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Qtc Prolongation and Use of Second-Generation Antipsychotics in the Geriatric Population

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Abstract

Prolongation of the QT interval is a potentially important and life-threatening complication of several second-generation antipsychotic medications. However, literature on this matter is equivocal and difficult to study because of its uncommon presentation. Herein, is described, a case study of an 82-year-old male patient with QTc prolongation secondary to olanzapine use. A comprehensive review of published literature was also performed to determine whether the purported relationship between olanzapine use and prolonged QT interval and subsequent risk of torsades de pointes (TdP) was clinically relevant. Based on this review, it can be concluded with reasonable certainty that there is a clinical link between second-generation antipsychotics and QTc prolongation. Therefore, it is recommended that baseline, steady-state, and periodic ECGs be obtained throughout treatment. Patients should be screened for risk, family history, comorbidities, and have a thorough medical/cardiac work-up prior to initiation of drug therapy. Future research needs to be performed to improve our understanding of QTc prolongation and subsequent TdP/ sudden cardiac death associated with individual second-generation antipsychotic, while also evaluating quality of life parameters with and without olanzapine treatment. Such studies would help providers better understand the mechanism and risk factors associated with second-generation antipsychotic induced QTc prolongation. Finally, these studies would need to include a risk-benefit comparison of whether the impact of SGAs on quality of life in the elderly outweighs the potential risks associated with therapy.

Keywords: second-generation antipsychotics (SGAs), QT prolongation, cardiac effects, olanzapine, elderly

QTc Prolongation and Second-Generation Antipsychotics in the Geriatric Population

Background

Antipsychotic medications are being more widely used as their approved indications have expanded beyond schizophrenia and include bipolar and major depressive disorder, delirium, dementia, and substance-induced psychosis (Stoner, 2017). The treatment of schizophrenia is predominantly challenging because the disease state itself is associated with increased cardiovascular morbidity and mortality rates. The risk of sudden cardiac death is estimated to be 2 to 4 times greater than in the general population (Buckley, & Sanders, 2000). An increased risk for coronary heart disease has been directly linked to schizophrenia (Buckley, & Sanders, 2000). Patients with psychosis and bipolar disorder are already prone to have a shortened life expectancy by 15 to 25 years because of an increased presence of cardiovascular disease and an increased likelihood of sudden cardiac death (SCD) (Correll, & Nielson, 2010). A primary concern when using antipsychotic medications is the possibility of potentially fatal cardiac-related adverse events (Stoner, 2017). Risk factors such as tobacco use, sedentary lifestyle, poor dental hygiene/dietary habits, and alcohol abuse are commonly observed in those with lower socioeconomic status and are also commonly observed in patients with serious mental illnesses such as schizophrenia and bipolar disorder (Stoner, 2017). These place this population at increased risk for cardiovascular disease (Stoner, 2017). In addition, many second-generation antipsychotics (SGAs) or atypical antipsychotics increase the risk of metabolic syndrome through weight gain, as well as elevations in blood sugar and cholesterol concentrations, which further compounds the cardiovascular concerns related to their use (Stoner, 2017).

SGAs are associated with an increased risk for metabolic side effects, including obesity, diabetes mellitus, and dyslipidemia (Stoner, 2017). The SGAs olanzapine and clozapine are associated with the greatest risk of weight gain (Stoner, 2017). Ziprasidone, lurasidone, and

aripiprazole confer a lower risk of metabolic side effects, specifically weight gain (Stoner, 2017). When taking into account the increased cardiovascular risk related to mental health conditions alone, it is also expected that there is an increased risk of metabolic disorders as well as cardiovascular events in patients taking SGAs (Stoner, 2017). Finally, a US Food and Drug Administration boxed warning states that both first-generation antipsychotics (FGAs) and SGAs present an increased mortality rate when used in elderly patients with dementia (Stoner, 2017). Risperidone and olanzapine were the first SGAs to be associated with increased mortality (Stoner, 2017). Further studies have implicated multiple antipsychotics across drug classes. The mortality increase is associated primarily with cerebrovascular-associated events, although a direct cardiac-related contribution is substantial (Stoner, 2017). The question however remains as to whether the impact (of treating psychosis in the elderly) on quality of life (QOL) outweighs the potential risks of therapy. Clinicians should individualize the assessment of safety risks against expected benefits when prescribing these medications to patients with dementia/psychosis. Pending such studies, the use of SGAs in the geriatric population should be accompanied by the need for heightened awareness and improved understanding of their potential side-effects. This is particularly important for cardiovascular disorders, especially prolongation of the QT interval and the subsequent risk/development of Torsades de Pointes (TdP) and possible sudden death (Stoner, 2017).

The QT interval, measured as the interval between the initiation of the Q wave and the termination of the T wave on an Electrocardiogram (ECG), is a measure of ventricular depolarization and repolarization (Chohan, Mittal, & Javed, 2015). Due to its variation with heart rate the QTc offers a more analytical value. A number of formulas including Bazzet's formula and Freidreich's formula can be used to calculate the QTc (Chohan, Mittal, & Javed,

2015). Normal values differ between males and females. Prolonged QTc is defined as >450msecs in males and >470msecs in females (Chohan, Mittal, & Javed, 2015). It is important to understand factors which could influence the QTc, and in order to do so, one must have basic biochemical knowledge of the ventricular action potential of the cardiac myocytes (Chohan, Mittal, & Javed, 2015). The incidence of prolonged QTc in one large study was 293 out of 41,649 patients (0.7%) (Yu, et.al., 2017).

This involves four phases as depicted in Fig.1 below. Phase zero represents initial repolarization with influx of sodium. Phase one represents early repolarization with inactivation of the sodium currents and onset of transient outward potassium currents. A balance between outwards potassium currents and inward calcium currents accounts for phase two, the plateau phase. Rapid repolarization (Phase Three) follows when calcium currents are inactivated whilst Potassium currents remain open. Finally, Phase Four represents the resting membrane potential (Chohan, Mittal, & Javed, 2015).

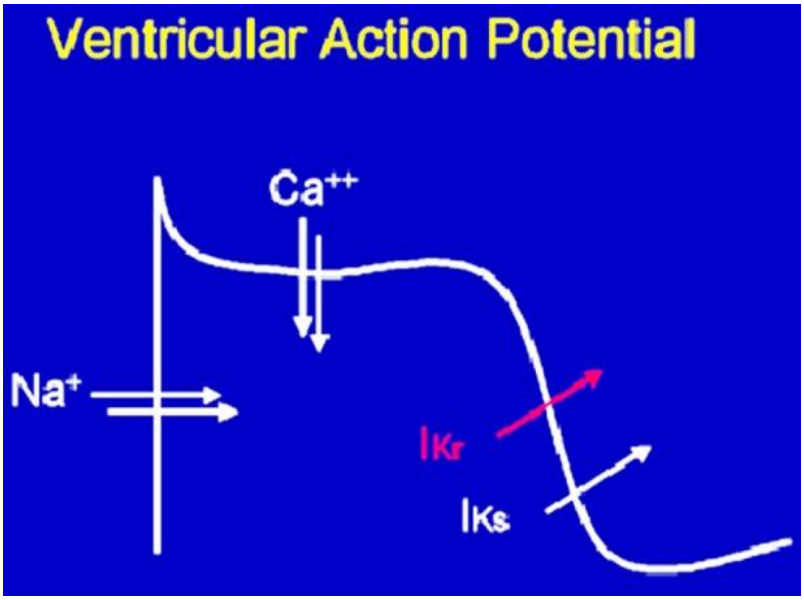

Figure 1: The Ventricular Action Potential

(Chohan, Mittal, & Javed, 2015)

Prolongation of the QT interval is rarely seen a de novo finding in normal adults and can lead to fatal consequences and sudden cardiac death (SCD) caused by arrhythmias such as TdP (Chohan, Mittal, & Javed, 2015). The mortality associated with this arrhythmia is estimated to be around ten percent and most of the mortality in the adult population is secondary to medication-related causes, including antipsychotic medications (Chohan, Mittal, & Javed, 2015). Hence, it is important for mental health providers to have knowledge of risk factors which could prolong the QTc. These risk factors can include, cardiac conditions such as congenital long QT syndrome and hypertension (Chohan, Mittal, & Javed, 2015). Systemic diseases such as hypothyroidism, liver disease and renal disease are also indicated as causative factors (Chohan, Mittal, & Javed, 2015). Further risk factors may include electrolyte imbalances, female gender and drugs (antiarrhythmics, antibiotics, antiemetics, antidepressants and antipsychotics) (Chohan, Mittal, & Javed, 2015). In this study, we describe a classic case of QT prolongation induced by a second-generation antipsychotic (SGAP), olanzapine, and review the relevant literature.

Case Report

The patient is an 82-year-old male patient with a past medical history of end stage renal disease on hemodialysis, diabetes, coronary artery disease, hypertension, and intracranial hemorrhages who was admitted related to hypoxic respiratory failure with oxygen saturation in the 70%'s. He was a resident of a nursing home. He typically has dialysis on Monday, Wednesday, Friday, but does not always finish his complete dialysis sessions and does not always attend. In addition, he has often refused his medications. His hemoglobin was low. He refused a recommended blood transfusion. Of note, he was initially admitted to the ICU due to a hypertensive emergency.

He has had prior psychiatric consultations, that indicated a neurocognitive disorder with psychosis. There was no documented mental health diagnosis. He was seen by the neuropsychologist during the hospitalization. It was determined that he had capacity to make his own medical decisions.

The Internal Medicine service requested a psychiatric consultation for suspected psychosis. On physical exam, he was oriented to place, date. His attention was fair. The patient reported that he had intermittent hallucinations. He stated that he believed they were improving. He was noted to endorse paranoid thoughts. He stated that he had never had a bypass and believed that the doctors were lying to him. He also stated that he was told that he has renal failure but does not believe this. He denied thoughts to harm himself or others. The patient was calm and cooperative during the interview. He appeared easily distractible. He was noted to have recent memory impairments. He was unable to recall 3/3 objects within only a few minutes. A complete MMSE was not performed.

Mental Status Exam: The patient was an 82-year-old Caucasian male. He was lying in bed. He was generally cooperative with the assessment. His speech was normal prosody and tone. His mood and affect were slightly irritable. His thought process was linear. He endorsed paranoia. He reported hallucinations within the past week. He denied homicidal or suicidal ideations. He was noted to have poor insight and impaired judgement. He was oriented to place and date. He had been seen in prior psychiatric consultation. Symptoms of paranoia and hallucinations had improved on olanzapine.

An ECG was obtained, and it showed that his QTc interval was prolonged with a QTc equal to 477. Baseline comprehensive metabolic panel to include electrolytes, serum magnesium levels, and testing for elevated cardiac enzymes were all unremarkable. It was considered very

likely that the second-generation antipsychotic medication (olanzapine) could further exacerbate the QTc interval and progress to TdP with sudden cardiac death.

The recommendation was made to withhold olanzapine and restart after QTc interval had normalized. It was recommended that the olanzapine may be restarted at 2.5mg once daily in the evening, and titrate as tolerated to 5mg daily. Serial ECGs were monitored for QTc interval prolongation.

Literature Review

For the sake of completeness and better understanding of whether this was a class effect of SGAs or whether there were differences seen between the SGAs, nine SGAs (amisulpride, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, and ziprasidone) listed in various CredibleMeds drug categories were included in this study. I searched PubMed in November 2019 for English language literature without setting any other limits. Search terms included the term second generation antipsychotics and QT OR QT prolongation OR QTc OR QTc prolongation OR torsades de pointes OR torsade OR TdP OR sudden cardiac death OR SCD. From the 254 results in PubMed, there were 70 articles that included second generation antipsychotics and QT, 38 articles that included second generation antipsychotics and QT prolongation, and 42 articles that included second generation antipsychotics and QTc interval. In addition, 61 articles included second generation antipsychotics and QTc prolongation, 3 articles included second generation antipsychotics and SCD, 13 articles included second generation antipsychotics and sudden cardiac death. Finally, only 4 articles included second generation antipsychotics and TdP, 11 articles included second generation antipsychotics and torsade, and 12 articles included second generation antipsychotics

and torsades de pointes and elderly. Of these 254 initial abstracts, I chose to focus in on articles that were specific to second generation antipsychotics and QT or QTc prolongation in the elderly as well as second generation antipsychotics and TdP or torsades de pointes and elderly which yielded 96 abstracts. Based on the review methodology utilized by Hasnain, & Vieweg (2014), I then focused in on the abstracts in four different categories.

Categories of Studies of SGAs Associated with the Risk of QTc Interval Prolongation and/or Torsade de Pointes (TdP)

A) QTc Prolongation-Specific Studies: Studies that specifically assessed QTc prolongation (or TdP) but were not toxicology studies. Most of these studies followed an open-label, non-randomized design, had a small sample size, and can be broadly categorized as observational or cross-sectional studies.
B) Toxicology Studies with Information on QTc Prolongation: Studies assessing the effects of toxic ingestion of SGAs on QTc interval or TdP. Overall, these studies followed a very similar design—analysis of ECGs of patients presenting with an overdose of the specified drug to determine changes in the QTc interval.
C) Efficacy and/or Safety Studies with Information on QTc Prolongation: Efficacy and safety studies that specifically reported QTc prolonging effects of the SGAs. Most of these studies were randomized and placebo-controlled, many were double-blinded, and several had an active comparator. Most of the studies excluded patients with cardiovascular or other medical comorbidities. Studies separately analyzing data from safety and efficacy trials for the effect of drug(s) on QTc interval were included in this category.

D) Studies specific to Olanzapine: Since the case study involved olanzapine, I focused particularly on studies exploring the drug related cardiac effects specific to olanzapine. I found 64 articles within this category utilizing the same database, PubMed when searching with search term "qtc prolongation and olanzapine". A further search restricted to the last 10 years yielded 34 articles. Of the 34 articles for the purpose of this study, I focused in on 8 articles that had access to in full text.

For the purposes of this literature review/discussion, I then focused in on these full-text articles involving olanzapine (category D above) as my case report dealt with this specific second-generation antipsychotic. Below is a description of 8 of these articles.

Discussion

In the study by Hasnain & Vieweg (2014), a review was completed comprehensively to assess the link between QTc interval prolongation and torsades de pointes for 11 second-generation antipsychotics. From this review that included thorough QT studies, QTc prolongation specific studies, and studies based on efficacy and safety trials did not link specific drug-associated QTc interval prolongation with TdP. They did show that specific drugs reviewed caused varying degrees of QTc interval prolongation, but the information was not clear and consistent enough to stratify individual drugs for this risk. It was found that TdP can occur at therapeutic doses of second-generation antipsychotics with a QTc interval less than 500 milliseconds. This comprehensive review was gathered utilizing PubMed and EMBASE related to antipsychotics such as iloperidone and ziprasidone, studies specifically designed to assess QTc interval prolongation or TdP, publications based on data from efficacy and safety trials, toxicology studies, and case reports (Hasnain, & Vieweg, 2014).

In the review by Chohan, Mittal, & Javed (2015), antipsychotic medication and QT prolongation is discussed. This study carried out an audit of patients under their service and out of one -hundred audited patients, five had a prolonged QTc interval on their most recent ECG; majority of these patients on a second-generation antipsychotic (clozapine). The review noted that up 90 percent of patients who develop torsades de pointes with psychotropic medication use have been shown to have a QTC interval greater than 500ms. A study they reviewed by Beach, Celano, Noseworthy, Januzzi, & Huffman (2013) noted that thioridazine, ziprasidone, and IV haloperidol were the antipsychotics with the greatest propensity for prolonging the QT interval associated with torsades de pointes. It has been widely suggested that second generation antipsychotics have a lower tendency to prolong the QT interval when compared to first generation antipsychotics (Chohan, Mittal, & Javed, 2015). Monitoring and managing patients on psychiatric medication for prolonged QT interval is imperative in order to reduce the risk of life-threatening complications. Obtaining a thorough clinical history from all patients is warranted; which should include a family history of cardiovascular disease, arrythmias, and sudden cardiac death. This study recommends obtaining a baseline ECG followed by annual ECGS to monitor patients on such medications (Chohan, Mittal, & Javed, 2015). Unless the QTc is greater than 500ms, rule out other causes for QT prolongation prior to stopping psychotropic medications. Taking this step could prevent compromise of the potential benefit from psychotropic medications. Advise should be sought from a cardiologist if the QTc is greater than 500ms, and the psychotropic medication should be discontinued. Concomitant use of two medications known to prolong the QT interval should be avoided (Chohan, Mittal, & Javed, 2015). "Although treatment with psychotropic medication such as antipsychotics is

associated with an increased risk for Sudden Cardiac Death, overall mortality remains lower than for patients who are left untreated" (Chohan, Mittal, & Javed, 2015, p. 1271).

In the study by Stoner (2017), management of serious cardiac adverse effects of antipsychotic medications are discussed. Three specific cases are discussed with side effects of QTc prolongation, myocarditis, and cardiomyopathy, as well as a case-crossover study that reviewed more than 17,000 cases of patients who developed ventricular arrythmias (VA) or who experienced sudden cardiac death (SCD) between 2001 and 2009 (Benjamin, Blaha, Chiuve, Cushman, Das, Deo, et.al, 2017). Stoner (2017), as previously stated discussed three specific cases. Risk factors for QTc prolongation include female sex, increased age, long QT syndrome, hypokalemia, hypomagnesemia, hypocalcemia, anorexia nervosa, bradycardia, heart failure, hypertension, renal and hepatic dysfunction, diabetes, genetic mutations, and obesity. First and second-generation antipsychotics have both been associated with QTc prolongation. Thioridazine is the antipsychotic most likely to result in QTc prolongation, followed by risperidone, olanzapine, haloperidol, and clozapine (Stoner, 2017). One study showed that risperidone and olanzapine are most commonly utilized. Risperidone and olanzapine were shown to be equally effective in reducing aggression/agitation (Ballard, & Waite, 2006). Risperidone was shown to be more effective in reducing psychosis in the elderly population (Ballard, & Waite, 2006). Clinicians should individualize the assessment of safety risks against benefits when prescribing these medications. A 7-year review from the US Food and Drug Administration reported cases of TdP most commonly with olanzapine, quetiapine, clozapine, ziprasidone, risperidone, haloperidol, droperidol, and amisulpride (Stoner, 2017). Within the case-crossover study that reviewed more than 17,000 cases of patients, patients who received antipsychotic treatment were at a 1.53-fold increased risk of developing VA or experiencing SCD. A higher risk was also

noted with first-generation antipsychotics as compared to second-generation antipsychotics. Atypical antipsychotics associated with higher risk of VA/SCD included quetiapine, and risperidone. Olanzapine also demonstrated an increased risk. It was also noted that short-term antipsychotic use also served as a greater predictor of VA/SCD-related events (Benjamin, Blaha, Chiuve, Cushman, Das, Deo, et.al, 2017). Given this information, implications from this study include a conservative practice-based approach including obtaining baseline ECG prior to starting an antipsychotic, once the drug is at a steady-state concentration, and then on a periodic base after (Stone, 2017). Serum electrolytes (BMP), to include serum potassium, calcium and magnesium, should be monitored (Stone, 2017). QTc-prolonging drugs should be avoided if baseline QTc is greater than 480ms in women and 470ms in men (Stone, 2017). If the QTc is normal, but an increase greater than 60ms is noted following administration, the drug should be discontinued (Stone, 2017).

The article by Shah, Aftab, & Coverdale (2014) discusses QTc prolongation with antipsychotics and ECG monitoring. This study was a literature review relevant to the topic at hand and was conducted utilizing the databases PubMed and Embase with various combinations of pertinent search words. They concluded that there was no definite evidence that atypical antipsychotics (second-generation) are associated with QTc interval prolongation, although all of the atypical antipsychotics are associated with QTc interval prolongation of varying degrees depending on specific drug and dose (Shah, Aftab, & Coverdale, 2014). While Ziprasidone showed the greatest amount of QTc prolongation among the atypical antipsychotics approved by the FDA, it is not commonly utilized in the geriatric population (Shah, Aftab, & Coverdale, 2014). Therefore, in absence of any cardiac risk factors, performing an ECG is not warranted. It should however be performed if the initial evaluation suggests increased cardiac risk or if the

antipsychotic to be prescribed has an established risk of TdP and sudden death. The ECG should be repeated for any patient who develops QTc prolongation while taking an antipsychotic medication. If QTc prolongation is noted, as previously stated, cardiac risk factors should also be assessed. If the QTc prolongation persists, discontinuation of the antipsychotic should be considered (Shah, Aftab, & Coverdale, 2014) balancing that decision with the fact that untreated psychosis is associated with severe impairment in cognition, poor quality of life and eventually debilitating morbidity and mortality.

In the review by Dietle (2015), QTc prolongation is discussed with antidepressants and antipsychotics. The determination for the following list of medications of higher risk of QTc prolongation at therapeutic doses was based on a review of literature and data from the comprehensive QT prolongation database, CredibleMeds (Dietle, 2015). While many drugs were systematically studied, of relevance to our case was the fact that olanzapine had clinically insignificant increases in QTc (3.6ms and 1.7ms), especially in patient above the age of 70 years (Dietle, 2015). The authors concluded that QT prolongation associated with SGAs is more prevalent in the elderly and these patients also have multiple identifiable risk factors and thus should be closely monitored while on therapy.

The study by Meyer-Massetti, Vaerini, Ratz Bravo, Meier, & Guglielmo (2011) reviewed and evaluated reports of QT prolongation, TdP, and/or cardiac arrest involving intravenous haloperidol versus other administration routes and the antipsychotics olanzapine and quetiapine. The study utilized WHO Global ICSR database VigiBase to critically evaluate these, utilizing all WHO safety reports (1972-2010) of cardiac reactions associated with haloperidol, quetiapine, and olanzapine. Findings included 365 cases (haloperidol), 489 cases (olanzapine, and 520 cases (quetiapine) that resulted in QT prolongation, TdP, and/or cardiac arrest (Meyer-Massetti, et. al,

2011). Olanzapine was associated with a slightly lower reporting odds ratio (Meyer-Massetti, et. al, 2011). The difference of the reporting odds ratio of haloperidol and quetiapine was not statistically significant (Meyer-Massetti, et. al, 2011).

The study by Suzuki, Ono, Sugai, Fukui, Watanabe, Tsuneyama, et. al. (2011) discussed dose-dependent effects of olanzapine on QT intervals. This study was an observational study that assessed the effect on olanzapine dose on QTc interval in 26 adult patients as their dose was increased. ECG was recorded at baseline and again when individual patients had been on an increased, stable dose of olanzapine for greater than 3 weeks. Olanzapine was increased from a mean dose of 7.1 to 18.1mg/day. Mean QTc interval increased significantly (8.0ms) between the two periods. None of the patients however exceeded the defined normal threshold within this study (430ms for males and 450ms for females) (Suzuki, et. al, 2011).

The study by Suzuki, Sugai, Fukui, Watanabe, Ono, & Tsuneyama, et. al. (2013) examined sex differences in the effect of olanzapine, risperidone, aripiprazole, or quetiapine on mean corrected QTc intervals among 222 patients with schizophrenia. Patients were either treated with olanzapine (n=69), risperidone (n=60), aripiprazole (n=62), or quetiapine (n=31). The mean QTc interval of quetiapine group (415.3ms) was significantly longer than that of risperidone (396.3ms), and aripiprazole groups (400.7ms). That of the olanzapine group (410ms) was significantly longer than that of the risperidone group. A switch to risperidone could be considered for this patient as it is relatively safer than olanzapine.

Implications

Second-generation antipsychotics (SGAs), in particular olanzapine, are commonly used in the treated of psychosis in the elderly. However, cardiac effects including QT prolongation and subsequent arrhythmias can be life-threatening in this population that tends to have multiple

comorbid risk factors. Providers should balance the risks of therapy-associated events against the risks of premature discontinuation of antipsychotic therapy (e.g. serious cognitive decline and associated worsening of QOL). Current literature does not provide sufficient and consistent information to stratify the different for their potential to prolong the corrected QTc interval and/or cause TdP. QTc interval prolongation associated with second generation antipsychotics is by itself not sufficient to cause TdP. TdP can occur at therapeutic doses of second-generation antipsychotics and with a QTc interval of less than 500 ms. Future research needs to improve its precision and broaden its scope to better understand the factors that facilitate or attenuate progression of second-generation antipsychotic associated QTc interval prolongation to TdP.

Antipsychotics have varying risk for QTc prolongation based on US Food and Drug Administration Guidelines antipsychotics. They are classified into three groups: high risk, moderate risk, and low to moderate risk. High risk drugs include chlorpromazine, IV haloperidol, and ziprasidone (UpToDate, 2019). Moderate risk includes clozapine, haloperidol (oral), olanzapine, quetiapine, risperidone, and thioridazine (UpToDate, 2019). Low to moderate risk include asenapine, iloperidone, palperidone, and pimavanserin (UpToDate, 2019). This information can assist clinicians in choosing an antipsychotic based on its risk profile for QTc prolongation.

Finally, the question remains: is routine ECG monitoring recommended with second-generation antipsychotic use? Whether or not QTc interval should be routinely monitored in patients receiving antipsychotics is a controversial issue, given logistic and financial dilemmas (Shah, Aftab, & Coverdale, 2014). There is a link between antipsychotic medications and prolongation of QTc interval, which is associated with an increased risk of torsade de pointes (TdP). The overall risk of TdP and sudden death associated with antipsychotics has been

observed to be low (Shah, Aftab, & Coverdale, 2014). Medications, genetics, gender, cardiovascular status, pathological conditions, and electrolyte disturbances have been found to be related to prolongation of the QTc interval (Shah, Aftab, & Coverdale, 2014). Conclusively, while electrocardiogram (ECG) monitoring is useful when administering antipsychotic medications in the presence of co-existing risk factors, it is not mandatory to perform ECG monitoring as a prerequisite in the absence of cardiac risk factors. An ECG should be performed if the initial evaluation suggests increased cardiac risk or if the antipsychotic to be prescribed has been established to have an increased risk of TdP and sudden death (Shah, Aftab, & Coverdale, 2014).

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