Int. j. adv. multidisc. res. stud. 2023; 3(6):880-890

Received: 16-10-2023
Accepted: 26-11-2023

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Prolonged QTc and Antipsychotic Medication

[1] Bharadwaj Adithya Sateesh, [2] Nicole Gousy, [3] Girma M Ayele, [4] Hari Devkota, [5] Mahlet Siraga, [6] Saad A Kareem, [7] Miriam B Michael

[1, 2] MD, Department of Clinical Sciences, American University of Antigua College of Medicine, St. Johns, Antigua and Barbuda

[3, 5, 7] MD, Internal Medicine, Howard University Hospital, Washington DC, USA

[4] Department of Internal Medicine, University of Maryland Medical Center Midtown Campus, Baltimore, USA

[6] Internal Medicine, University of Maryland School of Medicine, Baltimore, USA

Corresponding Author: **Miriam B Michael**

Abstract

Antipsychotic medications play a crucial role in managing various psychiatric conditions, but their use is associated with potential risks, notably prolonged QT intervals, which can lead to severe cardiovascular events. This comprehensive review analyzes current evidence on antipsychotic medication use in patients with prolonged QT intervals. Utilizing systematic review methodologies following PRISMA guidelines, the literature search identified relevant studies from PubMed and Science Direct databases. The review emphasizes the need for careful consideration of the benefits and risks associated with antipsychotic medications. Genetic variations, particularly in cytochrome P450 enzymes and ion channels, contribute to the susceptibility of QT prolongation. Patients with schizophrenia face an increased risk of cardiovascular events, necessitating close monitoring of the QT interval during antipsychotic treatment. Haloperidol and risperidone exhibit distinct QT effects, while quetiapine appears relatively safe. Recent studies also suggest a potential link between antipsychotic use, Brugada Syndrome, and other cardiac conditions in patients with schizophrenia. Elderly patients receiving antipsychotics require vigilant monitoring, particularly with polypharmacy regimens. In the emergency department, droperidol's safety for acute use is affirmed, challenging previous FDA warnings. Critical care and postoperative settings show varying effects of antipsychotics on QT intervals, with quetiapine demonstrating relative safety. Risk factors for QT prolongation in medical inpatients highlight the importance of routine monitoring. Psychiatric diseases present a gray area for QTc monitoring, prompting the need for risk stratification guidelines. Studies examining QTc in malignancy-related antiemetic regimens and the pediatric population underscore the importance of cautious antipsychotic use in these contexts. This review provides a comprehensive understanding of the multifaceted relationship between antipsychotic medications, QT prolongation, and cardiovascular risks, emphasizing the need for tailored monitoring strategies and further research to refine guidelines.

Keywords: Prolonged QTc, Antipsychotic, United States

Introduction

Antipsychotic medications are widely used to treat a range of mental health conditions, including schizophrenia and bipolar disorder. However, these medications can also lead to prolonged QT intervals, which increase the risk of serious cardiovascular events such as arrhythmias and sudden cardiac death. In this article review, we analyzed the current evidence on the use of antipsychotic medication in patients with prolonged QT intervals. Our review found that while antipsychotic medications can effectively treat mental health conditions, the potential risks of prolonged QT intervals must be carefully considered. We also identified a need for better monitoring and management strategies to minimize these patients' risk of adverse events. Overall, our review highlights the importance of considering both the benefits and risks of antipsychotic medication in the treatment of patients with prolonged QT intervals.

Methods

This systematic review strictly follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [2]. A search of the literature was performed on the 2nd of February, 2023, through the PubMed and Science Direct databases. The following query was used on the online databases: (qt prolongation in antipsychotics) yielded 797 results in Pubmed and 2743 ins Science Direct; Three thousand five hundred and forty publications were found and screened. Inclusion and exclusion criteria were applied, and only relevant research regarding our research question was considered.

Study selection included the following criteria: studies written in English and conducted on humans in the last five years(articles published between 2019 and 2023 were included) that were relevant to our topic and research question (the association of Qt prolongation in antipsychotics), peer-reviewed, full texts, including these study types: research articles, clinical trials, and observational studies (retrospective cohort and multi-center studies).

Duplicates of articles, articles not written in English, books and book chapters, letters to the editor, opinionated articles, editorials, letters, case reports, and *in vitro* or animal studies were excluded from the literature review. Articles that were strictly abstract or poster presentations were excluded. Narrative and systematic reviews, meta-analyses, and other literature reviews were excluded.

Regardless of our best efforts and a comprehensive search, we acknowledge that not all relevant research and studies may have been included in this review, and some articles may have been inadvertently omitted.

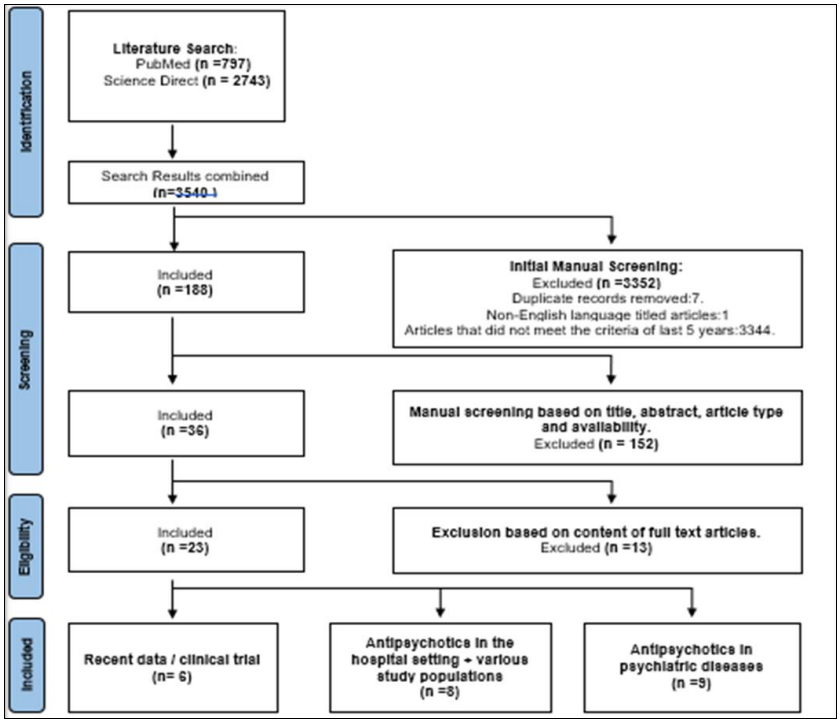

Fig 1: PRISMA flowchart describing the literature screening of studies related to Qtc prolongation in antipsychotic use. Screening was done as per the protocol described in the PRISMA statement [2]

Discussion

Overview of Recent Data/ Clinical Trials:

Drug-induced arrhythmias can occur as an adverse drug reaction that represents on an EKG as prolongations within the QT interval. QT prolongation is a significant risk factor for Torsades de Pointes, which can be fatal and lead to sudden cardiac arrest. While pre-existing cardiac disease and genetic variations in channelopathies can predispose patients to drug-induced arrhythmias, many medications can exacerbate or initiate prolongation within the QT interval, leading to fatal arrhythmias [3].

Recent studies in genetic variations in the pharmacokinetic-mediated susceptibility to QT prolongation suggest that those with an altered metabolism of QT-prolonging drugs play a significant role in how likely the development of significant QT prolongation in asymptomatic patients or those without any pre-existing diseases. One study by Martinez-Matilla *et al*. analyzed 96 genes encoding cytochrome P450 enzymes via massive parallel sequencing (MPS) to understand better the pharmacodynamic pathway associated with QT-prolonging drugs and sudden cardiac death. This revealed the possibility for altered drug metabolism in those with variants to the CYP2C19 and CYP2D6 could contribute to an arrhythmogenic phenotype. Additionally, they saw variants affecting the hERG channel, an important channel involved in the timing of myocyte repolarization through regulation of the Ikr current. It can also lead to arrhythmias when combined with QT-prolonging medications. Since drug-induced arrhythmias and channelopathies can predispose to fatal arrhythmias, knowing beforehand if a patient has one of these arrhythmogenic phenotypes can help prevent the development of sudden cardiac death [3]. Other studies have investigated molecular mechanisms leading to cardiomyopathies and channelopathies, with PKP2 and SCN5A particularly promising [3]. Pathogenic mutations within these genes can change contractile myofilament responses to Ca+2 influxes that can lead to arrhythmias and lead to altered responses to certain medications, such as antipsychotics, that can potentially prolongate the QT

interval. So, while drug-induced QT prolongation is undoubtedly multifactorial, those with genetic variability in ion channels or within the pharmacokinetic metabolism of QT-prolonging drugs may be at a higher risk for potentially fatal arrhythmias [3].

Patients with schizophrenia treated with antipsychotics are 2.3 times more likely in men and 2.1 times higher in women to die from cardiovascular disease [4]. Additionally, there is an increased incidence of sudden cardiac death in those taking antipsychotic medication compared to the general population. Specifically, those taking antipsychotics had a 4.5 to 5.8 times higher risk of sudden cardiac death than those not taking antipsychotic medication [4]. Because antipsychotics increase the QTc in a dose-dependent manner, close monitoring of the QT interval in those taking these medications is crucial in preventing the development of a fatal arrhythmia. Cao *et al*.'s case-control study showed that two genetic polymorphisms, EPB41L4A and LEP, were significantly associated with drug-induced QTc prolongation in Han Chinese patients taking antipsychotics [5]. EPB41L4A-AS1 is well known for its role in preventing tumor proliferation in many solid tumors. However, little is known about its role in developing antipsychotic-induced prolonged QTc. It is thought that EPB41L4A-AS1 may be related to the regulation of glycolysis and glutamine hydrolysis, thus how it controls tumorigenesis [5]. However, studies have also shown increased glycolysis in patients with right ventricular hypertrophy; thus, polymorphisms in EPB41L4A-AS1 may have a role in developing antipsychotic-induced QTc prolongation [5, 6]. LEP encodes for leptin on chromosome 7, which can regulate adipokine concentration within the bloodstream. Since elevated leptin levels can induce increased inflammation, insulin resistance, and oxidative stress, it is possible that polymorphisms that increase LEP expression may have a role in the development of QTc prolongation that is exacerbated by antipsychotic medications; however, further research on this is necessary [5].

Haloperidol is infamous for inducing derangements within the QT interval and within the RR interval (heart rate). However, of all the antipsychotics, QT prolongation is less commonly diagnosed from haloperidol use than in other antipsychotics, such as risperidone or sertindole [7]. Despite this, fatal arrhythmias have been reported even after a single dose of haloperidol. It has a higher risk of inducing ventricular arrhythmias despite a relatively modest increase in the QT interval upon administration. Due to its cardiotoxic effects, animal models have thoroughly studied it, consistently showing a drug-induced prolongation within the QTc. However, this is not the case, as most chronically-treated patients on haloperidol exhibit a normal QTc, despite having a higher incidence of ventricular arrhythmias. This suggests that chronic haloperidol use may deteriorate the adaptability of the QTc to changes in the heart rate. In a study by Vesely *et al*. the coupling between the QT interval and the RR interval was compared in chronic versus acute administration in guinea pig hearts. They revealed that chronic exposure to haloperidol does, in fact, significantly decrease the coupling between the QT and RR intervals suggesting an impaired ability to adapt to changes in the heart rate, leading to the development of ventricular arrhythmias.

Risperidone is another widely used antipsychotic with the potential for QTc prolongation with subsequent fatal arrhythmia development. Risperidone, like other QTc-prolonging antipsychotics, manipulates the potassium current in a reversible and dose-dependent manner. The inactivation of potassium currents also induces vasoconstriction and membrane depolarization, which can lead to sudden cardiac death [8]. On the other hand, quetiapine appears to be a relatively safe medication in terms of risk for QTc prolongation, despite it also affecting potassium channels. This is thought to be due to the effects of quetiapine and its metabolite, norquetiapine, on the human cardiac sodium channels (hNav1.5) and the hERG potassium currents [9]. It is thought that norquetiapine can block the hNav1.5 channel in a dose-dependent manner. This would then shorten the duration of the cardiac action potential and offset potential QTc prolongation through subsequent hERG inhibition. While inhibition of the hERG channel can potentially be pro-arrhythmic, the compensatory inhibition of the hNav1.5 channel acts predominantly as an antiarrhythmic, thus a reduced risk of QTc prolongation [9].

Interestingly, new research suggests that QT prolongation in those with schizophrenia may be due to an underlying Brugada syndrome. Brugada Syndrome is a rare, inherited cardiac condition that can lead to potentially fatal arrhythmias, characterized by specific ECG patterns, and has recently been associated with new-onset schizophrenia disorders [10]. In a study of 224 patients newly diagnosed with schizophrenia and had never been diagnosed with Brugada syndrome, 6.7% had ECG patterns suggestive of Brugada syndrome, compared to only 0.9% of the control group [10]. The study also found that patients with ECG patterns suggestive of Brugada Syndrome were more likely to have a family history of sudden cardiac death, a higher prevalence of suicidal ideation, and a lower body mass index than those without ECG patterns suggestive of Brugada Syndrome. The authors conclude that patients with recent onset schizophrenia spectrum disorders may have an increased risk of Brugada Syndrome or other cardiac conditions and that routine ECG screening may be useful in identifying at-risk patients. They also suggest that further research is needed to understand this association's underlying mechanisms and explore potential preventative and treatment strategies, especially when treatment strategies involving antipsychotics can potentially worsen underlying cardiac conditions.

Antipsychotics in the Elderly:

Regarding elderly care, the management of delirium is a central point of ensuring the safety and wellness of the patient, especially as up to 37% of hospitalized elderly patients develop delirium [castro, Jenraumjit]. Since antipsychotics, namely haloperidol, are the most effective way to treat and control delirium, critical care practice guidelines recommend close monitoring of electrolytes and EKG rhythms, specifically changes within the QT interval, especially when these medications are given intravenously [11]. Haloperidol, when given intravenously or at high doses is highly associated with QTc prolongation and the development of ventricular arrhythmias, which can initiate hesitation to administer the medication when necessary.

Because haloperidol is mostly given in low doses or administered orally to the elderly population, more studies are needed to see if the QT prolonging effects of haloperidol remain true in these settings.

In a prospective observational study by Castro *et al*., the differences in the QT interval were studied in hospitalized patients aged ≥70 years before and after they received low-dose haloperidol (1.5mg). They saw that patient with normal QTc duration during baseline showed a slight prolongation in QTc: haloperidol: +4, 4 ± 24 ms, P = 0.04 compared with baseline and control: +4, 5 ± 26 ms, P = 0.09. QTc duration in patients with borderline and abnormal QTc at baseline decreased [Castro]. In the patients with a borderline abnormal QTc, the mean QTc decrease was −15 ± 29 ms (P ≤ 0.001), and in those with an abnormal baseline QTc, the mean QTc decrease was −19 ± 27 ms (P = 0.004). Thus, those with a normal baseline QTc showed a slight QTc prolongation, while those with an abnormal or borderline baseline QT interval showed a QTc shortening [12]. While the mechanism of QTc shortening in those with an abnormal baseline QT interval is still unknown, it is thought that elevated CRP levels or dysautonomia, a common finding within the elderly population, might play a hand in these findings; however, more research is still necessary.

The need to monitor changes in an EKG in those taking antipsychotics may also not be necessary for all antipsychotics. In a study by Tariot *et al*., the effects of antipsychotic medications, including the atypical antipsychotic pimavanserin, were studied on those with psychosis attributable to Alzheimer's disease, Parkinson's disease, dementia, dementia with Lewy bodies, frontotemporal dementia, or vascular dementia [13]. Of note in the study was an asymptomatic prolongation of the QTc, affecting 1.3% of the patients. The QTc was 5.4±0.9 msec; 1 patient (0.3%) had an asymptomatic increase in the QTcF of more than 60 msec with pimavanserin. However, there were no other changes to the patient's vital signs or electrolyte balances. In a separate phase 1 QT/QTc study that evaluated the potential for the combination of olanzapine and samidorphan to prolong the QTc interval by Sun *et al*., they also found that this combination of antipsychotics had no clinically significant effects on the QT interval. Thus, monitoring EKGs and electrolyte levels may not always be necessary for all antipsychotic medications when low doses are administered [13, 14].

However, EKG monitoring is definitely necessary for elderly patients receiving polypharmacy therapies. In a study by Bo *et al*., the prevalence and variables associated with prolonged QT intervals were studied in patients over 65 on polypharmacy regimens, including antipsychotic medications. Their study revealed a prolonged QTc (on average 436.1 ± 26.6 ms) in approximately 25% of their patient population; however this was highly associated with the use of diuretics (p =.008) and male gender (p =.001) [15]. The average number of medications used daily by this cohort was 5.98 ± 2.81, with a wide variety of psychoactive medications used (antipsychotics, 24.5%; antidepressants, 33.8%; and benzodiazepines, 21.3%) [15]. However, according to their study, the association of prolonged QT intervals was only statistically significant with the use of diuretics and the male gender. While it is unclear why men would be more likely to have prolonged QT intervals, the use of diuretics and the risks of electrolyte abnormalities make routine EKG monitoring in those taking diuretics and antipsychotics crucial in the prevention of fatal arrhythmias or sudden cardiac death [15].

Antipsychotics in the ED

In the emergency department (ED), reducing a patient's psychiatric restlessness or agitation is a key step in managing patient care. This is commonly done by administering antipsychotics such as haloperidol; however, droperidol is another effective medication despite the FDA-issued black box warning for QTc prolongation in 2001 [16, 17]. With its anti-dopaminergic (D2 receptor antagonist) mechanism of action, in addition to its histamine and serotonin antagonist properties, droperidol is an inexpensive and rapidly acting medication that can reduce agitation in patients in addition to treating headache, nausea, acute pain, chronic pain, pain in the context of opioid tolerance and refractory abdominal pain [16, 17]. After the black-box warning was issued, the use of droperidol within the clinical armamentarium came to a complete stop. However, studies published in 2014 convinced the Clinical Guidelines Committee of the American Academy of Emergency Medicine that low-dose droperidol (under 2.5 mg) is safe for use in acute settings such as in the ED [16].

To further study the effect of droperidol on the QTc, a retrospective cohort study of all droperidol administrations by Gaw *et al*., showed that in the 6,000 ED visits studied, QTc prolongation was a rare occurrence after the administration of droperidol, with no clinically significant arrhythmias or deaths attributable to droperidol administration. Among the 1,674 patients who received an EKG less than 24 hours after receiving droperidol, approximately 3.6% had a QT greater than 500. Lastly, the only notable adverse effect after droperidol administration was akathisia, occurring in approximately 2.9% of patients in the study.

In a prospective cohort study of patients over 12 years of age who received droperidol for non-psychiatric reasons, Hernández-Rodríguez *et al*. revealed that only 12 patients out of 68 (17.6%) had an episode of QTc prolongation greater than 500 ms status post droperidol administration, and three patients (4.4%) had a delta QTc ≥ +60 ms. However, like the previous study, no clinically significant arrhythmias or deaths occurred due to droperidol administration, and the episodes of prolonged QT intervals were brief. Similarly, to the previous study by Gaw, the only notable side-effect was increased restlessness or anxiety (13.2%) [17]. Thus, despite the FDA black box warning on the QT-prolonging effects of droperidol, multiple studies, along with the Clinical Guidelines Committee of the American Academy of Emergency Medicine, declare that low doses of droperidol under 2.5mg do not have a clinically significant effect on the QT interval [16, 17].

Antipsychotics in the ICU/ Hospitalized/ Post-op

The management of restlessness and agitation in patients in critical care, and with the complex clinical histories of each patient, the use of potentially QT-prolonging medications can further complicate a case. However, this may not be so for all antipsychotic medications. In a prospective study conducted by Lee *et al*., the effect of the medication quetiapine on the prolongation of QTc intervals was studied in critically ill patients. The study involved monitoring QTc intervals in patients who received quetiapine and comparing them to a control group who did not receive the medication. They found no significant change in the QTc interval (a

measure of heart rhythm) before and after administering quetiapine, with an average change of 2.7 milliseconds. Compared to a control group that received melatonin, the difference in the average change in QTc was also insignificant. The study suggests that routine monitoring of QTc with electrocardiograms may not be necessary after administering quetiapine to critically ill patients, based on the study's findings of no significant change in QTc [18].

A retrospective cohort study by Hanna *et al*. aimed to evaluate the incidence of adverse events associated with using AAPs in a cardiac intensive care unit (CICU). The study analyzed data from 58 patients who received AAPs during their hospitalization in the CICU. The study analyzed data from 144 adult patients who were not receiving antipsychotics before admission and were subsequently treated with olanzapine (50 patients) or quetiapine (94 patients). The study evaluated the incidence of adverse events, including ventricular tachycardia, hypotension, and QTc prolongation. The results showed that 18% of patients experienced an adverse event, the most common being QTc prolongation (14%). Patients who received quetiapine had a higher rate of adverse events than those who received olanzapine, including QTc prolongation. However, the number of events was relatively low with both agents in a CICU cohort. The length of stay in the ICU was shorter for patients who received olanzapine.Overall, the study suggests that AAPs may be a viable treatment option for delirium in critically ill patients in the CICU, but further research is needed to establish their safety and efficacy [19].

Fox *et al*. conducted a prospective, open-label study that evaluated the effects of intravenous (IV) amisulpride on QTc interval prolongation at doses effective for managing postoperative nausea and vomiting (PONV). The study included 50 adult patients scheduled for elective surgery and at risk for PONV. The patients received a single dose of IV amisulpride 5 mg/kg within 10 minutes before the end of surgery. The study found that the mean change in QTc interval was 1.9 ms (95% confidence interval: -2.8 to 6.7 ms) at 5 minutes post-dose and 1.4 ms (95% confidence interval: -2.7 to 5.5 ms) at 15 minutes post-dose. These changes were not clinically significant, as the upper bounds of the confidence intervals were less than the threshold of 10 ms for clinically relevant QTc prolongation. The study concluded that IV amisulpride at doses effective for the management of PONV does not cause meaningful QTc interval prolongation. Therefore, the authors suggest that IV amisulpride could be a safe and effective option for the management of PONV in patients at risk for this condition [20].

Khan *et al*. conducted a cross-sectional study to determine the prevalence of risk factors for QT prolongation and associated drug-drug interactions (DDIs) in a cohort of 387 medical inpatients. The study found that 82% of the patients had at least one risk factor for QT prolongation, with electrolyte imbalances (53%), cardiovascular disease (30%), and liver disease (22%) being the most common. In addition, 22% of the patients were prescribed at least one drug known to cause QT prolongation, and 12% were prescribed two or more such drugs. The study also identified 40 DDIs that could potentially prolong the QT interval, the most common being antipsychotics and macrolides or fluoroquinolones.The study concluded that risk factors for QT prolongation and associated DDIs are highly prevalent in medical inpatients. Additionally, routine electrocardiogram monitoring may be warranted in patients with multiple risk factors for QT prolongation and those receiving multiple drugs that can cause QT prolongation [21].

Antipsychotics in Psychiatric Diseases

The management of QTc monitoring of QTc prolongation in adults with medical and psychiatric comorbidities is currently a gray area lacking a solid set of guidelines. Xiong *et al*. aimed to add more light to this by creating a set of guidelines with a risk score to be applied to patients. The authors emphasize the importance of identifying patients at risk for QTc prolongation due to various factors, including medications, electrolyte imbalances, and medical conditions such as cardiac disease and liver dysfunction, and come up with a risk score. The authors provide recommendations for monitoring QTc interval, including baseline electrocardiogram (ECG) before starting QTc-prolonging medications, routine ECG monitoring during treatment, and consideration of cardiac consultation in high-risk patients. The authors also highlight the need for clear communication and collaboration between medical and psychiatric providers to ensure the safe and effective use of QTc-prolonging medications in this patient population [22].

Antipsychotic medication is a mainstay in managing psychiatric diseases; however, those taking antipsychotic medications tend to have a higher risk for cardiovascular disease and increased mortality [4]. While the QT interval is a staple in monitoring EKG changes caused by antipsychotics, the deceleration capacity (DC) is another method to help track EKG changes seen with antipsychotic medication use. DC is an electrocardiographic marker that indicates cardiac autonomic function, and QTc is a measure of cardiac repolarization. A study by Okayasu *et al*. found that patients with schizophrenia who were taking antipsychotic medications had lower DC compared to those who were not taking these medications. They found that DC was negatively dose-dependent in patients with schizophrenia taking chlorpromazine, zotepine, olanzapine, and clozapine. In contrast, the use of carbamazepine increased DC in a dose-dependent manner. Typically, DC values <2.5 ms, 2.6 to 4.5 ms, and >4.5 ms represent high, moderate, and low mortality risks, respectively; thus, antipsychotics lowering the DC have a higher mortality risk. Previous reports show that lower DC levels indicate a higher mortality risk in those with a previous cardiac history; thus, its use in predicting fatal arrhythmia development may be useful. The findings showed that antipsychotic use, particularly with medications such as chlorpromazine, zotepine, olanzapine, and clozapine, was negatively associated with DC dose-dependent. However, there was no significant correlation between DC and QTc. Additionally, there was a significant correlation between QTc and DC in patients who were taking antipsychotic medications [4]. These findings suggest that antipsychotic use may affect cardiac autonomic function in patients with schizophrenia and that there may be a relationship between QTc prolongation and DC. Further research is needed to confirm these results and to investigate the clinical implications of these findings.

Another method to evaluate the depolarization and repolarization process of the heart is through evaluation of the frontal QRS-T angle. The frontal QRS-T angle is an electrocardiogram-based measure that reflects the overall orientation of the heart's depolarization and repolarization processes. Since cardiovascular disease is the most common

cause of death in patients with schizophrenia, this study was essential to establish and understand a baseline. In a study by Tekin *et al*., the frontal QRS-T angle was compared between patients with schizophrenia and healthy volunteers. The results of this study showed that the corrected QT interval and frontal QRS-T angle were significantly higher in patients with schizophrenia compared to healthy controls. The frontal QRS-T angle was positively correlated with age, duration of disease, negative symptom severity, and disease duration. These factors were independent predictors of the increased frontal QRS-T angle seen in patients with schizophrenia treated with antipsychotic medication. The study suggests that the frontal QRS-T angle could be a useful electrocardiogram parameter for evaluating cardiovascular disease risk in patients with schizophrenia, especially those on long-term treatment [23].

Prolonging the QT interval on an electrocardiogram (ECG) is a concern for many drugs because it can lead to a fatal arrhythmia known as torsades de pointes. However, not all antipsychotic medications warrant monitoring and testing for this complication [24]. For example, quetiapine's effects on the QT interval were evaluated in Japanese patients with bipolar disorder during the late stage of clinical development [24]. The study involved 93 Japanese patients with bipolar disorder who received quetiapine fumarate at doses ranging from 300 mg to 600 mg per day. The study results indicate that quetiapine fumarate has a minimal effect on the QT interval in Japanese patients with bipolar disorder. The concentration-QTc modeling and simulation approach predicted a maximum QTc prolongation of 7.1 milliseconds at the highest recommended dose of 600 mg daily, below the threshold for clinical concern. Additionally, no patients in the study experienced a QTc interval of greater than 500 milliseconds, which is considered a significant risk for torsades de pointes. The study suggests that quetiapine fumarate is safe for Japanese patients with bipolar disorder regarding QT prolongation. The concentration-QTc modeling and simulation approach used in the study may be useful for evaluating the potential for other drugs to cause QT prolongation in the future [24]. Further investigation into other antipsychotics utilizing this modeling and simulation approach should be considered to rule out unnecessary ECG monitoring and invasive testing for those prescribed these medications.

Antipsychotic Medication in Malignancy

Antipsychotic medications are also widely used in managing nausea and vomiting in malignancy; however, the most commonly used regimens contain domperidone, ondansetron, and olanzapine, all have the potential for inducing QT prolongation. To assess the arrhythmic potential of these medications, Kamath *et al*. conducted a prospective, observational, single-group, assessor-blinded study that evaluated the effect of this regimen on the QTc interval in patients with malignancy. They revealed a significant change in the QTc interval over time, with the QTc interval on the first day being higher than that at baseline, especially in females. However, no significant differences were observed in males. Two female patients had an absolute QTc prolongation (Bazett correction) of more than 500 ms, but no significant adverse events were reported. These findings indicate that QTc prolongation is a concern when using olanzapine alone or combined with domperidone and ondansetron. Further investigation is necessary to determine the long-term safety of this antiemetic regimen. The results suggest that the antiemetic regimen containing domperidone, ondansetron, and olanzapine did not significantly prolong the QTc interval in patients with malignancy [25].

Antipsychotics in the Pediatric Population

Antipsychotics are also widely used in the pediatric population; thus, investigations into the efficacy, safety, and tolerability of these medications are crucial. Ziprasidone is one of the most commonly prescribed antipsychotic medications for children and adolescents with mania in bipolar I disorder due to its effectiveness and tolerability. In a study evaluating QTc prolongation, Findling *et al*. saw that in those chronically taking ziprasidone, the mean Fridericia-corrected QT interval (QTcF) intervals in the group treated with ziprasidone were slightly longer compared to the group treated with placebo at all study visits. However, no participants in the ziprasidone group had QTcF intervals equal to or greater than 480 msec, which is considered a significant QT prolongation. Additionally, no participants in the ziprasidone group had increased QTcF intervals from their baseline measurement equal to or greater than 60 msec [26]. In another study by Das *et al*., the prevalence and risk factors associated with potential drug-drug interactions (PDDIs) was evaluated in children and adolescents receiving psychotropic medications that could lead to QT interval prolongation. They revealed that 37.8% of the study population was exposed to at least one PDDI. The most frequent combinations were between two antipsychotics or an antipsychotic and a selective serotonin reuptake inhibitor. Thus, those with PDDIs are more likely to develop a prolonged QT interval leading to a fatal arrhythmia. These studies highlight the need for careful monitoring and management of medication use in children and adolescents receiving psychotropic medications [1].

Table 1

S. No	Author	Study	Conclusions and findings
1	Okayasu *et al*.; 2023 [4]	Effect of antipsychotic use by patients with schizophrenia on deceleration capacity and its relation to corrected QT interval,	The study investigated the effect of antipsychotic use by patients with schizophrenia on deceleration capacity (DC) and its relation to the corrected QT interval (QTc). The study found that DC was significantly lower in patients with schizophrenia compared to healthy controls, and the use of antipsychotics was associated with further reductions in DC. The study also found a significant positive correlation between QTc and DC in patients with schizophrenia. The authors suggest that antipsychotics may contribute to increased risk for cardiovascular events in patients with schizophrenia by reducing DC. They also highlight the importance of routine monitoring of DC and QTc in patients with schizophrenia who are being treated with antipsychotics.
2	Findling *et al*.; 2022 [26]	Efficacy, Safety, and Tolerability of Flexibly Dosed Ziprasidone in Children	The study found that ziprasidone was significantly more effective than placebo in reducing manic symptoms in children and adolescents with bipolar I disorder,

		and Adolescents with Mania in Bipolar I Disorder: A Randomized Placebo-Controlled Replication Study.	and was generally well-tolerated with few adverse effects reported.
3	Hernández-Rodríguez *et al*.; 2022 [17]	Prospective real-time evaluation of the QTc interval variation after low-dose droperidol among emergency department patients	The study aimed to prospectively evaluate the QTc interval variation after low-dose droperidol administration among emergency department patients. The study found that low-dose droperidol did not cause significant QTc interval prolongation or torsades de pointes (TdP) in emergency department patients. The study also found that patients who received droperidol had a lower incidence of persistent nausea and vomiting than those who received other antiemetic agents. The authors conclude that low-dose droperidol is safe and effective for managing nausea and vomiting in emergency department patients. They also suggest that further research is needed to confirm these findings in larger, more diverse patient pop
4	Hanna *et al*.; 2022 [19]	Atypical Antipsychotic Safety in the CICU	The study aimed to evaluate the safety of atypical antipsychotics in critically ill cardiac patients (CICU). The study found that using atypical antipsychotics in CICU patients was associated with a significant increase in the risk of all-cause mortality and ventricular arrhythmias. The study also found that the use of atypical antipsychotics was associated with a higher risk of in-hospital adverse events and a longer length of stay in the CICU. The authors conclude that atypical antipsychotics in critically ill cardiac patients should be avoided or minimized whenever possible, and alternative treatments should be considered. They also suggest that further research is needed to understand better the risks and benefits of atypical antipsychotics in this patient population.
5	Das *et al*.; 2022 [1]	Potential drug-drug interaction prevalence and risk factors associated with QT interval prolonging psychotropic use in children and adolescents,	The study aimed to evaluate the prevalence of potential drug-drug interactions (PDDIs) and risk factors associated with QT interval prolongation in children and adolescents who were prescribed psychotropic medications. The study found that PDDIs were common among children and adolescents prescribed psychotropic medications, and these interactions were associated with an increased risk of QT interval prolongation. The study also found that certain patient factors, such as age, sex, and medical comorbidities, were associated with an increased risk of PDDIs and QT interval prolongation. The authors conclude that clinicians should be aware of the potential for PDDIs and QT interval prolongation when prescribing psychotropic medications to children and adolescents and should carefully consider The risks and benefits of these medications on an individual basis. They also suggest that further research is needed to understand better the factors that contribute to PDDIs and QT interval prolongation in this patient
6	Tekin *et al*.; 2022 [23]	Comparison of frontal QRS-T angle in patients with schizophrenia and healthy volunteers,	The study compared the frontal QRS-T angle in patients with schizophrenia and healthy volunteers to evaluate the relationship between this angle and the presence of schizophrenia. The study found that the frontal QRS-T angle was significantly wider in patients with schizophrenia than healthy volunteers, indicating a greater dispersion of ventricular repolarization. The authors conclude that the wider frontal QRS-T angle observed in patients with schizophrenia may indicate an increased risk of ventricular arrhythmias. Further research is needed to understand better the underlying mechanisms and clinical implications of this finding.
7	Jenraumjit *et al*.; 2021 [11]	Drug-related problems of antipsychotics in treating delirium among elderly patients: A real-world observational study	The study aimed to identify drug-related problems associated with using antipsychotics in treating delirium in elderly patients in a real-world setting. The study found that the most common drug-related problems were adverse drug reactions, inappropriate dosing, and drug interactions. The study also found that the use of antipsychotics was associated with a higher risk of adverse drug reactions compared to other drug classes. The authors conclude that the use of antipsychotics in treating delirium in elderly patients should be carefully monitored and that alternative treatment options should be considered to avoid potential drug-related problems. They suggest that future research should focus on identifying effective and safe treatment options for delirium in elderly patients that minimize the risk of drug-related problems.
8	Kamath A *et al*.; 2021 [25]	Effect of domperidone, ondansetron, olanzapine-containing antiemetic regimen on QT_Cinterval in patients with malignancy: a prospective, observational, single-group, assessor-blinded study.	The study aimed to evaluate the effect of an antiemetic regimen containing domperidone, ondansetron, and olanzapine on the QTc interval in patients with malignancy. The study found that the antiemetic regimen did not significantly prolong the QTc interval in most patients, with only a small proportion experiencing QTc prolongation beyond the normal range. The study also found that the antiemetic regimen effectively managed nausea and vomiting in patients with malignancy. The authors conclude that the antiemetic regimen containing domperidone, ondansetron, and olanzapine appears safe regarding QTc prolongation in most patients with malignancy. They suggest that further studies are needed to

			evaluate this antiemetic regimen's long-term safety and identify potential risk factors for QTc prolongation in patients with malignancy receiving antiemetic therapy.
9	Fox *et al*.; 2021 [20]	Intravenous Amisulpride Does Not Meaningfully Prolong the QTc Interval at Doses Effective for the Management of Postoperative Nausea and Vomiting.	The study aimed to evaluate the effect of intravenous amisulpride on the QTc interval in patients receiving doses effective for managing postoperative nausea and vomiting. The study found that intravenous amisulpride did not significantly prolong the QTc interval in these patients. The mean change in QTc interval was within the normal range and was not considered clinically relevant. The authors conclude that intravenous amisulpride, at doses effective for managing postoperative nausea and vomiting, does not meaningfully prolong the QTc interval. They suggest that intravenous amisulpride may be a safe and effective option for managing postoperative nausea and vomiting, especially in patients with a history of QTc prolongation or other cardiac risk factors.
10	Gaw *et al*.; 2021 [16]	**Effectiveness and safety of droperidol in a United States emergency department.**	The study aimed to evaluate the effectiveness and safety of droperidol for treating agitation and nausea in the emergency department. The study found that droperidol effectively treated agitation and nausea in most patients. The incidence of adverse events was low, with only a few patients experiencing sedation or respiratory depression. There were no reports of torsades de pointes or other serious cardiac events. The authors conclude that droperidol is a safe and effective option for treating agitation and nausea in the emergency department. They suggest that droperidol should be considered a first-line treatment option for these indications, especially in patients with contraindications or intolerance to other medications. However, the authors note that further studies are needed to confirm these findings and to evaluate the long-term safety of droperidol in this population.
11	*Tariot et al*.; 2021 [13]	*Trial of Pimavanserin in Dementia-Related Psychosis*	The study aimed to evaluate the efficacy and safety of pimavanserin, a selective serotonin inverse agonist, for the treatment of dementia-related psychosis. The study found that pimavanserin effectively reduced the severity of psychotic symptoms in patients with dementia, as measured by the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) psychosis subscale. The treatment group showed statistically significant improvements in psychosis symptoms compared to the placebo group. The authors conclude that pimavanserin is a safe and effective option for treating dementia-related psychosis. They suggest that pimavanserin has the potential to fill an important treatment gap in this population, As there are currently no FDA-approved treatments for this indication. However, the authors note that further studies are needed to evaluate pimavanserin's long-term safety and efficacy in this population and its potential use in other psychiatric disorders.
12	*Bo et al*.; 2021 [15]	*Prevalence, predictors and clinical implications of prolonged corrected QT in elderly patients with dementia and suspected syncope.*	Found that prolonged corrected QT (QTc) interval was prevalent in elderly patients with dementia and suspected syncope. The study also identified predictors of prolonged QTc interval, such as age and use of certain medications. The findings suggest that routine electrocardiogram (ECG) monitoring may be warranted in elderly dementia patients with suspected syncope in order to detect prolonged QTc intervals and prevent potential adverse cardiac events.
13	Sun *et al*.; 2020 [14]	Combination of olanzapine and samidorphan has no clinically relevant effects on ECG parameters, including the QTc interval: Results from a phase 1 QT/QTc study.	The study on the combination of olanzapine and samidorphan found that this combination had no clinically relevant effects on ECG parameters, including the QTc interval. The study was a phase 1 QT/QTc study that evaluated the potential for the combination of olanzapine and samidorphan to prolong the QTc interval, which measures the heart's electrical activity. The results suggest that the combination of olanzapine and samidorphan is unlikely to effectively reduce cardiac events in patients with schizophrenia or bipolar disorder treated with this combination therapy.
14	Castro *et al*.; 2020 [12]	Should we still monitor QTc duration in frail older patients on low-dose haloperidol? A prospective Observational cohort study.	The prospective observational cohort study investigated whether monitoring QTc duration is necessary for frail older patients on low-dose haloperidol. The study found that QTc duration did not increase during low-dose haloperidol treatment, even in frail older patients. The study suggests that routine QTc monitoring in frail older patients on low-dose haloperidol may not be necessary.
15	Xiong *et al*.; 2020 [22]	QTc monitoring in adults with medical and psychiatric comorbidities: Expert consensus from the Association of Medicine and Psychiatry,	The article provides expert consensus recommendations for QTc monitoring in adults with medical and psychiatric comorbidities. The recommendations include obtaining an ECG at baseline and during treatment initiation for patients with multiple risk factors for QTc prolongation, regularly monitoring QTc in high-risk patients, and using clinical judgment to adjust treatment plans based on QTc changes. The experts suggest that communication and collaboration between the medical and psychiatric teams are essential to ensure safe and effective care for patients with comorbidities.
16	Cao *et al*.; 2020 [5]	EPB41L4A and LEP gene polymorphisms are associated with antipsychotic-induced QTc interval	The study aimed to investigate whether EPB41L4A and LEP gene polymorphisms were associated with antipsychotic-induced QTc interval prolongation in Han Chinese. The results indicated that the rs12654778 variant

		prolongation in Han Chinese,	of the EPB41L4A gene and the rs6923472 variant of the LEP gene were significantly associated with antipsychotic-induced QTc interval prolongation. The study provides evidence that genetic factors may contribute to the variability of QTc prolongation induced by antipsychotics in Han Chinese patients.
17	Kim *et al*.; 2020 [9]	Norquetiapine blocks the human cardiac sodium channel Nav1.5 in a state-dependent manner,	The study found that norquetiapine, a metabolite of quetiapine, blocks the human cardiac sodium channel Nav1.5 in a state-dependent manner. It suggests this may be a potential mechanism for developing cardiac arrhythmias and QT interval prolongation associated with using quetiapine. The findings highlight the importance of monitoring the cardiac effects of atypical antipsychotic medications and understanding their underlying mechanisms.
18	Ryeol An *et al*.; 2020 [8]	Inhibition by the atypical antipsychotic risperidone of voltage-dependent K+ channels in rabbit coronary arterial smooth muscle cells,	The study aimed to investigate the effect of risperidone, an atypical antipsychotic, on voltage-dependent K+ channels in rabbit coronary arterial smooth muscle cells. The results showed that risperidone inhibited the voltage-dependent K+ channels in a concentration-dependent manner, leading to a reduction in the relaxation of rabbit coronary arterial smooth muscle cells. The authors concluded that the inhibition of voltage-dependent K+ channels by risperidone might contribute to the cardiovascular adverse effects associated with its use.
19	*Fukushi et al*.; 2020 [24]	*Approach to Evaluating QT Prolongation of Quetiapine Fumarate in Late Stage of Clinical Development Using Concentration-QTc Modeling and Simulation in Japanese Patients with Bipolar Disorder*	The results of the study showed that the risk of QT prolongation associated with quetiapine fumarate was low and that the drug was generally safe and well-tolerated in Japanese patients with bipolar disorder. The authors also suggested that concentration-QTc modeling and simulation could be useful for evaluating the cardiac safety of new drugs in clinical development.
20	Martinez-Matilla *et al*.; 2019 [3]	Genetic susceptibility in pharmacodynamic and pharmacokinetic pathways underlying drug-induced arrhythmia and sudden unexplained deaths,	The article discusses the genetic susceptibility factors contributing to drug-induced arrhythmia and sudden unexplained deaths. The authors analyzed various drugs' pharmacodynamic and pharmacokinetic pathways and identified genetic variants that may increase the risk of adverse drug reactions. They also discussed the importance of genetic testing in personalized medicine to identify individuals at risk for adverse drug reactions and adjust medication dosages accordingly. The findings of this study suggest that genetic factors play a significant role in drug-induced arrhythmia and sudden unexplained deaths, and personalized medicine could be an effective approach to reducing the risk of adverse drug reactions.
21	Lee S *et al*.; 2019 [18]	Impact of Quetiapine Therapy on QTc Prolongation in Critically Ill Patients.	Retrospective study of patients who received quetiapine during their hospital stay in a medical intensive care unit. They analyzed the QTc intervals before and after quetiapine administration and found that quetiapine therapy was associated with a significant increase in QTc intervals in critically ill patients. The authors suggest that clinicians should be cautious when using quetiapine in critically ill patients who are at risk of developing arrhythmias due to QTc prolongation. They also recommend monitoring QTc intervals regularly in patients receiving quetiapine therapy, especially those with pre-existing cardiac conditions or taking other medications that can prolong QTc intervals. The findings of this study highlight the potential risks of quetiapine therapy in critically ill patients and the importance of careful monitoring to prevent adverse drug reactions.
22	Sutterland et. al; 2019 [10]	Increased prevalence of ECG suspicious for Brugada Syndrome in recent onset schizophrenia spectrum disorders,	The study found that the prevalence of ECG abnormalities suspicious for Brugada Syndrome was significantly higher in patients with recent onset schizophrenia spectrum disorders compared to healthy controls. The authors suggest that routine ECG screening should be considered in patients with recent onset schizophrenia spectrum disorders to identify those at risk for sudden cardiac death.
23	*Khan* et. al; 2019 [21]	*Prevalence of the risk factors for QT prolongation and associated drug–drug interactions in a cohort of medical inpatients*	The study found that 23.7% of the patients had at least one risk factor for QT prolongation, with the most common being hypokalemia. The study also identified 244 potential drug-drug interactions, with the most common being between antibiotics and QT-prolonging drugs. The authors concluded that there is a high prevalence of risk factors for QT prolongation and associated drug-drug interactions in medical inpatients, highlighting the need for increased awareness and monitoring of this potentially life-threatening condition.

Conclusion

Antipsychotic medications have a wide variety of uses to a wide variety of the patient population and can be effective both acutely and given chronically. Thus, their effects on the QT interval need to be studied in each of these settings, as it appears that QT prolongation is not always a guaranteed occurrence after administration. By identifying when routine EKG monitoring is necessary after antipsychotic administration, we can save hospital and patient time and resources while avoiding unnecessary testing on the patient. Conversely, our review also found that while antipsychotic medications can be significantly effective in treating psychiatric disorders, there are still gaps in treatment management strategies that need to be filled to reduce the risk of adverse events in the patient population. Overall, our review highlights the importance of considering both the benefits and risks of antipsychotic medication in treating patients with prolonged QT intervals.

References

1. Das B, Rawat VS, Ramasubbu SK, Agnihotri A, Kumar B. Potential drug-drug interaction prevalence and risk factors associated with QT interval prolonging psychotropic use in children and adolescents. Progress in Pediatric Cardiology. 2022; 64:p101456.
2. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ. 2009; 339:b2700. Doi: 10.1136/bmi.b2700
3. Martinez-Matilla M, Blanco-Verea A, Santori M, Ansede-Bermejo J, Ramos-Luis E, Gil R, *et al*. Genetic susceptibility in pharmacodynamic and pharmacokinetic pathways underlying drug-induced arrhythmia and sudden unexplained deaths. Forensic science international. Genetics. 2019; 42:203-212. Doi: https://doi.org/10.1016/j.fsigen.2019.07.010
4. Okayasu H, Shinozaki T, Takano Y, Sugawara N, Fujii K, Yasui-Furukori N, *et al*. Effect of antipsychotic use by patients with schizophrenia on deceleration capacity and its relation to the corrected QT interval. General hospital psychiatry. 2023; 81:15-21. Doi: https://doi.org/10.1016/j.genhosppsych.2023.01.005
5. Cao H, Li S, Gao Y, Ma Y, Wang L, Chen B, *et al*. EPB41L4A and LEP gene polymorphisms are associated with antipsychotic-induced QTc interval prolongation in Han Chinese. Psychiatry research. Advance online publication. 2020; 286:p112851. Doi: https://doi.org/10.1016/j.psychres.2020.112851
6. Piao L, Fang YH, Cadete VJJ, *et al*. The inhibition of pyruvate dehydrogenase kinase improves impaired cardiac function and electrical remodeling in two models of right ventricular hypertrophy: resuscitating the hibernating right ventricle. J Mol Med. 2010; 88:47-60. Doi: https://doi.org/10.1007/s00109-009-0524-6)
7. Vesely P, Stracina T, Hlavacova M, Halamek J, Kolarova J, Olejnickova V, *et al*. Haloperidol affects coupling between QT and RR intervals in guinea pig isolated heart. Journal of Pharmacological Sciences. 2019; 139(1):23-28. Doi: https://doi.org/10.1016/j.jphs.2018.11.004
8. An JR, Seo MS, Jung HS, Li H, Jung WK, Choi IW, *et al*. Inhibition by the atypical antipsychotic risperidone of voltage-dependent K+ channels in rabbit coronary arterial smooth muscle cells. European Journal of Pharmacology. 2020; 874: p173027. Doi: https://doi.org/10.1016/j.ejphar.2020.173027
9. Kim DH, Park KS, Park SH, Hahn SJ, Choi JS. Norquetiapine blocks the human cardiac sodium channel Nav1.5 in a state-dependent manner. European Journal of Pharmacology. 2020; 885:p173532. Doi: https://doi.org/10.1016/j.ejphar.2020.173532
10. Sutterland AL, Blom MT, Ladee K, Lubbers JJM, Cohen D, de Haan L, *et al*. Increased prevalence of ECG suspicious for Brugada Syndrome in recent onset schizophrenia spectrum disorders. Schizophrenia research. 2019; 210:59-65. Doi: https://doi.org/10.1016/j.schres.2019.06.013
11. Jenraumjit R, Somboon J, Chainan S, Chuenchom P, Wongpakaran N, Wongpakaran T. Drug-related problems of antipsychotics in treating delirium among elderly patients: A real-world observational study. J Clin Pharm Ther. 2021; 46(5):1274-1280. Doi: 10.1111/jcpt.13423. Epub 2021 Mar 25. PMID: 33768628.
12. Castro E, Körver F, Merry A, van Moorsel F, Hazebroek M, Smid M, *et al*. Should we still monitor QTc duration in frail older patients on low-dose haloperidol? A prospective observational cohort study. Age Ageing. 2020; 49(5):829-836. Doi: 10.1093/ageing/afaa066. PMID: 32614955
13. Tariot PN, Cummings JL, Soto-Martin ME, Ballard C, Erten-Lyons D, Sultzer DL, *et al*. Trial of Pimavanserin in Dementia-Related Psychosis. N Engl J Med. 2021; 385(4):309-319. Doi: 10.1056/NEJMoa2034634. PMID: 34289275
14. Sun L, Yagoda S, Xue H, Brown R, Nangia N, McDonnell D, *et al*. Combination of olanzapine and samidorphan has no clinically relevant effects on ECG parameters, including the QTc interval: Results from a phase 1 QT/QTc study. Prog Neuropsychopharmacol Biol Psychiatry. 2020; 100:p109881. Doi: 10.1016/j.pnpbp.2020.109881. Epub 2020 Jan 28. PMID: 32004636.
15. Bo M, Ceccofiglio A, Mussi C, Bellelli G, Nicosia F, Riccio D, *et al*. Prevalence, predictors and clinical implications of prolonged corrected QT in elderly patients with dementia and suspected syncope. Eur J Intern Med. 2019; 61:34-39. Doi: 10.1016/j.ejim.2018.10.011. Epub 2018 Oct 25. PMID: 30482635.
16. Gaw CM, Cabrera D, Bellolio F, Mattson AE, Lohse CM, Jeffery MM. Effectiveness and safety of droperidol in a United States emergency department. Am J Emerg Med. 2020; 38(7):1310-1314. Doi: 10.1016/j.ajem.2019.09.007. Epub 2019 Nov 25. PMID: 31831345.
17. Hernández-Rodríguez L, Bellolio F, Cabrera D, Mattson AE, VanMeter D, Grush AE, *et al*. Prospective real-time evaluation of the QTc interval variation after low-dose droperidol among emergency department patients. The American Journal of Emergency Medicine. 2022; 52:212-219. Doi: https://doi.org/10.1016/j.ajem.2021.12.039
18. Lee S, Morris A, Kim S, Li F, Baumgartner L. Impact of Quetiapine Therapy on QTc Prolongation in Critically Ill Patients. Ann Pharmacother. 2019; 53(7):705-710. Doi: 10.1177/1060028019829494. Epub 2019 Feb 1. PMID: 30704263.
19. Hanna MP, Adie SK, Ketcham SW, Deshmukh A, Gondi K, Abdul-Aziz AA, *et al*. A typical Antipsychotic Safety in the CICU. The American Journal of Cardiology. 2022; 163:117-123. Doi: https://doi.org/10.1016/j.amjcard.2021.09.052
20. Fox GM, Albayaty M, Walker JL, Xue H, Darpo B. Intravenous Amisulpride Does Not Meaningfully Prolong the QTc Interval at Doses Effective for the Management of Postoperative Nausea and Vomiting. Anesth Analg. 2021; 132(1):150-159. Doi: 10.1213/ANE.0000000000004538. PMID: 31913911.
21. Khan Q, Ismail M, Haider I, Ali Z. Prevalence of the risk factors for QT prolongation and associated drug-drug interactions in a cohort of medical inpatients. Journal of the Formosan Medical Association = Taiwan yi zhi. 2019; 118(1):109-115. Doi: https://doi.org/10.1016/j.jfma.2018.01.016
22. Xiong GL, Pinkhasov A, Mangal JP, Huang H, Rado J,

Gagliardi J, *et al*. QTc monitoring in adults with medical and psychiatric comorbidities: Expert consensus from the Association of Medicine and Psychiatry. Journal of Psychosomatic Research. 2020; 135:p110138. Doi: https://doi.org/10.1016/j.jpsychores.2020.110138

23. Tekin A, Tanrıverdi Z, Kapıcı Y, Güc B, Karamustafalıoğlu O. Comparison of frontal QRS-T angle in patients with schizophrenia and healthy volunteers. Journal of Psychiatric Research. 2022; 149:76-82. Doi: https://doi.org/10.1016/j.jpsychires.2022.02.033
24. Fukushi R, Nomura Y, Katashima M, Komatsu K, Sato Y, Takada A. Approach to Evaluating QT Prolongation of Quetiapine Fumarate in Late Stage of Clinical Development Using Concentration-QTc Modeling and Simulation in Japanese Patients with Bipolar Disorder. Clin Ther. 2020; 42(8):1483-1493. Doi: 10.1016/j.clinthera.2020.06.002. Epub 2020 Aug 11. PMID: 32792252.
25. Kamath A, Rai KM, Shreyas R, Saxena PUP, Banerjee S. Effect of domperidone, ondansetron, olanzapine-containing antiemetic regimen on QTCinterval in patients with malignancy: A prospective, observational, single-group, assessor-blinded study. Sci Rep. 2021; 11(1):p445. Doi: 10.1038/s41598-020-79380-1 PMID: 33431995; PMCID: PMC7801395.
26. Findling RL, Atkinson S, Bachinsky M, Raiter Y, Abreu P, Ianos C, *et al*. Efficacy, Safety, and Tolerability of Flexibly Dosed Ziprasidone in Children and Adolescents with Mania in Bipolar I Disorder: A Randomized Placebo-Controlled Replication Study. J Child Adolesc Psychopharmacol. 2022; 32(3):143-152. Doi: 10.1089/cap.2021.0121. Epub 2022 Apr 7. PMID: 35394365.