Methdone, psychotropics and prolonged QT

Project ECHO/ROAM
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Disclosures

• Dr. Yuodelis Flores has no financial relationships that may be a conflict of interest.

• There will be no unannounced discussion of off-label uses of drugs, diagnostics, or biologics.
Q: You are evaluating a patient for methadone maintenance. The cardiogram shows a QTc of 498 msec. What is the next step?

- a. Begin methadone maintenance
- b. Refer the patient for opioid detoxification
- c. Refer the patient for cardiology consultation
- d. Begin methadone maintenance with target dose below 100 mg/d, obtain a second cardiogram in 30 days and make clinical decision regarding ongoing methadone treatment based on clinical information.
Acquired Long QT Syndrome

- Qtc >450 msec
  >500 msec

- Drugs that prolong QT do so by $I_{kr}$ potassium channel blocking activity in myocardium--prolongs cardiac repolarization.
Risk Factors for Acquired Long QT Syndrome & Torsades de Pointes

- Underlying cardiac abnormalities
  - Congenital long QT syndrome
  - Structural heart disease: LVH, MI, CHF, Low EF
  - Sinus bradycardia, heart block, incomplete heart block
- Hypothyroidism
- Electrolyte abnormalities (particularly K+ & Mg+)
- Female, elderly, eating disorders, substance abuse, polypharmacy
Risk Factors for Acquired Long QT Syndrome & Torsades de Pointes

- High doses or concentrations of QT prolonging drug
- Use of other drugs known to prolong QT
- Use of a QT prolonging drug with one that slows drug metabolism due to inhibition of P450 enzymes, such as *erythromycin*, *cimetidine*, & *grapefruit juice*. (Inhibits CYP3A4) (also CYP2D6 & CYP2B6).
Medications that prolong QT

- Methadone
- Levacetylmethadol (LAAM)
- Macrolides (especially erythromycin)
- Antifungals (ketoconazole)
- Fluoroquinolones
- Antiarrhythmic medications (Quinadine, Amiodarone)
- Antipsychotics
- Antidepressants
Antipsychotic medications that cause prolongation of QT interval

- **Haloperidol**—especially when it is administered IV or in higher doses than recommended.

- **Pimozide**

- **Phenothiazines** – Thioridazine & mesoridazine

**Atypical Antipsychotics:**

- **Ziprasidone (Geodon)**
- **Risperidone (Risperdal)**
- **Quetiapine (Seroquel)**
- **Clozapine (Clozaril)**
- **Olanzapine**
Antidepressants that prolong QT

• Tricyclics +++
• Trazodone +
• Nefazodone +++
• SSRIs ++
  – Citalopram-**most cardiotoxic +++
• SNRI: venlafaxine +
• Lithium +++
• Mirtazapine +
Potent CYP3A4 inhibitors that will increase serum methadone levels

- Ritonavir
- Amiodarone
- Diltiazem
- Quinidine
- Ciprofloxacin
- Dihydroergotamine
- Fluconazole/ketoconazole
- Macrolide antibiotics
- Metronidazole

- Cimetidine
- Ethanol
- Disulfiram
- Omeprazole
- Diazepam
- SSRIs
- Nefazodone
- Grapefruit juice
Conclusions Regarding Clinical Procedures

Expert Panel members agreed that, to the extent possible, every opioid treatment program should have a cardiac risk management plan that incorporates the following elements:
1. **Clinical Assessment**

- The assessment conducted at intake should include a complete medication history; personal and family history of structural heart disease (including long QT syndrome, sudden cardiac death, myocardial infarction, heart failure); any personal history of arrhythmia or syncope; and use of QT-prolonging drugs, including prescribed medications and illicit drugs such as cocaine.
2. **ECG Assessment**

- Routine ECG to assess for structural heart disease is not indicated in methadone treatment programs.

- A baseline ECG at the time of admission and within 30 days should be performed on patients with significant risk factors for QT prolongation, including a history of cardiac arrhythmia or prolonged QT interval; symptoms suggestive of arrhythmia, such as episodes of syncope, dizzy spells, palpitations, or seizures; medication history; family history of premature death or any other historical information suggestive of a possible cardiac arrhythmia.
Cardiac risk management plan

2. ECG Assessment

- Additional ECGs should be performed annually or whenever the methadone dose exceeds 120 mg/day.
- In addition to scheduled ECGs, any patient who experiences unexplained syncope or generalized seizures should have an ECG. If marked QT prolongation is documented, TdP should be suspected and the patient hospitalized for telemetry monitoring.
Cardiac risk management plan

3. Risk Stratification

• If the QT interval is more than 450 ms but less than 500 ms, methadone may be initiated or continued, accompanied by a risk-benefit discussion with the patient and more frequent monitoring.

• For methadone-maintained patients with marked QT prolongation (≥500 ms), strong consideration should be given to adoption of a risk minimization strategy (such as reducing the methadone dose, eliminating other contributing factors, transitioning the patient to an alternative treatment such as buprenorphine, or discontinuing methadone treatment).
4. *Drug Interactions*

- Physicians should be aware of interactions between methadone and other medications that also have QT-prolonging properties.
- Medications that suppress P450 enzymes (CYP 3A4) and thus raise methadone blood levels by slowing it’s metabolism.
Cardiac risk management plan

5. Administrative procedures

• Disclosure—informed consent. Clinicians should inform patients of arrhythmia risk when they prescribe methadone.

• Patients should receive educational materials that explain, in lay language, cardiac risk and its relationship to QT interval.

• Staff should be educated about risk factors for TdP and drug interactions with methadone.