Review Article

QT Interval Considerations for COVID-19 and Beyond

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Editors Note:

This manuscript was submitted to *JPSW* on June 5, 2020. While a hydroxychloroquine and azithromycin regimen is no longer recommended for COVID-19, the recent use of those medications was the catalyst for this manuscript.

Since the first case was reported to the World Health Organization (WHO) on December 31, 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease (COVID-19), has left few aspects of our society untouched.[1] As the death toll in the United States has risen to over 130,000 people, protective measures have been implemented to try to slow spread of the virus.[2,3] Many aspects of community pharmacy have changed due to COVID-19 to protect patients. Physically, stores and hospitals have changed by implementing barriers and mandatory masks for staff.[3] Yet, the biggest safeguards present in community and acute care pharmacies are the pharmacists who review medications for accuracy and appropriateness.

The status of pharmacists as gatekeepers to protect and educate the public, as well as fellow health care providers, about medications and their effects has become even more relevant as experimental regimens have been tried for COVID-19. This has been the case for one of the first experimental regimens, hydroxychloroquine (Plaquenil®), which may be prescribed concomitantly with azithromycin (Zithromax®). Fill rate data collected by GoodRx have shown a 367% increase in hydroxychloroquine prescriptions during March of 2020, and it has subsequently been added to the U.S. Food & Drug Administration (FDA) shortage list.[4,5] In April 2020, azithromycin was also added to the FDA shortage list, with many manufacturers citing "excess demand" as the cause.[5,6] However, like all medications, this regimen has risks that may pose more harm than benefit for certain patients. For hydroxychloroquine and azithromycin, a major concern is that both can cause QT prolongation alone, and this risk increases when used concomitantly.[7-9] Though this regimen is no longer recommended for patients with COVID-19, it brought attention to the dangers of QT-prolonging medications and the importance of pharmacist intervention in these cases.[10,11]

This article seeks to review medications that can cause QT prolongation and suggest interventions for pharmacists to help prevent Torsades de Pointes (TdP) in both the community and hospital settings.

QT Prolongation Clinical Review

The QT interval is measured by electrocardiogram (ECG) as the time from the beginning of the QRS complex to the end of the T wave, which represents the time from ventricular depolarization to repolarization.[7,9,12-13] Many health systems use a corrected QT interval, or QTc. There are several available formulas to calculate a patient's QTc; however, all calculations include the measured QT interval and the patient's heart rate or the patient's RR interval (the distance between R waves in subsequent heart beats). Changes in either of these parameters can falsely lengthen or shorten the QT interval observed on the ECG. For example, a patient with tachycardia may appear to have a normal or shortened QT interval due to the increased frequency of beats. The opposite would be true for a patient with bradycardia. A normal adult QT interval ranges from 400 to 440 milliseconds (ms); a QT interval longer than 500 ms is considered abnormally prolonged and puts the patient at risk for TdP. For patients with a baseline QT interval of 500 ms, the risk of developing TdP is 2 to 3 times higher than patients with a normal QT interval. The risk of developing TdP increases by 5% to 7% for every 10 ms over this threshold.[9]

Torsades de Pointes, or "twisting of the points," is characterized by ventricular tachycardia with a heart rate ranging from 160 to 250 beats per minute and cyclic twisting in the QRS complex around the horizontal axis every 2 to 5 beats.[7,9,12] The rhythm will appear irregular with varying QRS complex width and absent P waves. This is typically preceded by systolic pauses that continue to lengthen until the onset of TdP. The clinical presentation of TdP varies widely from asymptomatic to sudden cardiac death.

QT Prolongation Causes and Risk Factors

Three published methods for calculating a patient's risk of developing QTc prolongation and TdP include the pro-QTc algorithm developed by the Mayo Clinic, the RISQ-PATH score developed in University Hospitals Leuven in Belgium, and the Tisdale score developed by Indiana University.[13-17] This article will include risk factors assessed in each tool (Table 1), but will reference the ranges used to determine risk level in the Tisdale Score.[13] A Tisdale score of 6 points or less can be considered low risk for developing TdP, 7 to 10 points a moderate risk, and 11 points or higher a high risk.

Many medications are known to cause QT prolongation, even when taken at recommended doses.[8] Common medications seen in the community setting are antiarrhythmics, antibiotics, antipsychotics, opioid agonists, and anti-

TABLE 1. Factors that Result in Increased QT Interval and TdP Risk[13, 15-21]

Risk Factor	Explanation
Demographics	
Female	Testosterone shortens the QT interval.
Age ≥ 68 years	Testosterone decreases with age.
Tobacco use	Nicotine is a nonspecific blocker of potassium channels, causing a longer action potential and slower repolarization of cardiomyocytes.
Lab Values	
Serum potassium ≤ 3.5 mmol/L	Potassium is needed to repolarize cardiomyocytes.
Serum calcium < 4.65 mg/dL	Calcium is needed for cardiomyocyte contraction.
Serum magnesium < 1.7 mg/dL	Magnesium is needed for potassium uptake into cardiomyocytes; low magnesium leads to low potassium uptake and slower repolarization.
Serum C-reactive protein > 5 mg/L	Indicates inflammation. Inflammatory cytokines can interact with cardiomyocyte ion channels, affecting the length of action potentials.
Creatinine clearance ≤ 30 mL/min	Indicates renal impairment; excretion of QT-prolonging medications may be reduced, allowing for accumulation.
Electrocardiogram Results	
Presenting QT interval ≥ 450 milliseconds	Starting with a longer QT interval leaves less room for an increase before it becomes pathologically prolonged and may indicate other underlying risk factors.
Concurrent Medications	
Loop diuretic (e.g., furosemide, torsemide, bumetanide)	Loop diuretics can cause hypokalemia and may block potassium currents.
Number of QT-prolonging medications	Risk increases with each additional QT-prolonging medication.
Disease States	
Acute myocardial infarction (MI)	QT interval shortens during acute MI, but typically returns to normal after MI resolution.
Heart failure with reduced ejection fraction	Alterations in ventricular function increase the risk for QT prolongation; heart failure with preserved ejection fraction does not carry the same risk due to preserved ventricular function.
Sepsis	QT interval may become prolonged during an acute sepsis event, but typically returns to normal after resolution.
Liver failure	Metabolism of QT-prolonging medications may be reduced, extending and increasing their effect(s).
Hypothyroidism	Thyroid hormone regulates calcium concentrations in cardiomyocytes. Low thyroid hormone leads to increased calcium levels during repolarization, which slows the repolarization process.
Hypertension	Hypertension often leads to left ventricle hypertrophy, which can lead to delayed repolarization of the ventricles.
Diabetes mellitus	Hyperglycemia may affect potassium, sodium, and calcium channels in cardiomyocytes, lengthening the repolarization process.

emetics (Table 2). QT-prolonging effects may be increased at higher doses and when multiple QT-prolonging medications are taken together. CredibleMeds® (www.crediblemeds.org) is an online database that contains information for QT-prolonging medications identified through analysis of scientific publications, information in the official medication label, and reports submitted either to the CredibleMeds® website or to U.S. FDA Adverse Event Reporting System. This free resource can be used by pharmacists and prescribers when questioning the QT-prolonging potential of a certain medication.

Community Pharmacist Interventions

Though community pharmacists may not have access to ECG readings, they play a pivotal role in preventing QT prolongation and Torsades de Pointes. A study of 61 case reports of QT prolongation in elderly patients found that over 50% of them had 2 or more QT-prolonging agents prescribed.[25] Another study of 500 patients discharged from an academic medical center emergency department showed that nearly 2% of patients were given prescriptions with a contraindicated Category X drug-drug interaction, the most common being due to QT prolongation.[26] These data suggest a great opportunity for community pharmacists to reduce morbidity and mortality in their patients at risk for QT

prolongation.

In community pharmacies, a guidance document could be developed to ensure that pharmacists are assessing patients for QT prolongation risk factors (Appendix 1). The document could include information about looking at a patient's fill history to determine chronic conditions that increase their risk. For example, if a patient routinely fills lactulose or ursodiol, it is likely that they have liver disease. Or, if a patient is taking furosemide, lisinopril, and carvedilol, they may have heart failure, and they may be at risk for hypokalemia due to their furosemide usage. This risk is further compounded if the patient happens to be female or elderly. If a patient has multiple risk factors, it may be warranted to contact their provider to ensure they have assessed the patient's cardiac function before starting a new QT-prolonging medication. Community pharmacists could also add notes to patient profiles indicating their assessment of the patient's QT prolongation risk so that this information is readily available for future fills and documented to protect against possible liability claims.

An equally important step that community pharmacists should take is counseling patients on QT prolongation risks and symptoms.[11,27] Pharmacists have the valuable experience of counseling patients on severe risks without scaring them to the point of nonadherence, which is essential when counseling patients on QT prolongation. Though often asymptomatic, pharmacists can counsel patients to seek emergency care if they experience faintness or heart palpitations.[9,27] Because TdP can spontaneously resolve, the patient's symptoms may be intermittent. At each refill for QT-prolonging medications, pharmacists should assess for changes in the patient's QT-prolongation risk factors or if the patient has experienced any worrisome symptoms.[27]

Pharmacists can also discuss with patients how to reduce their risk of QT prolongation. Pharmacists can ask patients if they have ever had an ECG and if they have one scheduled for the future, especially if they are picking up a new QT-prolonging medication or their dose was increased.[22] For hydroxychloroquine in particular, it is recommended that

TABLE 2. Commonly Prescribed Medications and Risk of QT Prolongation[8,22-24]

Drug Class	*QT Prolongation Risk*		
	Medications known to cause prolonged QT and TdP	*Medications known to cause QT Prolongation but not TdP*	*Medications that may cause QT prolongation under certain circumstances**
Alpha-1 adrenergic blocker		Alfuzosin	
Anti-anginal			Ivabradine[a,b,d,e] Ranolazine[a-c,e]
Antiarrhythmic	Amiodarone Dofetilide Flecainide Sotalol	Quinidine	Propafenone[b-d]
Antibiotic (fluoroquinolone)**	Moxifloxacin Ciprofloxacin Levofloxacin	Gemifloxacin Ofloxacin	
Antibiotic (macrolide)**	Azithromycin Erythromycin Clarithromycin		
Antibiotic (miscellaneous)			Metronidazole[a,c]
Anticonvulsant		Felbamate	
Antidepressant (SSRI, SNRI, or SRIA)	Citalopram (SSRI) Escitalopram (SSRI)	Venlafaxine (SNRI)	Fluoxetine (SSRI)[a-d] Paroxetine (SSRI)[e] Sertraline (SSRI)[a-c,e] Trazodone (SRIA)[a-d]
Antidepressant (tricyclic or tetracyclic)		Mirtazapine (tetracyclic) Nortriptyline (tricyclic)	Amitriptyline (tricyclic)[a-e] Doxepin (tricyclic)[a,c,d]
Antiemetic	Ondansetron Prochlorperazine	Dolasetron Granisetron Palonsetron Promethazine	Metoclopramide[a,c]
Antifungal	Fluconazole		Itraconazole[c,e] Ketoconazole[b,c,e] Posaconazole[c,e] Voriconazole[a,c,e]
Antihistamine	Dimenhydrinate		Diphenhydramine[d] Hydroxyzine[a-d]
Antimalarial	Chloroquine Hydroxychloroquine		Quinine[a,c,d]
Antimanic		Lithium	
Antipsychotic	Haloperidol	Aripiprazole Clozapine Lurasidone	Olanzapine[a,c] Quetiapine[a-d] Risperidone[a-d] Ziprasidone[a-d]
Beta-3 agonist (overactive bladder)		Mirabegron	
Histamine-2 receptor antagonist			Cimetidine[e] Famotidine[a,c,d]
Immunosuppressant		Tacrolimus	
Muscle relaxant		Tizanidine Tolterodine	Solifenacin[a-c]

patients receive periodic ECG monitoring throughout the first 4 days of therapy.[28] If a patient has not had a baseline ECG, the pharmacist should then contact the prescriber to determine the next course of action. Pharmacists should advise their patient to attend all scheduled appointments with their physician to monitor their cardiac function and blood chemistries because, oftentimes, there are no apparent symptoms to alert the patient that something is wrong. These appointments may allow their physician to detect hypomagnesemia or hypokalemia and prescribe oral supplements before the situation progresses. However, there is not current data suggesting that all patients receiving QT-prolonging medications would benefit from an over-the-counter magnesium supplement; so, a recommendation as to whether community pharmacists should offer this option to patients cannot be made. Lastly, pharmacists should encourage patients to keep a current medication list, including over-the-counter medications, on their person to share with all their health care providers. A complete and current medication list helps ensure the risk of additive effects of QT-prolonging medications is not overlooked, especially in cases of polypharmacy or during transitions of care.[9,13]

TABLE 2 CONT. Commonly Prescribed Medications and Risk of QT Prolongation[8,22-24]

Drug Class	QT Prolongation Risk		
	Medications known to cause prolonged QT and TdP	Medications known to cause QT Prolongation but not TdP	Medications that may cause QT prolongation under certain circumstances*
N-methyl D-aspartate receptor antagonist		Memantine	
Opioid agonist	Methadone	Buprenorphine	Loperamide[d]
Opioid analgesic		Hydrocodone (extended release) Tramadol	
Phosphodiesterase 3 inhibitor	Cilostazol		
Proton pump inhibitor			Esomeprazole[a,c] Lansoprazole[a,c] Omeprazole[a,c] Pantoprazole[a,c]

Abbreviations: SNRI, serotonin/norepinephrine reuptake inhibitor; SRIA, serotonin reuptake inhibitor/antagonist; SSRI, selective serotonin reuptake inhibitor; TdP, Torsades de Pointes.
** Circumstances include use in patients with electrolyte abnormalities (a), patients with bradycardia (b), concomitant use with another QT-prolonging medication (c), doses that are higher than recommended (d), or decreasing the metabolism or elimination of other QT-prolonging medications (e).[8]*
*** Fluoroquinolones and macrolides are listed from most to least likely to cause QT prolongation.[23]*

Inpatient Pharmacist Interventions

Most inpatient pharmacists have the luxury of access to a patient's complete electronic health record, allowing them to perform risk assessments, like the Tisdale score, and confirm appropriate monitoring of patients for QT prolongation.[11,27] It may be helpful for pharmacists to use a checklist to ensure all risk factors have been considered. The University of Waterloo in Canada developed a stepwise approach to minimizing QT-prolongation risks.[27] These steps include the following:

1. Assess the patient to determine if they have a history of QT prolongation and/or TdP, if a baseline ECG has been performed, and if the patient has additional risk factors for QT prolongation.
2. Assess the drug to determine the indication, if safer therapeutic alternatives exist, and if the dose is appropriate considering drug-drug interactions and the patient's renal or hepatic function. If the Tisdale score is being used, it is strongly recommended to consider alternative medications if the patient's score is 11 or higher.[13]
3. Decide to verify or reject the medication order. If verified, ensure that proper monitoring is in place. Consider discontinuing the medication if the patient's QTc increases by 60 ms or increases past 450 ms for males or 460 ms for females.

There are a few steps that can be added to this algorithm to further improve patient safety. One step that could be added to this algorithm would be a conversation with the patient's care team to discuss the risks versus benefits of the proposed medication. In addition, the patient's serum concentrations of calcium, magnesium, and potassium should be monitored throughout the patient's admission along with a 12-lead ECG. In particular, it is recommended to increase the frequency of electrolyte and ECG monitoring in patients with a Tisdale score of 7 or higher.[13] Lastly, if this is a new chronic medication, proper patient education, including the counseling points mentioned in the community pharmacist section, should ideally occur before discharge.[13,27]

Managing COVID-19 and QT Prolongation

Although in-vivo studies in March 2020 of hydroxychloroquine with or without azithromycin showed improved clearance of SARS-CoV-2 from nasopharyngeal secretions, faster clinical recovery, and improved radiologic findings, the efficacy of these treatment options remains questionable at best.[29,30] These studies were limited to single institutions in France and China with sample sizes of less than 100 patients. There have also been recent and highly publicized data in the Lancet and New England Journal of Medicine suggesting higher mortality for patients receiving hydroxychloroquine alone or with a macrolide; these data were later retracted.[31,32]

Eventually, U.S. FDA and

National Institutes of Health (NIH) released statements discouraging hydroxychloroquine and azithromycin use in patients with COVID-19.[10,11] However, before these statements were released, a publication by Michael Ackerman and colleagues from Mayo Clinic included some guidance for prescribing of QT-prolonging medications in patients with COVID-19, which is also endorsed by CredibleMeds®.[33,34] Dr. Ackerman and colleagues noted that use of hydroxychloroquine or other QT-prolonging medications to treat COVID-19 should be evaluated in the context of a patient's risk-to-benefit profile; a patient with less severe disease and a QTc greater than 500 ms may elect to forgo hydroxychloroquine treatment, whereas in a patient with critical illness, the benefit of hydroxychloroquine therapy could outweigh the risk of arrhythmia with any possible QT prolongation. In these patients, increased countermeasures (e.g., closer telemetry monitoring, wearable defibrillator) should be implemented, and modifiable risk factors for drug-induced TdP (i.e., abnormal serum concentrations of calcium, potassium, and magnesium, and discontinuation of other QT-prolonging medications) should be addressed. Additionally, Mayo Clinic recommended in patients with QTc greater than 500 ms, hydroxychloroquine should be started over azithromycin, and combination therapy should be avoided.

The American College of Cardiology also posted guidance regarding use of hydroxychloroquine and azithromycin in patients with COVID-19 and related QT recommendations before FDA and NIH discouraged its use.[10,11,35] They linked to Dr. Ackerman's recommendations but also described some additional considerations, including use of Tisdale's validated risk score to predict risk of drug-associated QT prolongation to stratify cardiac monitoring during drug therapy.[35] In hospitalized patients who experienced QT prolongation to an absolute QTc greater than 500 ms or an increase of more than 60 ms from baseline, it was recommended to discontinue azithromycin and/or reduce the hydroxychloroquine dose, though no dose adjustments were provided.[35,36] If the QTc remained prolonged greater than 500 ms or increased 60 ms or more from baseline with daily ECG monitoring, discontinuation of hydroxychloroquine was recommended, or an electrophysiologist should be consulted for continued use. In the outpatient setting, it was recommended that a Tisdale score of 11 points or higher be a relative contraindication for use of hydroxychloroquine with or without azithromycin. If patients had a Tisdale score of 6 points or less with a baseline ECG of less than 500 ms, no further ECG monitoring was recommended with new prescriptions; if the score is 7 points or higher, a repeat ECG after 3 days, taken 2 to 3 hours after a dose of therapy, was recommended to further assess QT prolongation. Increases seen at that time were recommended to be measured against a lower threshold (i.e., continued prolongation of 500 ms or greater, more than a 30 to 60 ms increase from baseline) to consider discontinuing therapy due to the reduced opportunities for further monitoring. It was recommended that all patients have a baseline ECG regardless of setting of therapy; though, it is not always feasible for the community pharmacist to gain access to this information.

Considering FDA and NIH statements that discourages use of hydroxychloroquine in patients with COVID-19, there are some key considerations for both community and acute care pharmacists to ensure safe prescribing.[10,11] First, it is imperative to determine the indication for hydroxychloroquine and azithromycin prescriptions. For example, if the patient has a labeled indication for hydroxychloroquine (e.g., rheumatoid arthritis, lupus), then as long as the dose is appropriate, it is likely safe to dispense. Some pharmacies have added soft stops to their software, which require a pharmacist to check the indication and enter an override before dispensing these medications.

For hydroxychloroquine, triggers that may warrant further investigation into the indication include past fill history, total daily dose prescribed, and the number of refills. If a patient has past regular fills for hydroxychloroquine, it is likely being used for a chronic disease state. In addition, the presence of refills indicates that it is not being used to treat a temporary condition like COVID-19. Lastly, the dose and duration prescribed can indicate if the medication is being used for COVID-19 or a chronic inflammatory condition. When used for COVID-19, the total daily dose ranged from 400 to 800 mg for 4 to 7 days; total daily doses for inflammatory conditions range from 200 to 400 mg and are dispensed in 30 to 90 day quantities.[28] Thus, if a pharmacist receives a hydroxychloroquine prescription for higher-than-normal doses or with no refills, this should prompt evaluation of the indication.

For azithromycin, if no indication is mentioned on the prescription, pharmacists should ask the patient or contact prescribers to determine it. Azithromycin has many approved uses, including community-acquired pneumonia, otitis media, and acute chronic obstructive pulmonary disease exacerbation treatment.[28] If a prescriber wishes to use either medication for treatment of COVID-19, a conversation regarding current data and the need for monitoring should be initiated. In the outpatient setting, greater scrutiny is warranted due to the lack of continuous cardiac monitoring. These risks should be communicated to the provider to ensure that they have been considered.

Conclusion

The knowledge, skills, and patient relationships of pharmacists position them well to reduce the risks of QT prolongation in the outpatient and inpatient settings. Though the risk of QT prolongation with certain medications has gained newfound attention due to experimental COVID-19 regimens, it is an important consideration for all patients that should continue to be assessed beyond its implications for COVID-19 treatments. Patients with a QTc of 500 ms or greater are at the greatest risk for experiencing TdP with new or continued use of QT-prolonging medications, as well as patients who experience an increase of 60 ms or more from baseline after starting a new QT-prolonging medication. In addition, or in the case of the absence of ECG information, the Tisdale score would be fairly easy to adapt to any setting to stratify a patient's risk of QT prolongation into low (6 points or less), medium (7 to 10 points),

or high (11 points or higher), which can be helpful in evaluating new prescriptions for QT-prolonging medications, counseling patients, developing monitoring plans, or discussing concerns with prescribers. Recommendations released for COVID-19 treatments also suggest new actionable recommendations based on a patient's Tisdale score.

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References

1. Rolling updates on coronavirus disease (COVID-19). World Health Organization. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen. Updated May 8, 2020. Accessed May 11, 2020.
2. Provisional death counts for coronavirus disease (COVID-19). Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/nvss/vsrr/covid19/index.htm. Updated July 21, 2020. Accessed July 21, 2020.
3. Guidance for pharmacies. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/pharmacies.html. Updated April 14, 2020. Accessed May 8, 2020.
4. Marsh T. Live updates: fills and prices for unproven covid-19 treatments. GoodRx. https://www.goodrx.com/blog/covid-19-treatments-fill-increases-price-changes/. Updated April 28, 2020. Accessed May 4, 2020.
5. FDA drug shortages. U.S. Food & Drug Administration. https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Azithromycin%20Tablets&st=c&tab=tabs-1. Updated April 14, 2020. Accessed May 4, 2020.
6. Hydroxychloroquine sulfate tablets. American Society for Health-System Pharmacists Drug Shortages. https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortage-Detail.aspx?id=646&loginreturnUrl=SSOCheckOnly. Updated April 16, 2020. Accessed May 10, 2020.
7. Passman R, Kadish A. Polymorphic ventricular tachycardia, long Q-T syndrome, and torsades de pointes. *Med Clin North Am*. 2001;85(2):321-341.
8. CredibleMeds® [online database]. Oro Valley, AZ: AZCERT, Inc.; 2020. https://www.crediblemeds.org/index.php/login/dlcheck. Updated May 12, 2020. Accessed May 12, 2020.
9. Trinkley KE, Page RL, II, Lien H, Yamanouye K, Tisdale JE. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr Med Res Opin*. 2013;29(12):1719-1726.
10. Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and. Updated June 15, 2020. Accessed July 21, 2020.
11. Hydroxychloroquine plus azithromycin. National Institute of Health. https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/hydroxychloroquine-plus-azithromycin/. Updated July 17, 2020. Accessed July 21, 2020.
12. Sanoski CA, Bauman JL. The Arrhythmias. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill. Accessed May 21, 2020.
13. Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes: role of the pharmacist in risk assessment, prevention and management. *Cam Pharm J* (Ott). 2016;149(3):139-152.
14. Tisdale JE, Jaynes HA, Kingery JR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes.* 2013;6(4):479-487.
15. Haugaa KH, Bos JM, Tarrell RF, Morlan BW, Caraballo PJ, Ackerman MJ. Institution-wide QT alert system indentifies patients with a high risk of mortality. *Mayo Clin Proc.* 2013;88(4):315-325.
16. Vandael E, Vandenberk B, Vandenberghe J, Spriet I, Willems R, Foulon V. Development of a risk score for QTc-prolongation: the RISQ-PATH study. *Int J Clin Pharm*. 2017;39(2):424-432.
17. Tomaselli Muensterman E, Tisdale JE. Predictive analytics for identification of patients at risk for QT interval prolongation: a systematic review. *Pharmacotherapy*. 2018;38(8):813-821.
18. Akbarzadeh MA, Yazdani S, Ghaidari ME, et al. Acute effects of smoking on QT dispersion in healthy males. *ARYA Atheroscler*, 2014;10(2):89-93.
19. Antoniou CK, Dilaveris P, Manolakou P, et al. QT Prolongation and Malignant Arrhythmia: How Serious a Problem? *Eur Cardiol*. 2017;12(2):112-120.
20. Lazzerini PE, Laghi-Pasini F, Bertolozzi I, et al. Systemic inflammation as a novel QT-prolonging risk factor in patients with torsades de pointes. *Heart.* 2017;103(22):1821-1829.
21. Mayet J, Shahi M, McGrath K, et al. Left ventricular hypertrophy and qt dispersion in hypertension. Hypertension. 1996;28(5):791–796.
22. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of Torsades de Pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121(8):1047-1060.
23. Teng C, Walter EA, Gaspar DKS, et al. Torsades de pointes and qt prolongation associations with antibiotics: a pharmacovigilance study of the FDA adverse event reporting system. *Int J Med Sci.* 2019;16(7):1018-1022.
24. Kolesar JM, Vermuelen LC. Top 300 Pharmacy Drug Cards—2018/2019. McGraw Hill Education, 2018.
25. Jackobson G, Carmel NN, Lotan D, et al. Reckless administration of QT interval-prolonging agents in elderly patients with drug-induced torsade de pointes. *Z Gerontol Geriat*. 2018;51(1):41-47.
26. Jawaro T, Bridgeman PJ, Mele J, Wei G. Descriptive study of drug-drug interactions attributed to prescriptions written upon discharge from the emergency department. *Am J Emerg Med.* 2019;37(5):924-927.
27. Grindrod KA, Nagge J. Simplifying QT prolongation for busy clinicians. *Can Fam Physician*. 2019;65(4):268-270.
28. Lexi-Drugs® [online database]. Hudson, OH: Lexi-Comp, Inc.; 2013. https://online.lexi.com/lco/action/home. Accessed May 11, 2020.
29. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents.* 2020;56(1):105949.
30. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. [pending peer review]. *MedRxiv.* 2020. Doi: https://doi.org/10.1101/2020.03.22.20040758
31. Mehra MR, Desai SS, Kuy SR, et al. Retraction: cardiovascular disease, drug therapy, and mortality in Covid-19. *N Engl J Me.* 2020;382(26):2582.
32. Mehra MR, Desai SS, Ruschitzka F, Patel AN. Retraction: hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet*. 2020; S0140-6736(20)31180-31186.
33. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19. *Mayo Clin Proc.* 2020;95(6):1213-1221.
34. Recommendations re: COVID-19 treatments. CredibleMeds®. https://crediblemeds.org/blog/recommendations-re-covid-19-treatments/. Updated March 29, 2020. Accessed March 30, 2020.
35. Ventricular arrhythmia risk due to hydroxychloroquine-azithromycin treatment for COVID-19. American College of Cardiology. https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19. Updated March 29, 2020. Accessed April 2, 2020.
36. Arshad S, Kilgore P, Chaudry Z, et al. Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patient's Hospitalized with COVID-19. *Int J Infect Dis.* 2020;97:396-403.

APPENDIX 1. Guidance Document to Assess QT Prolongation in Community Pharmacy Settings[8,9,11]

Patient Risk Factor Assessment		
	Risk Factor	***Explanation***
Patient Demographics	Age	Risk increases if age ≥ 68 years
	Sex	Females are at higher risk than males
Risk Factors Inferred by Fill History	The prescribed QT-prolonging medication is new or was previously taken at a lower dose.	New QT-prolonging medications and/or larger doses of QT-prolonging medications increase the patient's risk
	Number of QT-prolonging medications that the patient is prescribed.	Each additional QT-prolonging medication increases the patient's risk. The Credible Meds® database and package inserts can be used to determine if a medication prolongs the QT interval or may interact with other QT-prolonging medications.
	Evidence of liver disease can be inferred with past fill history for lactulose (Generlac®) or ursodiol (Actigall).	Liver disease decreases elimination of QT-prolonging medications and can increase a patient's risk.
	Evidence of heart failure can be inferred with past fill history for loop diuretics, beta blockers (specifically, metoprolol, carvedilol, or bisoprolol), and angiotensin II converting enzyme inhibitors, angiotensin II receptor blockers, or angiotensin receptor neprilysin inhibitors	Heart failure and the medications used to treat it increase the risk of developing QT prolongation.
	Risk factors for hypokalemia can be inferred with past fill history for loop diuretics without potassium supplements	Hyperkalemia increases the risk of developing QT prolongation.
Patient Medical History and Monitoring Assessment		
	Questions to Ask Patients	***Actions to Take***
Medical History Assessment	If they have ever been told they have liver disease, kidney disease, or heart failure	Note this information in patient's file for ease of review during next refill.
Monitoring Assessment	If they have ever had an ECG and if they have follow-up appointments to check their electrolyte levels and repeat the ECG	If patient has not had an ECG and they have more than one risk factor above, call the prescriber to ensure appropriate monitoring will be performed.
Patient Counseling Points		
	Counseling Pearls	***Actions to Take***
Symptoms of QT Prolongation	QT prolongation may present as heart palpitations that may self-terminate, faintness, or may be completely asymptomatic	Instruct the patient to seek emergent care if these symptoms occur. Assess at each refill if the patient has experienced these symptoms since starting this medication.
Follow-up Cardiac and Electrolyte Monitoring	QT prolongation can occur without symptoms but still be life-threatening	Stress the importance of attending all follow-up appointments and scheduled laboratory monitoring. A physician may prescribe supplements to manage electrolyte deficiencies and reduce risk of QT prolongation.
Review Over-The-Counter (OTC) Medications and Suggest Alternatives if Applicable	Some over-the-counter medications can prolong the QT interval and/or interact with QT-prolonging medications.	Instruct patients to carry a list of all prescription and OTC medications so that they can share this with all of their healthcare providers. Instruct patients to ask their doctor or pharmacist before starting any new OTC medications. Example OTC Substitutions • Suggest cetirizine or loratadine instead of diphenhydramine for allergies. • Suggest antacids instead of proton pump inhibitors or histamine-2 receptor antagonists for gastroesophageal reflux disease. • Suggest meclizine or ginger instead of dimenhydrinate for motion sickness.