# A MULTI-INCIDENT ANALYSIS ON QT-PROLONGATION IN THE COMMUNITY

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## INTRODUCTION

The QT interval is the time measured from the initiation of the QRS complex to the termination of the T wave during an electrocardiogram (ECG).[1] This interval represents the time between ventricular depolarization until subsequent repolarization of the ventricles.[1] Long QT syndrome (LQTS) refers to a case in which the QT interval is abnormally long indicating an undesirable delay in cardiac repolarization. This syndrome can either be a result of genetic inheritance or is acquired.[1] The presence of a prolonged QT interval increases the risk of developing cardiac arrhythmias, most clearly torsades de pointes (TdP), a life threatening form of polymorphic ventricular tachycardia associated with rapid heart rates of 160 to 240 beats per minute.[1]

TdP may present with symptoms of palpitations, dizziness, shortness of breath or syncope and in some cases this can be transient.[1,2] However, in most other cases TdP will deteriorate into ventricular fibrillation that can result in sudden cardiac death.[1,2]

Drug therapy is the most common cause of acquired LQTS; although some associated with greater risks than others, there are over 100 drugs available that have the potential to cause QT prolongation and many of these drugs are amongst the top 100 medications prescribed in Canada (Table 1).[1,3,4]

*For a full list of QT-interval prolonging drugs see www.crediblemeds.org/

**Table 1: Examples of Top 100 Prescribed Drugs Associated with Risk of TdP**[3,4]

| | | |
|---|---|---|
| **Known TdP risk:** Drugs that prolong the QT interval and are clearly associated with a known risk of TdP even when taken as recommended. | | |
| • Azithromycin<br>• Ciprofloxacin<br>• Citalopram | • Clarithromycin<br>• Domperidone | • Donepezil<br>• Escitalopram |
| **Possible TdP risk:** Drugs that can cause QT prolongation but currently lack evidence for a risk of TdP when taken as recommended. | | |
| • Venlafaxine<br>• Risperidone | | |
| **Conditional TdP risk:** Drugs that are associated with TdP but only under certain circumstances of their use or by creating conditions that facilitate or induce TdP. | | |
| • Trazodone<br>• Sertraline<br>• Amitriptyline | • Paroxetine<br>• Pantoprazole | • Hydrochlorothiazide<br>• Furosemide |

The objective of this multi-incident analysis is to examine medication incidents involving QT prolongation interactions that are commonly encountered within the community setting. Common themes and potential contributing factors are identified and are presented along with suggested safety recommendations (Tables 2, 3, 4).

## METHODS

A qualitative, multi-incident analysis was conducted using anonymous reports submitted to the Institute for Safe Medication Practices Canada (ISMP Canada) Community Pharmacy Incident Reporting (CPhIR) Program.[5] Medication incidents reported with keywords "QT", "TdP", "Torsades de pointes", "Prolong*", and "QT-int*" were extracted from the CPhIR Program from April 2010 to June 2016. Ultimately, 92 incidents met the inclusion criteria and were included in this multi-incident analysis. At least two ISMP Canada analysts independently reviewed and analyzed the medication incidents.

## LIMITATIONS

The results available for this analysis may be limited due to the voluntary reporting nature of the CPhIR Program. The quality of data available may be influenced by reporter bias and the paucity of most reported incident descriptions. Some assumptions had to be made based on the analyst's knowledge and experience of community pharmacy practice. The "Incident Examples" provided in Tables 2, 3, and 4 were limited by what was inputted by pharmacy practitioners to the "Incident Description" field of the CPhIR program.

## RESULTS

**Table 2:** Theme 1 - Prescriber Triggered Potential for QT Prolongation

| Incident Examples | Commentary |
|---|---|
| A patient was prescribed both ciprofloxacin and clarithromycin for a lung infection. The combination of these drugs increases the risk of QT prolongation. The physician was notified and decided to only use clarithromycin. The physician was not aware this combo could potentially have a negative effect.<br><br>A patient was given a prescription for ciprofloxacin in the event a UTI develops. The patient has a history of tachycardia and MI and is currently on Sotalol and Elavil®. The pharmacy recognized the potential for QT prolongation given all the risk factors and drug interactions and [patient] was advised to return to prescriber for a different antibiotic.<br><br>A patient was prescribed octreotide acetate omega and domperidone. These two medications have a drug interaction of increasing QT prolongation risk. The prescriber was notified and they decided to cancel the domperidone. The prescriber indicated they only ordered it based on a recommendation from the gastroenterologist. | **The list of QT prolonging agents is vast and is frequently updated** as new evidence arises. Prescribers may not be familiar with every single agent.<br><br>**Despite the wide implementation of electronic medical records (EMR) software in ambulatory care, a majority of prescribers do not fully utilize the advanced functions provided (e.g. review electronic alerts such as drug dose and interactions).**[6]<br><br>**Episodic care (e.g. walk-in clinics) and transitions of care (e.g. specialists) may leave gaps of information transfer** regarding patient's medical history and medication history thus leading to potential risk of prescribing errors. |

**Table 3:** Theme 2 - Potentially Inappropriate Pharmacist Interventions

| Incident Examples | Commentary |
|---|---|
| A patient on quetiapine was prescribed Zithromax®. Pharmacy contacted prescriber to change it to amoxicillin due to QT prolongation.<br><br>A patient on citalopram was prescribed rabeprazole. Pharmacy noted they interact to increase QT interval. The prescriber was contacted and had rabeprazole changed to omeprazole.<br><br>Pharmacist noticed a patient was on omeprazole 20 mg and citalopram 60 mg. The combination of PPI & high dose citalopram may increase QT prolongation risk. The prescriber was contacted and agreed to decrease the citalopram dose. | Although pharmacies have interaction checkers, the **responsibility for evaluating the clinical significance of a detected interaction** and making the most appropriate intervention when necessary is on the onus of pharmacists.<br><br>Many pharmacists may rely heavily on technology for their clinical decision support capabilities. **The interventions made may lack clinical significance due to the absence of a comprehensive patient assessment.** (Note: Majority of the reporters had not indicated any apparent patient assessment prior to making an intervention. In reality, assessment may or may not have occurred.)<br><br>Potential consequences of acting on interaction alerts without proper patient assessment may include: **delayed treatments, switches to suboptimal therapies, and a waste of time and resources.** |

**Table 4:** Theme 3 - Patient Potentiated Risk for Harm

| Incident Example | Commentary |
|---|---|
| A patient had their prescription faxed to the pharmacy. The prescription was for an antibiotic to treat a UTI. Upon checking with their regular pharmacy for a medication list, it was found this antibiotic has a QT prolongation interaction with the patient's regular medications. The prescriber was contacted and the antibiotic was changed. | **When patients are consulting or seeking care from multiple prescribers (e.g. from the use of walk-in clinics or specialists clinics),** they may fail to fully communicate all pertinent medical and medication information needed for the clinician to safely prescribe.<br><br>**Attending multiple pharmacies** may potentiate harm by limiting pharmacists' access to a complete medication history of the patient. |

## SAFETY RECOMMENDATIONS

### FOR PRESCRIBERS

**Ensure that computerized physician order entry systems have programming or the functionality to detect drug-drug and drug-disease interactions and are updated regularly.[7]**

Use of a computer clinical decision support system (CDSS) incorporating identification of QT prolonging interactions will influence the prescribing of drugs with QT liability and reduce the risk of QT prolongation. The alerts will also act as a reminder to physicians to identify patients with TdP risk factors. Keep in mind that although some prescribers may already be using this software, ongoing evaluation of the alert frequency is essential to reduce alert fatigue.[8]

**Ensure a patient's complete medication record is obtained.**

As shown in the multi-incident analysis, most incidents involved interactions with short-term agents (e.g. antibiotics) which were commonly prescribed in episodic care such as walk-in clinics and urgent care centres. It is pertinent for the prescriber to be aware of the patient's current medical and medication information in order to prescribe safely. Additionally, all encounters should be documented and communicated to the patient's primary care physician if possible.

### FOR PHARMACISTS

**Evaluate and update alerts in the clinical decision support system (CDSS).[8]**

Use a reliable resource, such as Credible Meds (www.crediblemeds.org), to review the alerts that appear when an interaction is detected with a drug associated with QT prolongation. Regularly review and try to reduce the frequency of warnings that are not clinically significant. Be aware that filtering drug interactions may prevent alert fatigue, but may also limit the CDSS's ability to detect interactions if its settings are overly restrictive.[8] If modifications are made, inform all pharmacy staff of the alerts that have been added or removed.

**Avoid over-reliance on technology.[8]**

Do not base all clinical decisions solely on system alerts or notifications. Clinical decision support systems (CDSSs) are designed, as their name suggests, to provide support and should always be used in conjunction with the pharmacist's clinical assessment and professional judgement.

Over-reliance may lead to automation biases.[9] An absence of an alert does not mean there is absolutely no concerns or issues with the prescription or medication order; this could be affected depending on the system alert settings and how up-to-date the CDSS may be. On the contrary, a generated alert does not always imply clinical significance.

**Educate patients and caregivers. Monitor and provide regular follow-ups.[8]**

Ensure that patients are informed of the clinical symptoms of QT prolongation that should prompt them to seek immediate medical attention (e.g. palpitations, syncope, light-headedness, or dizziness).

Recommend patients to carry an updated medication list when interacting with healthcare professionals. Patients should also be educated to communicate their comorbid conditions or any changes of their existing medical conditions to clinicians of their circle of care.

Pharmacists can also play an integral part by routinely following up with patients and monitor their medication therapy management.

**Perform a risk assessment and ensure a standardized communication system is in place to notify prescribers of recommendations and interventions with respect to patient care.[7]**

Upon realization of a potential QT interval prolongation, perform a risk assessment (Appendix 1) to determine its clinical significance. To properly complete an assessment, an updated medication list and medical history should be obtained from the patient if not readily available. Interventions may or may not be required depending on the overall risk assessment.

A baseline ECG should be ordered prior to initiating therapy with a QT prolonging agent in an at-risk patient.[10,11] Discuss with prescriber to request one, if necessary. This will aid in subsequent monitoring efforts for TdP.

### FOR PATIENTS

**Carry an up-to-date medication list to share with healthcare providers in the circle of care.**

Ideally, patients should be aware of all the medications they are currently using so that an up-to-date medication list can be communicated to all healthcare providers in their circle of care. Realistically, carrying an accurate list of current medications that can be shared with healthcare providers would be the next best option. Consider the use of ISMP Canada's MyMedRec app (http://www.knowledgeisthebestmedicine.org/index.php/en/app/) for smartphones that can act as a portable health and medication record.[12]

## CONCLUSIONS

This multi-incident analysis has identified common areas where QT prolongation incidents may occur in community pharmacy practice. Vulnerabilities are recognized in different stages of the medication-use process. Prescribers, pharmacists, and patients can collaborate to prevent these medication incidents from happening in the future.

### SUGGESTED RESOURCES ON QT PROLONGATION

CredibleMeds - www.crediblemeds.org

Development and Validation of a Risk Score to Predict QT Interval Prolongation in Hospitalized Patients - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3788679/pdf/nihms490533.pdf

With the support of the Canadian Society of Hospital Pharmacists (CSHP) Foundation 2015 Education Grant, ISMP Canada is currently developing ToolQit, an evidence-based communication and decision-guiding tool for pharmacists to evaluate the complexities of QT prolongation. We are currently seeking pharmacists to help test and evaluate our prototype. If you are interested, please email ISMP Canada at qt@ismp-canada.org. For further information regarding ToolQit, please refer to https://www.ismp-canada.org/ToolQit_QTprolongation/.

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# APPENDIX 1: QT-PROLONGATION RISK FACTORS CHECK-LIST [1,2,3,4,5]

The following list is based on evidence from literature, which indicates that about 90% of drug interaction-induced TdP occurred in patients with at least one other risk factor, and 74% of cases have two or more risk factors.[1] Modifiable risk-factors should be reversed prior to administration if the drug-interaction cannot be avoided.[1]

*DISCLAIMER: The following check-list is intended to facilitate the practitioner's assessment, and is not intended as substitution for the practitioner's professional judgement. Pharmacist is highly encouraged to communicate his/her assessment with the prescriber, even if he/she does not believe an intervention is necessary, to facilitate continuity of care.*

| Patient-related | Drug-related |
|---|---|
| ☐ Female sex<br>☐ > 60 year old<br>☐ Structural heart disease – eg. HF, LVH<br>☐ Renal impairment (drug clearance)<br>☐ Hepatic impairment (drug metabolism)<br>☐ Borderline or prolonged baseline QTc interval (>450ms)<br>☐ Bradycardia (HR < 60 bpm)<br>☐ Genetic susceptibility (mutations in the KCNH2, KCNQ1, KCNE2 gene)<br>☐ Hypokalemia (< 3.5 mmol/L)<br>☐ *Low-normal baseline potassium (3.5–4 mmol/L)<br>☐ Hypomagnesemia (< 0.7 mmol/L) | ☐ Already on ≥ 2 QTc-liability drugs<br>☐ Antiarrhythmic:<br>☐ Antidepressant:<br>☐ Antipsychotic:<br>☐ Other: _____<br>☐ On a Class I or **III antiarrhythmic:<br><br>*** Relative risk amongst §macrolides:<br>Clarithromycin ≈ Erythromycin > Azithromycin<br>*** Relative risk amongst ¥fluoroquinolones:<br>Moxifloxacin ≥ Levofloxacin > Ciprofloxacin<br>*** Relative risk amongst antidepressants:<br>TCA > SSRI (Citalopram > Escitalopram ≥ sertraline ≈ fluoxetine ≈ fluvoxamine ≈ paroxetine) |

* Investigate for drug-causes (eg. loop and thiazide diuretics); may also present in patients with eating disorders, predisposing them to electrolyte disturbances

** Highly potent IKr channel blockers which exhibit concentration-independent QTc-prolongation

*** Based on retrospective studies and reports, in conjunction with pharmacodynamic and pharmacokinetic characteristics of the drug. Note: With the exception of Class III antiarrhythmics, drug-induced QTc-prolongation is a dose-dependent phenomenon.

§ Dual-risk mechanism: intrinsic IKr channel blockers and potent inhibitors of CYP3A4 (with exception of azithromycin) which is involved in metabolism of many QTc-prolonging agents

¥ Not predominantly metabolized by CYP450

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