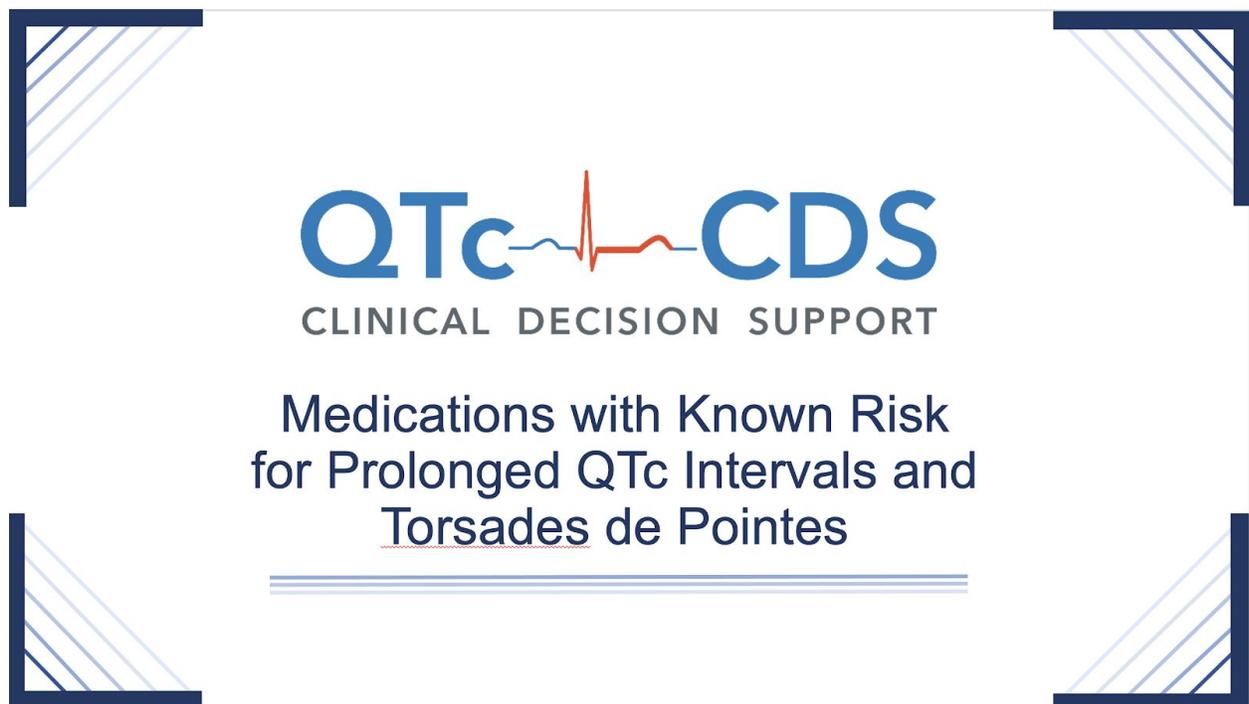


**QTc Risk Clinical Decision Support:
Medicines with Known Risk for
Prolonged QTc Intervals and Torsades de Pointes**



Thank you for your interest in this educational program
“QTc Risk Clinical Decision Support: Medicines with Known Risk for
Prolonged QTc Intervals and Torsades de Pointes.”

This educational module — number three in a series of four — will cover medications with known risk for prolonged QTc intervals and torsades de pointes (TdP).

SLIDE ONE: DRUG-INDUCED SUDDEN DEATH

Drug-Induced Sudden Death

Products Removed From Market Due to Torsades de Pointes

- Terfenadine (Seldane®)
- Astemizole (Hismanal®)
- Gatifloxacin oral (Tequin®)
- Sparfloxacin (Zagam®)
- Grepafloxacin (Rexar®)
- Levomethadyl (Orlaam®)
- Cisapride (Propulsid®)
- Mibefradil (Posicor®)
- Sertindole (Serlect®)
- Mesoridazine (Serentil®)
- Propoxyphene (Darvon®)
- Probucol (Lorelco®)

Many medications have been removed from the market due to their association with QT prolongation and sudden cardiac death. The medications on the above list have been removed owing to their

association with QT prolongation — some because of a direct effect — others because they inhibit the metabolism of certain drugs, and by that mechanism have been associated with Torsades de Pointes.

SLIDE TWO: MEDICATIONS AFFECTING QTc INTERVAL

Medications Prolonging QTc Interval

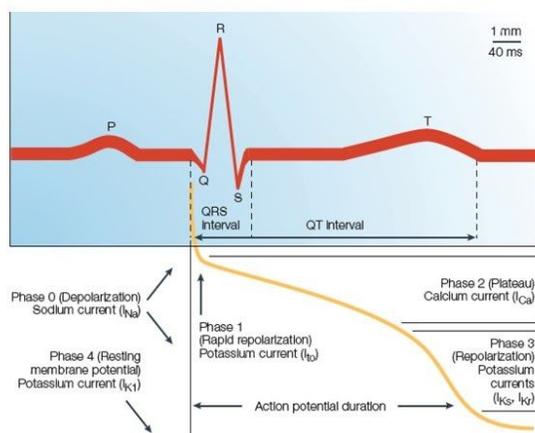


While a large number of medications have been removed from the market due to their effect on the QT interval, there are still many medications on the market that have this side effect. This owes to the fact that — although they can cause a side effect — the benefit of using these drugs currently outweighs the risk under certain circumstances.

SLIDE THREE: CARDIAC HERG SUBUNIT

Cardiac hERG Channel

- Many drugs inhibit the I_{kr} (hERG) current



The above image shows the relationship between cardiac action potentials, associated currents, and what is observed on an electrocardiogram. Displayed at the top is the electrocardiogram and the bottom shows the action potential. The flow of different ions through different channels drives the electrical activity seen in the electrocardiogram. When observing QT prolongation, the focus is on the I_{Kr} current which is related to cardiac repolarization.

**SLIDE FOUR: MECHANISM OF ACTION OF DRUG-INDUCED
PROLONGED QTc**

Mechanism of Drug-Induced Prolonged QTc

I_{Kr} Inhibition



**Delayed
Ventricular
Repolarization**



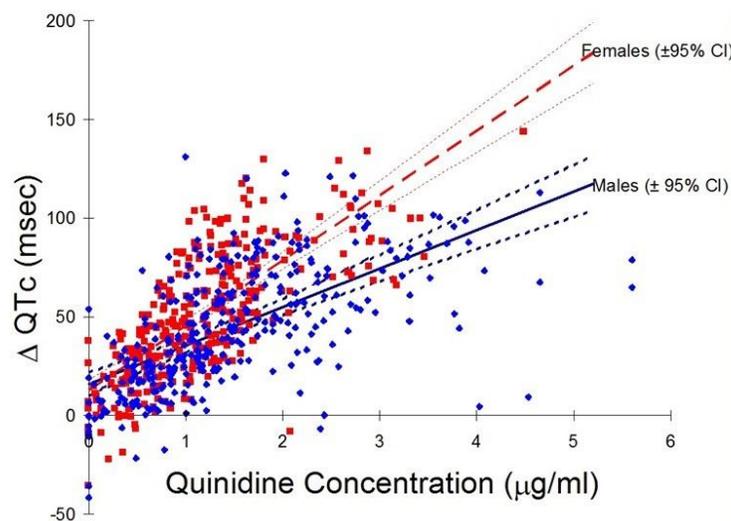
+/- RISK FACTORS

QT/QTc Prolongation

Drugs that can cause QT prolongation often inhibit the I_{Kr} current which leads to delayed Ventricular repolarization and then — when this is combined with other risk factors — can lead to severe QT prolongation.

SLIDE FIVE: CHANGE IN CORRECTED QT FOR MALES AND FEMALES AFTER QUINIDINE ADMINISTRATION

Females have greater QTs response to hERG blockers and TdP Risk

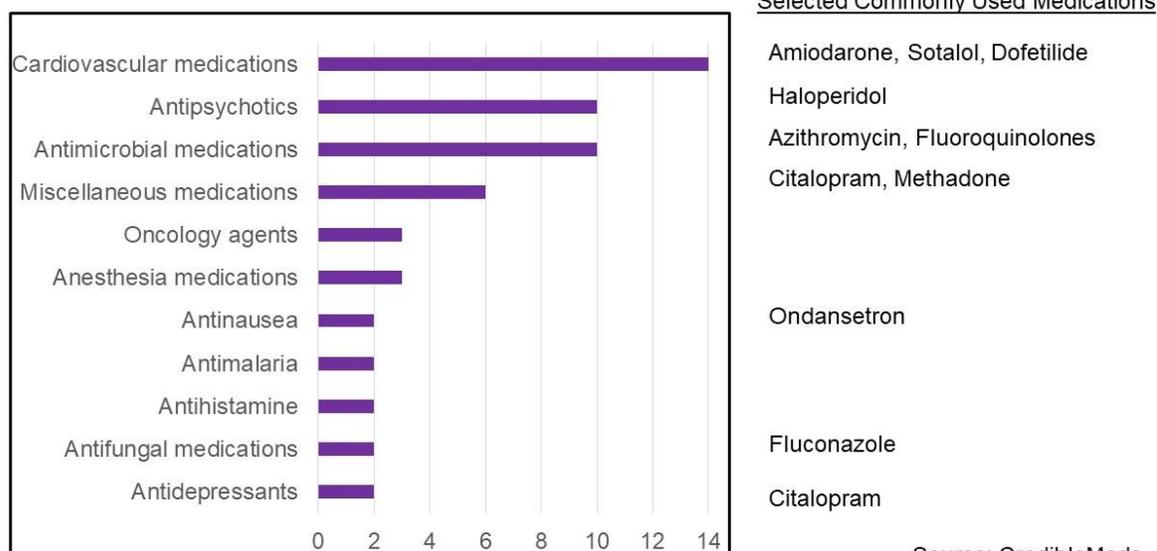


Benton et al. Clin Pharmacol Ther 2000; 67:413-8

Drugs that inhibit the QT interval often exhibit a dose response relationship such as the relationship displayed here. When the concentration of quinidine increases, it will lead to an increase in the QT interval; displayed above is the increasing trend at the higher concentration and QT interval. Also note, in the case of quinidine, females tend to exhibit a greater effect with this medication, and that is why the line is steeper for females than for males.

SLIDE SIX: MEDICATIONS WITH KNOWN RISK FOR PROLONGED QTc AND TORSADES DE POINTES

Medications with Known Risk of Torsades de Pointes



Medications with a known risk for prolonging QTc and torsades de pointes occupy many different drug classes, with the most common being cardiovascular medications, antipsychotics and antimicrobial medications. Some specific, commonly-used medications in practice include amiodarone, azithromycin, ondansetron, and fluconazole. These are just a few of the medications with a known risk.

SLIDE SEVEN: COMPREHENSIVE SOURCE FOR DRUG-INDUCED PROLONGED QTc

Comprehensive Source for Drug-Induced Prolonged QTc

The screenshot displays the CredibleMeds website homepage. At the top, the CredibleMeds logo is on the left, and a banner for mobile apps is on the right. Below the logo, it states 'A Trusted Partner Providing Reliable Information On Medicines'. The main navigation bar includes 'FOR EVERYONE', 'FOR HEALTHCARE PROVIDERS', and 'FOR RESEARCH SCIENTISTS'. A search bar is located at the top left, with 'Members Login' and 'Register Here' buttons below it. A 'QUICK LINKS' section is on the left side. The main content area features a 'Donate to AZCERT' button, a 'See News below!' link, and a 'List of QT Clinical Factors Launched - QTFactors.org' link. Below this is a 'Free Smartphone App for QTdrugs Lists (click here)' link. A 'QUICK SCAN for drugs on the QTdrugs Lists:' section contains two buttons: 'Click Here' for 'Quick Scan for one drug at a time (No registration required)' and 'Click Here' for 'Review all lists and download (Free, registration required)'. At the bottom, a note states: 'Visitors to the CredibleMeds® website can use Quick Scan to search for drugs on the QTDrugs lists. Access to download the lists of QTdrugs requires registration so that'.

CredibleMeds is a comprehensive source for information about drug-induced QT prolongation. The CredibleMeds website and smartphone applications publish medication lists for drugs associated with torsades de pointes. Drugs can be searched one at a time with a “quick scan” feature or users can register for a free account to be able access the complete drug list.

SLIDE EIGHT: MEDICATION RATING FOR RISK OF TORSADES

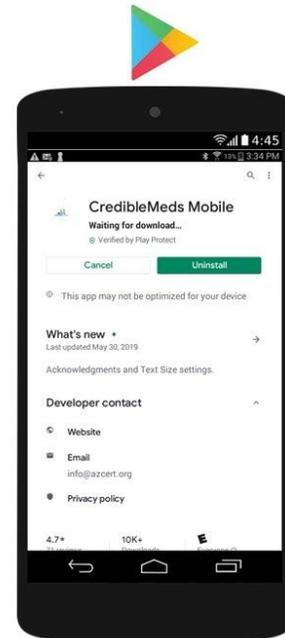
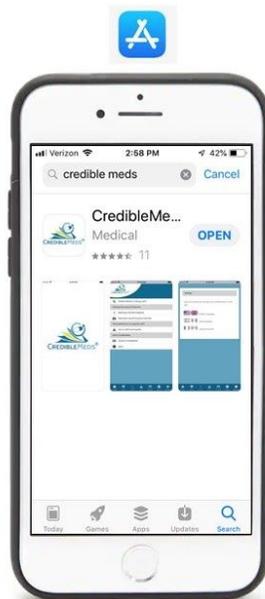
Medications with Risk of Torsades

| TdP Risk Categories | |
|---|---|
|  Known Risk of TdP | Clearly associated with known risk of TdP, even when taken as recommended |
|  Possible Risk of TdP | Can cause QT prolongation but lacks evidence for risk of TdP when taken as recommended |
|  Conditional Risk of TdP | Associated with TdP but only under certain conditions such as excessive dose, other risk factors |
|  Drugs to Avoid in Congenital Long QT | Any medication in above risk categories and other medications that have special risk due to mechanism of action |

Credible Meds rates the risk of torsade de pointes with different drug classifications. The first classification is **Known Risk of TdP** and those are drugs that are associated with torsades de pointes when taken as recommended. The next category is **Possible Risk of TdP** and those are medications that cause QT prolongation but do not show evidence of causing torsade de pointes when taken as recommended. The third category is drugs with a **Conditional Risk of TdP** under certain conditions, such as excessive dose or combined with other risk factors such as hypokalemia. The last category is a special category for drugs to avoid in congenital long QT and this list includes medications present on the other three lists, as well as other drugs that can pose a risk in patients with this condition.

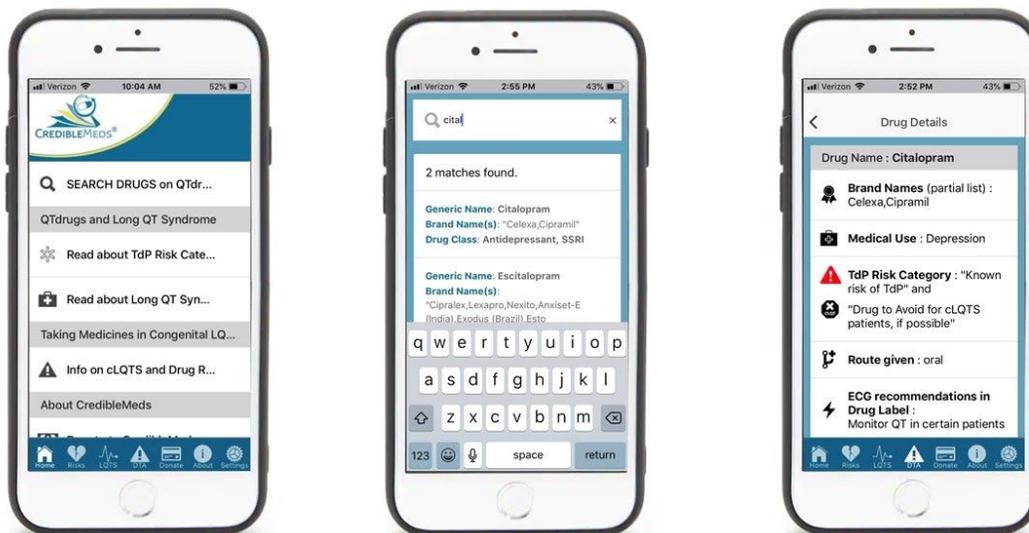
SLIDE NINE: CREDIBLEMEDS IN THE APPLE AND ANDROID APP STORES

Free
CredibleMeds
App in Apple
and Google
app stores



In addition to the CredibleMeds website, CredibleMeds is available as an app for smartphones and tablets on the Apple and Android platforms.

SLIDE TEN: CREDIBLEMEDS APP



To use the CredibleMeds app, tap on search drugs (displayed on the left side of this slide). Start typing the drug name you are searching for (displayed in the middle of this slide). The app will then show the results that match your search. Select the drug you are searching for and the app will provide the information for that specific drug including other brand names, medical uses, routes available and the risks of this drug with respect to torsades de pointes and QT prolongation (displayed on the right side of this slide). In this example, using citalopram, notice there is a known risk for torsades de pointes and at the bottom there are drug label recommendations for electrocardiogram monitoring.

To complete this module, please continue to the TOOLS section of this module's webpage for a short quiz that will test your knowledge of the presented information before advancing to Module FOUR.

[MODULE THREE KNOWLEDGE TEST](#)

Thank you for your time and for your interest in this educational program "QTc Risk Clinical Decision Support: Medicines with Known Risk for Prolonged QTc Intervals and Torsades de Pointes".

We hope you have enjoyed part three of this four-part educational series.



Thank you

QTc RISK CLINICAL DECISION SUPPORT:
A PRIMER FOR HEALTHCARE PROVIDERS
MODULE 3: Medications With Known Risk
for Prolonged QTc and TdP

