>
</tbody>
</table>

- Fluoxetine and paroxetine have failed to show any significant effects on QTc prolongation

Beach. Psychosomatics 2013.
FDA. 2012.

TCAs

- De Ponti et al.
  - Review of non-antiarrhythmic medications associated with QTc prolongation and TdP
  - Reviewed amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, and protriptyline
  - Included 13 case studies

- Results
  - All can prolong QTc interval
  - Most commonly amitriptyline and maprotiline
  - Least commonly clomipramine

Antipsychotic Overview

**Typical antipsychotics**

- Low potency antipsychotics are thought to carry a greater risk
  - Thioridazine and chlorpromazine

**Atypical antipsychotics**

- Most carry low to moderate increases in QTc interval

Typical Antipsychotics

- **Thioridazine**
  - Average increase in QTc of 30-35 msec
  - Moderate doses (300 mg/day) showed greatest prolongation of QTc
  - Periodic ECG monitoring recommended

- **Pimozide**
  - Mean QTc prolongation of 24 msec
  - Metabolized by 3A4
  - Periodic ECG monitoring recommended

- **Haloperidol**
  - Average increase in QTc of 4.7 msec for oral to 17.1 msec for IV
  - 2007 post-marketing: 229 cases of QTc prolongation and 73 cases of TdP

Atypical Antipsychotics

- **Ziprasidone**
  - Average increase in QTc of 15-20 msec
  - Incidence of QTc prolongation >500 msec has been estimated at less than 0.06%

- **Olanzapine, quetiapine, & risperidone**
  - Comparable to oral haloperidol
  - QTc prolongation ranged from 1-14 msec

Beach. Psychosomatics 2013.
FDA 2000.
Atypical Antipsychotics

- Iloperidone & paliperidone
  - Associated with QTc prolongation in presence of 2D6 and 3A4 inhibitors

- Aripiprazole
  - Not associated with prolonged QTc

- Clozapine
  - Associated with sudden cardiac death, but only associated with QTc prolongation in case reports

Pfizer Study 054

- Objective
  - To assess the effect of oral ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol on the QTc interval in patients with schizophrenia

- Methodology
  - Open-label, parallel group

- Intervention
  - Ziprasidone 20-80 mg BID
  - Risperidone 1-8 mg BID
  - Olanzapine 5-20 mg daily
  - Quetiapine 25-374 mg BID
  - Thioridazine 25-150 mg BID
  - Haloperidol 2-15 mg daily

Pfizer Study 054 Results

Study 054: QTc Mean Change from Baseline in Absence and Presence of Metabolic Inhibitor

FDA 2000.
Dose Relationship

- QTc prolongation shows a dose dependent relationship
- Dosages defined by chlorpromazine equivalents per day
  - Doses >2000 mg chlorpromazine equivalents per day associated with highest risk

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Chlorpromazine 2000 mg Equivalent (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>80</td>
</tr>
<tr>
<td>Risperidone</td>
<td>80</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>100</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1,500</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1,200</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>150</td>
</tr>
<tr>
<td>Clozapine</td>
<td>1,000</td>
</tr>
</tbody>
</table>


QTc Prolongation TdP

<table>
<thead>
<tr>
<th></th>
<th>QTc Prolongation</th>
<th>TdP</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>Thioridazine</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Haloperidol (IV)</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
<td>+++</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>Fluphenazine</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Haloperidol (PO/IM)</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Iloperidone</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Paliperidone</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>+</td>
</tr>
<tr>
<td>Low Risk</td>
<td>Asenapine</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Lurasidone</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td>+</td>
</tr>
<tr>
<td>Minimal Risk</td>
<td>Aripiprazole</td>
<td>-</td>
</tr>
</tbody>
</table>

Beach. Psychosomatics 2013.

Interventions
Treatment of TdP

- Discontinue QTc prolonging medication
- Magnesium sulfate IV
- Maintain potassium levels of 4.5-5 mmol/L
- Defibrillation if patient remains unstable
- Transvenous pacing to prevent recurrence
  - Useful if no response to magnesium or if TdP precipitates
  - Isoproterenol if temporary pacing not available
    - Contraindicated in patients with congenital LQTS or ischemic heart disease


Patient Case - PF

PF is a 56 year old male with a PMH significant for schizoaffective disorder, HTN, HLD, glaucoma, and GERD who reports for a follow up appointment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>5 mg BID</td>
<td>Schizoaffective d/o</td>
</tr>
<tr>
<td>Citalopram</td>
<td>40 mg daily</td>
<td>Schizoaffective d/o</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10 mg daily</td>
<td>HTN</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg BID PRN</td>
<td>HTN</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40 mg daily</td>
<td>HLD</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>1 drop in both eyes every evening</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg daily</td>
<td>GERD</td>
</tr>
</tbody>
</table>

Patient Case - PF

- The physician orders an ECG and the patient’s QTc interval was 492 msec, which increased from 479 msec on 8/2/15
- The physician asks your opinion about what to do with the patient’s medications. He states the patient’s symptoms are moderately controlled

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>52 (60-100 bpm)</td>
</tr>
<tr>
<td>K⁺</td>
<td>3.4 (3.5-5 mmol/L)</td>
</tr>
<tr>
<td>SCr</td>
<td>1.5 (0.6-1.4 mg/dL)</td>
</tr>
<tr>
<td>AST</td>
<td>67 (7-40 U/L)</td>
</tr>
<tr>
<td>ALT</td>
<td>54 (7-40 U/L)</td>
</tr>
</tbody>
</table>
Patient Case - PF

• What could you recommend?

Final Case

Patient Case - DG

• DG is a 29 year old female being discharged on 11/2/15 with a diagnosis of schizophrenia. DG discontinued olanzapine 10 mg daily due to weight gain in 2/2015.

• Upon discharge, the psychiatry resident wishes to start ziprasidone since it has less weight gain.

• PMH: MDD, insomnia, DM

<table>
<thead>
<tr>
<th>Medications</th>
<th>Initiation Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram 40 mg daily</td>
<td>5/2007</td>
</tr>
<tr>
<td>Trazodone 50 mg qHS</td>
<td>8/2001</td>
</tr>
<tr>
<td>Amitriptyline 50 mg qHS</td>
<td>1/2010</td>
</tr>
<tr>
<td>Metformin 1,000 mg BiD</td>
<td>9/2013</td>
</tr>
</tbody>
</table>
Patient Case - DG

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value (Range)</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>490 msec</td>
<td>11/2/15</td>
</tr>
<tr>
<td>QTc</td>
<td>486 msec</td>
<td>10/31/15</td>
</tr>
<tr>
<td>QTc</td>
<td>449 msec Baseline</td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>128/87 mmHg</td>
<td>11/2/15</td>
</tr>
<tr>
<td>HR</td>
<td>77 bpm</td>
<td>11/2/15</td>
</tr>
<tr>
<td>Sodium</td>
<td>142 mmol/L (135-145)</td>
<td>10/31/15</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.4 mmol/L (3.5-5.0)</td>
<td>10/31/15</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2.1 mg/dl (1.5-2.6)</td>
<td>10/29/15</td>
</tr>
<tr>
<td>Calcium</td>
<td>9.7 mg/dl (8.5-10.5)</td>
<td>10/29/15</td>
</tr>
<tr>
<td>SCr</td>
<td>0.85 mg/dl (0.6-1.4)</td>
<td>10/31/15</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>16/10 U/L (7-40)</td>
<td>10/29/15</td>
</tr>
<tr>
<td>Glucose</td>
<td>103 mg/dl (65-100)</td>
<td>11/2/15</td>
</tr>
<tr>
<td>LDL</td>
<td>85 mg/dl (0-100)</td>
<td>11/2/15</td>
</tr>
</tbody>
</table>

• Which risk factors does DG have for QTc prolongation?

• Which of her current medications prolong QTc interval?

• What recommendations do you have for the psychiatrist?

• What medication would you recommend instead?
Patient Case - DG

- What ECG monitoring would you recommend for DG?
  A. At baseline only
  B. At baseline and intermittently
  C. Only after the aripiprazole has been started
  D. Never
- Any other monitoring you would recommend?

Conclusion

- Practitioners should be aware of all medications and risk factors that can prolong QTc
- The link between prolonged QTc and TdP is not linear
- Certain medications are associated with QTc prolongation, but serious events can occur with an increase in risk factors
- The highest risk psychotropic medications are thioridazine, IV haloperidol, pimozide, and ziprasidone
- Pharmacists should take time to explain the risks and side effects

Shocking the Heart with Psychotropic Medications

Christie Hart, PharmD, MBA
Iowa City Veterans Affairs PGY1 Pharmacy Resident
References


11. LaPointe N. Unraveling Torsade de Pointes. CPNP presentation.


References Continued


