Clinical Guide for Community Pharmacists to Evaluate Risks and Manage QTc Prolongation Due to Drug-Drug Interactions

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Background

- Long QT syndrome (QT prolongation) is a condition where the interval between the beginning of the QRS complex to the end of the T wave is lengthened, reflecting delayed myocardial repolarization.[1]
- "QTc" denotes the QT interval corrected for a patient's heart rate.[2]
- QTc prolongation can precipitate to torsades de pointes (TdP), a life-threatening ventricular tachyarrhythmia that results in sudden death.[1]
- It is due to genetic susceptibility and medications.[1]
- Clinical significance of QTc prolongation is underestimated and overvalued.
- Currently, there are no validated risk scales that assess QTc prolongation risk for outpatient or ambulatory patients.

Objectives

1) To identify the recommendations posed by clinicians in evaluating QTc prolongation risks associated with three commonly-encountered drugs (citalopram, domperidone, ciprofloxacin) that may result in QTc prolongation alerts in the community pharmacy; and,

2) To develop a clinical algorithm or therapeutic thought process for community pharmacists to effectively evaluate and manage these drug-drug interactions (DDIs).

Methods

The recommendations were compiled through 2 methods.

1) Environmental Scan of National Regulatory Bodies and Clinical Guidelines

Regulatory Bodies
- Health Canada
- United States Food and Drug Administration (FDA)

Clinical Guidelines
- Canadian Network for Mood and Anxiety Treatments American Psychiatric Association (CANMAT)
- American Association of Gastroenterology (AAG)
- Canadian Journal of Urology (CJU)
- Canadian Thoracic Society (CTS)

2) Systematic Review of Primary Literature

MEDLINE (PubMed)

Search criteria: (qt prolongation OR prolonged qt OR qt interval OR qtc interval OR long qt syndrome) AND (citalopram OR domperidone OR ciprofloxacin)
222 articles

Time frame: 2006 – 2016, inclusive
156 articles

Patients ≥19 years old
153 articles

Randomized controlled trials, meta-analyses

Pre-programmed "Additional Filter" criterion	Manual perusal

7 articles total

Citalopram:	Domperidone:	Ciprofloxacin:
5 articles	1 articles	1 article

Results & Key Findings

Figure 1. Clinical guide for evaluation of general QTc prolonging drug-drug interactions.[3,4]

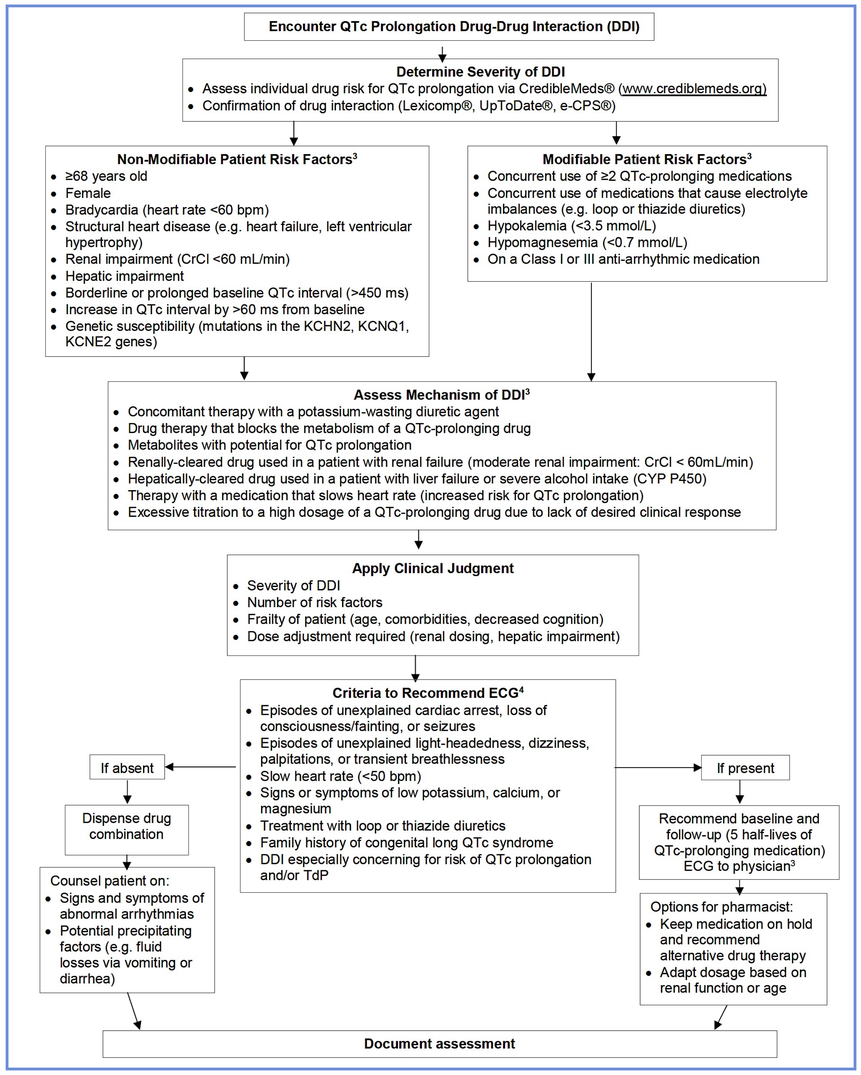

Table 1. Results from environmental scan and systematic review.[5-7]

Citalopram	Domperidone	Ciprofloxacin
▪ **Health Canada/FDA**: >40 mg should not be used (20 mg for elderly) due to dose-dependent QTc prolongation. ▪ **CANMAT**: SSRIs carry a very low risk of TdP and other arrhythmias. ▪ **Primary literature**: most showed increase in QTc interval; Beach et al considered 40mg as max dose to be overly conservative.[5]	▪ **Health Canada**: contraindicated in QTc prolongation, max daily dose 30 mg. ▪ **AAG**: suggest baseline ECG. ▪ **Primary literature**: Boyce et al demonstrated a 3-fold increase in domperidone concentrations with concomitant use with a CYP 3A4 inhibitor (ketoconazole) and recommended that the combination should not be administered.[6]	▪ **Health Canada/FDA**: minimal guidance. ▪ **CJU/CTS**: no mention. ▪ **Primary literature**: Tsikouris et al observed that ciprofloxacin is the least torsadogenic fluoroquinolone, and in healthy patients, a 7-day treatment does not increase the risk for TdP.[7]

Figure 2. Clinical guide for evaluation of citalopram QTc prolonging drug-drug interactions.[8]

Conclusions & Future Directions

- Evaluation of QTc prolonging drug-drug interactions is highly reliant on the clinical judgment of the community pharmacist, involving an analysis of the patient's risk factors and the severity of the drug-drug interaction
- Upon assessment, the community pharmacist should:
  - Place the medication on hold if the TdP risk is high
  - Recommend baseline and steady-state ECG testing (at 5 half-lives of the medication)
  - Provide alternative drug therapies, or dose-adjust based on the patient's renal or hepatic function
- Decision should always be documented and signs and symptoms of TdP should be communicated to the patient
- Point-of-care ECG testing may aid community pharmacists in the assessment of patients at risk for TdP

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