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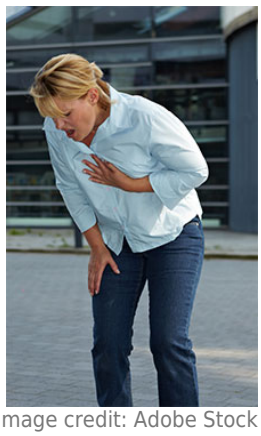
QT Prolongation from Psychiatric Medication: Information for Physicians



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Sommaire : QT prolongation from psychiatric medications leading to potentially fatal cardiac arrhythmias (such as Torsades de Point) is an uncommon but serious complication. Unfortunately, many psychiatric medications such as antidepressants and antipsychotics have a risk of prolonging QT. For patients at risk of QT prolongation, address modifiable risk factors, use caution with medications that may worsen QT intervals, and consider cardiology consultation. For patients with QT prolongation, stop any offending medications and address modifiable risk factors.

Case, Part 1

Jan is a middle-aged female in your practice. Several years ago, she had been diagnosed with anxiety, and treated with Citalopram, which she continues to take. A few months ago, the dosage was raised to 40 mg daily. She now presents to you with fainting spells and chest pains. What are you going to do?

What is a Normal QT Interval?

The QT interval on an ECG:

- Is the beginning of the QRS complex to the end of the T wave, and represents ventricular depolarization and repolarization.
- Varies with heart rate. Various formulas are used to correct the QT interval for heart rate, and once corrected, it is expressed as the QTc (“QT corrected”) interval -- **a normal QTc interval is < 440 ms.**

What is Prolonged QT?

QT prolongation is clinically significant as it is associated with an increased risk of torsades de pointes (TdP), a potentially fatal ventricular arrhythmia.

QTc may be

1. Borderline prolonged >440 ms and <500 ms	When borderline → Consider reducing the dosage of any QT-prolonging medications or changing to an alternative non QT-prolonging medication.
2. Prolonged QTc Interval >500 ms	When prolonged → Stop any medications that prolong the QT interval

What is a Significant Medication-Induced QTc Prolongation?

- Increase in baseline QTc < 5 ms = Not considered significant
- Increase in baseline QTc > 20 = Concerning
- Increase in baseline QTc > 60 ms = Very concerning
    - With familial long QT syndrome, for every 10 ms increase in QTc, there is a 5% increase in the risk of arrhythmic events.

Risk factors for QT prolongation

In cases of torsades de pointes, there are often multiple risk factors present, which include the following main risk factors:

- Potentially Modifiable Risk Factors
    - Electrolyte Disturbances (in particular hypokalaemia, hypomagnesemia and more rarely hypocalcemia).
    - Bradycardia
    - Using more than one medication that prolongs the QT interval
- Non-modifiable
    - Congenital long QT syndrome
    - Cardiac disease (e.g. bradycardia, heart failure, left ventricular hypertrophy, myocardial infarction)
    - Impaired hepatic/renal function (due to effects on medication metabolism)
    - Thyroid disease (more common with hypothyroidism and usually normalizes with treatment)
    - Female sex
    - Age > 65-yo

Clinical Presentation

- Ranges from no symptoms to presenting with cardiac symptoms.

Red Flags for ECG Screening

In primary care, there are so many medications that may potentially prolong QT, that it is not practical to do an ECG every time such medication is prescribed.

Consider ECG with the following red flags/risk factors

- For children and youth
    - Any young person with unexplained syncope, unexplained seizures or unexplained cardiac events (such as cardiac arrest, or sudden death)
    - Family history of
        - Unexplained syncope
        - Unexplained seizures
        - Sudden death in young people
- For adults
    - Age >65
    - Female sex
    - Electrolyte imbalances (specifically low serum potassium and magnesium levels)
    - High or toxic serum levels of the suspected medication
    - Preexisting cardiovascular impairment, such as bradycardia (Washington 2012)

- Taking two or more medications that may cause QT prolongation
- Myocardial infarction
- Heart failure
- Genetic polymorphism
- History of QT prolongation
- Brain injury (Abrishamkar, 2012)

If there are red flags or risk factors

- Do baseline ECG prior to starting potentially QT-prolonging medication
- Repeat ECG when the medication reaches a steady state at the target dose.

Medication-induced QT Prolongation

Epidemiology

- **Medication-induced QT prolongation is the most common cause of long QT syndrome**

Pathophysiology

- Due to taking one or more medications that prolong the QT interval
- Mechanisms of medication-induced QT prolongation
  - Pharmacodynamic Interaction: Using more than one medication that prolongs the QT interval increases the risk of torsades de pointes and ventricular arrhythmia.
  - Pharmacokinetic Interaction: Even medications that do not prolong the QT interval themselves can increase the risk of QT prolongation by inhibiting the metabolism of medications that do prolong the QT interval
    - E.g. macrolide antibiotics and antifungals which inhibit the CYP3A4 enzyme.
    - E.g antidepressants that may inhibit the CYP2D6 enzyme
  - Effects on Electrolytes: Hypokalaemia and hypomagnesemia can increase the risk of QT prolongation
    - E.g. diuretics can interact with QT-prolonging medications by causing hypokalaemia.
    - E.g. long term proton pump inhibitors may cause hypomagnesemia which can increase the risk for QTc prolongation

Medications with Higher RIsk of QTc Prolongation at Therapeutic Dosages

SSRIs	Citalopram (Celexa) > 40 mg daily (Washington, 2012) Escitalopram (Cipralex) Venlafaxine > 300 mg daily (Washington, 2012) Note: • **All SSRIs** at plasma concentration **above therapeutic level** are associated with QT prolongation
TCAs	Amitriptyline Imipramine Clomipramine Trimipramine Maprotiline Desipramine Nortryptyline
Second generation antipsychotics (SGA)	Ziprasidone (Zeldox in Canada / Geodon in USA) (most compared to other newer antipsychotics) Iloperidone Quetiapine (Seroquel)

First-generation antipsychotics	Thioridazine (Mellaril) Mesoridazine (Serentil) Chlorpromazine (Thorazine) Haloperidol (Haldol)

Reference: Dietle, 2015; Credible Meds (www.crediblemeds.org).

Medications with Lower Risk of QTc Prolongation at Therapeutic Dosages

SSRIs	Fluoxetine (Prozac) Fluvoxamine (Luvox) Sertraline (Zoloft) Paroxetine (Paxil)
SNRIs	Duloxetine (Cymbalta) Desvenlafaxine (Pristiq) Levomilnacipran Milnacipran
TCAs	Doxepin
Second generation antipsychotics (SGA)	Olanzapine Risperidone Paliperidone Aripiprazole Asenapine Clozapine Brexiprazole Lurasidone
First-generation antipsychotics	Loxapine

Reference: Dietle, 2015; Credible Meds (www.crediblemeds.org).

Assessment / History including Medication History

HPI	Any history of cardiac events or symptoms? Any history of disordered eating, vomiting or diarrhea that could cause electrolyte disturbance or bradycardia
Medication history	**A**ny psychiatric medications with a higher risk of QT prolongation? See Table above Are there drug interactions that can increase the level of a QT prolonging medication? Any medications that can alter serum electrolytes? What is the dose intensity of the QT prolonging medications?
Past Medical History	Risk factors for drug-induced TdP • Any congenital long QT syndrome? • Any previous TdP

Diagnosis of Medication-Induced QT Prolongation

Is the following present?

- Presence of QT prolongation, plus
- Presence of QT prolonging medications

If so, then:

- Make a presumptive diagnosis of medication-induced QT prolongation.
- Stop QT prolonging medications

Does the ECG normalize after this step?

- If so, this confirms the diagnosis of medication-induced QT prolongation.

Differential Diagnosis (DDx) of Medication-Induced QT Prolongation

Other conditions that may also cause QT prolongation are:

- Congenital/familial long QT syndrome
    - Patients with prolonged QT in absence of secondary causes for QT prolongation such as medication-induced (European Society of Cardiology, 2006)
    - Epidemiology
        - Rare; about 1 in every 7,000.
    - Presentation may be:
        - Asymptomatic with no symptoms suggesting that they have QT prolongation, OR
        - Symptomatic with cardiac symptoms such as
            - Syncope (the most common symptoms), often triggered by exertion or sound; usually the rhythm returns to normal within a minute, and the patient regains consciousness without disorientation.
            - Generalized seizure: When the long QT syndrome dysrhythmia persists longer, it may present with a generalized seizure.
            - Sudden death: In a small minority, the rhythm degenerates further into torsades de pointes and ventricular fibrillation, and unfortunately, some patients will present with sudden death as the first indication of QT prolongation.
        - Triggers include exercise, swimming or emotion, or simply sleeping at night.
    - Red flags for congential long QT syndrome
        - Any of these red flags that may indicate a congenital (familial) form of long QT syndrome, such as:
            - Hearing loss deficit
            - Family history of cardiac arrest and sudden death at early age
            - Long QT persist despite stopping medications causing prolonged QT
- Acquired QT prolongation from other risk factors and conditions such as:
    - Female Sex
    - Older age
    - Bradycardia
    - Electrolyte abnormalities
    - Low left ventricular ejection fraction, left ventricular hypertrophy
    - Myocardial infarction, myocardial ischemia,
    - Cerebral hemorrhage

Physical Exam

There are no pathognomonic findings on physical exam to indicate QT prolongation.

Nonetheless, physical exam is useful to rule out other potential reasons for arrhythmic and syncopal events in otherwise healthy people such as:

- Heart murmurs caused by hypertrophic cardiomyopathy
- Valve defects

Some patients may show:

- Excessive bradycardia for their age
- Hearing loss (congenital deafness), indicating the possibility of JLN syndrome.
- Skeletal abnormalities, such as short stature and scoliosis are seen in LQT7 (Andersen syndrome)
- Congenital heart diseases, cognitive and behavioral problems, musculoskeletal diseases, and immune dysfunction may be seen in those with LQT8 (Timothy syndrome)

Investigations

When there is suspicion, consider the following:

- ECG of the patient and family members
- Serum potassium and magnesium levels
- Thyroid function tests
- Genetic testing of the patient and family members
- Pharmacogenomic testing, to see if there are troubles metabolizing medications.

Management: Prevention of Medication-Induced QT Prolongation

Assess modifiable risk factors for QT prolongation	Modify risk factors such as • Bradycardia • Hypokalaemia ◦ Avoid medications that reduce serum potassium. ◦ Correct potassium deficiency. • Hypomagnesaemia • Avoid medications that reduce magnesium level. • Correct magnesium deficiency. • Hypocalcaemia • Drugs that induce QT interval prolongation.
Reduce risk factors	Use alternative agents that are purported to have less risk of QT prolongation such as • Lorazepam (Ativan) • Loxapine (Loxapac) • Lurasidone (Latuda) • Bupropion (Wellbutrin) • Vortioxetine (Trintellix) Are QT interval prolonging medications required? If so, use lowest effective dose. Correct underlying causes of electrolyte abnormalities or medication-induced bradycardia.
Monitor	Consider ECG: • At baseline prior to initiation or dose increase of QT interval prolonging medication • Once QT interval prolonging medication reaches steady state (5 half-lives). • Every month for 6 months, then every 6-12 months thereafter.
Educate the patient	Educate the patient to seek medical help if s/he has any of the following: • Palpitations • Lightheadedness • Dizziness • Syncope Educate the patient to inform any other healthcare professionals if they: • Have congenital long QT syndrome. • Have a previous history of medication-induced QT prolongation.

When and how to modify therapy	Where a patient has risk factors and is to be prescribed a QT prolonging medication, consider • Changing to an alternative medication that is not known to prolong the QT interval if possible. If baseline ECG shows QTc of 480 ms • Consider an alternative medication that does not cause QT prolongation. • Correct electrolyte imbalances. Does follow-up ECG show QTc ≥500 ms and/or absolute increase in QTc ≥60 ms? If so, then: • Discontinue QT prolonging medication. • Correct electrolyte imbalances. • Refer to cardiologist.

Reference: Trinkley, 2013; National Medicines Information Centre, 2015; NHS Greater Glasgow and Clyde Medicines Information Service, 2012

When and Where to Refer

Emergency Department

- Does patient have risk factors for QT prolongation AND experience a cardiac event (e.g. syncope, cardiac arrest)? If so, then refer for assessment in the Emergency Department.
- Has patient has taken an overdose of a QT-prolonging medication (such as an SSRI)? If so, then refer to Emergency Department for close cardiac monitoring.

Cardiology

- Is long QT persistent despite cessation of offending medications? Consider referring to cardiology to consider other causes (such as familial long QT syndrome).
- Is it a pediatric patient at high risk of QTc prolongation? If so, then consider referral to cardiology prior to initiating any psychotropic meds with a known side effects of QTc.

Case, Part 2

Jan is a middle-aged female in your practice. Several years ago, she had been diagnosed with anxiety and treated with Citalopram, which she continues to take. A few months ago, the dosage was raised to 40 mg daily. She now presents to you with fainting spells and chest pains. What are you going to do?

ECG shows QTc prolongation. You taper her Citalopram down to 10 mg daily, and you recommend counselling/therapy to ensure that he has non-medication strategies for her anxiety.

A repeat ECG shows no further QTc prolongation, thus confirming that her Citalopram may have been the cause of her QTc prolongation.

Patient Handouts

Acquired Long QT Syndrome
http://www.nhs.uk/conditions/long-qt-syndrome/documents/acquired-lqt-brochure06.pdf

Primary Care Reviews

Grindrod K, Nagge J: Simplifying QT prolongation for busy clinicians, Canadian Family Physician April 2019, 65(4) 268-270. Retrieved Apr 20, 2019 from http://www.cfp.ca/content/65/4/268

Practice Guidelines

ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. Retrieved Dec 29, 2016 from http://reference.medscape.com/medline/abstract/16935995

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Washington N: Which psychotropics carry the greatest risk of QTc prolongation, Current Psychiatry. 2012 October; 11(10): 36-39. Retrieved Dec 13, 2016 from http://www.mdedge.com/currentpsychiatry/article/64870/anxiety-disorders/which-psychotropics-carry-greatest-risk-qtc

Recommended Websites

Credible Meds
Up-to-date listings of medications that affect QT, including a downloadable app.
http://crediblemeds.org

About this Document

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Disclosures

The authors report no financial relationship with any company whose products are mentioned in this article or with

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