PALLIATIVE PEARLS
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Drug-induced QT Prolongation: A Review
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OVERVIEW

Understanding Drug Interaction Risk in Advanced Illness

Terminally ill adults often possess multiple characteristics that increase their risk for clinically significant drug interactions. Common risk factors include:[1]

- Advanced age
- Polypharmacy (the routine use of multiple medications)
- Addition of new medications for pain and symptom management
- Multiple chronic disease state comorbidities

Drug interactions can occur in several ways:

- Drug-drug interactions: between two or more medications
- Drug-disease interactions: between a medication and an underlying disease state
- Drug-food interactions: between a medication and food or beverages

Given the continually expanding number of available medications, it is unrealistic to remember every potential drug interaction. However, recognizing patient characteristics that increase interaction risk and being familiar with common high-risk medications can help clinicians develop safer and more effective care plans.

Long QT Syndrome and Drug-Induced QT Prolongation

Long QT syndrome (LQTS)(aka. QT prolongation), is a disorder of cardiac repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG).[2] LQTS can be congenital or acquired and is associated with an increased risk of polymorphic ventricular tachycardia, also known as torsades de pointes (TdP). TdP is a rare type of arrhythmia, however, is life-threatening thus warranting attention and recognition of precipitating risk factors. Drug-induced LQTS is the most common cause of acquired LQTS and will be the focus of this resource.[2,3]

UNDERSTANDING THE QT INTERVAL

Basic Cardiac Electrophysiology

The ECG reflects the heart's electrical conduction during each heartbeat and is represented by a series of waves and complexes:[4]

- At rest, cardiac cells are polarized, meaning there is no active electrical conduction. A heartbeat begins in the sinoatrial (SA) node, where an electrical impulse initiates a wave of depolarization that spreads through the atria, producing the P wave.
- The electrical impulse then travels through the atrioventricular (AV) node, His bundle, right and left bundle branches, and Purkinje fibers. This conduction results in atrial repolarization and ventricular depolarization, which are represented by the QRS complex.
- Ventricular repolarization completes the cardiac cycle and produces the T wave.

The ECG contains both waves and the intervals between them. The **QT interval** represents the total time required for ventricular depolarization and repolarization, measured from the beginning of the QRS complex to the end of the T wave.

- Because heart rate influences repolarization time, the QT interval is commonly adjusted for heart rate and reported as the rate-corrected QT interval (QTc). In this article, "QTc" denotes measured values, while "QT" is used for general references.
- At a heart rate of 60 beats per minute, a normal QTc is generally 420 milliseconds (msec) or less.[4]
- During the QT interval, sodium, potassium, and calcium ions move across cardiac cell membranes. Disruptions in these ion movements—such as excess sodium entry or reduced potassium exit—can delay repolarization, resulting in **QT interval prolongation**.[6] For a visual comparison of a normal ECG and one with a prolonged QT interval, refer to the Cleveland Clinic online article, Long QT Syndrome (LQTS).[5]
    - A prolonged QTc is generally defined as:[2]
        - ≥ 470 msec in adult males
        - ≥ 480 msec in adult females
    - The risk of serious cardiac events increases as the QTc lengthens. Ventricular arrhythmias like TdP are more commonly associated with a QTc greater than 500 msec.[6] For a side-by-side illustration of a normal ECG and the characteristic *twisting pattern* of TdP, refer to the Cleveland Clinic online article, Torsades de Pointes.[7]

Considerations in Hospice and Palliative Care

In hospice and palliative care, patient goals of care often do not include routine diagnostic procedures such as ECG monitoring. Without baseline or follow-up ECG measurements, clinicians must rely on the following to mitigate overall patient risk for TdP:

- Identification of patient-specific risk factors
- Recognition of symptoms suggestive of arrhythmia
- Careful medication review

RISK FACTOR ASSESSMENT

Multiple factors can contribute to or worsen QT prolongation. When these risk factors occur in combination with QT-prolonging medications, the likelihood of developing torsades de pointes increases substantially.[2,6,8]

The following table outlines common causes and potentiating factors associated with QT prolongation.

Table 1: Causes and Potentiators of LQTS (i.e., QT Prolongation)

Congenital		
• Jervell and Lange-Nielsen syndrome	• Romano-Ward syndrome	• Idiopathic
Acquired		
Metabolic disorders • Hypokalemia • Hypomagnesemia • Hypocalcemia • Starvation • Anorexia nervosa • Liquid protein diets • Hypothyroidism	Other conditions • Myocardial ischemia or infarction • Bradycardia* • Subarachnoid hemorrhage • HIV infection • Hypothermia	Other factors • **Medications** • Age > 65 years • Female gender** • Liver failure (e.g., cirrhosis)^ • Renal failure (GFR ≤ 30ml/min)^
* Slow heart rate prolongs repolarization ** Female baseline QT intervals are approx. 20 msec greater than male ^ QT-prolonging drug(s) may accumulate		

SYMPTOMS ASSOCIATED WITH ACQUIRED QT PROLONGATION

Torsades de pointes (TdP) can significantly reduce cardiac output, resulting in tissue hypoxia. Episodes lasting longer than 10 seconds may lead to syncope, seizure-like activity, or death if the arrhythmia does not spontaneously terminate. Shorter episodes may not cause loss of consciousness and can present with a range of symptoms that warrant recognition and further evaluation.[2,8]

Presyncope is the most common symptom associated with TdP and is often experienced as lightheadedness, with or without palpitations. Although palpitations can be associated with TdP, they are not specific to this arrhythmia. [2]

Key characteristics include:

- A prodromal or "near-fainting" sensation (occurs more frequently than syncope).[10]
- Symptoms that typically last seconds to minutes and are often described as:[10]
    - "Nearly blacking out"
    - "Nearly fainting"
- Associated manifestations may include: [10]
    - Lightheadedness
    - A feeling of warmth
    - Diaphoresis
    - Nausea
    - Visual blurring or temporary visual loss
- Pallor may be observed by caregivers or bystanders.[10]

Syncope is a transient, self-limited loss of consciousness that typically occurs when ventricular arrhythmias are faster or more sustained, resulting in hypotension and hemodynamic compromise.[2,11]

Important considerations include:

- Syncope may occur without preceding palpitations.[2]
- Episodes can indicate a higher-risk arrhythmia and warrant prompt assessment.

Cardiac arrest can occur when ventricular arrhythmias become rapid and sustained. This presentation may be more common in patients with underlying structural or functional heart disease or other significant cardiac comorbidities.[2]

IDENTIFYING QT-PROLONGING MEDICATIONS

Numerous medications have been associated with QT prolongation, making a systematic approach to medication assessment essential. The goal is to preserve therapeutic benefit while minimizing the risk of TdP.[9]

CredibleMeds® is a widely recognized resource that promotes the safe use of medications associated with QT prolongation. Its "QT Drugs List" categorizes medications according to their TdP risk: [9]

- Known Risk: Clear association, even when taken as recommended (*see Table 2*).
- Possible Risk: Currently lack evidence for risk of TdP when taken as recommended (*see Table 3*).
- Conditional Risk: Associated with TdP however;
    - Only under certain conditions, such as high doses, electrolyte abnormalities (e.g., hypokalemia), or concurrent use of interacting medications OR
    - Indirectly by causing electrolyte disturbances or by increasing the levels of QT-prolonging medications through drug interactions.

For the sake of brevity, examples of conditional risk medications are intentionally omitted from this clinical feature article and may be reviewed in the CredibleMeds® database; registration and access are free, and the content is updated regularly.[9]

Table 2: Palliative Medications with Known Risk of TdP[8,9]	
Class	Example Medications
Antiarrhythmics	• Class IA agents: quinidine, disopyramide, procainamide • Class III agents: sotalol, dofetilide, amiodarone, dronedarone
Antimicrobials	• Fluoroquinolones: ciprofloxacin, levofloxacin, moxifloxacin • Macrolides: erythromycin, azithromycin • Antifungals: fluconazole (Diflucan®), ketoconazole, itraconazole
Conventional Antipsychotics	• Haloperidol • Chlorpromazine • Thioridazine
Selective Serotonin Reuptake Inhibitors (SSRIs)	• Citalopram (Celexa®) • Escitalopram (Lexapro®)
Miscellaneous	• Donepezil (Aricept®) • Methadone • Ondansetron (Zofran®)[12]*
* Ondansetron dosage form consideration: TdP risk is associated predominantly with intravenous (IV) administration. To reduce risk, do not exceed 16mg IV as a single dose and follow recommended infusion rates.[12]	

Table 3: Palliative Medications with Possible Risk of TdP[9]	
Class	Example Medications
Select Analgesics	• Tramadol (Ultram®) • Buprenorphine (Butrans®) • Hydrocodone extended-release (Hysingla®, Zohydro®)
Atypical Antipsychotics	• Aripiprazole (Abilify®) • Clozapine (Clozaril®) • Pimavanserin (Nuplazid®)
Select Antidepressants	• Tricyclic Antidepressants (TCAs): Desipramine, Nortriptyline • Mirtazapine (Remeron®) • Venlafaxine (Effexor®)
Select Antiemetics	• Promethazine (Phenergan®) • Dolasetron (Anzemet®) • Granisetron (Kytril®) • Palonosetron (Aloxi®)

MEDICATION MANAGEMENT CONSIDERATIONS

There is no consistent approach among hospice and palliative care prescribers regarding QT-prolonging interactions. Some clinicians place little emphasis on them, while others actively adjust therapy in response.[13–15] A balanced approach is often most appropriate—one that neither dismisses all warnings nor overreacts to them, but instead prioritizes patient comfort and safety while minimizing unnecessary risks and medication burden. The following proactive considerations can help guide medication management in patients at risk for torsades de pointes (TdP) and mitigate potential harm:

- Actively address bothersome symptoms related to the interaction when they arise and jeopardize patient comfort (See *Symptoms Associated with Acquired QT Prolongation* section).
- Actively identify medication adjustment opportunities, when feasible (e.g., patients with longer prognoses), and within patient goals of care:
    - Use the lowest effective dose: Avoid high doses or concentrations of QT-prolonging drugs and administer orally – QT prolongation risk is route- and dose-dependent for several medications.[2,16]
    - Evaluate cytochrome P450 (CYP450) drug interactions: Recognize that many QT-prolonging medications are metabolized by CYP450. It's important to identify them as well as medications that may inhibit them.[6]
        - For example, ranolazine (Ranexa®) and grapefruit juice are inhibitors of isoenzyme 3A4. Methadone is a 3A4 substrate and concurrent use with either of these agents increases methadone concentrations and further increases the risk of QT prolongation.[1]
    - Avoid the use of multiple QT-prolonging medications: Avoid combining two or more QT-prolonging medications whenever possible, as additive effects can significantly increase the risk of TdP.[2,3,6,8,9]
    - Assess patients regularly for contributing factors to electrolyte disturbance(s): Electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) can increase susceptibility to QT prolongation and TdP. Assess patients for opportunities to deprescribe medications and for potentially reversible conditions. Examples:
        - Use diuretics purposefully; balance symptom management relief while preventing excessive fluid loss.[2,6,8,9]
        - Manage nausea and/or vomiting that contributes to decreased oral intake (food, liquids) and resulting dehydration.

SUMMARY

Although several commonly used palliative care medications are associated with QT prolongation, accurately predicting an individual patient's risk remains challenging. Pharmacists can play a critical role in identifying QT-prolonging medications, evaluating drug interactions, recommending therapeutic alternatives and helping clinicians balance treatment benefits against patient-specific risk factors.

CredibleMeds® is a valuable resource that provides medication-specific risk classifications, educational tools, literature references, and guidance for clinicians caring for patients with or at risk for LQTS.[9]

Equally important is thorough documentation of medication-related assessments, patient counseling, and communications with interdisciplinary team members. Clear documentation serves as both a historical record and a prospective care tool, helping to support ongoing monitoring, facilitate continuity of care, and reduce duplication of effort among team members.

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