Shocking the Heart with Psychotropic Medications

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

- Acquired prolongation of QT interval
  - Electrolytes
  - Medications
  - Disorders
  - Nutritional

**QTc Prolongation Definition**

<table>
<thead>
<tr>
<th>QTc (ms)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged</td>
<td>≥470 msec</td>
<td>≥480 msec</td>
</tr>
</tbody>
</table>

**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**
  \( \frac{QT}{\sqrt{RR^2+120}} \)
  - USE for HR outside of 60-100 bpm
- **Framingham**
  \( QT + 0.154(1 – HR) \)
  - 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**
    \( \frac{411}{\sqrt{79}} \approx 472 \) msec
  - **Fredericia**
    \( \frac{411}{\sqrt{79^2+120}} \approx 450 \) msec

- TF is a 57 year old male starting azithromycin for community acquired pneumonia
  - QT = 411 msec
  - HR = 48 bpm
  - **Bazett**
    \( \frac{411}{\sqrt{48}} \approx 367 \) msec
  - **Fredericia**
    \( \frac{411}{\sqrt{48^2+120}} \approx 382 \) msec
Let’s Visualize

- TF is a 57 year old male starting azithromycin for community acquired pneumonia
  - QT = 411 msec
  - HR = 79 bpm
- Bazett
  \[
  \frac{411}{\sqrt{79}} = 472 \text{ msec}
  \]
- Fredericia
  \[
  \frac{411}{\sqrt{77}} = 450 \text{ msec}
  \]

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>
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<tr>
<td>Quinidine</td>
<td>Erythromycin</td>
<td>Ketaconazole</td>
<td>Halofantrine</td>
<td>Vandentanib</td>
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<tr>
<td>Disopyramide</td>
<td>Clarithromycin</td>
<td>Granzolide</td>
<td>Fluconozole</td>
<td>Methadone</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Azithromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>Quinolones</td>
<td></td>
<td>Digoxin</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>Levofloxacine</td>
<td>Levofloxacine</td>
<td></td>
<td></td>
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<tr>
<td>Amiodarone</td>
<td>Moxifloxacine</td>
<td></td>
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<tr>
<td>Dofetilide</td>
<td></td>
<td></td>
<td>Ondansetron</td>
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<td>Furosemide</td>
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<tr>
<td>Procainamide</td>
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<td>Procainamide</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td></td>
<td></td>
<td></td>
<td></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

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

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

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>

*Glassman, JAMA 2002.*

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.*

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

*FDA 2000.*

**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

*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

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

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>

Interventions

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

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

What could you recommend?

Lab Value (Range)

<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 - 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>

Final Case
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</td>
<td>Baseline</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>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>

Patient Case - DG

- Which risk factors does DG have for QTc prolongation?
- Which of her current medications prolong QTc interval?

Patient Case - DG

- 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

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References

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