Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2024): 2.2
CiteScore® (2024): 5.2
www.biomolbiomed.com | blog.bjbms.org

REVIEW

Erkan et al: SGAs – Cardiac ion channel effects

Second-generation antipsychotics – Cardiac ion channel modulation and QT interval disturbances: A review

Orhan Erkan[1], Ayse Suna Dai[2], Nihal Ozturk[2], Semir Ozdemir[2*]

[1]Department of Biophysics, Faculty of Medicine, Kafkas University, Kars, Türkiye;

[2]Department of Biophysics, Faculty of Medicine, Akdeniz University, Antalya, Türkiye.

*Correspondence to Semir Ozdemir: osemir@akdeniz.edu.tr.

DOI: https://doi.org/10.17305/bb.2025.13405

ABSTRACT

Second-generation antipsychotics (SGAs) are frequently prescribed in psychiatry due to their efficacy and improved tolerability compared to first-generation agents. However, these medications are associated with significant cardiac adverse effects, particularly QT interval prolongation and torsades de pointes (TdP). This review aims to summarize the mechanisms by which SGAs affect cardiac ion channels and how these actions contribute to QT interval disturbances and increased arrhythmia risk. A narrative literature review was conducted using PubMed, Web of Science, and Google Scholar, without year restrictions, focusing on English-language experimental and clinical studies related to clozapine, olanzapine, risperidone, quetiapine, and ziprasidone. The findings indicate that all five SGAs inhibit the rapid delayed rectifier potassium current (I_{Kr}) mediated by the human ether-a-go-go-related gene (hERG) potassium channel. Notably, the observed variability in the ratio of half-maximal inhibitory concentration to maximum free plasma concentration ($IC_{50}/C_{max,free}$) reflects its dependence on both the degree of hERG inhibition and the pharmacokinetic properties specific to each SGA. Additionally, several SGAs affect other potassium, sodium, and calcium currents, which may either mitigate or exacerbate the consequences of I_{Kr} inhibition. In conclusion, QT interval prolongation associated with SGAs is primarily driven by hERG potassium channel blockade, although the degree of this effect varies significantly among different agents. This variability highlights the necessity for electrocardiogram (ECG) monitoring and individualized cardiac risk assessments, especially for vulnerable patient populations.

Keywords: Second-generation antipsychotics, QT prolongation, torsades de pointes, hERG potassium channels, sodium channels, calcium channels, repolarization reserve, ventricular arrhythmias.

INTRODUCTION

Antipsychotic drugs are an effective group of medications widely prescribed for the treatment of psychiatric diseases such as schizophrenia and bipolar disorder [1, 2]. They are used not only in the treatment of psychotic disorders but also in various neuropsychiatric conditions such as obsessive-compulsive disorder, delirium and treatment-resistant depression [3, 4].

Antipsychotic drugs are mainly divided into two groups: typical or first-generation antipsychotics (FGAs) and atypical or second-generation antipsychotics (SGAs) [5]. Discovered in the 1950s, FGAs have high affinity for dopamine D2 receptors and significantly affect dopaminergic neurotransmission even at low doses [2, 6, 7]. Following the use of FGAs, the inhibition of dopamine release leads to a reduction of positive symptoms such as delusions and hallucinations in the mesolimbic pathway, social withdrawal and loss of motivation in the mesocortical pathway, motor dysfunctions in the nigrostriatal pathway, and an increase in prolactin levels in the tuberoinfundibular pathway [8-10]. In FGAs with high extrapyramidal side effects (EPS), distressing motor disorders such as akathisia, dystonia, dyskinesia (tardive dyskinesia), and gradually developing parkinsonism are commonly observed [4, 11]. In addition, it is known to cause adverse effects related to the endocrine system such as galactorrhea, gynecomastia and osteoporosis by increasing prolactin levels [3].

SGAs are agents that show fewer EPS compared to FGAs and are generally better tolerated [3]. The discovery that clozapine binds with low affinity to the D2 receptor paved the way for the development of SGAs [12]. These drugs have a broader mechanism of action because they block not only dopamine D2 receptors but also serotonin 5-HT2A receptors [11]. Their greater effect on serotonergic receptors and short-term binding and dissociation from the D2 receptor (kiss and run) have led to the definition of SGAs as atypical and the occurrence of lower EPS [11, 13]. Various clinical studies have shown that SGAs ensure better patient compliance and increase long-term treatment continuation rates compared to FGAs [14]. Their lower risk of EPS and relatively greater therapeutic efficacy on negative symptoms have made them preferred over FGAs in clinical practice [2]. However, SGAs can increase the incidence of metabolic disorders such as weight gain, obesity, glucose intolerance, and dyslipidemia [15-17].

The side effects that arise depending on the receptor binding profiles of antipsychotic drugs are also of great clinical importance [18]. This is because antipsychotic drugs have affinities for many receptors at varying degrees. Current studies have not yet satisfactorily demonstrated which receptors they bind to and to what extent they alleviate psychosis. A good understanding of the specific pharmacodynamic and pharmacokinetic properties of these drugs can enable accurate assessment of both their clinical efficacy and side effect profiles. The side effects observed in this group of drugs can be classified as restlessness, insomnia, sedation, dizziness, sexual dysfunction, obesity, metabolic syndrome, dyslipidemia, diabetes, and weight gain [3, 19].

Although SGAs stand out with their better tolerability and lower risk of EPS compared to FGAs, their potential effects on the cardiovascular system should not be ignored. These drugs have long been known to be associated with cardiac arrhythmias and the risk of sudden cardiac arrest. Such arrhythmias generally manifest themselves with clinical findings such as QT interval prolongation (long QT syndrome; LQTS), ventricular tachycardia, and torsade de pointes (TdP) on the electrocardiogram (ECG). QTc prolongation caused by antipsychotic drugs is a major concern because epidemiological findings and case-control studies have shown that the risk of sudden death is increased in psychiatric patients using these drugs [20-23]. Consistently, many studies have shown that these drugs can interact with ion channels regulating heart rhythm and cause various electrocardiographic changes [24-26]. Therefore, investigating the effects of SGAs on cardiac ion channels is of critical importance for the prevention of possible cardiac complications and the safe use of these drugs. This review aims to discuss current findings regarding modulation of ion channels as cellular mechanisms underlying the effects of SGAs on the electrical activity of the heart. Clozapine, olanzapine, risperidone, quetiapine and ziprasidone, which are widely used new generation antipsychotics that have been suggested to have cardiac side effects in experimental and clinical studies, were included in the study. During the preparation, a comprehensive literature search was conducted in PubMed, Web of Science and Google databases without any year limitation. All relevant publications with sound methodology published in English were used. The keywords employed during the literature search included "second-generation antipsychotics," "QT prolongation," "torsade de pointes," "cardiac side effects," "hERG channels," "cardiac

ion channels," "sodium channels," "potassium channels," "L-type and T-type calcium channels," "action potential," "electrophysiology," "patch-clamp" and "cardiac myocytes,".

Electrophysiological changes observed in second-generation antipsychotics

Cardiovascular diseases and psychiatric disorders, which are increasingly prevalent, are very important health problems that affect each other's progression [27]. Autonomic nervous system disorders frequently accompanying psychiatric problems, genetic predispositions, smoking, unhealthy diet, and chronic inflammation are factors that can adversely affect the cardiovascular system. On the other hand, stress and the physical and physiological consequences of lifestyle changes in individuals with cardiovascular disease can lead to the emergence of psychiatric symptoms or exacerbate existing disorders [28, 29]. Indeed, previous studies have shown that the risk of developing cardiovascular diseases is significantly higher in individuals diagnosed with schizophrenia than in healthy individuals [30, 31].

Although SGAs are considered safer than FGAs in terms of EPS, they likely pose serious risks to cardiac electrophysiological markers, and therefore their side effects have been extensively studied since their invention. Consistently, the use of these drugs has shown to cause remarkable changes in heart rhythm, autonomic nervous system function, and cardiac conduction. The most frequently reported cardiac effects associated with SGAs include sinus tachycardia, QT interval prolongation, TdP, disturbances in heart rate variability (HRV), myocarditis, orthostatic hypotension, cardiomyopathy, and sudden cardiac death [32-36]. Interestingly, SGAs have been reported to not only have more pronounced cardiac side effects compared with FGAs but may also cause some new adverse effects specific to this group of drugs [37].

The QT interval covers the duration from the beginning of the Q wave to the end of the T wave on the ECG and reflects the depolarization and repolarization of the ventricles. However, the QTc parameter, which is calculated with different formulas to eliminate the effect of heart rates varying between individuals on QT, provides a more definitive and reliable value [38]. To evaluate physiological processes that influence this interval, it is critical to understand the electrophysiological dynamics in the membrane that generates the cardiac action potential (AP). The major membrane

currents that can alter the QT interval include Na^+ currents responsible for the AP depolarization phase, Ca^{2+} currents effective in the plateau phase, and various K^+ currents that determine the repolarization phase. Pathological changes occurring in these currents or channels will lead to changes in the QT interval on the ECG. Antipsychotic drugs mostly prolong the QT interval by blocking the delayed-rectifier potassium currents (I_{Kr}) (also known as hERG channels, $K_v11.1$), which are responsible for the late repolarization of the AP [39, 40]. Such prolongation increases the risk of arrhythmias such as TdP, defined as polymorphic ventricular arrhythmia, and ventricular fibrillation, which can eventually result in cardiac arrest or sudden cardiac death [41, 42]. Table 1 summarizes the effects of SGAs (and selected metabolites) on ion channels, showing how they inhibit cardiac Na^+ and Ca^{2+} currents along with K^+ currents (hERG/I_{Kr}, I_{to}, I_{K1}) in heterologous systems and native myocytes.

Antipsychotic drugs differ significantly from each other in terms of chemical structures and pharmacological properties. Due to their different receptor binding profiles, their effects on ion channels, QT interval, and AP will also differ. Therefore, specific studies of each drug will allow for a better understanding of their cardiac side effects. In this context, the effects of five commonly prescribed antipsychotic drugs on ion channels were reviewed based on published research findings, and the potential risks of each on cardiac function were discussed in detail.

Pharmacological and electrophysiological characteristics of SGA

Second-generation antipsychotics (SGAs) share common therapeutic mechanisms but differ markedly in their receptor binding affinities, metabolic characteristics, and effects on cardiac ion channels. These pharmacological and electrophysiological differences underlie both their clinical efficacy and their distinct cardiac risk profiles, particularly regarding QT prolongation. Below, we summarize the key pharmacological and ion channel-related features of five widely used SGAs.

CLOZAPINE

Clozapine, first discovered in 1959, is the first atypical antipsychotic with a chemical structure similar to tricyclic antidepressants (Figure 1) [43]. In a study conducted in

Finland after its widespread use, surprisingly agranulocytosis developed in 16 patients and 8 of them died after severe infection [44, 45]. Although this report significantly reduced the use of clozapine in Europe, it continued to be used cautiously in patients who did not respond to other drugs. Moreover, it was not completely dismissed because of its ability to improve both positive and negative symptoms of psychosis and its lower risk of EPS compared with chlorpromazine, which was widely used at the time. After being reintroduced in 1989, the risk of agranulocytosis decreased to 0.38% with careful use in treatment-resistant schizophrenia [46]. However, in further various side effects such as weight gain, diabetes, and myocarditis were also reported [16].

Clozapine has a complex receptor-binding profile, and this receptor-ligand interaction contributes to both its clinical efficacy and side effect profile. Unlike the D2 receptor blockade observed in typical antipsychotics, clozapine exerts its effects through serotonergic, noradrenergic, and glutamatergic receptors [5, 47]. The wide spectrum of pharmacological action of clozapine on different receptor subtypes is also exhibited in its cardiac side effect profile. In particular, by affecting voltage-dependent ion channels in cardiomyocytes, it prolongs the QT interval and predisposes to potentially fatal ventricular arrhythmias. Real-world data indicate that QTc prolongation occurs more frequently in clozapine-treated patients than previously assumed. In a 2024 Australian clinical study, QTc prolongation was identified in 36.5% of individuals receiving clozapine, and this finding was significantly associated with higher heart rate and elevated clozapine serum levels [48].

Effects of clozapine on potassium currents

Although clozapine is a powerful antipsychotic used in the treatment of distinct schizophrenia patients, its cardiac side effects should be taken into consideration due to hERG channel inhibition and effects on K_v channels [49]. It has been shown to cause QT prolongation and increase the risk of TdP due to significant suppression of I_{Kr} current by inhibiting hERG channels [50].

The effects of clozapine on the hERG channel activity have been carefully examined in different experimental models. Studies in Xenopus oocytes have shown that clozapine inhibits hERG channels in a voltage-dependent manner, and the measured

IC_{50} values varied depending on the applied voltage; at -40 mV the IC_{50} value was 39.9 μM, decreasing to 28.3 μM at 0 mV and 22.9 μM at +40 mV. On the other hand, in electrophysiological measurements performed on hERG channels expressed in HEK-293 cells, the IC_{50} value of clozapine was found to be 2.5 μM [49]. Furthermore, an increased ability to inhibit hERG channels was observed at higher membrane potentials, suggesting that clozapine binds more strongly to channels that are open or inactivated [50]. This value indicates that clozapine can inhibit hERG channel even at therapeutic plasma concentrations, which is thought to significantly increase the risk of QT prolongation [51]. In studies conducted on guinea pig ventricular myocytes, a 24.7% decrease in I_{Kr} current was measured with 1 μM clozapine, while the decrease reached 79.6% with 5 μM [49]. Moreover, hERG currents were suppressed in both voltage- and time-dependent manner in the presence of clozapine. The IC_{50} values obtained in the same study implicate that even therapeutic doses can achieve a significant suppressive effect on hERG channels and I_{Kr}, suggesting that clozapine is likely to increase the risk of arrhythmia [49].

Understanding the binding and dissociation kinetics of drugs is critically important for more accurately assessing the risk of causing LQTS. In a study investigating drug interaction kinetics with the $K_v11.1$ potassium channel in Chinese hamster ovary (CHO) cells, clozapine was shown to inhibit $K_v11.1$ channels in a dose-dependent manner (IC_{50} = 2.8 μM) and further Markov model was developed to explain the binding and unbinding kinetics of clozapine [50]. The model included drug-bound open (O-D) and drug-bound inactivated (I-D) states in addition to open (O) and inactivated (I) states. In the model, the dissociation constant (K_d) for binding to the open state was determined as 1.46 μM, and for the inactivated state as 1.63 μM. These findings correctly predicted the experimental IC_{50} values and explained the kinetic structure of clozapine binding to $K_v11.1$ channels [50]. In fact, the study emphasizes that the kinetic effects of conventional IC_{50} measurements can be ignored, as drugs with slow binding/dissociation kinetics may have greater effects at low heart rates [50].

In a study conducted on rabbit coronary artery smooth muscle cells, clozapine was found to inhibit K_v channels in a concentration-dependent manner, with an IC_{50} value calculated as 7.84 μM [52]. Analyses on cells revealed that clozapine strongly

inhibited the $K_v1.5$ subtype, while partially suppressing $K_v2.1$ and K_v7 channels [52]. Experiments conducted to observe whether the inhibition was channel-specific showed that clozapine exerted a specific effect on the $K_v1.5$ channel subtype [53]. Following inhibition of $K_v2.1$ and K_v7 channels, the effect of clozapine decreased from 45% to 21% and from 45% to 19%, respectively, indicating that these channels also play a significant role in the effect of clozapine [52].

In summary, clozapine inhibits Kv channels in both cardiac myocytes and vascular smooth muscle cells, leading to significant changes in cardiac and vascular physiology. These findings indicate that clozapine is an SGA drug that should be carefully monitored, especially in patients with cardiovascular pathologies, as it exhibits significant ionic effects even at therapeutic doses [49-52]. However, it is not yet known whether clozapine has an effect on transient-outward potassium currents (I_{to}), another K^+ current that may affect QT duration.

Effects of clozapine on calcium currents

The effects of clozapine on cardiac Ca^{2+} channels have also been extensively studied. In particular, its inhibitory actions on T-type Ca^{2+} channels $Ca_v3.1$ (α1G) and L-type $Ca_v1.2$ are noteworthy [51, 54]. In a study by Choi and Rhim, clozapine was shown to inhibit $Ca_v3.1$ current in HEK-293 cells in a dose-dependent manner (IC_{50} = 23.7 μM) [54]. In addition, the rate of inhibition of $Ca_v3.1$ current by clozapine varied in a voltage-dependent manner: at -100 mV, 10 μM clozapine inhibited $Ca_v3.1$ current by 23% (IC_{50} = 23.7 μM), while at -75 mV, a more physiologically relevant voltage, the same concentration inhibited 52% (IC_{50} = 8.8 μM) [54]. This suggests that inhibitory effect of clozapine on Ca^{2+} current is stronger at more physiological voltage levels. Additionally, channel inhibition has been reported to be use-dependent, with channel blockade occurring more rapidly with increasing stimulation frequency. Furthermore, clozapine did not alter the activation kinetics of the channel but significantly slowed its deactivation, thereby increasing Ca^{2+} influx [54]. Clozapine also dramatically shifted the steady-state inactivation curve of $Ca_v3.1$ channels to more negative potentials and slowed the inactivation kinetics. Since $Ca_v3.1$ channels play an important role in regulating cardiac pacemaker activity, this inhibitory effects has been associated with ventricular tachycardia, one of the cardiac side effects of clozapine [54]. On the other hand, in a study conducted by Le Marois et al. in CHO

cells, clozapine was shown to inhibit $Ca_v1.2$ L-type Ca^{2+} currents (I_{CaL}), with an IC_{50} value determined as 9.2 μM [51]. Of note, therapeutic plasma concentrations of clozapine have been suggested to be in the range of 1-4 μM [54-59], which is relatively low compared to the IC_{50} values, but local effects may be more pronounced due to accumulation in cardiac tissue. Consistently, 10–24 times higher clozapine levels has been observed compared to plasma concentrations in heart, liver and brain tissues, which implicates an effective concentration range of 10–100 μM in clinical conditions [54, 60]. Therefore, these findings suggest that clozapine can cause significant inhibition and kinetic modulation of $Ca_v3.1$ channels even at clinically therapeutic concentrations and may result in cardiac side effects.

Effects of clozapine on sodium currents

When the effect of clozapine on cardiac ion channels was examined in terms of voltage-gated sodium channel ($Na_v1.5$) inhibition, it was shown that it inhibited both peak and late current components of this channel [51]. In the study by Le Marois et al., a dose response curve was plotted by applying clozapine at concentrations ranging from 0.12 μM to 100 μM, and the IC_{50} values were calculated as 8.7 μM for late sodium current (I_{NaL}) and 10 μM for peak current [51]. Although it is thought that clozapine will reduce the depolarization rate of the AP due to inhibition of Na^+ channels and thus lead to a slowing of conduction in myocardium, it does not seem likely to cause a significant blockade in the treatment dose range when the therapeutic plasma concentration is considered to be approximately 1–2 μM [51]. On the other hand, clozapine inhibits not only the $Na_v1.5$ channel but also repolarizing K^+ currents, including $K_v11.1$, whose blockade is one of the most important factors that can lead to QT prolongation [50]. Furthermore, while clozapine is expected to prolong action potential duration (APD) and QT interval due to blockade of repolarizing K^+ currents, concurrent inhibition of depolarizing $Na_v1.5$ and $Ca_v1.2$ may counteract this effect [51].

A clinical factor that should be emphasized is that clozapine has been reported to accumulate in cardiac tissue [61], suggesting that, although no significant Na^+ channel inhibition has been observed experimentally at therapeutic plasma concentrations, it may cause cardiac conduction slowing at high doses or with prolonged use. This may explain the association of clozapine with bradycardia or conduction defects [51]. On

the other hand, clinical data suggest that while clozapine may cause QT prolongation, it does not significantly increase the incidence of TdP [62]. It has been suggested that due to clozapine's similar inhibition of depolarizing and repolarizing currents, the prolongation of AP and QT interval will be minimal, resulting in a reduced risk of TdP. Consequently, although clozapine inhibits multiple cardiac ion currents, the balance among these currents suggests that its TdP risk may be lower compared with other SGAs [51]. Nevertheless, considering its potential for tissue accumulation, regular monitoring of patients receiving clozapine is still recommended.

OLANZAPINE

Olanzapine is a clinically effective SGA that exerts antagonistic effects at dopamine and serotonin receptors [63], and its chemical structure, along with its major metabolites, is shown in Figure 2. Pharmacologically and structurally, it is similar to clozapine. Unlike FGAs, it binds loosely to dopamine receptors and thus allows normal dopamine neurotransmission to be maintained. Olanzapine received approval for use in the treatment of schizophrenia in 1996. It is also widely used, with FDA approval, in the treatment of bipolar disorder and depression [11, 64]. In addition, off-label uses include the treatment of acute agitation, delirium, anorexia nervosa, and chemotherapy-induced nausea and vomiting (CINV) [65-68]. In vitro studies show that olanzapine has effects on serotonergic (5-HT2A/C), dopaminergic (D1–4), histamine (H1), adrenergic (α1), and muscarinic (M1–5) receptors [69, 70].

Among the most common adverse effects associated with olanzapine use are increased appetite, marked weight gain, elevations in blood glucose, and the development of diabetes [15]. In addition, similar to other atypical antipsychotics, it can lead to unpredictable effects on the cardiovascular system [71]. Its cardiovascular effects are generally associated with increased sympathetic activity, vagal inhibition, and QTc prolongation [72].

In one study, olanzapine use led to an average increase of 10 bpm in heart rate as sympathetic activity became predominant [73]. Olanzapine generally causes a mild prolongation of QTc duration. In a clinical study, the mean QTc prolongation in patients using olanzapine was found to be around 10–15 ms [74]. In another study, QTc duration did not prolong significantly with olanzapine and generally remained

below 500 ms [75]. The effects of olanzapine on cardiac repolarization have also been examined in experimental animal models. A study in anesthetized dogs showed that olanzapine did not cause QT prolongation, but at high doses it increased heart rate and caused vagal inhibition [76]. In recent inpatient data, olanzapine was associated with QTc prolongation in 15.4% of patients [77]. Although the relative risk increase did not reach statistical significance, these findings indicate that olanzapine can remarkably affect QTc in a subset of patients.

Effects of olanzapine on potassium currents

In a study investigating the effect of olanzapine on hERG channels in HEK-293 cells, it was shown to inhibit hERG tail currents in a concentration-dependent manner (−50 mV) [78], and the IC_{50} for these currents was calculated as 8.0 μM, a value well above therapeutic concentrations. Besides, it exhibited concentration-dependent inhibition (1 μM olanzapine 15.9%; 3 μM 31.7%; 10 μM 56.4%; 30 μM 78%; 100 μM 91.2%) with increased channel activation and shifted the steady-state activation and inactivation curves to more hyperpolarized potentials. In addition to concentration dependence, hERG channel inhibition by olanzapine also showed a voltage-dependent effect (−30 mV 31.4%; −10 mV 49.1%). However, at more depolarized potentials (between 0 and +50 mV) where channels are fully activated, olanzapine inhibition occurred independently of voltage. These findings indicate that hERG channel inhibition by olanzapine is voltage-, state-, and concentration-dependent [78]. Nevertheless, it has been reported that the IC_{50} value obtained for olanzapine, with plasma concentrations ranging from 3.8–665.7 nM, is approximately 30 times higher than therapeutic levels [79]. However, olanzapine has been shown to accumulate in tissues up to 4–46 times the plasma level [78], and that the heart/plasma ratio can reach 2.7 in guinea pigs [80], suggesting that hERG inhibition may become clinically relevant with long-term use or at high doses [78].

Another study in HEK-293 cells showed that olanzapine and its metabolites (2-hydroxymethyl, N-desmethyl) blocked hERG current amplitude in a concentration-dependent manner, but to a lesser extent than thioridazine and sertindole [25]. The IC_{50} values for olanzapine, 2-hydroxymethyl, and N-desmethyl were calculated as 0.23 μM, 11.6 μM, and 14.2 μM, respectively [81]. A significant correlation was also observed between hERG blockade and QTc prolongation. It was shown that, at

clinical plasma concentrations, olanzapine causes approximately 14% hERG blockade and leads to a 1.7 ms QT prolongation, while 2-hydroxymethyl, and N-desmethyl have smaller effects on the QT interval [25, 82]. In another study conducted by Mow et al. in CHO cells, olanzapine showed dose-dependent I_{Kr} blockade on $K_v11.1$, with an IC50 value of 27 μM, which was lower than other atypical antipsychotics (sertindole > haloperidol > risperidone > olanzapine) [83]. These results suggest that olanzapine is unlikely to trigger an arrhythmia due to hERG inhibition, but may have proarrhythmic potential at very high doses. In experiments conducted on human atrial cardiomyocytes to observe its effects on K^+ channels, the IC_{50} value was found to be >5 μM for Ito, whereas it was >10 μM for sustained potassium current (I_{sus}) and inwardly rectifying potassium current (I_{K1}). Based on these findings, it was stated that olanzapine does not cause clinically significant inhibition, and therefore, the likelihood of a cardiac risk from blockade of these channels is low [25]. Consequently, it is likely to assume that the observed QT prolongation due to olanzapine is almost entirely related to the hERG channel.

Lehmann and colleagues argued that estimating TdP risk from QTc is not very reliable. Instead, the ratio of the hERG channel's half-maximal inhibitory concentration (hERG IC_{50}) to the peak serum concentration of unbound drug (C_{max}) is widely used in preclinical drug development to screen for chemicals likely to cause TdP. In their meta-analysis using the hERG IC_{50}:C_{max} ratio, they found that this value for olanzapine was 1345, well above the threshold of 80, which represents a negligible risk for TdP, and thus suggesting that olanzapine exhibit no risk for TdP [84].

Overall, although olanzapine is an SGA that may not have a significant effect on the QT interval and has a low risk of causing TdP, it should still be used with caution at high doses or in patients with cardiac risk factors [25, 75, 76, 78, 83-86].

Effects of olanzapine on sodium currents

Studies have shown that olanzapine has minimal effects on Na^+ channels. In myocytes obtained from human right atrial tissues, olanzapine's capacity to block $Na_v1.5$ channels was found to be very low, with an IC_{50} value greater than 10 μM [25]. These findings indicate that olanzapine does not inhibit Na^+ channels at clinically

remarkable levels and therefore carries a low risk of Na^+-current-related cardiac adverse effects. However, due to the limited number of studies on these channels, the current findings are insufficient to provide a definitive assessment of the cardiac risks. Therefore, comprehensive studies using different experimental models are needed. Finally, due to the lack of experimental evidence demonstrating the effects of olanzapine on Ca^{2+} channels, which play a central role in both electrical and contractile activity of the heart, this issue has not been discussed in this review; therefore, studies targeting these shortcomings are of critical importance.

RISPERIDONE

Risperidone is a benzisoxazole derivative SGA drug approved by the FDA in 1993 (Figure 3). It strongly blocks dopamine D2 and serotonin 5-HT2 receptors [81, 87, 88]. It is used in the treatment of various psychotic disorders, primarily schizophrenia and acute bipolar disorder [89]. In addition, it is suggested to cause a significant reduction in the severity and incidence of EPS such as dystonia, akathisia, Parkinsonism, and tardive dyskinesia [90, 91].

Among the most common dose-dependent adverse effects are weight gain, hyperprolactinemia, sedation, dyslipidemia, hyperglycemia, and risk of diabetes [15, 17]. Cardiovascular adverse effects may include TdP as a result of QT prolongation, orthostatic hypotension, and tachycardia [92-94]. There is extensive research on risperidone-related QT prolongation, showing that in patients it prolongs QTc duration on average by 20–30 ms [95], and it has been suggested that the risk of QT prolongation becomes pronounced especially at high doses. In fact, it has been reported that risperidone, which is considered to be directly related to QT prolongation and the risk of developing TdP [96], significantly prolongs the QTc period and leads to the development of TdP following its use in an elderly patient [97]. Nevertheless, in a 2025 cohort study, QTc prolongation occurred in 8.45% of risperidone users with the Fridericia formula and 14.08% with Bazett, although no cases exceeded 500 ms and no serious arrhythmias were observed [98].

To better understand the changes occurring in the cardiovascular system and to elucidate the electrophysiological mechanisms associated with QTc prolongation, it is

necessary to focus specifically on the cardiac ionic currents that play a role in these physiological processes.

Effects of risperidone on potassium currents

The effects of risperidone on cardiac electrophysiology have been examined in detail in different cellular and animal models. Due to its actions on cardiac ion channels, risperidone can lead to marked changes in the repolarization process. In particular, it has been shown to cause QT prolongation through $K_v11.1$ channel inhibition [99] and to produce a pronounced delay in repolarization due to strong inhibition of I_{Kr} [26, 100]. In studies on HEK-293 cells investigating hERG channel inhibition by risperidone, the IC_{50} value was determined as 0.12 µM [99]. This value indicates that risperidone can produce a marked hERG inhibition even at therapeutic plasma concentrations. In experiments on human atrial myocytes, 5 µM risperidone reduced I_{Kr} current by 60% and significantly prolonged APD [26].

In a study conducted in guinea pig papillary muscles, risperidone was shown to prolong the APD in a concentration-dependent manner. After application of E-4031 (a selective I_{Kr} blocker) and chromanol 293B (a selective I_{Ks} blocker), a more pronounced prolongation of AP was observed. The fact that the impact on APD observed with K^+ blockers was greater than that with risperidone alone suggests that this effect is achieved by concomitant suppression of Ca^{2+} currents that balance the repolarization of AP [24]. Accordingly, in rabbit ventricular myocytes, risperidone prolonged APD in a concentration- and frequency-dependent manner, and in recordings from Purkinje fibers, early afterdepolarization (EAD) waves were observed in 6 out of 7 fibers [101]. In addition to its strong inhibitory effect on I_{Kr}, it has been shown to modulate G-protein-activated inwardly rectifying K^+ (GIRK) channels [102]. Risperidone had no marked effect on I_{K1} current, but inhibited GIRK1/2 and GIRK1/4 channel currents expressed in Xenopus oocytes by 35% [102]. In meta-analyses evaluating its contribution to TdP risk through hERG inhibition, the hERG IC_{50}:C_{max} ratio was calculated as 34 [84], and it has therefore been argued that it should be included among high-risk drugs for TdP. Clinical studies show that QT prolongation associated with risperidone use is pronounced and that some clinical cases associated with TdP have been reported [103-105].

In an experimental study on the electrophysiological effects of risperidone in CHO cells, it was shown that, like other antipsychotic drugs, it can inhibit I_{Kr} in a dose-dependent manner via the $K_v11.1$ channel and IC_{50} value was measured as 1.6 μM [83]. On the other hand, in HEK-293 cells, Fossa et al. demonstrated that risperidone inhibited the hERG current by 11% at a therapeutic concentration of 8 nM, with an IC_{20} value of 11 nM, a relatively low value. The study aimed to demonstrate that the electrical alternans parameter (beat-to-beat changes in APD), measured in anesthetized guinea pig hearts, may be particularly useful in distinguishing which drugs have a higher risk of arrhythmia. The magnitude of alternans reflects the extent to which drugs affect the hERG channel and the potential for this effect to trigger arrhythmias. At BCL-200 (basic cycle length = 200 ms), risperidone caused a very small increase in alternans (less than 2 ms). However, at BCL-140 (a faster heart rate cycle), alternans decreased significantly by 16 ms [100]. Consistent with these, although risperidone markedly inhibited hERG current in HEK-293 cells at high doses, no increase in alternans was observed; indeed, at high doses (74 times the clinical dose) alternans decreased. This suggests that risperidone may display an antiarrhythmic tendency and that other protective mechanisms (e.g., autonomic nervous system modulation or intracellular Ca^{2+} dynamics) may be at play [100]. In ventricular cells isolated from New Zealand rabbits, the potential of risperidone to cause long QT syndrome was assessed by the degree of I_{Kr} inhibition, and 1 μM risperidone reduced I_{Kr} tail current by 28%, which was identified as one of the main mechanisms responsible for APD prolongation. It was also determined that risperidone had no effect on I_{K1} current [106]. In the study conducted by Magyar et al., on dog ventricular myocytes and guinea pig papillary muscles, a concentration-dependent decrease in I_{Kr} currents (IC_{50}=0.92 μM) was observed, while only a 9.6% decrease in I_{Ks} currents was shown at a high risperidone concentration of 10 μM [107]. They concluded that the prolongation of AP observed in both dog ventricular myocytes and guinea pig papillary muscle was related to the reductions in these currents [107]. On the other hand, risperidone inhibited the hERG channel by 17% in HEK-293 cells and the IC_{50} value was measured as 0.148 μM [25]. In addition, the IC_{50} value of risperidone for I_{to} current was >5 μM, and no clinically meaningful inhibition was detected. Similarly, the inhibition potentials on I_{sus} and I_{K1} were low, with IC_{50} values >10 μM. Therefore, the cardiac risk associated with inhibition of I_{to}, I_{sus}, and I_{K1} channels by risperidone was suggested to be low [25].

In conclusion, since risperidone does not cause a significant reduction in I_{to}, I_{sus}, or I_{K1} currents at clinical concentrations, there is no significant cardiac risk associated with inhibition of these channels. However, it should be noted that risperidone is an antipsychotic that potently inhibits the hERG channel and suppresses the I_{Kr} current, thereby prolonging the QT interval and increasing the risk of TdP. Therefore, due to clear evidence demonstrating a significant reduction in I_{Kr} current even at therapeutic doses, risperidone should be used with caution, particularly in individuals with cardiovascular disease [24, 83, 84, 99-102, 104, 106].

Effects of risperidone on calcium currents

The effects of risperidone on Ca^{2+} currents, in addition to K^+ currents, have been extensively examined [24, 100]. Although it has been shown to inhibit L-type Ca^{2+} channels in HEK-293 cells, it is unlikely to have a significant effect on these channels at therapeutic plasma concentrations due to its high IC_{50} value of 116 µM [100]. In a study on guinea pig papillary muscle, the effects of risperidone on APD were examined and shown to cause a concentration-dependent prolongation. Investigating the ionic currents responsible for this phenomenon, Christ et al. observed a significant prolongation of AP with the application of I_{Kr} and I_{Ks} blockers (chromanol 239B and E-4031) while the prolongation of AP following risperidone administration was more limited compared to that produced by these blockers. Accordingly, they also demonstrated that risperidone decreases L-type Ca^{2+} currents in a concentration-dependent manner, and this effect may play a compensatory role in the prolongation of APD. These findings suggest that the effect of risperidone on AP cannot be explained solely by inhibition of K^+ channels but is modulated by compensatory ionic mechanisms such as L-type Ca^{2+} channel blockade. Therefore, risperidone-induced I_{CaL} inhibition was considered the most likely explanation for its limited effect on APD [24].

Effects of risperidone on sodium currents

Although its impacts on cardiac electrophysiology have been primarily associated with hERG channel inhibition, the effects of risperidone on Na^+ channels have also been investigated, and its affinity for the $Na_v1.5$ channel has been found to be low [25]. In this study, the IC_{50} value of risperidone on Na^+ channel was shown to be

above 10 μM in isolated human atrial cells [25]. These findings indicate that it is unlikely for risperidone to produce a clinically relevant Na^+ channel inhibition. From a clinical perspective, risperidone has negligible effects on Na^+ channels and is therefore not expected to significantly interfere with AP formation or conduction [25].

QUETIAPINE

Quetiapine, a dibenzodiazepine-derived SGA, was developed in 1985 and approved by the FDA in 1997 for the treatment of schizophrenia. It is also widely used in the treatment of manic episodes in bipolar individuals and in bipolar depression, although it has relatively higher toxicity and mortality rates compared with other SGAs [108-111]. In many countries, it is used off-label in combination with antidepressants in the treatment of major depressive disorder [112]. Quetiapine is also prescribed off-label for mental disorders such as anxiety disorder, delirium, psychotic disorders associated with dementia, and obsessive-compulsive disorders [113]. It is widely preferred worldwide because it is FDA approved and can be used not only in the treatment of schizophrenia and depression but also in the treatment of various psychiatric disorders.

Quetiapine is a broad-spectrum SGA that can bind to numerous targets [114]. Compared with dopamine D1 and D2 receptors, it shows a higher binding affinity especially for 5-HT2A receptors in the serotonergic system [115, 116]. In addition, while it has a strong tendency to bind to histamine and α-adrenergic receptors, its affinity for muscarinic receptors is lower [117, 118]. Quetiapine exhibits various pharmacological effects at different dose levels and its interaction with multiple receptors determines the side effect profile of the drug. Norquetiapine is the active metabolite of quetiapine and, despite having similar chemical structures, they can exert different pharmacological effects (Figure 4) [119, 120]. Of particular note are its inhibition of the norepinephrine transporter (NET) and its partial antagonist effects on 5-HT2C, 5-HT7, α2, and 5-HT1A receptors [121, 122].

Persistent somnolence, orthostatic hypotension, and dizziness are among the most common adverse effects of quetiapine [123, 124]. In particular, it has been shown to cause weight gain and lipid metabolism disturbances, and to increase cardiovascular risk factors such as sinus tachycardia, myocarditis, cardiomyopathy, and QTc prolongation [125]. Real-world data from 2024 show that quetiapine is associated

with a modest mean QTc increase of ~18 ms, while severe QT prolongation (QTc >500 ms or ΔQTc >60 ms) occurred in 13% of users. These patients also demonstrated significantly higher rates of ventricular arrhythmias and sudden cardiac death, indicating that quetiapine-related QT risk becomes clinically relevant in vulnerable individuals [126].

Effects of quetiapine on potassium currents

Although quetiapine is considered a less potent hERG inhibitor compared to other SGAs, some studies have shown that it has significant effects on the cardiac repolarization [127]. A study by Erkan et al. showed that 10 μM quetiapine decreased the I_{to} current density by 17%, while 100 μM quetiapine produced a 23% reduction. Furthermore, the I_{sus} current density was significantly reduced at both low and high concentrations [127]. Although quetiapine's potential to prolong the QT interval, similar to other atypical antipsychotics, has been largely attributed to inhibition of the hERG channel, these findings suggest that its effects on potassium currents such as I_{to} and I_{sus} may also contribute to prolongation of QT [127]. However, further experimental and clinical studies are needed to confirm quetiapine's effects on the human heart.

In smooth muscle cells obtained from the coronary arteries of male New Zealand rabbits, quetiapine was also shown to inhibit K_v channels in a concentration-dependent manner (48% inhibition at +60 mV, IC_{50} = 47.98 μM). Although it did not alter the steady-state activation curve, it caused a negative shift in the steady-state inactivation curve. To test which subtypes of channel contribute to the total K_v current and which of these subtypes may underlie the effect of quetiapine, selective inhibitors of K_v1.5 (DPO-1), K_v2.1 (guangxitoxin), and K_v7 (linopirdine) were applied. After pretreatment with DPO-1 and linopirdine, quetiapine shows similar inhibition, whereas in the presence of guangxitoxin this additional effect decreased markedly, suggesting that K_v1.5/K_v7 are not the primary targets (44% and 43% in the presence of DPO-1 and linopirdine, respectively), while K_v2.1 plays a partial role (34% in the presence of guangxitoxin) [128].

In another study in which hERG potassium currents were examined, both quetiapine and norquetiapine were shown to inhibit these currents in a concentration-dependent

manner (IC_{50} = 8.3 and 10.8 µM, respectively). At high potentials where the channel is fully open, the effect of norquetiapine was voltage-independent, and the steady-state inactivation curve of hERG currents shifted to more hyperpolarized potentials in the presence of norquetiapine. As a result, it was suggested that quetiapine and norquetiapine have equal potency in inhibiting hERG tail currents [129].

Effects of quetiapine on calcium currents

Studies focusing on the effects of quetiapine on Ca^{2+} channels in the cardiovascular system are very rare, with only one study available [127]. This study, conducted in Wistar rat ventricular myocytes, demonstrated that quetiapine achieved significant inhibition of I_{CaL} by 12% at 10 µM and 21% at 100 µM concentration [127]. Moreover, while there was no significant change in inactivation kinetics at low concentrations, the inactivation time was dramatically prolonged at higher concentrations (τ value increased from 95 ms to 189 ms). Consistent with these findings, quetiapine was found to directly affect the contractile activity of ventricular myocytes [127]. Slowed inactivation of channel especially at high concentrations may also contribute to this effect. These findings support the thesis that quetiapine directly affects L-type Ca^{2+} channels, thereby reducing contractility of ventricular myocytes. However, further experimental and clinical studies are needed to elicit the underlying mechanism and to confirm quetiapine's effects on the human heart.

Effects of quetiapine on sodium currents

When quetiapine's effect on cardiac Na^+ channels was examined, its active metabolite, norquetiapine, was shown to effectively inhibit $Na_v1.5$ channels [130]. In this study, Kim et al. used HEK-293 cells expressing the $Na_v1.5$ channel, and comprehensively evaluated the effects of both quetiapine and norquetiapine on Na^+ channels under different experimental conditions. The effect of quetiapine on $Na_v1.5$ was determined to be voltage-dependent, with an IC_{50} value of 504.8 µM at a holding potential of -120 mV and 29.6 µM at -90 mV [130]. These findings suggest that quetiapine is unlikely to cause clinically significant Na^+ channel blockade. Conversely, IC_{50} values for norquetiapine were found to be much lower, measured as 36.8 µM at -120 mV and 5.9 µM at -90 mV. Besides, norquetiapine has been shown to block the $Na_v1.5$ channel with higher affinity, particularly in the inactivated state [130]. This suggests a

mechanism similar to that of antiarrhythmic drugs. Its use-dependent blockade (increasing with stimulation frequency) suggests that it may cause conduction defects, particularly in cardiac cells stimulated at higher frequencies. Active metabolites of antipsychotics may exhibit similar or different pharmacodynamic/pharmacokinetic properties compared to the parent compound; they may be responsible for all or part of the therapeutic effect, and may even reverse or neutralize the specific activity. This is primarily due to the stronger binding of norquetiapine to the inactivated state of $Na_v1.5$ than quetiapine, which slows recovery from inactivation. Norquetiapine shifts the channel's steady-state inactivation to a more negative potential, facilitating the transition to the inactivated state and increasing the effectiveness of the blockade. Furthermore, norquetiapine's lower $1/K_i$ value (affinity for binding to the inactivated state) suggests that the drug may remain in the channel longer (dissociate slowly), thus strengthening the blocking effect [130].

ZIPRASIDONE

Ziprasidone is a second-generation antipsychotic approved by the FDA in 2001 and structurally classified as a benzisothiazolylpiperazine derivative (Figure 5). Like other atypical antipsychotics, ziprasidone strongly blocks dopamine D2 and serotonin 5-HT2 receptors. However, it has eight times higher affinity for the 5-HT2A receptor than for the D2 receptor [131]. This increases the antipsychotic effect while reducing the risk of EPS. In addition, its 5-HT1A agonist effect improves negative symptoms by increasing dopamine in the frontal cortex and reduces EPS caused by D2 antagonism [132]. Ziprasidone causes a sedative effect by binding to histamine-1 receptors with moderate affinity and orthostatic hypotension by binding to alpha-1-adrenergic receptors [131].

Ziprasidone was approved by the FDA for the treatment of acute manic or mixed episodes associated with schizophrenia and bipolar disorder [133]. It is considered safe because it does not produce clinically significant metabolic side effects and has minimal or no effect on prolactin levels and anticholinergic side effects [134]. Publications regarding its cardiovascular side effects have conflicting results. A study by Timour et al. suggested that it is a drug with a high risk of QTc prolongation and TdP development. Ziprasidone has been reported to prolong the QTc interval by an average of 20-30 ms in patients and that its effect is dose-dependent [95]. Indeed,

recent clinical data have confirmed that ziprasidone exerts the highest QTc prolongation risk among commonly used second-generation antipsychotics, supporting preclinical findings that strong hERG channel blockade underlies its proarrhythmic potential [135, 136]. Conversely, some studies have reported that it does not cause TdP even at high doses exceeding 160 mg/day, and no arrhythmias have been observed even in cases of intentional overdose [137, 138]. However, antipsychotic use, including ziprasidone, has been associated with increased mortality in dementia-related psychosis, leading the FDA to issue a "Black Box" warning for this population. A warning was subsequently added to the product label stating that the drug should not be given to patients with serious cardiovascular disease, electrolyte imbalances, or those taking other medications that may prolong the QT interval [139]. To resolve these uncertainties, the most logical and scientific approach is to examine ionic currents, which can provide a more detailed understanding of the mechanisms underlying the QT interval alterations.

Effects of ziprasidone on potassium currents

It has been thought that ziprasidone, like other antipsychotics, may prolong the QT interval by inhibiting the hERG current. However, despite its consistent hERG inhibitory potency in experimental conditions, clinical data on cardiac adverse events remain inconclusive [47, 140]. On the other hand, electrophysiological studies in HEK-293 cells have shown that it can inhibit the hERG channel in a concentration-dependent manner. At concentrations of 0.01, 0.1, 1, and 10 μM, it inhibited the hERG current by 22.1%, 41.4%, 64.7%, and 80.8%, respectively (IC_{50} = 0.24 μM). These findings indicate that ziprasidone is a highly potent hERG channel inhibitor [141].

Another study examining the effect of ziprasidone on the hERG channel reported that it is one of the most potent hERG inhibitors after sertindole [25]. The IC_{50} value for the hERG channel was found to be quite low at 0.125 μM, and it was shown to cause 22.7% blockade at plasma concentrations. This level of blockade resulted in a 15.9 ms prolongation of the QT interval. Lehmann et al. also measured an IC_{50} value of 169 nM and C_{max} of 1.64 nM for hERG channels expressed in HEK-293 cells [84]. Additionally, they suggested that ziprasidone carries a minimal risk for TdP because the hERG IC_{50}:Cmax ratio, calculated to assess the risk of TdP induction, was found

to be 103 [84]. In this context, ziprasidone was reported to have a lower TdP risk than some antipsychotics such as risperidone (4.13) and haloperidol (51), but a higher risk than olanzapine (1345). On the other hand, in human atrial myocytes I_{to}, I_{sus}, and I_{K1} currents were examined, and the IC_{50} value for I_{to} was found to be >5 μM, and this high value was not associated with clinically significant inhibition [25]. Similarly, the IC_{50} values for the I_{sus} and I_{K1} currents were found to be >10 μM, reinforcing the view that it would not cause clinically significant inhibition through these channels. Taking together, it seems that the cardiac risks that ziprasidone may cause are most likely due to hERG channel blockade.

Effects of ziprasidone on sodium currents

The effects of ziprasidone on I_{NaL} are of particular interest. Wu et al. demonstrated that ziprasidone may increase proarrhythmic potential by increasing I_{NaL} [142]. In this study, monophasic APD ($MAPD_{90}$) was measured in cells taken from the left ventricular wall of female New Zealand rabbits, and the effects of ziprasidone were assessed by increasing I_{NaL} with ATX-II toxin. Ziprasidone significantly prolonged $MAPD_{90}$ at a concentration of 1 μM, and this effect was more pronounced when used in conjunction with ATX-II [142]. These findings emphasize that ziprasidone should be used with caution, especially in patients with low repolarization reserve, as the increase in I_{NaL} may cause intracellular Na^+ and Ca^{2+} overload, thus triggering arrhythmias such as EAD and ventricular tachycardia [142].

Another study examining the effects of ziprasidone found that it had an inhibitory effect on $Na_v1.5$ in cells isolated from human atrial myocytes, but the IC_{50} was higher than 10 μM [25]. Based on these findings, it was suggested that clinical doses of ziprasidone are unlikely to cause significant inhibition of the Na^+ channel. Namely, ziprasidone has a very low capacity to block the fast Na^+ current that initiates AP, and therefore, it is not expected to have a significant effect on the fast depolarization phase. In fact, clinically, no evidence was found that ziprasidone induces cardiac conduction delay due to Na^+ channel blockade [25].

CONCLUSION

It appears that SGAs exert distinct electrophysiological effects on ion channels in cardiac myocytes. This class of antipsychotic drug tends to prolong the cardiac repolarization phase primarily by inhibiting potassium currents (I_{Kr}, the hERG channel current). Some degree of hERG channel blockade has been reported in all SGAs, and this effect prolongs the APD and thus the QT interval, generating a mechanism that can trigger potentially fatal ventricular arrhythmias such as TdP. However, there are significant differences in the affinity for the hERG channel and the degree of blockade among SGAs. For example, clozapine, risperidone, and ziprasidone exhibit potent I_{Kr} inhibition at very low concentrations, significantly suppressing the I_{Kr} current even at therapeutic doses and thus potentially leading to QT prolongation. In contrast, SGAs such as olanzapine and quetiapine, due to their low inhibition of the hERG channel, have a low risk of proarrhythmia associated with I_{Kr} blockade. In general, SGAs may slow repolarization through the hERG channel, but the risk of QT prolongation and arrhythmias for each drug is not similar at clinical doses.

The data presented in Table 2 demonstrate that the affinities of SGAs for the hERG channel differ significantly from the free drug concentrations achieved at therapeutic doses. These variations help explain why the clinical risk of QT prolongation differs among agents, as the relevant parameter is not solely the IC_{50} value, but rather its relationship to the circulating free drug concentration. Accordingly, the $IC_{50}/C_{max,free}$ ratio serves as a critical pharmacological safety index that estimates the likelihood of hERG channel inhibition under therapeutic conditions. An $IC_{50}/C_{max,free}$ ratio greater than 30 indicates a wide safety margin for hERG channel inhibition, whereas a low ratio indicates a notable change in repolarization and a risk of QT prolongation. This consideration enables a more integrated interpretation of the electrophysiological impact of SGAs on cardiac ion channels.

The effects of SGAs on cardiac ion currents other than hERG were generally observed at higher concentrations and were of less clinical significance at therapeutic levels. Most SGAs do not produce marked inhibition of I_{to}, I_{K1}, and I_{sus}. For example, in human cardiac myocytes both risperidone and ziprasidone block I_{to} and I_{K1} currents at high concentrations with IC_{50} values >5–10 μM, so the functions of these channels

are likely unchanged at therapeutic doses. Clozapine has been shown to inhibit some K_v channels, a subtype of potassium channel, at micromolar levels, while the clinical relevance of this is unclear. Regarding calcium channels, SGAs have also been reported to affect L-type ($Ca_v1.2$) and T-type ($Ca_v3.1$) Ca^{2+} currents. Risperidone can block L-type Ca^{2+} channels only in the high dose range (IC_{50} = ~ 10 μM), and its effects on these channels are negligible at therapeutic plasma levels. Clozapine, on the other hand, is thought to inhibit $Ca_v3.1$ only at high concentrations. However, studies in HEK-293 cells have shown that clozapine significantly inhibits the $Ca_v3.1$ channel in the ~ 1–10 μM range, and this effect becomes more pronounced at physiological membrane potentials [54]. It has also been suggested that the inhibition of T-type Ca^{2+} currents, which play a role in cardiac pacemaker activity, may be associated with ventricular tachycardia, a known cardiac side effect of clozapine. In addition, some SGAs exert a blocking effect on the fast Na^+ current ($Na_v1.5$) that initiates the early phase of the AP. However, this effect is generally limited at therapeutic levels and is therefore not expected to cause clinically significant conduction slowing. On the other hand, quetiapine and its active metabolite, norquetiapine, can only block Na^+ channels at high concentrations and under repetitive stimulation, and therefore are not thought to exert a significant effect on the human heart under therapeutic conditions [130]. Although clozapine can inhibit both the peak and late components of Na^+ channels, this effect is not expected to cause a conduction defect with routine treatment, as its IC_{50} value is ~8–10 μM. Due to the limited number of electrophysiological studies, it is not possible to have a definitive conclusion about the effects of ziprasidone on cardiac ion channels. The relatively few studies on its effects on sodium and potassium currents, as well as the lack of studies on whether it causes changes in calcium currents, are important shortcomings that need to be addressed.

Due to their multifaceted effects on cardiac ion channels, SGAs can, on the one hand, predispose to QT prolongation via I_{Kr} blockade, while on the other, they can limit arrhythmia-triggering mechanisms by suppressing certain depolarizing currents. In particular, although clozapine can effectively inhibit seven different cardiac ion currents, due to the similarity of these inhibitions, there is no significant change in the total duration of the AP, and consequently, QT prolongation remains minimal [51]. Thus, despite inhibition of the hERG channel, clozapine has exhibited a relatively safe cardiac profile in clinical practice. Previous reports have indicated that clozapine may

prolong the QT interval but does not cause a significant increase in the incidence of TdP. Similarly, in other SGAs that affect multiple ion channels, the presence of counter-balancing alterations in ionic currents may result in a lower proarrhythmic potential than would be predicted based solely on hERG channel blockade.

In summary, second-generation antipsychotics affect cardiac repolarization primarily through I_{Kr} channel inhibition. Although they can also modulate Ca^{2+}, Na^{+}, and other K^{+} channels at high doses, their effects observed at therapeutic plasma concentrations are generally mild and, in most cases, produce clinically insignificant changes. Nevertheless, the simultaneous multichannel effects of these drugs can lead to unexpected and surprising consequences. In conclusion, while the combined effects of SGAs on ion channels reduce the incidence of serious arrhythmias in the general population, they can cause critical symptoms in patients with cardiac disease or those taking multiple QT-prolonging medications. Therefore, ECG monitoring and individual assessment of arrhythmia risk are recommended during SGA treatment.

Conflicts of interest: Authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

Submitted: October 20, 2025

Accepted: December 4, 2025

Published online: December 11, 2025

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TABLES AND FIGURES WITH LEGENDS

Table 1. Inhibitory potency of second-generation antipsychotics on cardiac ionic currents/channels

Drugs	Metabolite	Experimental Model	IC_{50} (μM)	Effect at [conc.]	Notes	Ref.
Clozapine		CHO/hERG	2.8		Inhibition of hERG	[50]
		XO/hERG	28.3		Inhibition of hERG	[49]
		HEK-293	2.5		Inhibition of hERG	[49]
		Guinea-pig ventricular myocyte		24.7% [1 μM]	Inhibition of I_{Kr}	[49]
		Guinea-pig ventricular myocyte		79.6% [5 μM]	Inhibition of I_{Kr}	[49]
		Coronary arterial smooth muscle cells	7.84		Inhibition of I_{Kv}	[52]
		HEK-293	23.7		Inhibition of I_{CaT}	[54]
		CHO	9.2		Inhibition of I_{CaL}	[51]
		HEK-293	10		Inhibition of I_{Na}	[51]
		HEK-293	8.7		Inhibition of I_{NaL}	[51]
		CHO	4.1		Inhibition of I_{Kr}	[51]
		CHO	11		Inhibition of I_{Ks}	[51]

		CHO	54	Inhibition of I_{to}	[51]
		CHO	118	Inhibition of I_{K1}	[51]
		Human atrial myocyte	51.7	Inhibition of I_{to}	[25]
		Human atrial myocyte	28.2	Inhibition of I_{Na}	[25]
		Human atrial myocyte	>100	Inhibition of I_{K1}, I_{sus}	[25]
		HEK-293	0.320	Inhibition of hERG	[25]
Olanzapine		HEK-293/hERG	8	Inhibition of hERG	[78]
		HEK-293/hERG	0.23	Inhibition of hERG	[81]
		CHO/hERG	6	Inhibition of hERG	[143]
		Human atrial myocyte	>100	Inhibition of I_{to}, I_{Na}, I_{sus} and I_{K1}	[25]
		HEK-293	0.231	Inhibition of hERG	[25]
		CHO/hERG	27	Inhibition of hERG	[83]
	2-hydroxymethyl	HEK-293	11.6	Inhibition of hERG	[81]
	N-desmethyl	HEK-293	14.2	Inhibition of hERG	[81]
Risperidone		CHO/hERG	0.26	Inhibition of hERG	[99]
		Human atrial		29% [30 Inhibition of	[26]

	myocyte		μM]	I_{to}	
	Human atrial myocyte		28.7% [3 μM]	Inhibition of I_{sus}	[26]
	Human atrial myocyte		47.4% [30 μM]	Inhibition of I_{sus}	[26]
	HEK-293	0.39		Inhibition of hERG	[144]
	HEK-293	25.5		Inhibition of I_{to}	[144]
	CHO	9.7		Inhibition of I_{Ks}	[144]
	CHO/hERG	1.6		Inhibition of hERG	[83]
	HEK-293		11% [8 nM]	Inhibition of hERG	[100]
	Rabbit ventricular myocyte		28% [1 μM]	Inhibition of I_{Kr}	[106]
	Canine ventricular myocyte	0.92		Inhibition of I_{Kr}	[107]
	HEK-293	0.148		Inhibition of hERG	[25]
	Human atrial myocyte	60		Inhibition of I_{Na}	[25]
	CHO/hERG	0.167		Inhibition of hERG	[143]
	Guinea-pig ventricular myocyte	116		Inhibition of I_{CaL}	[100]
Quetiapine	Rat ventricular myocyte		17% [10 μM]	Inhibition of I_{to}	[127]
	Rat ventricular myocyte		18.6% [10 μM]	Inhibition of I_{sus}	[127]
	Rat ventricular		12% [10	Inhibition of	[127]

		myocyte		μM]	I_{CaL}	
		Rabbit coronary arterial smooth muscle cells	47.98		Inhibition of I_{Kv}	[128]
		CHO/hERG	5.7		Inhibition of hERG	[143]
		HEK-293	8.3		Inhibition of hERG	[129]
		HEK-293	29.6		Inhibition of I_{Na}	[130]
	Norquetiapine	HEK-293	10.8		Inhibition of hERG	[129]
	Norquetiapine	HEK-293	5.9		Inhibition of I_{Na}	[130]
Ziprasidone		HEK-293	0.24		Inhibition of hERG	[141]
		CHO/hERG	0.169		Inhibition of hERG	[143]
		HEK-293	0.125		Inhibition of hERG	[25]
		Human atrial myocyte	>10		Inhibition of I_{to}, I_{K1}, I_{Na} and I_{sus}	[25]

Abbreviations: CHO: Chinese hamster ovary; hERG: Human ether-a-go-go-related gene; XO: Xenopus oocytes; HEK-293: Human Embryonic Kidney-293.

Table 2. Comparison of hERG inhibition potency and pharmacokinetic parameters of SGAs

Drug	IC_{50} (hERG, μM)	~f_u	~$C_{max, total}$ (μM)	~$C_{max, free}$ (μM)	~$IC_{50}/C_{max, free}$
Clozapine	0.32-28.3	0.05	1.53	0.076	4.2-370
Olanzapine	0.23-27	0.07	0.50	0.035	6.6-771
Risperidone	0.14-1.6	0.15	0.02	0.003	42-481
Quetiapine	5.7-10.8	0.17	2.09	0.36	15.8-30
Ziprasidone	0.12-0.24	0.01	0.79	0.008	15-30

Abbreviations: IC_{50}: Half-maximum inhibitory concentration of the hERG channel; f_u: Unbound fraction (1-protein binding); $C_{max, total}$: Peak serum concentration; $C_{max, free}$: Peak unbound concentration; SGAs: Second-generation antipsychotics; hERG: Human ether-a-go-go-related gene potassium channel.

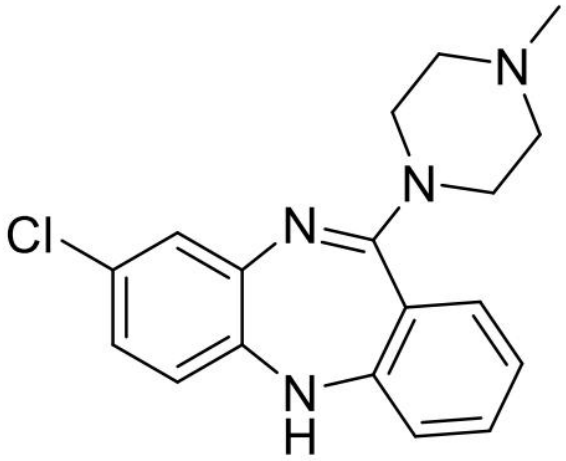


Figure 1. Chemical structure of clozapine. Clozapine is the first atypical (second-generation) antipsychotic, characterized by a tricyclic dibenzodiazepine scaffold structurally related to tricyclic antidepressants.

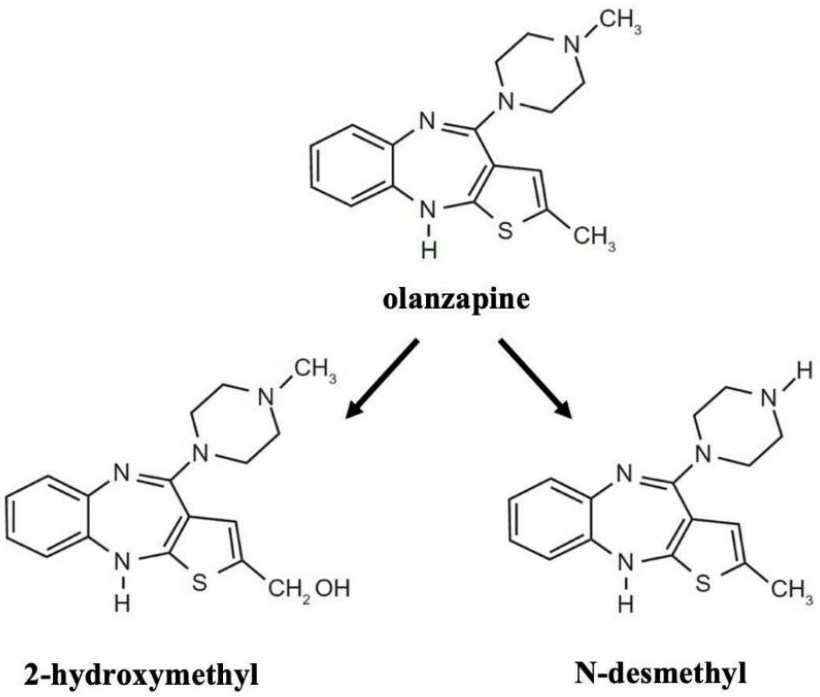


Figure 2. Chemical structures of olanzapine and its metabolites. Olanzapine and its major metabolites 2-hydroxymethyl-olanzapine and N-desmethyl-olanzapine are shown, all retaining the thienobenzodiazepine core that underlies the pharmacological similarity of olanzapine to clozapine.

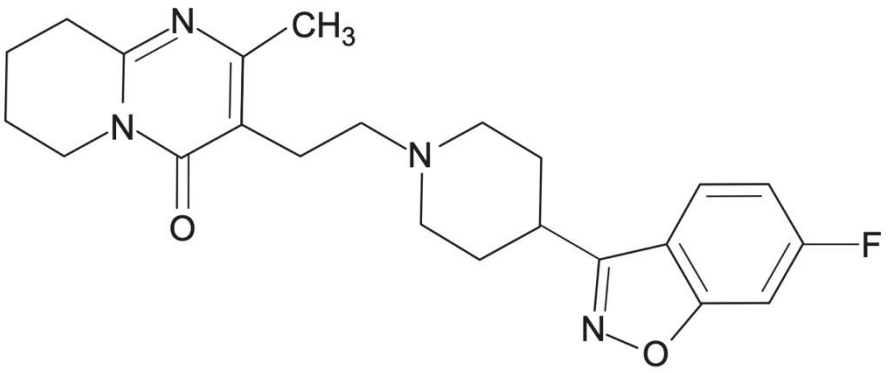


Figure 3. Chemical structure of risperidone. Risperidone is a benzisoxazole-derived second-generation antipsychotic that acts as a potent dopamine D2 and serotonin 5-HT2 receptor antagonist, and is widely used in the treatment of schizophrenia and acute bipolar disorder.

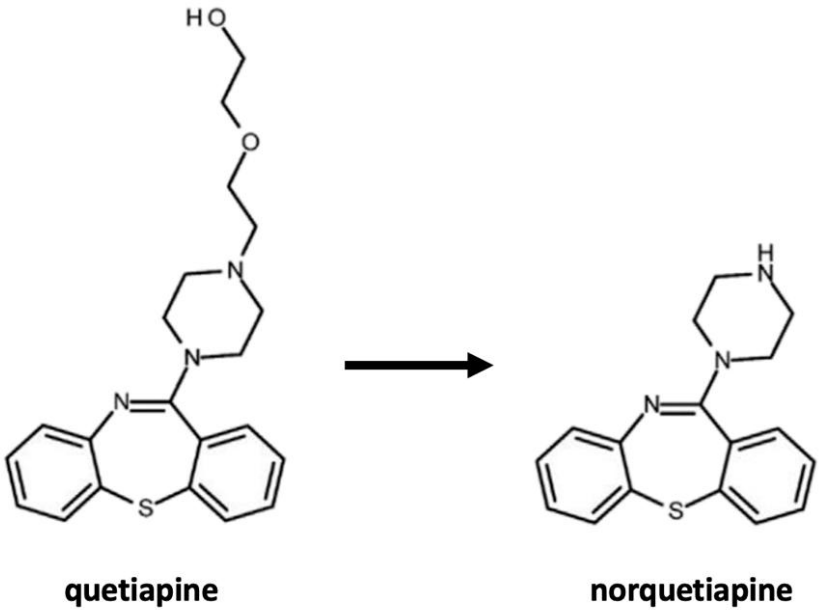


Figure 4. Chemical structures of quetiapine and norquetiapine. Quetiapine and its active metabolite norquetiapine are shown; despite their closely related structures, norquetiapine displays a distinct pharmacological profile, including inhibition of the norepinephrine transporter and partial agonist/antagonist actions at several serotonergic and adrenergic receptor subtypes.

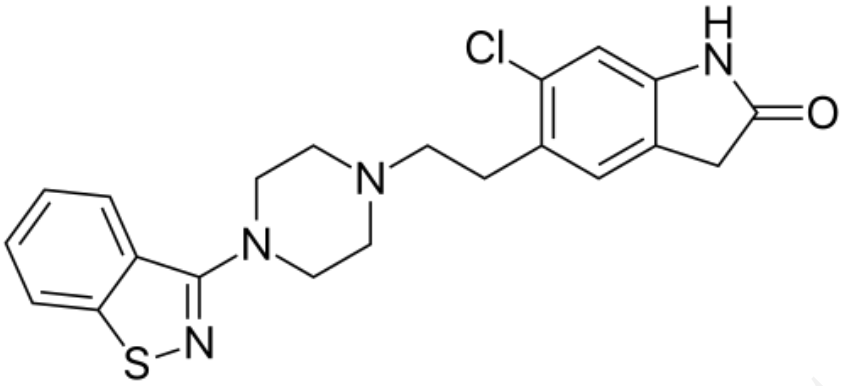
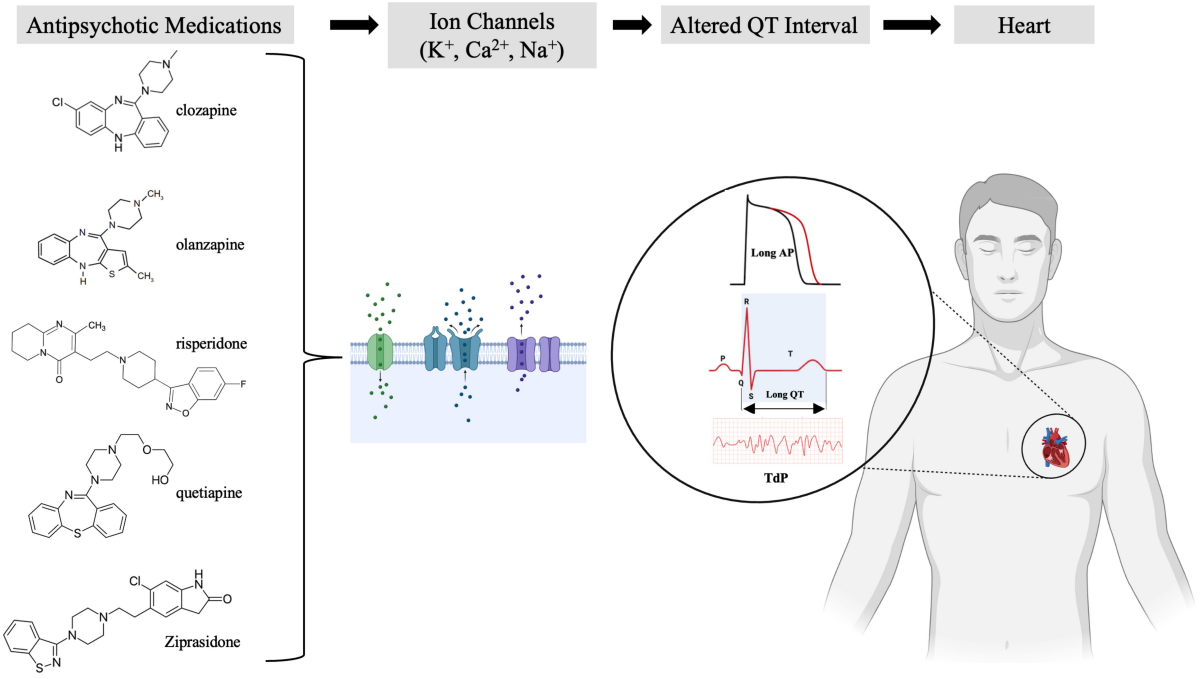


Figure 5. Chemical structure of ziprasidone. Ziprasidone is a benzisothiazolylpiperazine-derived second-generation antipsychotic with markedly higher affinity for serotonin 5-HT2A than dopamine D2 receptors, a profile that supports its atypical antipsychotic properties and relatively lower risk of extrapyramidal side effects.

SUPPLEMENTAL DATA

Graphical abstract



Graphical abstract. Schematic representation of the effects of five commonly used second-generation antipsychotic drugs (clozapine, olanzapine, risperidone, quetiapine, and ziprasidone) on cardiac electrophysiology. These agents influence cardiac K^+, Ca^{2+}, and Na^+ channels leading to prolongation of action potential duration and the QT interval, thereby increasing susceptibility to arrhythmogenesis.