Resource Document on QTc Prolongation and Psychotropic Medications

Approved by the Joint Reference Committee, June 2018

"The findings, opinions, and conclusions of this report do not necessarily represent the views of the officers, trustees, or all members of the American Psychiatric Association. Views expressed are those of the authors." -- *APA Operations Manual*.

Margo C. Funk, M.D., M.A.,[1] Scott R. Beach, M.D.,[2,3] Jolene R. Bostwick, PharmD, BCPS, BCPP,[4] Christopher M. Celano, M.D.,[2,3] Mehrul Hasnain, M.D.,[5] Ananda Pandurangi, M.B.B.S., M.D.,[6] Abhisek C. Khandai, M.D., M.S.,[7] Adrienne Taylor, M.D.,[7] James L. Levenson, M.D.,[6] Michelle Riba, M.D.,[8] and Richard J. Kovacs, M.D.[9]

[1]Mental Health Service Line, Veterans Affairs Southern Oregon Rehabilitation Center and Clinics, White City, OR; [2]Department of Psychiatry, Massachusetts General Hospital, Boston, MA; [3]Harvard Medical School, Boston, MA; [4]Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, MI; [5]Mount Pearl, Newfoundland, Canada; [6]Department of Psychiatry, Virginia Commonwealth University, Richmond, VA; [7]Department of Psychiatry and Behavioral Sciences, Northwestern Feinberg School of Medicine, Chicago, IL; [8]Department of Psychiatry, University of Michigan Medical School, Ann Arbor, MI; [9]Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN

Corresponding Author: Margo C. Funk, M.D., M.A., 8495 Crater Lake Avenue, White City, OR, 97503. Phone: (541) 826-2111 ext.3394. Email: margo.funk@va.gov

ABSTRACT

OBJECTIVE: Psychiatrists and other clinicians frequently prescribe psychotropic drugs that may prolong cardiac repolarization, thereby increasing the risk for torsades de pointes (TdP). The corrected QT interval (QTc) is the most widely used and accepted marker of TdP risk. This resource document was created in response to the paucity of strong evidence to guide clinicians in best practice prescription and monitoring of psychotropic medications that may increase risk of TdP.

METHOD: The American Psychiatric Association (APA) Council on Consultation-Liaison Psychiatry, in collaboration with the American College of Cardiology (ACC), convened a workgroup of experts to summarize the current literature and to create this set of clinical considerations for the practicing clinician.

RESULTS: This resource document includes a summary of basic electrocardiography, psychopharmacology and drug safety, special practice settings including the intensive care unit and under-resourced clinics, special populations including children and patients with cardiac implantable electronic devices, and the approach to TdP risk stratification and mitigation.

CONCLUSIONS: There is no absolute QTc interval at which a psychotropic should not be used, rather a comprehensive risk-benefit analysis should include assessment of pharmacologic and non-pharmacologic risks for TdP versus the risk of failure to control high-risk psychopathology or of psychiatric decompensation.

INTRODUCTION

Psychiatrists frequently prescribe psychotropic drugs that may prolong cardiac repolarization, thereby increasing the risk for torsades de pointes (TdP). The heart-rate corrected QT interval (QTc) on the electrocardiogram (ECG) is the most widely used and accepted marker of TdP risk by drug safety boards. Over the past decade, there has been increased attention by the medical community about the role of QTc interval monitoring in the prescription of psychotropic medications.

The incidence of TdP is difficult to study in a systematic way. Although rigorous testing of new drugs for the tendency to prolong the QTc interval has been in place for more than 10 years, classification systems that catalogue medications according to 'level of risk' are based on variable levels of evidence, including case reports or retrospective cohorts, which cannot be used to compare drugs and are difficult to generalize into clinical practice. Though TdP is thought to be a fairly rare event, active surveillance systems suggest the incidence of TdP may be 10 to 100-fold higher than estimated by spontaneous report (1). Furthermore, most studies use the Bazett correction. Though it is the most widely used correction formula, it is well established that Bazett overestimates the QTc interval at high heart rates, underestimates the QTc interval at low heart rates, and is consistently cited to be the least reliable method of correction.

Given the paucity of strong evidence to guide clinicians in best practice prescription and monitoring of psychotropic medications that may increase risk of TdP, to date there are no practice guidelines endorsed by the American Psychiatric Association (APA) or the American College of Cardiology (ACC). The APA Council on Psychosomatic Medicine, in collaboration with the ACC, convened this workgroup of experts in the field to summarize the current literature and to create a set of clinical considerations for the practicing clinician. This resource document is not intended to be a practice guideline, rather an educational tool for clinicians to use when prescribing psychotropic medications.

QTc INTERVAL AND TORSADES DE POINTES

Drug-Induced TdP and the Association with QTc Interval

TdP (literally meaning twisting of points) is a very rare form of polymorphic ventricular tachycardia characterized by the twisting of QRS complexes around the isoelectric line (Figure 1.A). The phenomenon was described by Desertennes and colleagues in 1966 in a group of patients that exhibited a long QT interval, a long cycle/short cycle sequence prior to the arrhythmia, and macroscopic T wave alternans (2). The clinical arrhythmia had also been described in a series of patients exposed to the

antiarrhythmic drug quinidine (3). TdP usually occurs in unsustained bursts that terminate spontaneously. These bursts can recur and may progress to a fatal ventricular arrhythmia. When not quickly fatal, it is clinically characterized by palpitation, dizziness, and syncope. Chest pain, shortness of breath, and sweating may be present as non-specific symptoms.
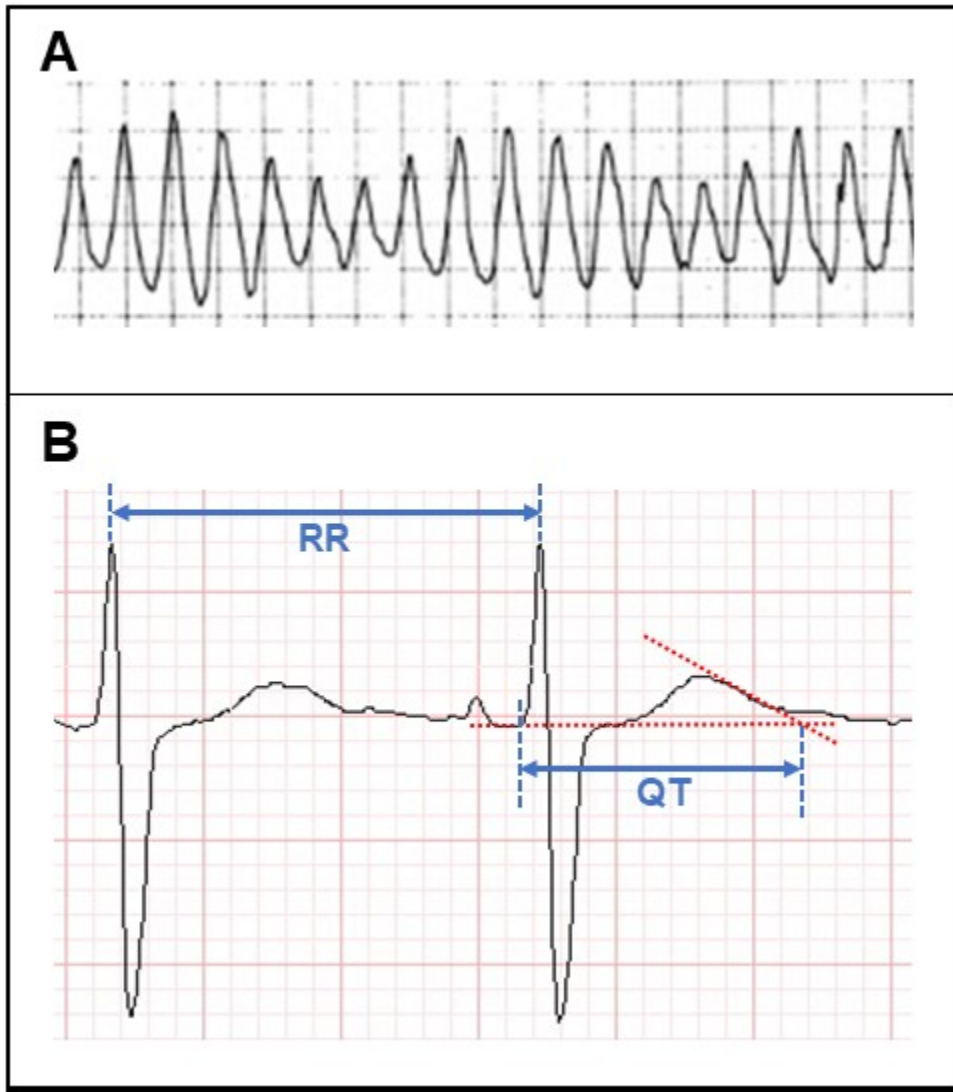

Figure 1. Torsades de Pointes and Use of the Tangent Method for Reliable QT-Interval Measurement[a]

 [a]Panel A shows an example of torsades de points from surface telemetry monitoring. Panel B shows ECG intervals relevant for QT interval measurement and heart-rate correction. The dotted red lines represent the intersection of the tangent to the steepest downward slope of the T-wave and the isoelectric baseline. Use of this intersection to define the end of the T-wave is a reliable and well-accepted method for QT interval measurement.

The burst-pattern of drug-induced TdP makes it very difficult to capture on a standard 10 second ECG. Pre-mortem diagnosis by ECG requires prolonged monitoring and sometimes a bit of luck. Sudden cardiac death attributable to drug-induced TdP is likewise difficult to adjudicate without concomitant ECG evidence of the arrhythmia. Therefore, surrogate markers and risk models have been used to inform prescribers of drugs that might produce TdP in an individual patient. Since TdP is characterized by a prolonged QTc interval by definition, QTc interval prolongation has been the major surrogate marker for the clinical arrhythmia. In a major Rotterdam prospective population-based cohort study, prolonged QTc interval (as defined in Table 1) was associated with a three-fold (8-fold for those ≥68 years age) increased risk of sudden cardiac death over a 6.7-year follow-up period (4). The link between drug-induced QTc interval prolongation and TdP is so strong that regulatory agencies responsible for drug approval worldwide have mandated that every new drug with significant systemic bioavailability be thoroughly tested for the possibility of drug-induced QTc interval prolongation (www.ich.org, product guidelines) (5). The American Heart Association, the American College of Cardiology and other organizations have published strategies to reduce TdP risk in hospitalized patients based on QTc interval prolongation as a surrogate marker for arrhythmia risk (6). These and other similar data have contributed to using QTc interval primarily as the most important (but imprecise) surrogate marker for TdP. Other less researched and less often used surrogate markers include T-wave shape and morphology and J-T interval.

Table 1. Bazett-corrected QTc interval measurements (6, 10).

Rating	Adult men (ms)	Adult women (ms)
Normal	< 430	< 450
Borderline	431-470	451-480
Prolonged	> 470	> 480

The Genesis of the QTc Interval

Mechanical activity of the heart is linked to electrical activity in a complex interplay between the depolarization and repolarization of excitable tissue and contraction and relaxation of the myocardium. The ECG represents the body surface findings of the sum of the cardiac cycle of depolarization and repolarization. Figure 2.A shows an ECG lead II waveform with descriptions of ECG intervals and the

electrophysiological events represented.

Figure 2.B-C provides a simplified description of ionic events occurring at a cellular level. Sodium (Na^+), calcium (Ca^{2+}), and potassium (K^+) ionic movements underlie the processes of depolarization and repolarization. A resting potential is maintained by sodium-potassium pump and other mechanisms resulting in uneven distribution of ions between the interstitium and interior of the cardiac myocyte (7). Cellular depolarization (QRS interval on the surface ECG; Figure 2.B-C) derives mostly from a net inward flux of sodium and then calcium ions. Cell repolarization (JT/QT interval on the surface ECG; Figure 2.B-C) derives from a net outward flux of potassium ions. Ventricular tissue is vulnerable to polymorphic ventricular tachycardia (e.g., TdP) during the latter part of the repolarization phase and the risk increases if ventricular repolarization is prolonged. The majority of drugs associated with QTc interval prolongation and TdP are linked to pharmacological blockade of hERG (human-Ether-a-go-Related Gene) potassium channels (Figure 2.D), which produce a repolarizing current termed the delayed rectifier current (IKr) (8). The role of magnesium (Mg^{2+}), known to be a first line intervention for acute TdP, is unclear mechanistically, but may serve to stabilize the cardiac myocyte membrane potential via interaction with calcium and potassium channels (Figure 2.C).
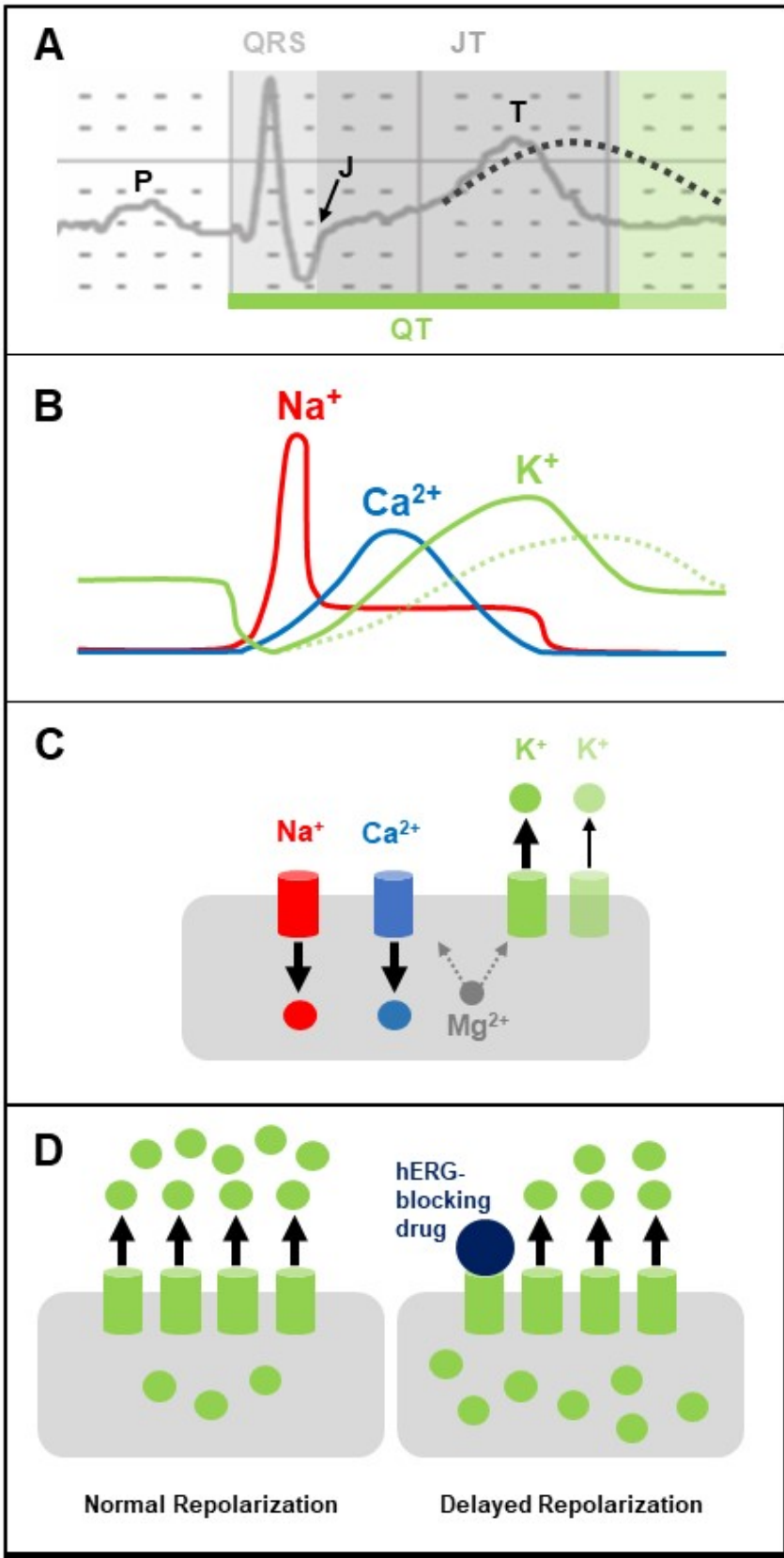
Figure 2.   Electrocardiogram (ECG) Waveforms and Intervals Corresponding to Ionic Activity During Cardiac Depolarization and Repolarization[b]

[b]Panel A shows a surface ECG waveform with intervals relevant to monitoring for TdP. The dotted line demonstrates delayed repolarization manifesting as a prolonged T-wave/U-wave, represented on the ECG as QT prolongation. The solid line shows the tangent to the steepest downward slope of the T-wave, defining the end of the T-wave by the intersection of the tangent with the baseline. Panel B shows the relationship of sodium (Na^+), calcium (Ca^{2+}) and potassium (K^+) action potentials to the surface ECG (panel A). Panel C demonstrates the net influx of sodium (Na^+) and calcium (Ca^{2+}) into the cardiac myocyte during depolarization and the net efflux of potassium (K^+) during both normal and delayed repolarization. The role of magnesium (Mg^{2+}) is unclear, however it may promote stabilization of the membrane potential during repolarization via interactions with calcium and potassium channels. Panel D compares the rate of potassium efflux through various potassium channels during normal repolarization versus in the presence of a hERG channel blocking drug.

Correcting QT Interval for Heart Rate

The duration of QT interval varies depending upon the heart rate, and the QT interval needs to be "corrected" (QTc) for heart rate to make it more consistent and clinically meaningful. A number of different formulae, each with its own set of limitations, exist to correct the QT interval for heart rate. It is important to recognize there is a lack of consensus as to which technique is optimal, and none are perfect. When doing serial comparisons of QTc interval, the same correction technique should be used throughout.

Bazett's formula ($QTcB = QT/\sqrt{RR}(Sec.)$) (9) is the most common method used to correct QT interval for heart rate, and is programmed into most ECG machines in clinical use. The RR interval, which is a proxy for heart rate, is input into the formula in seconds. The standard "normal" and "at risk" values for QTc interval are studied and based on this formula as well (10) (Table 1). A major limitation of Bazett's formula is that it overestimates QTc interval at any heart rate much higher than 60 beats per minute (bpm) and underestimates QTc interval at rates lower than 60 bpm (11). As many patients who are being treated with potentially QTc-prolonging medications in the hospital setting are tachycardic due to agitation or systemic medical conditions, this overcorrection becomes clinically meaningful. Bazett's formula was a standard for pharmaceutical research but the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) recently identified it as "an inferior method" and recommended using Fridericia's formula (or another suitable method) instead

(www.ich.org). Fridericia's formula uses a cube root (instead of square root) of HR ($QTcF = QT/\sqrt[3]{RR}$) and is less influenced by extremes of HR. Other formulas (e.g., Framingham's and Hodges') or statistical methods (population- or individual-corrected QTc interval) are also available but are used less frequently. In some cases of drug-induced QTc interval prolongation, the uncorrected QT interval may be a better predictor of clinical events (12).

Technical Aspects of Recording and Measuring QT interval on the ECG

Since the QT interval is, by definition, an ECG measurement, a properly recorded and measured ECG must be the basis for clinical decision making regarding QTc interval prolonging drugs. Interpretation of the ECG, including quantitation of the electrocardiographic intervals, should be performed according to the local institutional standards. In most hospital settings, board-certified cardiologists provide the interpretations, but in many practice settings this may not be feasible. ECG interpretation should be available by a person qualified by experience or training to interpret the ECG. Most modern ECG machines provide computer-derived interval measurements, as well as interpretive statements. These automated measures differ from machine to machine, but most often are derived from "representative complexes" or "median complexes" that take advantage of signal averaging techniques and automated threshold detection. Prescribers need to be aware of the limitations of machine-derived intervals, as well as the difference of measurements from machine to machine (13). In general, if the patient's ECG pattern is normal and free of artifact, the computer-derived intervals, including QTc interval, are reliable. If the patient's ECG is abnormal the computer-derived intervals are less reliable, and prescribers should consider performing manual measurement. Widening of the QRS complex is a common abnormality seen with bundle branch block, ventricular pacing, or use of certain medications (e.g. tricyclic antidepressants) and leads to prolongation of the QT interval without perturbation of repolarization. In such cases, clinicians should not only perform manual measurements, but also consider alternative methods to assess for TdP risk. In all cases, manual measurement remains the best approach, and is a skill that should be encouraged among all clinicians involved in caring for patients who may receive ECGs in the course of their clinical care (14).

How to measure the QT interval

The QT interval is defined as the distance from the beginning of the QRS complex to the end of the T-wave. A standardized approach to define the end of the T-wave is the intersection of the tangent to the steepest downward slope of the T-wave with the isoelectric baseline (Figure 1.B). When using Bazett's or Fridericia's formulae to correct for heart rate, the RR interval from the preceding cycle length is used

(14).

The recommendations above apply to the standard 12-lead ECG, which is a 10 second recording of cardiac electrical activity. Many other techniques capture ECG information in other formats and may have utility in monitoring the QTc interval. Hospital telemetry systems record single or multi-lead ECG data continuously from patients. Many of these systems have automated QTc interval measurement algorithms, some even providing real time assessment of the QTc interval. The American Heart Association has published standards regarding these systems, and the practitioner should be familiar with the local systems if they are used to make clinical decisions (15). Ambulatory monitors (e.g., Holter, event, and implanted loop) can also provide measurements of the QTc interval, but similar to the 12-lead ECG, require noise-free signals and are more reliable in patients with normal ECGs. The use of ambulatory monitors for measurement of the QTc interval is discouraged because of the difficulty obtaining a noise-free signal in the ambulatory patient. Similarly, single-lead measurement with a mobile device is not a substitute for a 12-lead ECG. Ambulatory monitors and single-lead mobile devices may be useful for monitoring/screening at-risk patients for arrhythmias, however.

Non-drug risk factors for QTc interval prolongation and TdP

Medications are only one of the several possible risk factors for QTc interval prolongation and these increase the risk of TdP independently. Well-established non-drug risk factors based on literature are included in Table 2.

Table 2. Risk for TdP (16-18)

Non-modifiable risk factors	Modifiable risk factors
- Female sex - Advanced age - Congenital long QT syndrome (LQTS) - Personal history of drug-induced QTc interval prolongation - Personal history of structural or functional cardiac disease (e.g., heart failure with reduced ejection fraction) - Metabolizer status	- Concurrent use of more than one QTc interval prolonging drug - Pharmacokinetic drug-drug interactions - Drug toxicity - Rapid intravenous infusion of QTc interval prolonging drugs - Severe acute illness - Bradycardia - Starvation - Inadequate dose adjustment of

	hepatically-metabolized drugs in patients with hepatic cirrhosis
	• Inadequate dose adjustment of renally-eliminated drugs in patients with acute kidney injury or chronic kidney disease
	• Risk or presence of hypokalemia, hypomagnesemia, or hypocalcemia

Combinations of these risk factors have been shown to correlate with subsequent prolongation of the QTc interval in at-risk patients (19); therefore, potential cumulative effects must be seriously considered. The odds of provoking TdP with a non-cardiac drug alone are very low, but co-existing risk factors can increase the odds dramatically (20, 21). It is essential to be aware of these risk factors to assess and monitor patients accordingly if a drug with a risk to prolong QTc interval is being considered or prescribed.

Most of the non-modifiable risk factors are self-explanatory and can be documented through clinical interview or past clinical records. Prior unexplained syncope should be investigated thoroughly as to the cause. While abnormal QT behavior in the absence of other risk factors may suggest congenital LQTS, it is important to recognize that some patients will show no evidence of LQTS until exposed to a QTc interval prolonging agent or clinical situation (22). If in doubt, a cardiologist can be consulted.

Pharmacodynamic and pharmacokinetic drug-drug interactions are probably the most common risk factors that can be easily modified (or prevented) in many instances. The pharmacodynamic interaction would result when drugs with a potential to prolong QTc interval are prescribed concurrently. A pharmacokinetic interaction would occur if a drug or a substance (e.g., nicotine, drug of abuse) is added or removed resulting in a metabolic interaction that results in slow or inhibited metabolism and consequent higher plasma concentrations of the drug associated with QTc interval prolongation. Given the vastness of possible drug-drug interactions, the best clinical approach would be to consult with a pharmacist.

Toxic drug plasma concentrations can result from a slow (or rapid, i.e., if a parent drug requires activation via CYP enzymes to an active drug) metabolizer status, pharmacokinetic drug-drug interaction, or from an intentional or accidental overdose. Patients in such a situation will need to be monitored depending upon the level of toxicity and extent of other risk factors for QTc interval

prolongation. Dose-related QTc interval prolongation is an important consideration, so medications administered intravenously that achieve higher plasma concentrations more rapidly, may increase this risk compared with oral administration. Presence of hepatic cirrhosis and/or renal insufficiency will add to the QTc interval prolonging effect of the drug by impairing its metabolism and/or excretion, resulting in higher than usual (or toxic) drug plasma concentrations. In states of mild insufficiency, the effect may be negligible for one drug, but the risk will be cumulative if more than one drug associated with QTc interval prolongation is prescribed concurrently.

Hypokalemia, hypomagnesemia and hypocalcemia can add to the risk of TdP. Several medications and/or procedures (e.g., diuretics and dialysis) can potentially disrupt electrolyte balance, and patients taking them will need to be monitored in this regard (23). Maintaining communication with the physician prescribing such drugs and establishing responsibility about electrolyte monitoring will facilitate the process and minimize duplication. Acute medical conditions (e.g., gastroenteritis, endocrinopathies), physiological conditions (e.g., gravida emesis, strenuous exercise), or fasting can also cause electrolyte disruption. Furthermore, certain diagnoses can be accompanied by behaviors (e.g., purging and/or dietary restriction in eating disorders, binge drinking in alcohol use disorder, use of dietary supplements) that would pose a risk for electrolyte derangement; these need to be considered during risk stratification.

PSYCHOPHARMACOLOGY

It is worth noting that the following discussion of psychotropic medication classes, and in some cases, individual medications, is meant to highlight the importance of performing a comprehensive risk-benefit evaluation through the application of current data, knowledge of the clinical relevance of absolute QTc interval calculations, and consideration of historical regulatory recommendations in the context of other non-medication risk factors.

CredibleMeds publishes a widely used, freely available online list of drugs known to prolong the QTc interval, divided into four categories (https://crediblemeds.org/) (24): drugs with known risk of TdP; drugs with possible risk of TdP; drugs with conditional risk of TdP (i.e., can cause TdP under certain conditions); and drugs to be avoided by patients with congenital long QT. The lists are produced by consensus of a board of experts who utilize available data from product labeling, the FDA, published literature, and other sources. A link to the website is included in many guidelines of the American Heart Association and American College of Cardiology. However, the inclusion and classification are not

systematic, as it is based on evidence of quite variable quality, ranging from double blind, randomized placebo-controlled trials with intensive ECG monitoring to single case reports that often include other risks that may account for the reported association. In some cases, supporting citations provide no actual evidence of the association. In our opinion, the classification on crediblemeds.org should not be accepted uncritically, but considered as a general list of drugs with possible potential for causing TdP. For all drugs that have a potential to prolong QTc interval, the risk of QTc interval prolongation and TdP increases when other risk factors for QTc interval prolongation are also present.

Several other points are important to remember when reviewing studies related to QTc interval prolongation. First, it is critical to understand the population being studied (e.g., healthy vs. medically or psychiatrically ill), the method of QTc interval measurement used (e.g., Bazett, Fridericia, use of a nomogram), the timing of QTc interval measurement (e.g., following a single dose of a medication vs. at steady-state), the dose of the medication, and the presence of other medications that might alter the metabolism of the medication being studied. These vary widely among studies and can impact the degree of QTc interval prolongation reported. Second, while most studies report mean QTc interval prolongation, this arguably is less important than the percentage of participants who experience clinically meaningful QTc interval prolongation, since, in these instances, a change in medication can make a substantial impact on QTc interval. Finally, it is important to recognize the strengths and weaknesses of different study types. Case reports, for example, are important for identifying potentially important side effects, but they often are fraught with confounders and may be in the setting of overdose, which limits their utility. Thorough QTc interval studies, in contrast, can clearly illustrate causal relationships between medications and QTc interval prolongation; however, these are performed in healthy adults with minimal QTc interval risk factors and so have limited generalizability. Given the wide variability in methodology and study samples, we have chosen to refrain from providing mean QTc interval prolongation for specific medications in table form. Instead, we hope to highlight relevant studies that provide guidance for making recommendations regarding medication selection in patients at risk for QTc interval prolongation. It is important clinicians understand the inherent limitations of available data and how this applies to their own practice as well as how this may impact guidance provided by regulatory agencies.

Regulatory Agencies and Drug Safety Monitoring

Agencies in many countries regulate the drug (and therapeutic devices) approval process through establishing efficacy and safety of the drug (device) and monitoring them for any potential concerns

after they become available for use. A few examples of such agencies include the Food and Drug Administration (FDA) in the USA, Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom, Health Canada, and the Therapeutic Goods Administration (TGA) of Australia. Over the last decade, these agencies have issued safety warnings related to the risk of QTc interval prolongation and TdP associated with some psychotropic drugs. In some cases, the warnings followed data based on thorough QTc interval studies and in other instances warnings were based on data from post-marketing reports and surveillance. While some degree of general consensus exists between various agencies, they tend to differ in fine details and occasionally more dramatically. The differences stand out more noticeably when data are limited and/or difficult to interpret reliably. This is the case with regards to the risk of QTc interval prolongation and TdP associated with psychotropic drugs, as we highlight with a few examples below.

Citalopram and escitalopram underwent a thorough QTc interval study after post-marketing reports of QTc interval prolongation and TdP associated with citalopram emerged (25, 26). A dose-dependent QTc interval prolongation was observed both for citalopram (mean 8.5 ms with 20 mg/day dose and mean 18.5 ms with 60mg/day dose) and escitalopram (mean 4.5 ms with 10 mg/day dose and mean 10.7 ms with 30mg/day dose). The increase, based on predefined terms, was significant for citalopram but not for escitalopram. Following these data, all four regulatory agencies mentioned above issued a safety warning for citalopram. The MHRA considered the data for escitalopram concerning enough to issue a safety warning for escitalopram as well. This highlights that safety of psychotropics (or lack thereof) is not a dichotomous matter (21). Interestingly, in the aforementioned thorough QTc interval study (25), QTc interval was calculated using Bazett's method, which now is considered an "inferior method" and Fridericia's method (or another suitable method) is recommended for use in such studies (27).

The FDA and the TGA both have issued safety warning about quetiapine based on post-marketing data. The evidence was not strong or clear enough for the FDA to issue a "boxed" safety warning, however, a warning is included within the text of the FDA label for quetiapine. The FDA label notes "there were cases reported of QTc interval prolongation in patients who overdosed on quetiapine, in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QTc interval" (28). The TGA safety warning is based on a very similar observation and notes "Post-marketing reports of QTc interval prolongation associated with quetiapine treatment have occurred not only in the context of overdose, but also with concomitant illness and in patients taking other drugs known to cause electrolyte imbalances or increase the QTc interval" (29). A recent comprehensive

review has substantiated these concerns noticing that while quetiapine toxicity is associated with QTc interval prolongation, all three cases of TdP (out of 16 case reports of QTc interval prolongation) reported up till 2013 had occurred at therapeutic doses of quetiapine (21).

This document does not specifically cover safety warnings issued by various regulatory agencies. Above we have only provided a few examples to draw attention to this matter. Our understanding of psychotropic drug associated QTc interval prolongation and TdP is evolving. Further safety warnings and/or modification of existing warnings is expected as data emerge. We advise clinicians to stay informed and follow the safety warnings pertinent to their country of practice.

Selective Serotonin Reuptake Inhibitors (SSRIs)

For many years, SSRI antidepressants were considered safe from a QTc interval prolongation perspective, despite occasional case reports of QTc interval prolongation for all agents in this class. To date, studies examining QTc interval prolongation effect for fluoxetine, fluvoxamine, and paroxetine have provided no compelling evidence of QTc interval prolongation (30). Sertraline remains the agent with the best-established track record in cardiac populations (31, 32).

As previously stated, on August 2011, the FDA issued a warning for QTc interval prolongation with citalopram based on a thorough QTc interval study demonstrating prolongation of 8.5ms at doses of 20mg and 18.5ms at doses of 60mg (25). Subsequent studies, including a meta-analysis, a large retrospective study of an ECG database, and a randomized placebo-controlled study, have suggested that citalopram may be more likely than other SSRIs to cause QTc interval prolongation, and may prolong the QTc interval at a similar magnitude to that demonstrated in the FDA study (33-36). The FDA currently advises practitioners to not utilize doses of citalopram greater than 40mg in all patients, and to use doses of 20mg or lower in patients over the age of 60 years or with liver dysfunction. Though most studies suggest that the risk of QTc interval prolongation and TdP increases with higher doses, at least one large study found higher doses to be associated with fewer adverse outcomes, though QTc interval was not specifically examined and the authors did not control for other known risk factors (37).

Several studies have suggested that escitalopram may have QTc interval prolonging properties, with a thorough QTc interval study estimating prolongation of 4.5ms at 10mg and 10.7ms at 30mg daily (30). However, a large meta-analysis of nearly 3300 patients demonstrated a mean prolongation of only 3.5ms for all doses (38).

When applying these results to real-life clinical practice, it is essential to consider that QTc interval changes in the range of 10-20ms, as found in the citalopram studies, are below the limits of detection on an individual ECG and may only yield a signal in large samples. QTc interval changes in the range of 30-60ms would be considered potential signals; changes >60ms should be considered unusual and signals of concern. Hence, though the QTc interval changes with citalopram separate out from the other SSRIs, the clinical impact in isolation of other risk factors is insignificant.

It is also important to keep in mind that, for some patients, the risk of QTc interval prolongation with 60mg of citalopram is not as significant as the risk of psychiatric decompensation with a lower dose. There is evidence to suggest that the FDA warning has not reduced all-cause or cardiac mortality, but has led to increased rates of psychiatric hospitalizations for patients whose dose was reduced reflexively (39). Another study found that patients who had their dose of citalopram reflexively reduced were more likely to be prescribed sedatives or anxiolytics and had higher healthcare utilization (40). These studies highlight the importance of comprehensively considering all factors contributing to the risk-benefit ratio when prescribing "at-risk" medications.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Among SNRIs, venlafaxine, the oldest agent in this class, has the most evidence to support concerns with the risk for dose-related QTc interval prolongation, in both therapeutic doses (150 mg or 300 mg daily) and in overdose situations (41-44), some of which have proven fatal (45, 46). With that stated, the overall risk of QTc interval prolongation and TdP at therapeutic doses and in overdose situations is low (47), though elderly patients may be at greater risk (48). One study comparing the risk of sudden cardiac death or near death when venlafaxine was compared to other antidepressants found no increase in risk with the use of venlafaxine (49).

The paucity of data on the remaining available SNRIs, including duloxetine, desvenlafaxine, and levomilnacipran, limit any conclusions regarding the QTc interval prolongation risk among these agents (41). Duloxetine's effects on the QTc interval have been studied in therapeutic and supratherapeutic doses. Overall, studies have found a decrease in the QTc interval when studied in healthy adults (50, 51). When corrected for heart rate, there is a slight increase in QTc interval values, however, study authors deemed this is not clinically significant (51).

One published study, reviewing overdoses of desvenlafaxine identified no cases of QTc interval prolongation in doses up to 3500 mg (52). In a systematic review and meta-analysis of levomilnacipran, this agent was found to increase QTc interval compared to placebo when Bazett's formula, but not when

Fridericia's formula, was used (53), suggesting these findings may have been driven by increases in heart rate. Among users of levomilnacipran, no patients experienced a QTc interval greater than 500 ms (53). Notably, some studies evaluating the QTc interval risk of levomilnacipran were further limited by the exclusion of patients with a baseline abnormal ECG (54, 55).

Tricyclic and Tetracyclic Antidepressants (TCAs)

TCAs are known to prolong the QTc interval via blockade of sodium channels leading to QRS widening, in addition to effects on the delayed potassium rectifier current. Clinically significant QTc interval prolongation tends to occur at therapeutic doses only in the setting of pre-existing cardiac disease, or in overdose (56). A meta-analysis suggested the average QTc interval prolongation associated with TCAs is 13 ms compared to placebo (31). Among TCAs, amitriptyline and maprotiline have been most commonly associated with TdP in case reports (57).

Other Antidepressants

At therapeutic doses, the use of bupropion has demonstrated a reduction in QTc interval (33, 58, 59) and may be considered a reasonable option in patients at high risk for ventricular arrhythmias (60). On the other hand, similar to venlafaxine, bupropion has been linked to QTc interval prolongation, particularly in overdoses (61-64). Reports of QTc interval prolongation with bupropion may be confounded by tachycardia and reported concomitant medications or substances (41). Importantly, in one key study, none of the patients that exhibited prolonged QTc interval experienced any type of arrhythmia (62).

Evaluating the risk of QTc interval prolongation with mirtazapine, studies have demonstrated a greater risk of mirtazapine for cardiac sudden death and ventricular arrhythmias in elderly patients when compared with paroxetine or citalopram (65, 66). However, other studies demonstrate low risk of mirtazapine for cardiovascular adverse drug reactions, including arrhythmia, when compared to other antidepressants (60, 67) or in overdose (68, 69). Given these conflicting results, mirtazapine should be used cautiously in patients at risk for QTc interval prolongation, which is in alignment with the FDA warning in product labeling.

Continuing on with newer antidepressants, data on the risk of QTc interval prolongation with use of vilazodone is very limited, however initial data does not support an increase in risk (41, 70, 71). With regard to vortioxetine, data fail to demonstrate a risk associated with therapeutic and supratherapeutic doses in healthy adult males (72). Further, in short-term studies of adults with major depressive disorder

17

treated with vortioxetine, changes in QTc interval (Fridericia) were similar to that of placebo (73). It is important to keep in mind that broader exposure is limited due to the novelty of these two agents.

Antipsychotic Medications

Both typical and atypical antipsychotic medications also have been associated with QTc interval prolongation and its sequelae of TdP and sudden cardiac death (SCD). Among the typical antipsychotics, low-potency phenothiazines--especially thioridazine--lead to the greatest risk of QTc interval prolongation and sudden cardiac death (74-76). In a randomized trial of six antipsychotic medications, thioridazine led to 30.1 ms of QTc interval prolongation, which was numerically greater than the prolongation associated with haloperidol (7.1 ms), ziprasidone (15.9 ms), quetiapine (5.7 ms), olanzapine (1.7 ms), or risperidone (3.6 to 3.9 ms) (74).

Aside from thioridazine, haloperidol's QTc interval prolonging properties have received the most attention. Haloperidol is available in oral, intramuscular, and intravenous formulations, and each formulation is typically used in different clinical situations. While oral and intramuscular haloperidol are typically used for the management of psychosis or agitation in medically stable patients, intravenous haloperidol is often used for the management of delirium in medically ill patients. As noted above, in individuals without significant medical illness, orally administered haloperidol 15mg daily is associated with a mild (~7 ms) increase in QTc interval at steady state (34). Intravenous haloperidol may cause a greater degree of QTc interval prolongation and confer a greater risk for TdP than orally administered haloperidol (77), though the difference between these medications may be explained--at least in part-- by their uses in different clinical populations, as noted above (78). Due to its links to QTc interval prolongation and TdP, the FDA recommends cardiac monitoring of patients in the setting of intravenous haloperidol use (79).

Other typical antipsychotic medications also prolong the QTc interval. Both chlorpromazine and pimozide are associated with clinically significant QTc interval prolongation (77, 80, 81), and pimozide has been linked to TdP in overdose (82). Loxapine appears to be less likely to cause significant QTc interval prolongation, as two recent thorough QTc interval studies found that inhaled loxapine leads to mild (~5ms) increases in the QTc interval (83, 84). Finally, while the effects of perphenazine on QTc interval have not been studied, a retrospective cohort study found that perphenazine was associated with a similar risk of sudden death/ventricular arrhythmia and a lower risk of all-cause mortality compared to olanzapine (85).

Like the typical antipsychotics, nearly all atypical antipsychotic medications have been associated with

QTc interval prolongation to some degree. While it is difficult to rank atypical antipsychotic medications based on QTc interval risk due to differing study methodologies (21), ziprasidone appears to carry a particularly high risk of QTc interval prolongation (86). Thorough QTc interval studies suggest that ziprasidone leads to 10-21 ms increases in the QTc interval on average (74, 87), with over 20% of individuals experiencing >60 ms increases in QTc interval, a substantial and clinically meaningful increase (88).

The remaining atypical antipsychotic medications prolong QTc interval to a lesser degree. Iloperidone has been linked to Fridericia-corrected QTc interval increases of 8.5 ms (at a dose of 8mg BID) to 15.4 ms (at a dose of 24mg daily) in cardiovascular healthy adults (87). As previously highlighted, thorough QTc interval studies suggest that quetiapine leads to small to moderate (1.3-14.5 ms) increases in QTc interval at doses of up to 750mg daily, and the FDA has issued a warning due to quetiapine's propensity to prolong QTc interval (74, 87-90). These same trials found olanzapine to prolong QTc interval by 1.7-6.8 ms at up to 20mg/day and risperidone to prolong QTc interval by 3.6-11.6 ms at doses of 6-16mg/day (74, 88). QTc interval prolongation from paliperidone, lurasidone, and asenapine range from 4.5 ms (asenapine) to 12.3ms (paliperidone) (91), and a recent meta-analysis found that these three medications did not cause significant QTc interval prolongation compared to placebo (86). Though the effect of clozapine on QTc interval has been studied rarely, a retrospective review of patients who had switched treatment from another antipsychotic (>80% were atypical antipsychotics) to clozapine found no significant changes in QTc interval following the switch, suggesting that the risk of QTc interval prolongation between clozapine and other atypical antipsychotic medications is similar (92). Finally, aripiprazole appears to be the least likely atypical antipsychotic medication to cause QTc interval prolongation, with a recent meta-analysis finding that aripiprazole led to significant reductions in QTc interval compared to both placebo and active controls (93).

The link between atypical antipsychotics and TdP is less clear. While these medications have only been linked to TdP in case reports and FDA adverse events reports (21, 94), atypical antipsychotics have been associated with an increased risk of sudden death in population-based studies (95, 96), which may be explained by the association between these medications and ventricular arrhythmias. Furthermore, in elderly patients with dementia, they have been associated with mortality related to cardiac events, which has led the FDA to issue a boxed warning related to this complication.

Other Psychotropics

Lithium

There have been conflicting reports concerning lithium's effect on QTc interval prolongation. A retrospective study showed lithium had no significant association with QTc interval prolongation (97). However, another report showed lithium in concentrations above 1.2 mmol/L can markedly prolonged the QTc interval (98). Multiple regression analysis revealed that sex, lower serum potassium concentration, and, especially, higher serum lithium concentration were determinants for the prolongation of the QTc interval (99).

Antiepileptic Drugs

Major antiepileptic drugs have not been found to significantly precipitate prolongation of QTc interval. Valproate was found to lower QTc interval dispersion, which might indicate that valproate may have some preventative effects and stabilization in cardiac conduction (100). Studies with lamotrigine or topiramate have not shown any clinically significant changes on individual QTc interval, except for slight decreases in QTc intervals with lamotrigine (101, 102). Though carbamazepine has sodium-channel blocking properties, at least one study suggests decreasing QTc interval with increasing carbamazepine concentrations (103). In a double-blind, placebo- and active-controlled trial, gabapentin enacarbil, a transported prodrug of gabapentin, was not associated with QTc interval prolongation in healthy adults (104).

Stimulants

Stimulants have multifactorial potential in addition to just QTc interval prolongation. The increase of catecholamines by CNS stimulants results in a rise in heart rate (HR) and blood pressure (BP), which would be expected to increase the risk of ventricular arrhythmia or sudden cardiac death (105). Clinical trials have found no statistically or clinically significant changes to the QTc interval over short and long-term treatment with methylphenidate and amphetamine drugs (106, 107). Atomoxetine has been shown to be associated with life-threatening long QT syndrome (108). Evidence shows that atomoxetine inhibits cardiac potassium channel currents causing action potential prolongation and increasing risk of acquired long QT syndrome (109). However, a pooled analysis of five randomized double-blind trials showed no clinically significant increase in QTc interval prolongation (110).

Modafinil has been shown to cause infrequent significant increases in BP and HR. However, there has been no evidence that it has any clinically significant effect on QTc interval prolongation (111). While not considered stimulants, it is worth noting there are also no statistically or clinically significant increases in QTc interval associated with clonidine and guanfacine (112).

Although the cardiovascular impact of stimulant use is minimal in healthy patients, prescribers should use caution in patients with underlying heart disease, other atrial or ventricular arrhythmias, symptoms of undiagnosed disease (e.g., syncope), or prescription of other like cardiac medications. Given their effects on the sympathetic nervous system, patients receiving stimulants should have routine monitoring of HR and BP.

Trazodone

Trazodone has rarely been associated with QTc interval prolongation (113). However, there have been a few case reports highlighting risk of transient QTc interval prolongation in the setting of trazodone overdose, especially in patients taking other QTc interval prolonging agents or with underlying cardiovascular disease (113, 114).

Benzodiazepines and Buspirone

Although there may be effects on other cardiac parameters, there appears to be little effect on QTc interval from benzodiazepines and none reported with buspirone (115).

Acetylcholinesterase Inhibitors and Amantadine

Medications commonly used in dementias also have a relationship with prolonged QTc interval. Acetylcholinesterase inhibitors, such as donepezil, have cholinergic effects which may lead to adverse reactions in the cardiovascular system. Cardiac arrhythmias, QTc interval prolongation and TdP in patients prescribed donepezil have been highlighted in case reports (116). However, these case reports include patients age 80 years or older, with several medical comorbidities. The dopaminergic activity of amantadine has potential for induction of malignant arrhythmias resulting in amantadine-induced TdP in the setting of overdose and co-ingestions (117, 118).

Methadone

Methadone is well-known to be strongly associated with both QTc interval prolongation and TdP (119-121). TdP associated with methadone use was first reported in a retrospective case series of 17 patients receiving high dose treatment (119). Several case-control, cross-sectional, and prospective cohort studies have assessed the incidence of methadone-associated QTc interval prolongation and shown significant effects on the QTc interval (120). Unfortunately, the prevalence of QTc interval prolongation and TdP in methadone-treated patients is not clear; this gap in knowledge represents a major public health concern, especially in light of the burgeoning opioid epidemic. Guidelines from the American Pain Society can be helpful in identifying approaches to mitigating the risk of QTc interval prolongation

associated with methadone, which may include dose reduction and discontinuation of other agents that may prolong the QTc interval (122). Concomitant use with other medications with known risk for prolonging the QTc interval (e.g., citalopram) or in the context of electrolyte disturbances warrants cautious consideration of augmented risk for TdP (123). Further, as newer agents are developed in the management of opioid addiction, risks associated with these medications and how they compare with the QTc interval prolongation risks of methadone will be important.

Buprenorphine

In general, QTc interval prolongation is not considered a consequence of the use of other narcotics. Buprenorphine has been found to be less likely to cause QTc interval prolongation than methadone (124). However, some studies have shown that induction with buprenorphine was still followed by an increase in QTc interval (125).

Special Population: Children and Adolescents

Our workgroup has chosen to limit our review to studies involving adults over the age of 18. While psychotropic medications can cause QTc interval prolongation in children and adolescents, there are few studies evaluating these effects. Importantly, additional research is necessary within this population to guide clinical decision-making and avoid "overcautious interpretation" of ECGs among children and adolescents, which may lead to non-treatment (126). Further, extrapolation of adult data is not appropriate. One example includes data surrounding the use of methadone among pediatric patients and young adults, which suggest methadone may be safe, though additional prospective data are needed (127, 128). Antipsychotic medications have received the greatest attention in the pediatric population, where a systematic review found ziprasidone to be linked to the greatest degree of QTc interval prolongation and aripiprazole to lead to a significant reduction in QTc interval, consistent with studies in adults (129). Use of antipsychotic medications or other medications that may prolong the QTc interval in the context of eating disorders within this population requires specific consideration. One article highlights the importance of additive risk in the context of anorexia related to bradycardia and/or electrolyte abnormalities and the impact correction equations may have on normalizing the QTc interval, thereby underestimating the true severity of the repolarization abnormality (130). Additional monitoring is recommended in this population as well as those with bulimia who may purge and be pre-disposed to electrolyte abnormalities. Caution and repeat ECGs are advised as medications posing risk for QTc interval prolongation are added or doses are adjusted, or additional risk factors for QTc interval prolongation arise over the course of treatment.

In contrast, there are very few studies evaluating the effects of antidepressants or mood stabilizers on QTc interval in pediatric populations (101, 131). Pediatric patients represent a special challenge to the measurement and correction of the QTc interval. Pediatric patients may not be able to maintain the quiet supine posture needed for good quality ECG recording. The QTc interval varies with age and sex, and there is a sharp inflection in the relationship between age and QTc interval around puberty. Heart rate and the effect of heart rate on the performance of QT correction factors is more variable in the pediatric age range, and published reference ranges for QTc interval values have been developed in populations that may not reflect modern society's mix of races (132). For these reasons, the practitioner caring for pediatric patients may wish to consult with a local cardiologist with the experience and/or training to deal with the complex issues present in the pediatric population. Given the limitations in the literature, as well as complexities related to categorizing risk in children and adolescents of different age, making broad recommendations regarding the assessment and minimization of QTc interval prolongation in pediatric populations is difficult and beyond the scope of this resource document.

Non-Psychiatric Medications and QTc prolongation

While this resource document is focused on psychotropics, these represent only a subset of QTc interval prolonging medications. Over 100 non-psychotropic medications have also been shown to prolong the QTc interval and/or be associated with TdP, particularly anti-arrhythmic medications, certain antibiotics (e.g., macrolides and fluoroquinolones), antivirals (HIV medications), anti-emetics (e.g., ondansetron), acid blockers, antihistamines (e.g., hydroxyzine and diphenhydramine) and some anti-cancer medications. While a full discussion of QTc interval prolongation risk of all these medications is well outside the scope of this document, a few salient points are made below.

It is important to note that non-psychotropic QTc interval prolonging medications are frequently administered or prescribed in a variety of settings, often more so than psychotropics. In the intensive care population, 3-30% of patients received QTc interval prolonging medications, the most frequently administered being amiodarone, along with high use of fluoroquinolones (levofloxacin) and macrolides (azithromycin) (133, 134). A study in emergency departments found the top nine administered or prescribed QTc interval prolonging medications as non-psychotropic, particularly diphenhydramine, azithromycin, and ondansetron; ondansetron alone was prescribed in almost 10% of ED visits, despite being officially FDA-approved only for post-operative and chemotherapy-associated nausea and vomiting (135). In outpatients, a study of a national pharmaceutical claims database found almost a quarter of prescriptions involving QTc interval prolonging medications, the top three being

clarithromycin, erythromycin, and levofloxacin (66).

Of particular concern is the co-administration of two or more QTc interval prolonging medications, as this significantly increases the risk of QTc interval prolongation (136-138). This is particularly salient given the often-significant medical co-morbidity of the psychiatric population, and the resultant comingling of psychotropics and QTc interval prolonging non-psychotropics. In intensive care, almost one in five patients were co-administered two or more QTc interval prolonging medications; particularly frequent combinations included amiodarone and haloperidol, as well as amiodarone or haloperidol with macrolides or fluoroquinolones (133). In outpatients, close to 10% of patients received 2 or more QTc interval prolonging medications concurrently, particularly antidepressants such as fluoxetine and amitriptyline with macrolides or fluoroquinolones (139). Clinicians should also take care to inquire about over-the-counter medications, supplements, and imported drugs not approved in the U.S. Many useful tools exist online for the clinician to track potential drug-drug interactions prolonging the QTc interval, such as the Medscape Multi-Drug Interaction Checker (http://reference.medscape.com/drug-interactionchecker).

Minimization of QTc prolongation risk must involve a thorough assessment of the entire medication list, as well as balancing risks/benefits of psychotropics against those of other medications, and potential drug-drug interactions using appropriate reference tools.

CLINICAL CONSIDERATIONS

When to Obtain an ECG?

A wide variety of physiologic and pharmacologic factors can influence the QTc interval; it is therefore recommended that QTc interval measurement should be no more than one month prior to the decision point, and no substantial changes in medications, electrolytes, or cardiovascular status (e.g., an episode of heart failure or an acute MI) should have occurred subsequent to the measurement. ECGs are noninvasive, inexpensive, and readily available in most clinical settings, so if there is uncertainty on the patient's status, an ECG should be considered. Clinicians should consult any guidelines surrounding the ECG monitoring for specific medications. For example, the methadone safety guidelines published by the American Pain Society provide detailed information regarding recommendations for baseline and follow-up ECG monitoring, when to avoid methadone use, and alternative medications to consider for patients at high risk for QTc interval prolongation or TdP (122).

In resource-poor settings ECGs may not be easily accessible. Practitioners should not let the absence of

an ECG preclude the prescription of a psychotropic medication; rather they must carefully consider known risks vs. benefit of prescribing the medication. In settings where clinicians have access to an ECG machine in the absence of a cardiology overread, clinicians of any medical specialty should feel comfortable with measurement, calculation, and documentation of the QTc interval.

Additional Monitoring

It is important to monitor electrolytes in patients that may have risk of electrolyte dysfunction, specifically hypokalemia or hypomagnesemia. Electrolyte monitoring is particularly indicated in patients with severe diarrhea or vomiting, alcohol use disorder, susceptible to rapid fluid shifts as in dialysis, and in individuals receiving certain medications such as loop and thiazide diuretics, amphotericin B, and proton-pump inhibitors. Empiric supplementation with a bio-available magnesium preparation may be considered in patients at risk of chronic electrolyte deficiency. Renal and/or liver function, depending on the medication utilized and the patient's status, should be monitored to determine if renal or hepatic impairment may increase the risk for dose-dependent QTc interval prolongation. As always, monitoring for the addition or removal of specific medications that may affect drug concentrations of any offending medication(s) should also occur.

Intensive Care Unit (ICU)

Patients in the ICU setting are at increased risk of TdP given the very nature of having severe medical/surgical illness. In one survey, 18.2% of patients admitted to a coronary care unit had a QTc interval > 500 ms (134). Patients are more likely to have multiple risk factors for QTc interval prolongation, including concurrent use of medications associated with QTc interval prolongation, parenteral administration of such medications, electrolyte disturbance, hepatic/renal dysfunction, older age, and underlying cardiac illness.

It is essential for all members of the ICU team, psychiatry, cardiology and other specialty services to work collaboratively and broadly to approach risk stratification and risk mitigation in ICU patients. Clinical conversations about risk stratification in the ICU may superficially focus on the question: "does the patient have a QTc interval > 500 ms?" often stopping short of an all-inclusive evaluation of all pertinent risks, benefits and risk-mitigation strategies. There is no absolute QTc interval at which a psychotropic should not be used. The decision of where to draw the line requires a comprehensive risk-benefit assessment.

An important risk/benefit consideration is the risk of not appropriately controlling agitation which may

result in harm to patient via self-removal of external devices including vascular access, monitoring devices, temporary pacing wires, endotracheal tubes, etc. It is critical that antipsychotics are not inappropriately under-dosed for agitation out of concern for QTc interval prolongation. The intensive care unit should be considered the "safest" place in the hospital where patients are closely monitored and staff are equipped to rapidly manage arrhythmias. In very high-risk cases (e.g., patient with history of past TdP, on high-risk antiarrhythmic medication, and severe agitation requiring parenteral haloperidol) the team may consult cardiology for temporary over-drive pacing to prevent bradycardia. Re-intubation may be considered in patients with uncontrollable agitation.

When to Consult Cardiology

Routine cardiology consultation is not indicated when prescribing QTc interval prolonging medications to a patient without cardiac risk factors; however, many higher-risk clinical scenarios are best approached with cardiology input. In patients with known heart disease and one or more risk factors for drug-induced TdP, the clinician may consider consulting with the existing cardiologist when starting a medication with liability. In higher risk scenarios including co-administration of high-risk medications (e.g., amiodarone and parenteral haloperidol), marked QTc interval prolongation (>500ms), or a sudden increase of QTc interval (>60 ms from baseline), referral to cardiology is appropriate. Patients on a known offending drug who experience cardiac symptoms such as syncope, dizziness, and palpitations should immediately be referred to cardiology. Again, a team-based care approach with open communication between specialties is paramount.

Approach to the Patient with a Pacemaker or Implantable Cardioverter Defibrillator

Practitioners commonly assume that the presence of a pacemaker (PPM), implantable cardioverter defibrillator (ICD), or cardiac resynchronization therapy (CRT) device is protective against TdP, regardless of QTc interval prolongation. Specifically, clinicians may suppose that such devices will prevent TdP by pacing, or that a single appropriate shock could terminate a ventricular arrhythmia without complication.

It should be first considered that patients with a cardiovascular implantable electronic device (CIED) are already at increased risk for TdP by the mere nature of having pre-existing cardiac disease. It is important to remember that all CIEDs have intrinsic pacing function; however, to prevent accelerated PPM battery depletion and unnecessary ventricular strain, most pacemakers are not set to pace until

the heart rate drops below 40-50 beats/minute. A review of all published case reports of TdP in patients with PPMs over a 24 year period found a pacing rate of 55+/-11 beats/min when TdP occurred (140). Hence, typical pacing parameters will not prevent TdP. Tachycardia pacing (>70 beats/min) is an accepted approach that may effectively prevent TdP and may be strategically used, in collaboration with cardiology colleagues, in the setting of acute medical/surgical illness requiring higher-risk psychotropic medication (e.g., parenteral haloperidol for delirium in the cardiac intensive care unit).

ICDs and CRTs both have the capability to recognize TdP and deliver appropriate shock therapy. Though the goal of defibrillation is to terminate the ventricular arrhythmia, in most settings a single shock is not enough to stabilize the patient. Recalling that TdP typically occurs in a milieu of multiple risk factors, often including hypokalemia, hypomagnesemia, and medications that prolong ventricular repolarization, TdP may continue, despite repeated defibrillation, until the underlying milieu is corrected. Patients may experience a phenomenon known as "ICD storm" in which the ICD/CRT delivers repeated shocks in an attempt to abort the arrhythmia. ICD storm can result in additional comorbidity, including posttraumatic stress disorder (PTSD), increased anxiety and reduced quality of life (141, 142). When prescribing medications known to increase risk of TdP to patients with a CIED, the clinician should not assume that the patient is "protected," rather the presence of a cardiac device should trigger increased vigilance (143).

CONCLUSIONS

- The most widely used correction formula (Bazett), programmed into most ECG machines, is not a consistently reliable method of correction. It overestimates QTc interval at high heart rates and underestimates it in bradycardia. Manual measurement with heart-rate correction using Fridericia or an alternative population-based nomogram is more consistently reliable across a range of clinical scenarios.

- Currently available sources that classify drugs according to 'level of risk' are based on evidence of very variable quality and validity.

- Medications are only one of the several possible risk factors for QTc interval prolongation, each of which can increase the risk of TdP independently. Combinations of these risk factors can create cumulative risk. The co-administration of two or more QTc interval prolonging medications is of particular concern.

- There is not unanimity in the guidelines and warnings among the Food and Drug Administration

(FDA) in the USA and analogous bodies in other countries.

- In patients with significant cardiac risk factors, psychotropic drugs with a known risk to prolong QTc interval or those with a regulatory warning in this regard should be avoided when relatively safer alternatives are available.

- Though there is no absolute QTc interval at which a psychotropic drug should not be used, the risk-benefit ratio in patients with pretreatment QTc intervals >500ms must be assessed comprehensively with careful attention to risk mitigation strategies. The treatment team must consider risk of failure to control high risk psychopathology or of psychiatric decompensation.

- Routine cardiology consultation is not indicated when prescribing QTc interval prolonging medications to a patient without cardiac risk factors. When significant cardiac disease is present and/or when other risk factors for QTc interval prolongation are present, cardiology input should be considered.

REFERENCES

1.   Sarganas G, Garbe E, Klimpel A, Hering RC, Bronder E, Haverkamp W. Epidemiology of symptomatic drug-induced long QT syndrome and Torsade de Pointes in Germany. Europace. 2014;16:101-108.

2.   Dessertenne F. La tachycardie ventriculaire a deux foyers opposes variables. Arch Mal Coeur. 1966;59:263-272.

3.   Selzer A, Wray HW. Quinidine Syncope. Paroxysmal Ventricular Fibrillation Occurring during Treatment of Chronic Atrial Arrhythmias. Circulation. 1964;30:17-26.

4.   Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol. 2006;47:362-367.

5.   Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. Prog Cardiovasc Dis. 2001;43:1-45.

6.   Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM, Zareba W, American Heart Association Acute Cardiac Care Committee of the Council on Clinical C, Council on Cardiovascular N, American College of Cardiology F. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol. 2010;55:934-947.

7.   Fu EY, Clemo HF, Ellenbogen KA. Acquired QT Prolongation: Mechanisms and Implications. Cardiology in review. 1998;6:319-324.

8.   Hancox JC, McPate MJ, El Harchi A, Zhang YH. The hERG potassium channel and hERG screening for drug-induced torsades de pointes. Pharmacol Ther. 2008;119:118-132.

9.   HC B. An analysis of the time-relations of electrocardiograms. Heart. 1920;7:35-70.

10.   Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". J Cardiovasc Electrophysiol. 2006;17:333-336.

11.   Patel PJ, Borovskiy Y, Killian A, Verdino RJ, Epstein AE, Callans DJ, Marchlinski FE, Deo R. Optimal QT interval correction formula in sinus tachycardia for identifying cardiovascular and mortality risk: Findings from the Penn Atrial Fibrillation Free study. Heart rhythm. 2016;13:527-535.

12.   Tisdale JE, Kovacs R, Mi D, McCabe GP, Cariera BL, Sharma N, Rosman H. Accuracy of uncorrected

versus corrected QT interval for prediction of torsade de pointes associated with intravenous haloperidol. Pharmacotherapy. 2007;27:175-182.

13.   Kligfield P, Badilini F, Rowlandson I, Xue J, Clark E, Devine B, Macfarlane P, de Bie J, Mortara D, Babaeizadeh S, Gregg R, Helfenbein ED, Green CL. Comparison of automated measurements of electrocardiographic intervals and durations by computer-based algorithms of digital electrocardiographs. Am Heart J. 2014;167:150-159 e151.

14.   Postema PG, De Jong JS, Van der Bilt IA, Wilde AA. Accurate electrocardiographic assessment of the QT interval: teach the tangent. Heart rhythm. 2008;5:1015-1018.

15.   Sandau KE, Funk M, Auerbach A, Barsness GW, Blum K, Cvach M, Lampert R, May JL, McDaniel GM, Perez MV, Sendelbach S, Sommargren CE, Wang PJ. Update to Practice Standards for Electrocardiographic Monitoring in Hospital Settings: A Scientific Statement From the American Heart Association. Circulation. 2017;136:e273-e344.

16.   Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. Therapeutic advances in drug safety. 2012;3:241-253.

17.   Chorin E, Hochstadt A, Viskin S, Rozovski U, Havakuk O, Baranchuk A, Enriquez A, Strasberg B, Guevara-Valdivia ME, Marquez MF, Gonzalez-Pacheco H, Hasdemir C, Rosso R. Female gender as independent risk factor of torsades de pointes during acquired atrioventricular block. Heart rhythm. 2017;14:90-95.

18.   Rosso R, Adler A, Strasberg B, Guevara-Valdivia ME, Somani R, Baranchuk A, Halkin A, Marquez MF, Scheinman M, Steinvil A, Belhassen B, Kazatsker M, Katz A, Viskin S. Long QT syndrome complicating atrioventricular block: arrhythmogenic effects of cardiac memory. Circulation Arrhythmia and electrophysiology. 2014;7:1129-1135.

19.   Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, Kovacs RJ. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circulation Cardiovascular quality and outcomes. 2013;6:479-487.

20.   Viskin S, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by noncardiac drugs. Prog Cardiovasc Dis. 2003;45:415-427.

21.   Hasnain M, Vieweg WV. QTc interval prolongation and torsade de pointes associated with second-generation antipsychotics and antidepressants: a comprehensive review. CNS drugs. 2014;28:887-920.

22.   Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. The New England journal of medicine. 1992;327:846-852.

23.   Johri AM, Baranchuk A, Simpson CS, Abdollah H, Redfearn DP. ECG manifestations of multiple electrolyte imbalance: peaked T wave to P wave ("tee-pee sign"). Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc. 2009;14:211-214.

24.   Therapeutics ACfEaRo: CredibleMeds.

25.   Administration: UFaD: FDA safety communication: abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). 2011.

26.   Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC. QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics. 2013;54:1-13.

27.   Vandenberk B, Vandael E, Robyns T, Vandenberghe J, Garweg C, Foulon V, Ector J, Willems R. Which QT Correction Formulae to Use for QT Monitoring? Journal of the American Heart Association. 2016;5.

28.   Administration USFaD: Highlights of Prescribing Information. 2010.

29.   Administration AGDohTG: Medicines Safety Update, Volume 5, Number 1. 2014.

30.   Funk KA, Bostwick JR. A comparison of the risk of QT prolongation among SSRIs. The Annals of pharmacotherapy. 2013;47:1330-1341.

31.   Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, Noseworthy PA, Huffman JC. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. The Journal of clinical psychiatry. 2014;75:e441-449.

32.   Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT, Jr., Krishnan KR, van Zyl LT, Swenson JR, Finkel MS, Landau C, Shapiro PA, Pepine CJ, Mardekian J, Harrison WM, Barton D, McLvor M. Sertraline treatment of major depression in patients with acute MI or unstable angina. Jama. 2002;288:701-709.

33.   Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, Erb JL, Churchill SE, Kohane IS, Iosifescu DV, Smoller JW, Perlis RH. QT interval and antidepressant use: a cross sectional study of electronic health records. BMJ (Clinical research ed). 2013;346:f288.

34.   Drye LT, Spragg D, Devanand DP, Frangakis C, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Pollock BG, Porsteinsson AP, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG. Changes in QTc interval in the citalopram for agitation in Alzheimer's disease (CitAD) randomized trial. PloS one. 2014;9:e98426.

35.   Kogut C, Crouse EB, Vieweg WV, Hasnain M, Baranchuk A, Digby GC, Koneru JN, Fernandez A, Deshmukh A, Hancox JC, Pandurangi AK. Selective serotonin reuptake inhibitors and torsade de pointes: new concepts and new directions derived from a systematic review of case reports. Therapeutic advances in drug safety. 2013;4:189-198.

36.   Zhang Y, Baranchuk A, Hancox JC. Towards limiting QT interval prolongation and arrhythmia risk in citalopram use. Cardiology journal. 2014;21:454-457.

37.   Zivin K, Pfeiffer PN, Bohnert AS, Ganoczy D, Blow FC, Nallamothu BK, Kales HC. Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. American Journal of Psychiatry. 2013.

38.   Thase ME, Larsen KG, Reines E, Kennedy SH. The cardiovascular safety profile of escitalopram. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2013;23:1391-1400.

39.   Rector TS, Adabag S, Cunningham F, Nelson D, Dieperink E. Outcomes of Citalopram Dosage Risk Mitigation in a Veteran Population. The American journal of psychiatry. 2016;173:896-902.

40.   Gerlach LB, Kales HC, Maust DT, Chiang C, Stano C, Choe HM, Zivin K. Unintended Consequences of Adjusting Citalopram Prescriptions Following the 2011 FDA Warning. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2016.

41.   Jasiak NM, Bostwick JR. Risk of QT/QTc prolongation among newer non-SSRI antidepressants. The Annals of pharmacotherapy. 2014;48:1620-1628.

42.   Bavle A. Venlafaxine induced QTc interval prolongation in a therapeutic dose. Asian journal of psychiatry. 2015;16:63-64.

43.   Letsas K, Korantzopoulos P, Pappas L, Evangelou D, Efremidis M, Kardaras F. QT interval prolongation associated with venlafaxine administration. International journal of cardiology. 2006;109:116-117.

44.   Howell C, Wilson AD, Waring WS. Cardiovascular toxicity due to venlafaxine poisoning in adults: a

review of 235 consecutive cases. British journal of clinical pharmacology. 2007;64:192-197.

45.   Hojer J, Hulting J, Salmonson H. Fatal cardiotoxicity induced by venlafaxine overdosage. Clinical toxicology (Philadelphia, Pa). 2008;46:336-337.

46.   Bosse GM, Spiller HA, Collins AM. A fatal case of venlafaxine overdose. Journal of medical toxicology : official journal of the American College of Medical Toxicology. 2008;4:18-20.

47.   Isbister GK. Electrocardiogram changes and arrhythmias in venlafaxine overdose. British journal of clinical pharmacology. 2009;67:572-576.

48.   Kok R, Nolen W, Heeren T. Cardiovascular changes associated with venlafaxine in the treatment of late-life depression. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2007;15:725; author reply 726.

49.   Martinez C, Assimes TL, Mines D, Dell'aniello S, Suissa S. Use of venlafaxine compared with other antidepressants and the risk of sudden cardiac death or near death: a nested case-control study. BMJ (Clinical research ed). 2010;340:c249.

50.   Zhang L, Chappell J, Gonzales CR, Small D, Knadler MP, Callaghan JT, Francis JL, Desaiah D, Leibowitz M, Ereshefsky L, Hoelscher D, Leese PT, Derby M. QT effects of duloxetine at supratherapeutic doses: a placebo and positive controlled study. Journal of cardiovascular pharmacology. 2007;49:146-153.

51.   Wernicke J, Lledo A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo-controlled studies. Drug safety. 2007;30:437-455.

52.   Cooper JM, Brown JA, Cairns R, Isbister GK. Desvenlafaxine overdose and the occurrence of serotonin toxicity, seizures and cardiovascular effects. Clinical toxicology (Philadelphia, Pa). 2017;55:18-24.

53.   Huang Q, Zhong X, Yun Y, Yu B, Huang Y. Efficacy and safety of multiple doses of levomilnacipran extended-release for the treatment of major depressive disorder. Neuropsychiatric disease and treatment. 2016;12:2707-2714.

54.   Montgomery SA, Mansuy L, Ruth A, Bose A, Li H, Li D. Efficacy and safety of levomilnacipran sustained release in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled, proof-of-concept study. The Journal of clinical psychiatry. 2013;74:363-369.

55.   Asnis GM, Bose A, Gommoll CP, Chen C, Greenberg WM. Efficacy and safety of levomilnacipran

sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: a phase 3, randomized, double-blind, placebo-controlled study. The Journal of clinical psychiatry. 2013;74:242-248.

56.   Glassman AH. Cardiovascular effects of tricyclic antidepressants. Annual review of medicine. 1984;35:503-511.

57.   Vieweg WV, Wood MA. Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. Psychosomatics. 2004;45:371-377.

58.   Kiev A, Masco HL, Wenger TL, Johnston JA, Batey SR, Holloman LC. The cardiovascular effects of bupropion and nortriptyline in depressed outpatients. Annals of Clinical Psychiatry. 1994;6:107-115.

59.   Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. The Journal of clinical psychiatry. 1983;44:174-175.

60.   Teply RM, Packard KA, White ND, Hilleman DE, DiNicolantonio JJ. Treatment of Depression in Patients with Concomitant Cardiac Disease. Prog Cardiovasc Dis. 2016;58:514-528.

61.   Franco V. Wide complex tachycardia after bupropion overdose. The American journal of emergency medicine. 2015;33:1540.e1543-1545.

62.   Isbister GK, Balit CR. Bupropion overdose: QTc prolongation and its clinical significance. The Annals of pharmacotherapy. 2003;37:999-1002.

63.   Curry SC, Kashani JS, LoVecchio F, Holubek W. Intraventricular conduction delay after bupropion overdose. The Journal of emergency medicine. 2005;29:299-305.

64.   Druteika D, Zed PJ. Cardiotoxicity following bupropion overdose. The Annals of pharmacotherapy. 2002;36:1791-1795.

65.   Leonard CE, Bilker WB, Newcomb C, Kimmel SE, Hennessy S. Antidepressants and the risk of sudden cardiac death and ventricular arrhythmia. Pharmacoepidemiology and drug safety. 2011;20:903-913.

66.   Danielsson B, Collin J, Jonasdottir Bergman G, Borg N, Salmi P, Fastbom J. Antidepressants and antipsychotics classified with torsades de pointes arrhythmia risk and mortality in older adults - a Swedish nationwide study. British journal of clinical pharmacology. 2016;81:773-783.

67.   Spindelegger CJ, Papageorgiou K, Grohmann R, Engel R, Greil W, Konstantinidis A, Agelink MW, Bleich S, Ruether E, Toto S, Kasper S. Cardiovascular adverse reactions during antidepressant treatment:

a drug surveillance report of German-speaking countries between 1993 and 2010. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP). 2014;18.

68. Kelly CA, Dhaun N, Laing WJ, Strachan FE, Good AM, Bateman DN. Comparative toxicity of citalopram and the newer antidepressants after overdose. Journal of toxicology Clinical toxicology. 2004;42:67-71.

69. Berling I, Isbister GK. Mirtazapine overdose is unlikely to cause major toxicity. Clinical toxicology (Philadelphia, Pa). 2014;52:20-24.

70. Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, Pae CU. A review of current evidence for vilazodone in major depressive disorder. International journal of psychiatry in clinical practice. 2013;17:160-169.

71. Edwards J, Sperry V, Adams MH, Gallipoli S, Thorn MD, Longstreth J, Boinpally R. Vilazodone lacks proarrhythmogenic potential in healthy participants: a thorough ECG study. International journal of clinical pharmacology and therapeutics. 2013;51:456-465.

72. Wang Y, Nomikos GG, Karim A, Munsaka M, Serenko M, Liosatos M, Harris S. Effect of Vortioxetine on Cardiac Repolarization in Healthy Adult Male Subjects: Results of a Thorough QT/QTc Study. Clinical pharmacology in drug development. 2013;2:298-309.

73. Baldwin DS, Chrones L, Florea I, Nielsen R, Nomikos GG, Palo W, Reines E. The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies. Journal of psychopharmacology (Oxford, England). 2016;30:242-252.

74. Harrigan EP, Miceli JJ, Anziano R, Watsky E, Reeves KR, Cutler NR, Sramek J, Shiovitz T, Middle M. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. J Clin Psychopharmacol. 2004;24:62-69.

75. Mehtonen OP, Aranko K, Malkonen L, Vapaatalo H. A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. Acta psychiatrica Scandinavica. 1991;84:58-64.

76. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003;89:1363-1372.

77. Ozeki Y, Fujii K, Kurimoto N, Yamada N, Okawa M, Aoki T, Takahashi J, Ishida N, Horie M, Kunugi H.

QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia. Progress in neuro-psychopharmacology & biological psychiatry. 2010;34:401-405.

78.   Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, Huffman JC. QT Prolongation, Torsades de Pointes, and Psychotropic Medications: A 5-Year Update. Psychosomatics. 2017.

79.   Meyer-Massetti C, Cheng CM, Sharpe BA, Meier CR, Guglielmo BJ. The FDA extended warning for intravenous haloperidol and torsades de pointes: how should institutions respond? Journal of hospital medicine. 2010;5:E8-16.

80.   Glassman AH, Bigger JT, Jr. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. The American journal of psychiatry. 2001;158:1774-1782.

81.   Gulisano M, Cali PV, Cavanna AE, Eddy C, Rickards H, Rizzo R. Cardiovascular safety of aripiprazole and pimozide in young patients with Tourette syndrome. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2011;32:1213-1217.

82.   Krahenbuhl S, Sauter B, Kupferschmidt H, Krause M, Wyss PA, Meier PJ. Case report: reversible QT prolongation with torsades de pointes in a patient with pimozide intoxication. Am J Med Sci. 1995;309:315-316.

83.   Cassella JV, Spyker DA, Yeung PP. A randomized, placebo-controlled repeat-dose thorough QT study of inhaled loxapine in healthy volunteers. International journal of clinical pharmacology and therapeutics. 2015;53:963-971.

84.   Spyker DA, Voloshko P, Heyman ER, Cassella JV. Loxapine delivered as a thermally generated aerosol does not prolong QTc in a thorough QT/QTc study in healthy subjects. Journal of clinical pharmacology. 2014;54:665-674.

85.   Leonard CE, Freeman CP, Newcomb CW, Bilker WB, Kimmel SE, Strom BL, Hennessy S. Antipsychotics and the Risks of Sudden Cardiac Death and All-Cause Death: Cohort Studies in Medicaid and Dually-Eligible Medicaid-Medicare Beneficiaries of Five States. Journal of clinical & experimental cardiology. 2013;Suppl 10:1-9.

86.   Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lassig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet (London, England).

2013;382:951-962.

87.   Potkin SG, Preskorn S, Hochfeld M, Meng X. A thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. J Clin Psychopharmacol. 2013;33:3-10.

88.   Administration USFaD: Briefing Document for Zeldox Capsules. 2000.

89.   Hasnain M, Vieweg WV, Howland RH, Kogut C, Breden Crouse EL, Koneru JN, Hancox JC, Digby GC, Baranchuk A, Deshmukh A, Pandurangi AK. Quetiapine and the need for a thorough QT/QTc study. J Clin Psychopharmacol. 2014;34:3-6.

90.   Hasnain M, Vieweg WV, Howland RH, Kogut C, Breden Crouse EL, Koneru JN, Hancox JC, Digby GC, Baranchuk A, Deshmukh A, Pandurangi AK. Quetiapine, QTc interval prolongation, and torsade de pointes: a review of case reports. Therapeutic advances in psychopharmacology. 2014;4:130-138.

91.   Chapel S, Hutmacher MM, Haig G, Bockbrader H, de Greef R, Preskorn SH, Lalonde RL. Exposure-response analysis in patients with schizophrenia to assess the effect of asenapine on QTc prolongation. Journal of clinical pharmacology. 2009;49:1297-1308.

92.   Grande I, Pons A, Baeza I, Torras A, Bernardo M. QTc prolongation: is clozapine safe? Study of 82 cases before and after clozapine treatment. Human psychopharmacology. 2011;26:397-403.

93.   Polcwiartek C, Sneider B, Graff C, Taylor D, Meyer J, Kanters JK, Nielsen J. The cardiac safety of aripiprazole treatment in patients at high risk for torsade: a systematic review with a meta-analytic approach. Psychopharmacology. 2015;232:3297-3308.

94.   Poluzzi E, Raschi E, Moretti U, De Ponti F. Drug-induced torsades de pointes: data mining of the public version of the FDA Adverse Event Reporting System (AERS). Pharmacoepidemiology and drug safety. 2009;18:512-518.

95.   Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. The New England journal of medicine. 2009;360:225-235.

96.   Jolly K, Gammage MD, Cheng KK, Bradburn P, Banting MV, Langman MJ. Sudden death in patients receiving drugs tending to prolong the QT interval. British journal of clinical pharmacology. 2009;68:743-751.

97.   Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet (London, England). 2000;355:1048-1052.

98.   Hsu CH, Liu PY, Chen JH, Yeh TL, Tsai HY, Lin LJ. Electrocardiographic abnormalities as predictors for over-range lithium levels. Cardiology. 2005;103:101-106.

99.   Mamiya K, Sadanaga T, Sekita A, Nabeyama Y, Yao H, Yukawa E. Lithium concentration correlates with QTc in patients with psychosis. Journal of electrocardiology. 2005;38:148-151.

100.   Kurt E, Emul M, Ozbulut O, Guler O, Erdur F, Saglam H, Gecici O. Is valproate promising in cardiac fatal arrhythmias? Comparison of P- and Q-wave dispersion in bipolar affective patients on valproate or lithium-valproate maintenance therapy with healthy controls. Journal of psychopharmacology (Oxford, England). 2009;23:328-333.

101.   Kwon S, Lee S, Hyun M, Choe BH, Kim Y, Park W, Cho Y. The potential for QT prolongation by antiepileptic drugs in children. Pediatric neurology. 2004;30:99-101.

102.   Dixon R, Job S, Oliver R, Tompson D, Wright JG, Maltby K, Lorch U, Taubel J. Lamotrigine does not prolong QTc in a thorough QT/QTc study in healthy subjects. British journal of clinical pharmacology. 2008;66:396-404.

103.   Saetre E, Abdelnoor M, Amlie JP, Tossebro M, Perucca E, Tauboll E, Anfinsen OG, Isojarvi J, Gjerstad L. Cardiac function and antiepileptic drug treatment in the elderly: a comparison between lamotrigine and sustained-release carbamazepine. Epilepsia. 2009;50:1841-1849.

104.   Chen D, Lal R, Zomorodi K, Atluri H, Ho J, Luo W, Tovera J, Bonzo D, Cundy K. Evaluation of gabapentin enacarbil on cardiac repolarization: a randomized, double-blind, placebo- and active-controlled, crossover thorough QT/QTc study in healthy adults. Clinical therapeutics. 2012;34:351-362.e353.

105.   Schelleman H, Bilker WB, Kimmel SE, Daniel GW, Newcomb C, Guevara JP, Cziraky MJ, Strom BL, Hennessy S. Methylphenidate and risk of serious cardiovascular events in adults. The American journal of psychiatry. 2012;169:178-185.

106.   Weisler RH, Biederman J, Spencer TJ, Wilens TE. Long-term cardiovascular effects of mixed amphetamine salts extended release in adults with ADHD. CNS Spectr. 2005;10:35-43.

107.   Adler LA, Orman C, Starr HL, Silber S, Palumbo J, Cooper K, Berwaerts J, Harrison DD. Long-term safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: an open-label, dose-titration, 1-year study. J Clin Psychopharmacol. 2011;31:108-114.

108.   Yamaguchi H, Nagumo K, Nakashima T, Kinugawa Y, Kumaki S. Life-threatening QT prolongation in

a boy with attention-deficit/hyperactivity disorder on atomoxetine. European journal of pediatrics. 2014;173:1631-1634.

109.   Scherer D, Hassel D, Bloehs R, Zitron E, von Lowenstern K, Seyler C, Thomas D, Konrad F, Burgers HF, Seemann G, Rottbauer W, Katus HA, Karle CA, Scholz EP. Selective noradrenaline reuptake inhibitor atomoxetine directly blocks hERG currents. British journal of pharmacology. 2009;156:226-236.

110.   Wernicke JF, Faries D, Girod D, Brown J, Gao H, Kelsey D, Quintana H, Lipetz R, Michelson D, Heiligenstein J. Cardiovascular effects of atomoxetine in children, adolescents, and adults. Drug safety. 2003;26:729-740.

111.   Roth T, Schwartz JR, Hirshkowitz M, Erman MK, Dayno JM, Arora S. Evaluation of the safety of modafinil for treatment of excessive sleepiness. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2007;3:595-602.

112.   Martinez-Raga J, Knecht C, Szerman N, Martinez MI. Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. CNS drugs. 2013;27:15-30.

113.   Levenson JL. Prolonged QT interval after trazodone overdose. The American journal of psychiatry. 1999;156:969-970.

114.   Dattilo PB, Nordin C. Prolonged QT associated with an overdose of trazodone. The Journal of clinical psychiatry. 2007;68:1309-1310.

115.   Goodnick PJ, Jerry J, Parra F. Psychotropic drugs and the ECG: focus on the QTc interval. Expert Opin Pharmacother. 2002;3:479-498.

116.   Kitt J, Irons R, Al-Obaidi M, Missouris C. A case of donepezil-related torsades de pointes. BMJ case reports. 2015;2015.

117.   Sartori M, Pratt CM, Young JB. Torsade de Pointe. Malignant cardiac arrhythmia induced by amantadine poisoning. Am J Med. 1984;77:388-391.

118.   Manini AF, Raspberry D, Hoffman RS, Nelson LS. QT prolongation and Torsades de Pointes following overdose of ziprasidone and amantadine. Journal of medical toxicology : official journal of the American College of Medical Toxicology. 2007;3:178-181.

119.   Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsade de pointes associated with very-high-dose methadone. Ann Intern Med. 2002;137:501-504.

120.   Abramson DW, Quinn DK, Stern TA. Methadone-Associated QTc Prolongation: A Case Report and Review of the Literature. Prim Care Companion J Clin Psychiatry. 2008;10:470-476.

121.   Vieweg WV, Hasnain M, Howland RH, Clausen T, Koneru JN, Kogut C, Crouse EL, Hancox JC, Fernandez A, Pandurangi AK. Methadone, QTc interval prolongation and torsade de pointes: Case reports offer the best understanding of this problem. Therapeutic advances in psychopharmacology. 2013;3:219-232.

122.   Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, Inturrisi C, Knight JR, Otis-Green S, Marcus SM, Mehta D, Meyer MC, Portenoy R, Savage S, Strain E, Walsh S, Zeltzer L. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. The journal of pain : official journal of the American Pain Society. 2014;15:321-337.

123.   Digby GC, Pérez Riera AR, Barbosa Barros R, Simpson CS, Redfearn DP, Methot M, Femenía F, Baranchuk A. Acquired long QT interval: a case series of multifactorial QT prolongation. Clinical cardiology. 2011;34:577-582.

124.   Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007;167:2469-2475.

125.   Krantz MJ, Garcia JA, Mehler PS. Effects of buprenorphine on cardiac repolarization in a patient with methadone-related torsade de pointes. Pharmacotherapy. 2005;25:611-614.

126.   Roessner V, Wolff N, Ehrlich S, Waltereit R. Need for a more developmental perspective: QTc prolongation under psychotropic medication. European child & adolescent psychiatry. 2017;26:871-873.

127.   Anghelescu DL, Patel RM, Mahoney DP, Trujillo L, Faughnan LG, Steen BD, Baker JN, Pei D. Methadone prolongs cardiac conduction in young patients with cancer-related pain. Journal of opioid management. 2016;12:131-138.

128.   Madden K, Park M, Liu D, Bruera E. The frequency of QTc prolongation among pediatric and young adult patients receiving methadone for cancer pain. Pediatric blood & cancer. 2017;64.

129.   Jensen KG, Juul K, Fink-Jensen A, Correll CU, Pagsberg AK. Corrected QT changes during antipsychotic treatment of children and adolescents: a systematic review and meta-analysis of clinical trials. Journal of the American Academy of Child and Adolescent Psychiatry. 2015;54:25-36.

130.   Ritchie B, Norris ML. QTc prolongation associated with atypical antipsychotic use in the treatment

of adolescent-onset anorexia nervosa. Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie canadienne de psychiatrie de l'enfant et de l'adolescent. 2009;18:60-63.

131.   Uchida M, Spencer AE, Biederman J, Castro VM, Kenworthy T, Chan J, Rosales AM, Newton-Cheh C, Perlis RH. A Systematic Evaluation of the QTc Interval and Antidepressants in Youth: An Electronic Health Record Study. J Dev Behav Pediatr. 2015;36:434-439.

132.   Rautaharju PM, Zhou SH, Wong S, Calhoun HP, Berenson GS, Prineas R, Davignon A. Sex differences in the evolution of the electrocardiographic QT interval with age. The Canadian journal of cardiology. 1992;8:690-695.

133.   Freeman BD, Dixon DJ, Coopersmith CM, Zehnbauer BA, Buchman TG. Pharmacoepidemiology of QT-interval prolonging drug administration in critically ill patients. Pharmacoepidemiology and drug safety. 2008;17:971-981.

134.   Tisdale JE, Wroblewski HA, Overholser BR, Kingery JR, Trujillo TN, Kovacs RJ. Prevalence of QT interval prolongation in patients admitted to cardiac care units and frequency of subsequent administration of QT interval-prolonging drugs: a prospective, observational study in a large urban academic medical center in the US. Drug safety. 2012;35:459-470.

135.   Tay KY, Ewald MB, Bourgeois FT. Use of QT-prolonging medications in US emergency departments, 1995-2009. Pharmacoepidemiology and drug safety. 2014;23:9-17.

136.   Vandael E, Vandenberk B, Vandenberghe J, Spriet I, Willems R, Foulon V. Risk management of QTc-prolongation in patients receiving haloperidol: an epidemiological study in a University hospital in Belgium. International journal of clinical pharmacy. 2016;38:310-320.

137.   Digby G, Machaalany J, Malik P, Methot M, Simpson CS, Redfearn D, Baranchuk A. Multifactorial QT interval prolongation. Cardiology journal. 2010;17:184-188.

138.   Digby GC, Perez Riera AR, Barbosa Barros R, Simpson CS, Redfearn DP, Methot M, Femenia F, Baranchuk A. Acquired long QT interval: a case series of multifactorial QT prolongation. Clinical cardiology. 2011;34:577-582.

139.   Curtis LH, Ostbye T, Sendersky V, Hutchison S, Allen LaPointe NM, Al-Khatib SM, Usdin Yasuda S, Dans PE, Wright A, Califf RM, Woosley RL, Schulman KA. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. Am J Med. 2003;114:135-141.

140.   Pinski SL, Eguia LE, Trohman RG. What is the minimal pacing rate that prevents torsades de pointes? Insights from patients with permanent pacemakers. Pacing and clinical electrophysiology : PACE. 2002;25:1612-1615.

141.   Passman R, Subacius H, Ruo B, Schaechter A, Howard A, Sears SF, Kadish A. Implantable cardioverter defibrillators and quality of life: results from the defibrillators in nonischemic cardiomyopathy treatment evaluation study. Arch Intern Med. 2007;167:2226-2232.

142.   Freedenberg V, Thomas SA, Friedmann E. Anxiety and depression in implanted cardioverter-defibrillator recipients and heart failure: a review. Heart failure clinics. 2011;7:59-68.

143.   Brojmohun A, Lou JY, Zardkoohi O, Funk MC. Protected from torsades de pointes? What psychiatrists need to know about pacemakers and defibrillators. Psychosomatics. 2013;54:407-417.