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Cardiovascular Side Effects of New Antidepressants and Antipsychotics: New Drugs, old Concerns?

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Abstract

The cardiovascular toxicity of older generation of tricyclic antidepressants (e.g. imipramine, desipramine, amitriptyline, clomipramine) and neuroleptics (e.g. haloperidol, droperidol, thioridazine, pimozide) is well established. These drugs inhibit cardiovascular Na⁺, Ca²⁺ and K⁺ channels often leading to life-threatening arrhythmia.

To overcome the toxicity of old generation of antidepressants and antipsychotics, selective serotonin reuptake inhibitor antidepressants (SSRIs: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, venlafaxin) and several new antipsychotics (e.g. clozapine, olanzapine, risperidone, sertindole, aripiprazole, ziprasidone, quetiapine) were introduced during the past decade. Although these new compounds are not more effective in treating psychiatric disorders than older medications, they gained incredible popularity since they have been reported to have fewer and more benign side effect profile (including cardiovascular) than predecessors.

Surprisingly, an increasing number of case reports have demonstrated that the use of SSRIs and new antipsychotics (e.g. clozapine, olanzapine, risperidone, sertindole, aripiprazole, ziprasidone, quetiapine) is associated with cases of arrhythmias, prolonged QTc interval on electrocardiogram (ECG) and orthostatic hypotension in patients lacking cardiovascular disorders, raising new concerns about the putative cardiovascular safety of these compounds. In agreement with these clinical reports these new compounds indeed show marked cardiovascular depressant effects in different mammalian and human cardiovascular preparations by inhibiting cardiac and vascular Na⁺, Ca²⁺ and K⁺ channels. Taken together, these results suggest that the new generation of antidepressants and antipsychotics also have clinically important cardiac as well as vascular effects. Clinicians should be more vigilant about these potential adverse reactions and ECG control may be suggested during therapy, especially in patients with cardiovascular disorders.

The primary goal of this review is to shed light on the recently observed clinically important cardiovascular effects of new antidepressants and antipsychotics and discuss the mechanism beyond this phenomenon.

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Keywords

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INTRODUCTION

Cardiovascular mortality in psychiatric patients is high. Reports of sudden unexplained death in those taking psychotropic drugs, including neuroleptics and antidepressants, have raised the concern that part of this excess may be due to drug-induced arrhythmias, since many of these drugs have cardiac electrophysiological effects similar to those of quinidine. Indeed, it has recently been established that old generation of antidepressants (tricyclic antidepressants (TCAs) and antipsychotics (e.g. haloperidol, droperidol, thioridazine, pimozide) can be associated with increased risk of cardiac arrhythmias and sudden death [reviewed in 1–7].

In contrast, new generation of selective serotonin reuptake inhibitor antidepressants (SSRIs: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, venlafaxin) and several new antipsychotics (e.g. clozapine, olanzapine, risperidone, sertindole, aripiprazole, ziprasidone, quetiapine risperidol) are considered to be free from the cardiotoxicity of their predecessors. However, there are increasing number of case reports on various arrhythmias and syncope associated with the use of these new compounds [reviewed in: 3, 5–9]. In addition recent studies have demonstrated that the new SSRIs and antipsychotics also exert potent cardiovascular depressant effects in various mammalian and human cardiovascular preparations by inhibiting cardiac and vascular Na^+ , Ca^{2+} and K^+ channels. This review is concerned with the cardiovascular effects of new antidepressants and antipsychotics.

1. CARDIOVASCULAR EFFECTS OF ANTIDEPRESSANTS**1.1. Clinical Evidence**

1.1.1. Cardiovascular Effects of Tricyclic Antidepressants (TCAs)—The cardiovascular effects and toxicity of tricyclic antidepressants have been well documented in depressed patients without pre-existing cardiac disease [1, 3, 10–11]. The most common manifestation of such effect is the slowing of intraventricular conduction, manifested by prolonged PR, QRS and QT intervals on the standard ECG, and orthostatic hypotension [12–15]. The prolonged conduction can be dangerous in overdose and depressed patients with preexisting conduction defect and in patients who have already been treated with a class I (Na^+ -channel blocking) antiarrhythmic agent [16–17]. In overdose, delayed conduction may result in a complete heart block or ventricular reentry arrhythmias. Any of these complications, or a combination of both, may lead to death [18–20]. Depressed patients with conduction disease, particularly bundle branch block, being treated with TCAs at therapeutic plasma levels, are at a higher risk of developing symptomatic AV block than those of free from conduction disorders [16–17]. Tricyclic antidepressants have also been found to exert I/A class antiarrhythmic effects [21–23]. Children seem to be especially vulnerable to cardiotoxic effects of high doses of tricyclic compounds. Death has occurred in children after accidental or deliberate overdose with only a few hundred milligrams of drug [24]. Since tricyclic antidepressants can cause orthostatic hypotension, induce arrhythmia at higher doses or tissue concentrations, and interact unpredictably with other drugs, as do the serotonin-reuptake inhibitors, they must be used with great caution in patients with cardiac disease [16–17].

1.1.2. Cardiovascular Effects of Selective Serotonin Reuptake Inhibitors (SSRIs)—The most human clinical studies with SSRIs like fluoxetine, fluvoxamin, paroxetine, sertraline and citalopram showed significant advantages over TCAs in producing fewer

cardiotoxic, anticholinergic and antihistaminergic side effects in the treatment of major depressive disorders [reviewed in ³]. These newer compounds exhibited lower risk of inducing hypotension and a higher margin of safety in acute overdose than tricyclics [reviewed in ³]. However, it is interesting to note that the results of some animal studies were not always so clear cut. For example, early preclinical studies in cats with the highly selective serotonin reuptake inhibitor, citalopram, showed TCA-like cardiac effects at high doses [²⁵], and the development of citalopram was delayed by reports of cardiotoxicity in dogs, eventually attributed to a species-specific metabolite not found in humans [²⁶].

The SSRI drug, of that the most information is available, is fluoxetine [²⁷] used for oral administration; it is chemically unrelated to tricyclic, tetracyclic antidepressant agents. Several clinical studies showed that compared to tricyclic antidepressants, fluoxetine causes significantly fewer anti-cholinergic, antihistaminergic and cardiovascular side effects [reviewed in: ^{3, 8-9}]. However, even with fluoxetine one must be cautious in the conclusions drawn because the patients that have been carefully studied are, in general, depressed patients free of cardiovascular disease, and only very limited information is available in patients having cardiovascular disease as well [²⁸⁻³¹]. The SSRIs do have cardiac effects, the best demonstrated of those being a mild bradycardia observed during chronic treatment with fluoxetine, fluvoxamin, paroxetine [reviewed in ^{3, 8}]. This usually amounts to only a few beats per minute but it is the opposite of the tachycardia that has been associated with tricyclic drugs. Analysing large number of ECG recordings from citalopram-treated patients Enemark [³²] reported that citalopram-treatment also reduced the heart rate. This reduction occurred within the first week of the treatment without further reduction later. In a small group of citalopram-treated patients (3–4%) with normal heart rate at baseline bradycardia was developed. Furthermore, citalopram treatment was associated with a non-specific, insignificant prolongation of QT interval irrespective of age. In younger group of the patients a statistically significant decrease in T-wave amplitude was also demonstrated [³²]. Moreover, there are increasing number of case reports on dysrhythmia and syncope associated with fluoxetine and another SSRIs treatment and overdose [³³⁻⁵⁸]. A multicenter case-control study has shown that in the elderly the consumption of fluoxetine was significantly associated with an excess risk of syncope and orthostatic hypotension [⁵⁹]. A significant blood pressure lowering effect of fluoxetine was reported in DOCA-hypertensive rats [⁶⁰]. The authors suggested that a central action of fluoxetine on vasomotor center may be responsible for the reduction of blood pressure, but the possible direct cardiac and/or vascular effects of fluoxetine were not excluded or determined. Interestingly, several recent studies have provided evidence that fluoxetine and citalopram directly inhibit Ca²⁺ entry into vascular and intestinal smooth muscles resulting in vasodilation and intestinal relaxation, effects, which could be of significant therapeutic importance. [⁶¹⁻⁶⁴]. Surprisingly results from recently published retrospective studies show that the use of new SSRIs, similarly to the old TCAs, increases the risk of falls and hip fracture among elderly people [reviewed in ⁹].

1.2. Cellular Electrophysiological Effects

Electrophysiological studies (using a broad range of *in vitro* models) demonstrated that both antidepressants and antipsychotics exerted their cardiac actions by modifying the different cardiac ionic currents during the action potential (Fig. 1).

1.2.1. Cellular Electrophysiological Effects of TCAs—In electrophysiological studies on isolated mammalian multicellular cardiac preparations and single myocytes, TCAs, such as imipramine, chlorimipramine amitriptyline, desipramine, dibenzepin, lofepramine and amoxapine, were demonstrated to reduce the maximum velocity of depolarization (V_{max}) of the action potential, an indirect index of the fast inward sodium current, I_{Na} . [⁶⁵⁻⁶⁹]. Furthermore, imipramine also blocks the outward delayed rectifier K⁺ current (I_K) and the

inward slow Ca^{2+} (I_{Ca}) currents in guinea-pig ventricular myocytes and transient outward K^+ current (I_{to}) in rabbit atrial cells [70–72]. These direct membrane effects explain a variety of characteristic ECG abnormalities like prolongation of PQ, QRS, and QT, and cardiac adverse effects including tachyarrhythmias, heart block, congestive heart failure, observed during tricyclic antidepressants treatment and overdose [1, 3, 10–14, 19]. The effects of imipramine on action potential duration (APD) show important species dependence. In bovine ventricular [75] and Purkinje fibers [65], guinea-pig papillary muscles [76–77] and isolated ventricular myocytes [70] imipramine shortened the APD, whereas in rabbit and rat atrial fibers [78–79] it lengthened the APD. The different effects of imipramine on APD can be explained by the important differences in the ionic currents responsible for the repolarization among animal species. In guinea-pig ventricular myocytes where I_{to} is relatively little [74], the APD is controlled by the interaction between inward (I_{Na} and I_{Ca}) and outward currents (I_{K} and I_{K1}). Imipramine decreased the I_{Na} [81], I_{K} and I_{Ca} but did not modify the I_{K1} [70, 75]. The reduction of the APD in bovine and guinea pig ventricular preparations could be explained mainly by inhibition of I_{Ca} [65, 70, 75, 77]. In contrast, in rat, rabbit and human atria [64, 80, 82] and rat ventricular myocytes the I_{K} is negligible and I_{to} appears to be the most important outward K^+ current responsible for action potential repolarization. Thus the reduction of I_{to} could explain the prolongation of the APD observed in above-mentioned species. More recently several antidepressants with different chemical structures (imipramine, amitriptyline, mianserine, maprotiline and trazodone) were reported to block transient outward K^+ current (I_{to}) [73].

1.2.2. Cellular Electrophysiological Effects of SSRIs

1.2.2.1. Effects of SSRIs on Cardiac Action Potentials (APs) In vitro: We previously demonstrated that fluoxetine elicited a concentration dependent depression of the amplitude of action potential (APA), overshoot (OS) and the maximum rate of rise of depolarization phase (V_{max}) in multicellular ventricular preparations of rats, rabbits and dogs without changing the resting membrane potential (RP) [84–85]. The significant threshold concentrations were more or less similar (3–10 μM) in various species (including the most sensitive isolated canine myocytes). Fluoxetine caused a nearly similar shortening of the duration of ventricular action potential (APD) in three species (guinea pig, rabbit, canine), but not in rats. Fluoxetine caused a concentration-dependent decrease in force of contraction in rat right ventricular papillary muscle with a calculated IC_{50} value of 9.86 μM . Citalopram similarly to fluoxetine elicited a concentration-dependent (10–100 μM) reduction of V_{max} , decrease of APA, OS and shortening of APA in guinea-pig ventricular papillary muscle [86]. Fluoxetine and citalopram produced a dose-dependent decrease of V_{max} (an indirect indicator of the fast Na^+ channel activity), which suggests that they inhibited the activation of fast Na^+ channels and exhibited class I anti-arrhythmic effects. A possible explanation of the decrease in APA and OS and shortening of the early part of repolarization (APD_{50}) can be the inhibition of the calcium current (I_{Ca}). This latter mechanism may also be responsible for the negative inotropic effect of fluoxetine. The inhibitory effect of fluoxetine on peak Ca^{2+} current was proven in voltage clamped canine ventricular myocytes by IC_{50} value of 5.4 μM . This effect may cause lengthening of atrioventricular conduction. Considering its Na^+ and Ca^{2+} currents inhibitory action, fluoxetine may have antiarrhythmic as well as pro-arrhythmic properties (due to impairment of atrioventricular or intraventricular conduction). As far as the different effects of fluoxetine on rat ventricular APD are concerned, these can be explained by the unique ion regulation characteristic to ventricular repolarization phase of rat markedly different from that of other mammalian species [87]. Similar cardiac electrophysiological effects with venlafaxine were observed in guinea-pig cardiac myocytes [88]. These direct cardiac effects of fluoxetine and citalopram are similar to those found by us for TCA clomipramine [86] and previously reported for the tri- and tetracyclic antidepressants [3].

1.2.2.2. Effects of SSRIs on Cardiac Ion Channels: Previous and recent studies demonstrated that fluoxetine and other SSRIs possess potent antagonistic properties on voltage-dependent ion channels in different tissues [84–85, 89–106]. The IC_{50} values of SSRIs for Na^+ , Ca^{2+} and K^+ channels of mainly cardiac tissues are summarized in Table 1. Fluoxetine inhibited L-type of Ca^{2+} (Ca_L^{2+}) current in both rat and canine ventricular myocytes, but its potency was twice as high in rat (IC_{50} 2.8 μ M) than in canine myocytes (IC_{50} 5.4 μ M) [84, 95]. It is interesting to note that sertraline also inhibited the Ca_L^{2+} current in rat myocytes and its inhibitory activity (IC_{50} = 2.3 μ M) was similar to that of fluoxetine, while citalopram inhibited Ca_L^{2+} current of guinea-pig myocytes at much higher concentration (100 μ M) [95, 105]. These data provide evidence that inhibition of cardiac Ca_L^{2+} current could play an important role in reducing cardiac contractility, heart rate and atrio-ventricular conduction. The proposed mechanism may explain the prolonged PR interval, AV block, hypotension, which are common cardiovascular complications of fluoxetine therapy.

Fluoxetine and citalopram have a high inhibitory potency (IC_{50} =3.1, 1.5 and 3.97 μ M, respectively) on HERG potassium channel [94, 105]. The *human ether-a-go-go-related gene*, HERG, is believed to encode the protein, which underlies the rapid component of the delayed rectifier K^+ current I_{Kr} . HERG encoded I_{Kr} plays an important part in the repolarization of the cardiac action potential. Pharmacological inhibition of either heterologously expressed HERG or native I_{Kr} would thus be expected to correlate with ventricular action potential prolongation and associated prolongation of the QTc interval on ECG. Thus the HERG current inhibition by fluoxetine and citalopram may give an explanation for the arrhythmogenic side effects (ventricular tachycardias) of these drugs. It is very important to note that this current inhibition can occur at nearly therapeutic levels of these drugs, thus this effect should be considered during the therapy.

SSRIs also exhibit potent inhibitory effects on various voltage-dependent ion channels in non-cardiac tissues. Some of these effects are summarized in the Table 1, but the detailed description is beyond the scope of this review.

The inhibitory concentrations of SSRIs on cardiac APs and ion current were in the upper range of the therapeutic plasma levels [107]. However, it is difficult to relate *in vivo* plasma concentrations to *in vitro* concentrations as pharmacokinetic properties (tissue accumulation, metabolites) of the drug must also be considered. Under certain conditions (e.g. in case of drug interactions or reduced metabolism in elderly) the plasma concentration of SSRIs can reach even higher levels. Thus, a significant inhibition of various cardiovascular ion channels by SSRIs may occur in patients chronically treated with these compounds, resulting in certain pro- or arrhythmic effects. [reviewed in 3].

2. CARDIOVASCULAR EFFECTS OF NEUROLEPTICS

2.1. Clinical Evidence

The aim of this part of the review is to organise the available evidences on cardiac/ cardiovascular side effects; proarrhythmic potential of antipsychotic drugs and to discuss their actions on cardiac ion currents as proposed explanation of their proarrhythmic effects.

Antipsychotic drugs represent a chemically various group of compounds. Antipsychotic drugs can be classified typical (older drugs acting on dopamine D_1 , D_2 , adrenergic α_1 , muscarinic cholinergic, 5-HT₂ and histamine H_1 -receptors and associated with different side effects) and atypical (newer drugs inhibiting mainly both D_2 and 5-HT_{2A} receptors and have a higher efficacy and fewer side effects) groups. Among atypical antipsychotics clozapine shows marked difference from the others binding more to D_4 , 5-HT₂ and α_1 receptors than to D_2 receptor. [108]. Aripiprazole is a first member of a new class of atypical antipsychotics have

also unique properties showing a combined partial agonist activity at D₂ and 5-HT_{1A} receptors with an antagonism at 5-HT_{2A} receptors [109–111].

Antipsychotic drugs have long been known to be associated with risk of cardiac arrhythmia and cardiac arrest. These arrhythmias are often reflected as changes in the electrocardiogram (ECG), prolongation of the QT interval, ventricular tachycardias, torsades de pointes (TdP). TdP is a potentially life-threatening ventricular tachyarrhythmia that is associated with syncope and sudden death. TdP is characterized by a twisting morphology of the QRS complex around the isoelectric baseline and can occur in congenital and acquired form induced by various cardiac and non-cardiac drugs. Among antipsychotics haloperidol, droperidol, pimozide, sertindole, thioridazine were found to cause definitively TdP [112–118]. Several other antipsychotics including typical (chlorpromazine, fluphenazine, mesoridazine, prochlorperazine, trifluoperazine, sultopride) [119–121] (quetiapine, olanzapine, risperidone, ziprasidone) [122–127] have been reported to prolong the corrected QT interval (corrected for heart rate)(QTc). Both an Australian and a Finnish study of neuroleptic poisoning demonstrated that thioridazine caused the most frequently tachycardia, prolonged QTc, widened QRS, arrhythmias and sudden death [120, 128]. Thioridazine and droperidole were found to be associated with prolongation of QTc even at dosage used for therapy [129] and based on this study the indications of thioridazine were restricted and droperidol was voluntarily discontinued by the manufacturer in UK [114]. Pimozide, sultopride and droperidole also prolong QTc interval and have been associated with TdP and sudden death, but far fewer data are available [121, 130]. The high-potency drug haloperidole can prolong QTc interval, causes TdP and sudden death at normal therapeutic doses [131], but the frequency by which these effects occur is less than with thioridazine [128]. Similar cardiovascular risks of traditional antipsychotics used at therapeutic dosage were published in the USA in a retrospective study investigating 481,744 persons (aged 15–84 years, from 1988 to 1993) [132].

The new atypical antipsychotics have greater efficacy and fewer side effects than older neuroleptics and with the exceptions of sertindole and ziprasidone they have not caused consistent statistically significant lengthening of QT or sudden cardiac death at therapeutic concentrations [118, 133]. Sertindole has been proven to be associated with a QT prolongation at therapeutic concentrations [117, 124], and both increasing evidence of unexplained sudden cardiac death and serious arrhythmias found by the Committee on Safety of Medicine in the United Kingdom resulted in a voluntary withdrawal of the drug by the manufacturer [134]. Albeit the known correlation between schizophrenia and increased cardiovascular mortality it may difficult to estimate the sudden death due to particular neuroleptics at therapeutic doses [135, 136]. Clozapine beyond the well-known agranulocytosis risk, is being associated with myocarditis, cardiomyopathy and arrhythmogenesis risk [137, 138]. It also reduced measures of heart rate variability associated with parasympathetic control [124]. In the study of overdoses, clozapine overdose was associated with sinus tachycardia (more than 66% of the patients) however, in the case of risperidone overdose more than 66% of the patients were asymptomatic [139]. However, there are data suggesting that risperidone could cause sudden death [125]. Neither olanzapine nor quetiapine had been implicated in cases of TdP or sudden death.

Ziprasidone is a new atypical drug with less side effects and in comparison with olanzapine and risperidone it does not appear to cause weight gain, hyperlipidemia and hyperglycaemia but prolongs the QT interval more than haloperidol, olanzapine, quetiapine and risperidone [127]. Although it was not associated with cardiac events during premarketing trials the appearance of unexpected life-threatening arrhythmias can not be excluded when the drug enters widespread use.

2.2. Mechanism of the Lengthening of QT Interval

The QT interval includes both depolarization and repolarization. Q wave represents the onset of ventricular depolarization, while T wave is the sign of the repolarization. Because the QT interval shortens with increasing heart rates, it is usually corrected for heart rate (QTc).

Depolarization of ventricular cells is the result of a rapid influx of sodium ions through selective Na^+ channel and its duration measured by the QRS interval. Repolarization involves calcium, sodium, and different potassium channels. Whereas the participation of these ion channels in the repolarization is highly dependent on species, mainly potassium channels are responsible for this parameter. Concerning the specificity of QT prolongation as a marker of an effect on cardiac repolarisation, it should be kept in mind that the duration of the QT interval may be affected by both the velocity of repolarisation and ventricular conduction velocity. Class I antiarrhythmics as sodium channel blockers, decrease ventricular conduction velocity, cause widening of QRS complex and therefore lengthen the QT interval [140]. Similar action can be observed in the case of tricyclic antidepressants which by blocking Na^+ as well K^+ channels widen both the QRS and the QTc. The potassium channels (among them I_{Kr}) are most often involved in drug-induced QT prolongation and TdP. Drug blocking the I_{Kr} channel can induce QT prolongation and TdP and sometimes sudden death [141]. However, there is no close correlation between QTc interval prolongation and occurrence of TdP. Not all drugs that prolong the QTc interval produce TdP. Amiodarone, a class III antiarrhythmic drug, produces marked prolongation of QTc interval but does not evoke TdP. The calcium-channel blocker verapamil has been shown to prolong QT interval in a manner that is linearly correlated to its plasma concentration [142] but there are few described cases of verapamil-induced TdP [143]. No clear-cut dose-dependency can also be observed for QT prolongation or occurrence of TdP. In some cases the QT prolongation and occurrence of TdP is dose dependent but these parameters can also be observed at normal plasma levels of drugs, too [144]. In the latter several factors (hypokalaemia/magnesaemia, mutation of K^+ channels) reducing the repolarization reserve of a given subject greatly increase the proarrhythmic potential of relatively low plasma level [5, 7].

The link between the lengthening of QT interval and TdP is seemingly very complex and affected by several factors including electrolyte imbalance, age, gender, disease (myocardial ischemia, infarction, hypertension, hypothyroidism, diabetes, renal or hepatic dysfunction) and concomitant medications.

2.3. Cellular Electrophysiological Effects of Neuroleptics

Most of antipsychotics are generally lengthen the action potential duration (APD) and inhibit the rapid component of the delayed rectifier current (I_{Kr}) but some of the typical antipsychotics including chlorpromazine and haloperidol, beyond their inhibitory effect on K^+ current inhibit also Na^+ and Ca^{2+} channels [81]. Such effects could be antiarrhythmic or cardiotoxic, depending on the health (e.g. post myocardial infarct) of the myocardium. The net effect on APD of antipsychotics depend on the overall balance between inward and outward currents during the plateau phase of AP and their relative sensitivity to the particular agent in question. Table 2. summarizes the inhibitory potency of antipsychotic drugs on K^+ (I_{Kr} , I_{to} , I_{K1} , HERG) and other ion (Na^+ , Ca^{2+}) currents. In human I_{Kr} is carried by the human ether-a-go-go (HERG) K^+ channel, which can be expressed in homologous and heterologous cells in order to assess the potency (IC_{50}) of a drug in inhibiting this channel. Haloperidol and droperidol prolong APD in guinea-pig ventricular myocytes and inhibit I_{Kr} and HERG with IC_{50} values of 20 nM-1.36 μM and 32.2 μM , respectively and the effects of haloperidol on HERG are over five or twenty times more potent than its effects on I_{Na} and I_{CaL} , respectively [81, 145-146, 150, 163]. Thioridazine also lengthened APD in guinea-pig ventricular myocytes and potently inhibited I_{Kr} and HERG (IC_{50} values of 1.25 μM , 191 nM and 1 μM) [147, 149]. Comparative

study showed that newer atypical antipsychotic ziprasidone, olanzapine, risperidone block HERG and I_{Kr} in a more or less similar concentration range [148].

Figures (2 and 3) show that risperidone concentration-dependently increased APD in both guinea-pig ventricular muscle (Fig. 2A) and canine ventricular myocytes (Fig. 3B). This effect was most prominent on terminal phase of repolarization (APD₉₀) (with EC₅₀ values of 0.29 μ M and 0.48 μ M in guinea pig and canine myocytes, respectively) (Fig. 3C) and showed reverse rate dependence (Fig. 2B). Haloperidol had similar effect on APD (Fig. 2C) but reduced also the maximum velocity of depolarization (V_{max}) (indirect indicator of Na⁺ channel activity) (Fig. 2D) while risperidone was ineffective on this parameter. We found that risperidone concentration-dependently inhibited I_{Kr} with an IC₅₀ of 0.92 μ M and practically had no effect on the other K⁺ currents (I_{to} with IC₅₀ >10 μ M, I_{K1} with IC₅₀ >100 μ M) [151]. Similar effects of risperidone on both APD and I_{Kr} in rabbit ventricular myocardium and myocytes were observed [152], while lower IC₅₀ values (167 and 261 nM, respectively) were found in HERG channel by others [147, 155].

Sertindole was found to be a high affinity antagonist of the human cardiac K⁺ channel HERG (IC₅₀= 3 and 14 nM) but was less active at blocking other K⁺ currents (I_{Kv} 1.5, I_{to} with IC₅₀=2.1 and 10 μ M, respectively) [147, 148, 153].

Pimozide potently inhibited cardiac HERG K⁺ channel (IC₅₀ values of 18 and 174 nM) [147, 150], increased the risk of TdP [154] and also blocked I_{CaL} in rat ventricular myocytes [156]. Beyond the inhibitory action on HERG channel sertindole and pimozide also blocked the human brain K⁺ channel erg3. Sertindole blocked erg3 channel currents with an IC₅₀ of 43 nM, while pimozide had an IC₅₀ value of 103 nM [157]. It was suggested that this inhibition of erg3 related K⁺ channels in the brain might contribute to their efficacy/side effect profiles.

Comparing the HERG channel inhibitory activity of seven antipsychotics drugs (olanzapine, pimozide, quetiapine, risperidone, sertindole, thioridazine, ziprasidone) to their binding affinities for D₂ and 5-HT_{2A} receptors the following selectivity rank was found: olanzapine > risperidone > ziprasidone > thioridazine > pimozide > sertindole. Sertindole and pimozide had the highest HERG channel inhibitory activity, while the lowest inhibitory activity can be observed in the case of olanzapine and quetiapine. These results also showed that sertindole, pimozide, thioridazine displayed little or no selectivity for dopamine D₂ or 5-HT_{2A} receptors relative to their HERG channel affinities, and olanzapine had the greatest selectivity for dopamine D₂ and 5-HT_{2A} receptor binding compared to the HERG channel. In the case of quetiapine the selectivity was not calculated due to its lack of affinity for the dopamine D₂ receptor. Examining the relationship between plasma levels and QT prolongation for these drugs [127] the authors also found a good correlation between the ratio of total plasma drug concentration to HERG IC₅₀ and their QTc prolongation effect [147]. Based upon this *in vitro* results drug's selectivity (between their target receptor affinity and their HERG channel IC₅₀ value) seems to be a predictive factor for appearance of QT prolongation in clinic. It would be expected that olanzapine and risperidone, displaying high selectivity, would have the least potential to produce QT prolongation in clinical settings.

However, it is widely accepted that most QT prolonging drugs inhibit I_{Kr} but the potency of drug-induced block of I_{Kr} does not show a clear correlation with the risk of QT prolongation and occurrence of TdP. In isolated feline hearts haloperidol prolongs QT interval more than sertindole [159], while sertindole is 10–300 times more potent as a blocker of HERG than haloperidole (Table 2). In addition, some authors found that thioridazine and chlorpromazine have similar potencies for inhibition of HERG [158] and in stepwise regression analysis of 495 psychiatric patients thioridazine was associated with QT prolongation, but chlorpromazine was not [128]. These data suggest that more than one drug-induced mechanisms exist that makes

the heart vulnerable to (or protected from) QT prolongation by inhibition of the HERG K^+ channel.

2.4. Perspectives

It is a widely held concept that most QT prolonging non cardiac drugs are potassium channel blockers, inhibit I_{K_r} and induce TdP. IC_{50} values for inhibiting I_{K_r} in human or other mammalian systems are important to gain insight into the mechanism of drug action, although extrapolation to the clinical setting must carefully consider concentration ranges and possible additional pharmacological effects. Antipsychotic drugs with complex pharmacological actions on different receptors (dopamine, serotonin, muscarinic) and moreover with additional inhibitory effects on Na^+ , Ca^{2+} channels may exert various antiarrhythmic/proarrhythmic actions and their effects on the QT interval *in vivo* may be quite variable depending on the animal species and experimental model. It is postulated that some antipsychotics (olanzapine, risperidone), having higher difference between concentration required for I_{K_r} inhibition and their therapeutic plasma levels will only cause cardiac complications in population of vulnerable patients [160] or patients suffering from other disorders (cardiac, or hepatic disease). Therefore, the inhibition of HERG/ I_{K_r} at cellular level is an important, but not always a predictive arrhythmogenic property of a drug *in vivo*. The merits of various testing strategies in preclinical phases, including the advantages and limitations of preclinical assays and the current regulatory guidelines scrutinize these drugs, have recently been detailed [161–163]. Current strategies for the development of new psychotropic drugs should include voltage clamp experiments (using HERG) as well as *in vivo* QT animal models.

As far as the QT prolongation is concerned this sign per se does not necessary mean that the risk/benefit balance of an antipsychotic drug is negative. The final balance depends on other factors that must carefully be considered [2] and the various drugs do differ in their QT-prolonging potential. QTc interval is usually around 400 msec in duration. Greater duration than 440 msec can be considered abnormal. Considering a new drug showing a small or modest QT interval prolongation several questions arise. The first one is whether the prolongation is dose-dependent, because some patients will undoubtedly be either slow metabolizers or given unusually high doses (especially psychiatric patients). To predict the potential for drug-interactions it is also important to know the metabolic pathway of the drug.

The major problem that there is no consensus on the degree of QT prolongation which is clinically significant. It is very difficult to interpret the clinical data as case reports are sometimes questionable, inadequate, some of them involve extreme overdose and cannot be directly extrapolated to routine clinical practice. Some data derived from combination of different drugs, where the concomitant drug's effect on QT prolongation or occurrence of TdP can not be excluded.

CONCLUSIONS

Collectively, results of numerous recent basic research and clinical studies suggest that the new generation of anti-depressants and antipsychotics also have clinically important cardiac as well as vascular effects. Clinicians should be more vigilant about these potential adverse reactions and ECG control may be suggested during therapy, especially in patients with cardiovascular disorders. The recent advances in our understanding of the cellular and molecular basis for the cardiac effects of antidepressants and antipsychotic drugs may help specialists in the better selection of the appropriate drugs for the given patient to avoid the unexpected, sometimes life-threatening cardiac arrhythmias.

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ABBREVIATIONS

TCA(s)	Tricyclic antidepressant(s)
SSRI(s)	Selective serotonin reuptake inhibitor antidepressant(s)
ECG	Electrocardiogram
5-HT	5-hydroxytryptamine
APD	Action potential duration
APD₅₀	Action potential duration measured at 50% and APD ₉₀ and 90% of repolarization
OSP	Overshoot potential
APA	Action potential amplitude
V_{max}	Maximum velocity of depolarization during the action potential upstroke
RP	Resting membrane potential
I_{Na}	Inward Na ⁺ current
I_{Ca}	Inward Ca ²⁺ current
I_{to}	Transient outward K ⁺ current
I_{Kr}	Rapid component of outward delayed rectifier K ⁺ current
I_{Ks}	Slow component of outward delayed rectifier K ⁺ current
I_{sus}	Sustained outward K ⁺ current
I_{K1}	Inward rectifier K ⁺ current
TdP	

Torsade de pointes type ventricular tachycardia

HERG

Human ether-a-go-go related gene

CHO

Chinese hamster ovary cells

HEK-293

Human embryonic kidney cells

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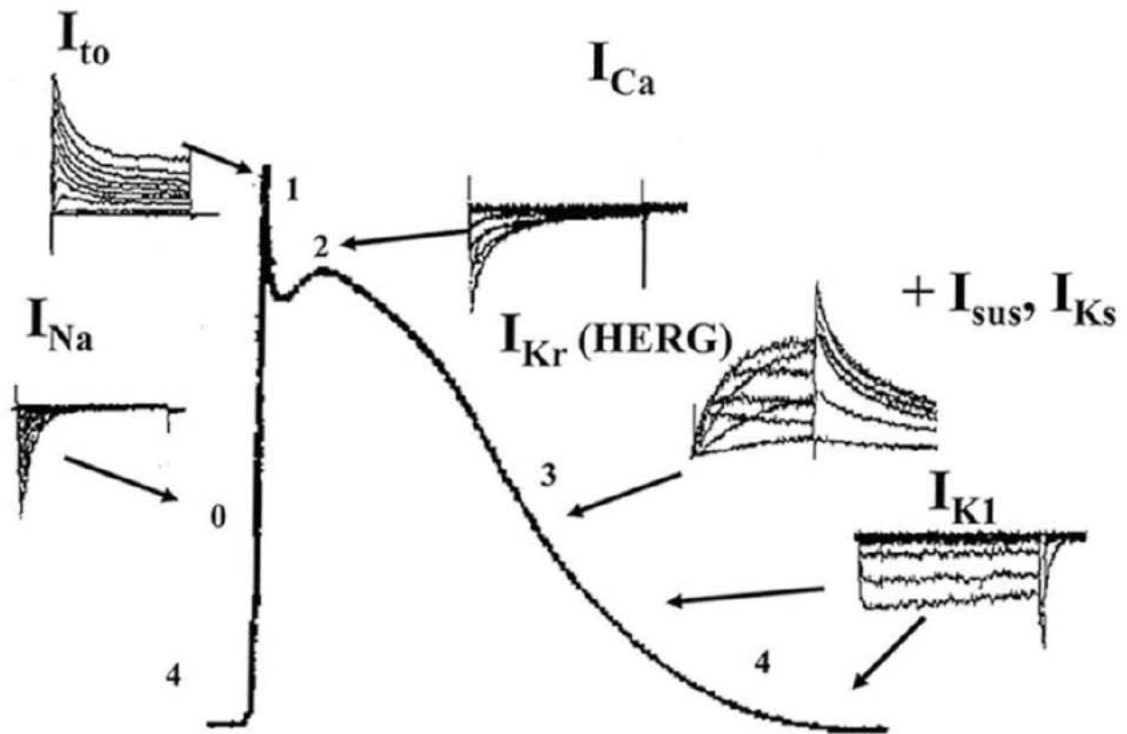


Fig. 1. Ionic currents during cardiac action potential. Downward represents inward (depolarizing), upward shows outward (repolarizing) currents. I_{Na} = inward sodium current; I_{Ca} = inward calcium current; I_{to} = transient outward potassium current; I_{Kr} = rapid component of outward delayed rectifier potassium current; I_{Ks} = slow component of outward delayed rectifier potassium current; I_{sus} = outward sustained potassium current; I_{K1} = inward rectifier potassium current.

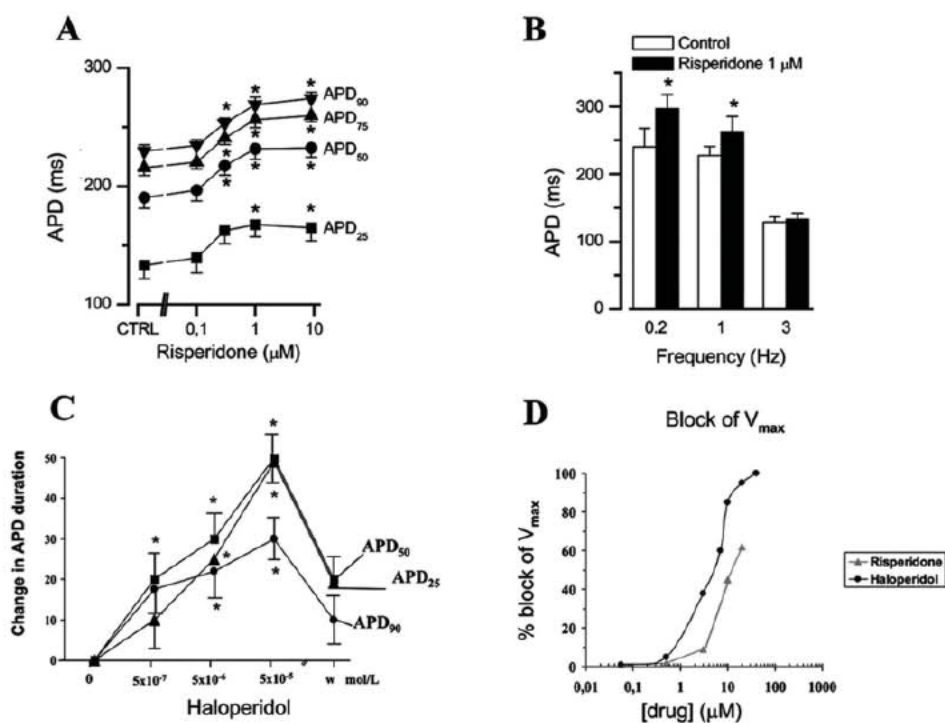


Fig. 2.

Cumulative concentration-dependent effects of risperidone (A, $n=9$) and haloperidole (C, $n=5$) on action potential duration measured at various levels of repolarization in guinea-pig ventricular papillary muscles. The preparations were treated with each concentration of drugs and paced at frequency of 1 Hz. B: Frequency-dependence of the lengthening effect of 1 μM risperidone on APD₉₀ studied in night guinea-pig ventricular preparations. D: Comparison of the effect of haloperidole (\bullet) and risperidone (\blacktriangle) on the maximal velocity of depolarization of AP (V_{max}). The effect was demonstrated as the percent change of decrease of V_{max} .

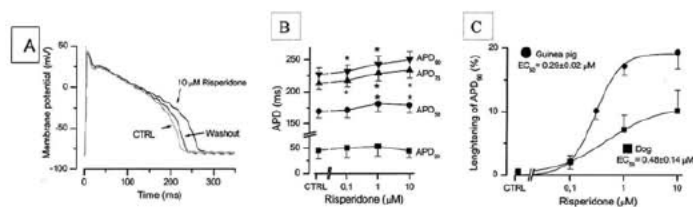


Fig. 3. Effects of risperidone (10 μ M) on action potential configuration in single canine ventricular myocytes paced a 1 Hz recorded 5 min after the drug superfusion (A). B: Cumulative concentration-dependent effects of risperidone on action potential duration measured at various level of repolarization in canine myocytes (n=5). C: Comparison of the APD prolongation effect of risperidone in canine ventricular myocytes (n=5) and guinea-pig papillary muscles (n=9). The risperidone induced prolongation of APD₉₀ was normalized to control APD₉₀ and expressed as its percent. Solid lines were obtained by fitting the data to the two-state Boltzmann model in order to determine EC₅₀ values.

Table 1
IC₅₀ Values of Antidepressants for Ionic Currents/Channels

Compound	Model system	Potassium channels/currents			HERG	Calcium channels/ current Ca _L	Sodium channels/ currents	References
		KV/delayed rectifier (rapid) I _{Kr}	Transient outward I _{to}					
TRICYCLIC DRUGS								
Imipramine	Guinea-pig ventricular myocytes				≥ 1 μM	≥ 1 μM	≥ 1 μM	71
	Rabbit atrial myocytes		≥ 1 μM				≥ 1 μM	72
	Guinea-pig ventricular myocytes							70
	Guinea-pig ventricular myocytes						3 μM	166
	Human cardiomyocytes						≥ 1 μM	167
	Rat ventricular myocytes						5 μM	95
Amitriptyline	CHO				3.4 μM	4 μM		168
	CHO				~4 μM			169
	Rabbit atrial and ventricular myocytes				4.7 μM			168
	Rat ventricular myocytes						≥ 1 μM	170
					3.75 μM			95
SELECTIVE SEROTONIN REUPTAKE INHIBITORS								
Fluoxetine	Rat pheochromocytoma (PC12) cell	16 μM						171
	HEK - 293				1.5 μM 3.1 μM	13.4 μM	25.6 μM	103 94
	Rat ventricular myocytes							95
	Canine ventricular myocytes		40 μM			2.8 μM		84
Citalopram	HEK - 293				5.97 μM	5.4 μM		105
	Rat ventricular myocytes							172
Sertaline	Rat ventricular myocytes					≥ 10 μM		95
Venlafaxine	Guinea-pig ventricular myocytes		38 μM			2.3 μM	~8 μM	88

Table 2
IC₅₀ Values of Antipsychotics for Ionic Currents/Channels

Compound	Model system	Potassium channels/currents				HERG	Calcium channels/ current	Sodium channels/ currents I _{Na}	References
		KV/delayed rectifier I _{Kr}	Transient outward I _{to}	Inward rectifier I _{K1}	I _{CaL}				
Chlorpromazine	CHO				1.47 μM			157	
Clozapine	HEK-293		>50 μM		320 nM		29 μM	148	
Droperidol	Ventricular myocytes HEK-293				32.2 μM			145	
Flupipiridone	Xenopus oocytes				2.34 μM			150	
Haloperidol	PC12 cells					20 μM		164	
	Ventricular myocytes HEK-293		>10 μM	>100 μM	26.8 nM		5 μM 14.4 μM	81 148	
	Xenopus oocytes				20 nM			165	
	Xenopus oocytes				1.36 μM			150	
	Xenopus oocytes				1.0 μM			146	
Olanzapine	HEK-293 CHO		>100 μM	>100 μM	731 nM 6013 nM		>100 μM	148 147	
Pimozide	HEK-293 Xenopus oocytes CHO		>100 μM	>100 μM	54.6 nM 1.74 μM 18 nM		21.9 μM	148 150 154	
Quetiapine	CHO				5765 nM			147	
Risperidone	canine ventricular myocytes HEK-293 CHO CHO		>100 μM	>100 μM	0.92 μM 148 nM 167 nM 261 nM		>50 μM	151 148 147 155	
Sertindole	HEK-293 HEK-293 CHO		>10 μM	>10 μM 21 μM	14 nM 14.7 nM 3 nM		>10 μM	148 153 147	
Thioridazine	Ventricular myocytes IsA201 CHO CHO HEK-293				1.25 μM			149	
Ziprasidone	HEK-293 CHO		>10 μM	>10 μM	125 nM 169 nM		>10 μM	148 147	

CHO = Chinese hamster ovary cells; PC12 cells = rat pheochromocytoma cells; HEK-293 = Human embryonic kidney cells.