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Electrophysiological and clinical fundamentals of QTc prolongation induced by antipsychotic medications

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Abstract
Patients with psychiatric disorders undergoing antipsychotic treatment are at an elevated risk for adverse cardiovascular events, including arrhythmias and sudden cardiac death. While the precise mechanisms linking cardiovascular diseases and psychiatric conditions remain unclear, QTc prolongation is suspected to be a contributing factor. The human ether-à-go-go-related gene (hERG, or KCNH2), which affects potassium channels, is implicated in the cardiotoxicity of various medications, including antipsychotics. This gene plays a critical role in determining whether a drug will be approved for market use. This paper elucidates the electrophysiological basis of QTc prolongation and reviews the evidence concerning which antipsychotics may exacerbate QTc prolongation and which may offer a safer profile. Generally, second-generation antipsychotics, especially aripiprazole, exhibit a more favorable profile concerning QTc prolongation. Nonetheless, we advocate for further research, particularly into the newest antipsychotics, to establish more robust, evidence-based guidelines for psychiatrists.

Keywords: Antipsychotic medications, QTc prolongation, electrophysiological and clinical fundamentals

Introduction
Cardiovascular disease [1] and psychiatric illnesses [2] are two significant health concerns that often coexist, influencing each other's outcome [3]. Meanwhile, in 2019, 970 million individuals globally suffered from psychiatric disorders, including 24 million people with schizophrenia [2]. The relationship between psychiatric disorders and cardiovascular health is bidirectional [3]. On one hand, the chronic stress associated with managing a cardiovascular condition, along with physiological changes and lifestyle adjustments, can contribute to the onset or exacerbation of psychiatric disorders [3]. On the other hand, psychiatric illnesses can adversely affect cardiovascular health through mechanisms such as chronic inflammation, dysregulation of autonomic function, and unhealthy lifestyle behaviors like smoking, poor diet, and physical inactivity [3-6]. For example, patients with schizophrenia are at 2 to 3 times greater risk of developing cardiovascular disorders. Additionally, some psychotropic medications have been linked to an increased risk of cardiovascular mortality [3, 6]. Moreover, some psychotropic medications have been associated with increased risk of cardiovascular mortality [7].

Antipsychotic drugs, while effective in treating psychiatric symptoms, can carry significant cardiovascular risks [7, 8]. These medications can exacerbate preexisting cardiovascular abnormalities and potentially lead to the emergence of new cardiac issues such as arrhythmias, cardiac arrest, and even sudden cardiac death (SCD) [9, 10]. The exact mechanisms by which antipsychotics increase cardiovascular risk remain a subject of ongoing research, though alterations in the QTc interval have been identified as a major contributing factor [9, 10].

Electrophysiology of QTc interval
Expanding on the pioneering work of Augustus Waller, who laid the groundwork for electrocardiography, the development of the modern electrocardiograph (ECG) is credited to Willem Einthoven, a Nobel laureate in 1924.

Einthoven's invention and description of the ECG in early 1900s revolutionized the field of cardiology by enabling the precise measurement of cardiac electrical activity [11, 13].

The early application of the ECG quickly led to significant discoveries in cardiac physiology, including the relationship between the QT interval and heart rate [14]. The QT interval (see Figure 1) represents the duration from the start of the Q wave to the end of the T wave on an electrocardiogram (ECG), reflecting the time taken for ventricular electrical activity [14, 17]. Specifically, the QRS complex corresponds to ventricular depolarization, while the T wave corresponds to ventricular repolarization.

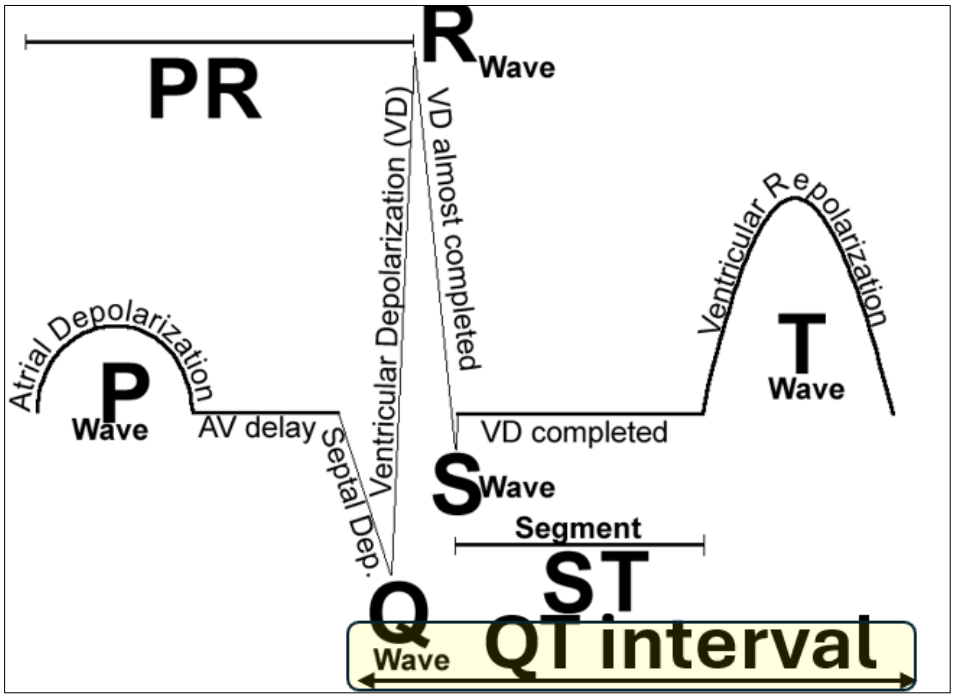

Fig 1: Schematic representation of ECG waves and QT interval

The QT interval primarily reflects the exchange of three ions—sodium (Na+), potassium (K+), and calcium (Ca++)—in ventricular cardiomyocytes. Among these, sodium and potassium play the major roles in shaping the QT interval (see Figure 2).

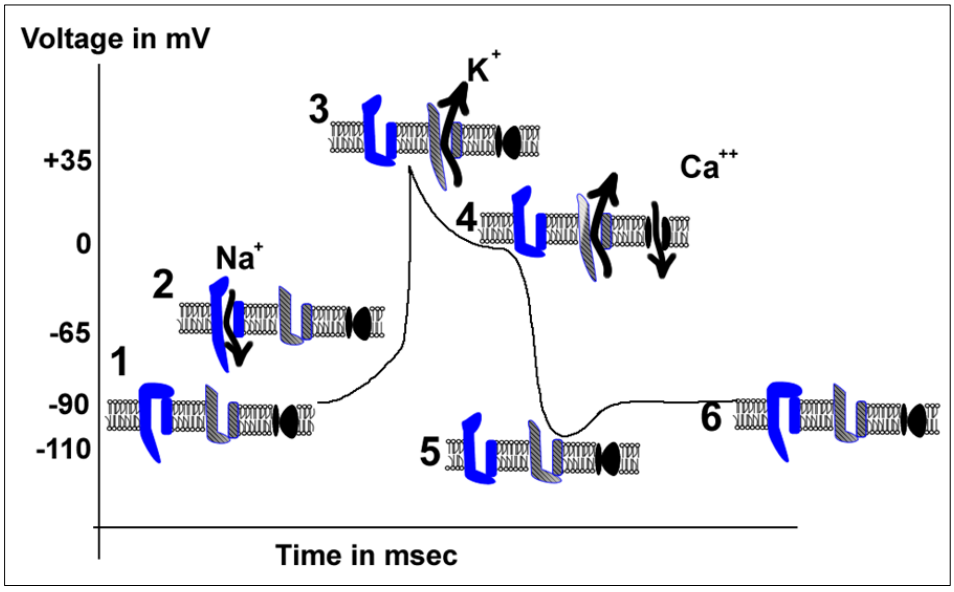

Fig 2: At a resting membrane potential of approximately -90 mV (1), voltage-gated channels for sodium (Na+), potassium (K+), and calcium (Ca++) are all in a closed state(1). As the membrane potential depolarizes to -65 mV (2), voltage-gated Na+ channels begin to open, allowing sodium ions to rush into the cell. This influx of sodium ions rapidly depolarizes the membrane potential to around +35 mV (2). Once the membrane potential reaches +35 mV (2), Na+ voltage-gated channels quickly close, halting the influx of sodium ions. Concurrently, K+ voltage-gated channels, which were already closed, begin to open, allowing potassium ions to exit the cell (3). This outward movement of potassium ions contributes to the repolarization of the membrane potential. Simultaneously, at around +35 mV (4), voltage-gated Ca++ channels start to open. The influx of calcium ions into the cell opposes the efflux of potassium ions, leading to a slower reduction in membrane potential compared to the rapid repolarization phase mediated by potassium ions [18].

Unlike the relatively consistent duration of the QRS complex, the QT interval can vary under physiological or pathological conditions, presenting challenges for precise measurement. In 1920, two researchers—Henry Cuthbert Bazett of England [19] and Danish physician Louis Sigurd Fridericia [20, 21], independently reported their observations on this relationship [22]. Bazett noted a proportional relationship between the QT interval and the square root of the RR interval (QTc = QT / √RR), while Fridericia observed a similar relationship using the cube root of the RR interval (QTc = QT / $\sqrt[3]{RR}$). These findings led to the development of corrected QT (QTc) intervals, denoted as QTcB and QTcF, respectively [23, 24].

The QT interval, representing the duration from the start of the Q wave to the end of the T wave on an ECG, is influenced by heart rate variations. Bradycardia (slow heart rate) tends to prolong the QT interval, whereas tachycardia (rapid heart rate) typically shortens it. However, accurately determining the precise onset of the QRS complex and the end of the T wave can be challenging due to variability in ECG morphology and interpretation [23, 24].

While Bazett's and Fridericia's methods (QTcB and QTcF) are widely used in clinical practice, alternative correction formulas have also been developed over time. For instance, the Framingham method adjusts the QT interval using a linear formula based on the RR interval, while the Hodges method incorporates a more complex adjustment to account for heart rate variability. Despite these advancements, QTcB and QTcF continue to be commonly utilized due to their historical significance and practical utility in clinical settings.

The typical upper thresholds for the rate-corrected QT interval (QTc) on an ECG are less than 430 milliseconds in males and less than 450 milliseconds in females. QTc intervals exceeding 450 milliseconds in males and 470 milliseconds in females indicate prolonged QT intervals[25]. Extended QT intervals are associated with a heightened susceptibility to Torsades de Pointes (TdP), an increase of 60 milliseconds in the QTc interval from baseline predisposes a patient to adverse cardiac outcomes. A QTc interval of over 500 milliseconds significantly increasing the risk of TdP [26]. When action potential duration (APD) is shorter at a fast heart rate, it is known as reverse frequency dependence. In this phenomenon, the shortening of APD at higher heart rates predisposes individuals to arrhythmias. Drugs with high frequency dependence bind to ion channels during fast heart rates, blocking Na+ channels during tachycardia. Conversely, drugs with reverse frequency dependence bind to ion channels during slow heart rates, thereby increasing the risk of arrythmias. For example, the blockade of hERG channels by chlorpromazine exhibits reverse frequency dependent [27]. An increase of 60ms of QTc from baseline predisposes a patient to adverse cardiac outcomes.

Lower transport of K+ to repolarize the myocyte membrane can result in QT prolongation. Depolarization of cardiomyocytes leads to the opening of Na+ channels, resulting in an action potential (AP). At the peak of the AP, voltage-gated K+ channels open, with the rapid delayed rectifier current (IKr) contributing to rapid repolarization and returning the membrane potential to its resting state (see Figure 2). The hERG gene (human ether-à-go-go-related gene, also known as KCNH2) encodes channels that facilitate the rapid delayed rectifier potassium current (IKr). Aberrations in IKr, such as mutations in the hERG gene, can lead to QT interval prolongation and potentially result in Torsades de Pointes (TdP) [28-29]. Selectivity for hERG channel inhibition is a critical factor in evaluating cardiotoxicity, and drugs that inhibit hERG are less likely to be marketed[29]. Approximately 60% of drugs in development may have such an effect [29]. A drug is considered high risk if it has less than 30-fold selectivity to its target [28, 30, 31]. For example, olanzapine exhibits 100 to 1,000 times more selectivity for the D2 receptor than for the hERG channel [32]. Despite these measures, 15% of drugs on the market can still prolong the QT interval and lead to TdP [29].

Antipsychotic agents are implicated in prolonging the QTc interval, although the precise mechanisms underlying this effect remain poorly understood [5, 7, 10, 26, 27]. Prolongation of the QTc interval increases the likelihood of premature ventricular contractions occurring during the vulnerable period of ventricular repolarization. This vulnerable period, located on the descending limb of the T wave (see Figure 3), is characterized by myocardial cells being in a state of relative refractoriness [18].

The serious concern arises when a premature ventricular contraction coincides with the vulnerable period, a phenomenon known as "R on T." This synchronicity can trigger a re-entry current in the myocardium, potentially leading to serious arrhythmias such as Torsades de Pointes, ventricular fibrillation, and even sudden cardiac death [18]. Since the descending limb of the T wave corresponds to the relative refractory period, a premature beat occurring during this phase (see Figure 3) can initiate a re-entry current. This re-entry current has the potential to degenerate into ventricular fibrillation [18].

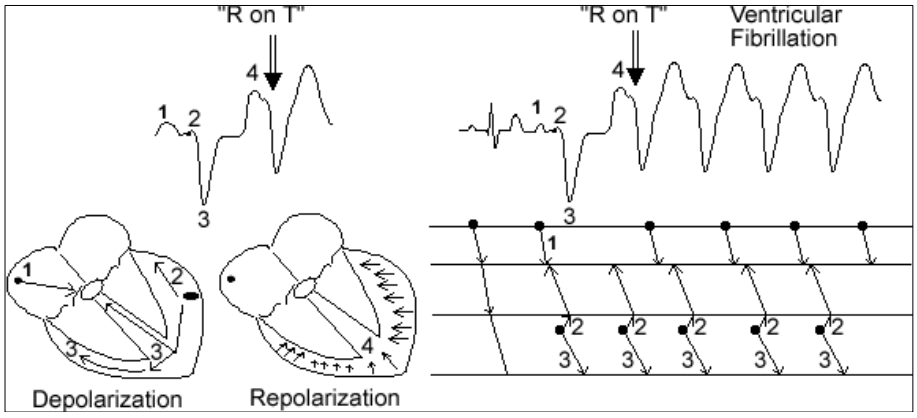

Fig 3: If an R wave reaches cardiac tissue that is not in the refractory period, it can give rise to the "R on T" phenomenon, which may subsequently lead to Torsades de Pointes (TdP)

Antipsychotics and QTc prolongation

Prolongation of QT intervals with antipsychotics is well documented in medical literature. Kongsamut *et al*. evaluated receptor binding and hERG channel affinity for a number of antipsychotic drugs [32]. The half-maximal inhibitory concentration (IC_{50}), representing the amount of a particular chemical needed to inhibit the activity of a channel by 50%, was used to assess this affinity [33]. In their study, Kongsamut *et al*. found that hERG channel currents were affected at the following IC50 values (with 95% confidence intervals) for various antipsychotics [25]:

- Sertindole: 2.7 nM (2.1-3.5 nM)
- Pimozide: 18 nM (14-22 nM)
- Risperidone: 167 nM (128-215 nM)
- Ziprasidone: 169 nM (133-212 nM)
- Thioridazine: 191 nM (162-224 nM)
- Quetiapine: 5765 nM (4688-7079 nM)
- Olanzapine: 6013 nM (5140-7030 nM)

These findings indicate that sertindole, pimozide, and thioridazine are less selective for the receptors of interest (D2 and 5-HT2A) than for hERG. This lack of selectivity is reflected in the observed changes in QTc interval for these drugs [25]:

- Thioridazine: +29.6 ms
- Ziprasidone: +15.5 ms
- Quetiapine: +4.8 ms
- Risperidone: +3 ms
- Olanzapine: +1.1 ms

Consistent with these findings, thioridazine is notably associated with a significant increase in the QTc interval compared to other antipsychotic medications. Introduced in 1959, thioridazine (Mellaril®) was linked to the first reported deaths associated with antipsychotic medications in 1963, two years before the description of Torsades de Pointes (TdP). In a study involving 24,000 patients, 49 patients died of sudden cardiac death (SCD), with 46 of them on phenothiazines and 28 on thioridazine [26]. Harring *et al*. reported that thioridazine use prolonged the QTc interval by an average of 30.1 milliseconds (ms) [34]. While haloperidol has also been positively associated with TdP, the increase in QTc (7.1 ms) with haloperidol is not as substantial as with thioridazine. In the same study by Harring *et al*., other antipsychotics were associated with QTc prolongations of:

- Ziprasidone: 15.9 ms
- Quetiapine: 7.1 ms
- Risperidone: 5.7 ms
- Olanzapine: 3.9 ms

Thioridazine's significant impact on QTc prolongation underscores its higher risk for adverse cardiac events compared to these other antipsychotics. Sertindole is associated with an average QTc prolongation of 19 milliseconds. It was never approved in the United States and was discontinued in Europe due to an increased risk of sudden cardiac death [35].

Prolongation of the QTc interval is associated with several risk factors, including the presence of other heart diseases, being older than 65 years of age, female gender, the use of multiple medications that prolong the QTc interval, and hypokalemia [36]. Lin *et al*. reported that female gender, age, and higher doses of certain medications were associated with greater QTc prolongation, with first-generation antipsychotics causing a more pronounced increase in [37].

Given these variables, it remains challenging to precisely establish the severity of QTc prolongation for each antipsychotic. However, it is generally believed that first-generation antipsychotics are associated with more significant QTc prolongation compared to newer agents. Prolongation of the QTc interval with ziprasidone is well documented, but the clinical significance of this association remains uncertain [38]. Although the incidence of sudden cardiac death with ziprasidone is not significantly different from that of placebo (0.6 sudden deaths per 100 patient-years of exposure), ziprasidone has been associated with a QTc prolongation of 20.3 milliseconds. This is compared to an increase of 11.6 milliseconds for risperidone, 6.8 milliseconds for olanzapine, 14.5 milliseconds for quetiapine, 35.6 milliseconds for thioridazine, and 4.7 milliseconds for haloperidol. Although ziprasidone causes a greater QTc prolongation compared to some other medications, this effect does not appear to be dose-dependent [39].

Clozapine, a medication known for its superior efficacy in treating schizophrenia, is associated with several cardiac adverse effects, including myocarditis and a potential for QTc [25]. Although clozapine does increase QTc in a dose-dependent manner, the clinical significance of this increase remains uncertain. Kang *et al*. found that 13.6% of patients exhibited ECG abnormalities on other antipsychotics, which increased to 31.1% after switching to clozapine. This risk was higher in older patients, though orthostatic hypotension and tachycardia did not appear to have an effect. Most of the new abnormalities were not clinically significant, and some resolved even with continued clozapine use [40]. Grande *et al*. did not find a significant difference in QTc intervals over 18 months of clozapine treatment in their sample of over 80 patients [41]. Additionally, the combination of clozapine with other antipsychotics resulted in some increase in QTc interval of undetermined clinical significance. A systematic review by Takeuchi *et al*. of 21 studies reported an ambiguous effect of antipsychotic polypharmacy on QTc prolongation, although caution against polypharmacy was advised [25].

Among second-generation antipsychotics, aripiprazole stands out for its minimal effect on the QTc interval. Torres-Yaghi *et al*. (in their review of QTc interval prolongation with therapies used to treat Parkinson's disease Psychosis) reported that aripiprazole has the smallest effect on QTc, with an average increase of only 0.4 milliseconds. Other studies suggest that aripiprazole might have a negative effect on QTc, with decreases ranging from -0.43 to -3.38 milliseconds. Some studies [42] even indicate no significant effect on QTc, with potential changes in QTc of only about 0.1%.

Conclusion

Although antipsychotics have significantly improved the quality of life for patients with a range of psychiatric disorders, these medications are associated with QTc prolongation, arrhythmias, and potential sudden cardiac death. This is a critical consideration for every psychiatrist. The ambiguity in clinical data complicates the creation of specific guidelines. However, understanding the basic mechanisms of QTc prolongation, including factors such as hERG inhibition by certain psychotropic drugs and other

risk factors that predispose patients to QTc prolongation, can aid providers in selecting the most appropriate medication for their patients.

First-generation antipsychotics generally carry a higher risk of QTc prolongation compared to second-generation antipsychotics. Although aripiprazole appears to have a better QTc profile, further studies are needed to provide conclusive guidance on prescribing these medications, particularly for patients with cardiovascular diseases (CVDs). Despite the ongoing ambiguity regarding the normal QTc range and the inconclusive effects of some second-generation antipsychotics on QTc prolongation, continued evaluation and caution are essential for ensuring patient safety.

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