Concurrent Use of Multiple QT-Prolongating Agents in Members of UnitedHealthcare Community Plan

An Analysis of the Point-of-Sale Drug Interaction Edit

QT prolongation is an established adverse effect of numerous medications. Most patients with drug-induced QT prolongation are asymptomatic, however, a prolonged QT interval can cause cardiac arrhythmias such as torsades de pointes (TdP), a potentially life-threatening ventricular arrythmia. TdP is usually short-lived and terminates spontaneously, however, some patients experience palpitations, syncope, seizures, ventricular fibrillation (VF), cardiac arrest, and sudden death.[1,2]

A number of factors have been identified as increasing the risk of QT interval prolongation, in addition to genetic susceptibility. When patients with non-pharmacologic risk factors are prescribed one or more QT-prolonging drugs, they have an increased risk of QT prolongation.[3]

Non-Pharmacologic Risk Factors[3]	• Advanced age • Female gender • Electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia) • Hepatic or renal dysfunction
Pharmacologic Risk Factors[4]	• High drug doses or concentrations of QT-prolonging drugs • Rapid intravenous infusion of QT-prolonging drugs • **Concurrent use of > 1 QT-prolonging drug** • Use of QT-prolonging drug with one that slows drug metabolism due to inhibition of hepatic CYP P450 enzymes • Diuretic treatment (correlated with electrolyte abnormalities, heart failure)
ECG Abnormalities[3, 4]	• Baseline QT prolongation of T wave lability • Development of marked QT prolongation (QTc >500 milliseconds), T wave lability, or T wave morphologic changes • Cardiac conditions (bradycardia, heart block, heart failure, heart disease) • Congenital Long QT Syndrome or “silent” genetic mutations

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Many structurally and pharmacologically unrelated drugs have been implicated as a cause of acquired QT prolongation, and additional medications continue to be identified.[4] The major classes of drugs that prolong QT interval include antiarrhythmics, antimicrobials, antipsychotics, antihistamines, antidepressants, antiemetics, and gastric motility agents.[3]

Because of the increased pharmacologic risk of QT prolongation with concurrent use of more than one QT prolonging drug, United HealthCare Community Plan implemented an edit at the Point of Sale (POS) for known and possible risk QT-prolongating agents on August 1st, 2020. This QT prolongation edit is a soft edit, meaning it can be overridden by the pharmacist at the POS with the appropriate National Council For Prescription Drug Programs (NCPDP) codes. During the 4th quarter of 2020, 74% of UHC implemented soft edit claims that hit a drug-drug interaction edit were claims for members receiving more than one QT-prolongating agent. Of these QT-prolongating drug-drug interactions, 30% were resolved at the POS by the pharmacist, and the member did not receive two medications concurrently that could potentially cause QT prolongation.

QT-Prolonging Drugs to Hit the UnitedHealthcare Community Plan Drug-Drug Interaction Edit During 4th quarter 2020

Top 10 Individual Medications	Top 10 Medication Pairs
1. Escitalopram	1. Escitalopram + Trazodone
2. Citalopram	2. Escitalopram + Quetiapine
3. Ondansetron	3. Citalopram + Trazodone
4.Trazodone	4. Fluconazole + Metronidazole
5. Fluconazole	5. Escitalopram + Aripiprazole
6. Quetiapine	6. Escitalopram + Hydroxyzine
7. Hydroxyzine	7. Escitalopram + Risperidone
8. Aripiprazole	8. Escitalopram + Mirtazapine
9. Hydroxychloroquine	9. Citalopram + Quetiapine
10. Metronidazole	10. Ondansetron + Trazodone

Patients receiving one or more QT-prolonging therapies are at increased risk and should be monitored for changes in QT interval by electrocardiogram (ECG). If QT prolongation occurs, discontinuation or substitution of the causative medication should be considered in addition to correcting any electrolyte abnormalities. Impaired hepatic and renal function may increase the patient's exposure to QT-prolonging medications putting them at increased risk as well.[2] It is recommended that providers become familiar with these QT-prolonging drugs, avoid these agents if necessary, and closely monitor at-risk patients.

CredibleMeds.org is a valuable resource for a complete list of QT-prolonging agents and their risk stratification including known, possible, and conditional risk of TdP.[5] A patient's risk of a fatal ventricular arrhythmia may be reduced with increased prescriber awareness of risk factors, vigilant ECG monitoring, recognition of drugs known to cause QT prolongation, and detection of specific drug interactions.[3]

The UnitedHealthcare Community Plan drug utilization review program is administered to promote the safe and efficacious use of medications. These interventions do not take into consideration patient-specific variables. The intent of this newsletter is to bring attention to potential medication related issues that have been found during an analysis of the DUR data regarding concomitant use of QT-prolonging agents. UnitedHealthcare Community Plan is committed to continuing to provide the best possible care for our members.

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[1]Schwartz, Peter J., and Raymond L. Woosley. "Predicting the Unpredictable: Drug-Induced QT Prolongation and Torsades de Pointes." Journal of the American College of Cardiology, vol. 67, no. 13, 2016, pp. 1639-1650., doi: 10.1016/j.jacc.2015.12.063.
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[2]Berul, Charles I. "Acquired long QT syndrome: Definitions, causes, and pathophysiology." UpToDate, 6 Nov. 2020, https://www.uptodate.com/contents/acquired-long-qt-syndrome-definitions-causes-andpathophysiology?search=qt%20prolongation&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
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[4]Miranda, Derick G, et al. "Medication-Induced QT-Interval Prolongation and Torsades de Pointes." U.S. Pharmacist, 18 Feb. 2011, www.uspharmacist.com/article/medication-induced-qt-interval-prolongation-and-torsades-de-pointes.
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[5]Crediblemeds. www.crediblemeds.org/.

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