Published in final edited form as:
Curr Pharm Des. 2004 ; 10(20): 2463–2475.

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

Pal Pacher[1,2,*] and **Valeria Kecskemeti**[2,*]

1*National Institutes of Health, National Institute on Alcohol Abuse & Alcoholism, Laboratory Physiologic Studies, Bethesda, MD 20892-8115, USA*

2*Department of Pharmacology and Pharmacotherapy, Semmelweis University of Medicine, Faculty of Medicines, Budapest Hungary*

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^+, Ca^{2+} 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^+, Ca^{2+} 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.

*Address Correspondance to these authors at the Department of Pharmacology and Pharmacotherapy, Semmelweis University, Faculty of Medicine, Nagyvárad tér 4, P.O.Box 370, Budapest H 1445, Hungary; Tel: 36-1-2102930/6265; Fax: 36-1-2104412; E-mail: kecsval@pharma.sote.hu and National Institutes of Health, NIAAA, Park Bldg., Rm. 445, 12420 Parklawn Drive, MSC-8115, Bethesda, MD2 20892-8115 USA; Tel: 301-496-6777; Fax: 301-480-0257; E-mails: ppacher@lycos.com.

Keywords

antidepressants; neuroleptics; antipsychotics; QT prolongation; arrhythmia; cardiac ion channels; repolarization

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 risperidal) 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 ANTIDEPRES-SANTS

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 othostatic 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, sertaline 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 Ca^{2+} 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 (Vmax) 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 (Ito) 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 Ica [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 Vmax, 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 impairement 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 μM) than in canine myocytes (IC_{50} 5.4 μM) [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 μM) was similar to that of fluoxetine, while citalopram inhibited Ca_L^{2+} current of guinea-pig myocytes at much higher concentration (100 μM) [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 μM, 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-HT_2 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-HT_2 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 D_2 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, trifluperazine, 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, sultopiride 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 IKr 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 (APD_{90}) (with EC_{50} values of 0.29 μM and 0.48 μM 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 IC_{50} of 0.92 μM and practically had no effect on the other K^+ currents (I_{to} with IC_{50} >10 μM, I_{K1} with IC_{50} >100 μM) [151]. Similar effects of risperidone on both APD and I_{Kr} in rabbit ventricular myocardium and myocytes were observed [152], while lower IC_{50} 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 (IC_{50}= 3 and 14 nM) but was less active at blocking other K^+ currents (Kv 1.5, I_{to} with IC_{50}=2.1 and 10 μM, respectively) [147, 148, 153].

Pimozide potently inhibited cardiac HERG K^+ channel (IC_{50} 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 IC_{50} of 43 nM, while pimozide had an IC_{50} 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 D_2 and 5-HT_{2A} receptors the following selectivity rank was found: olanzepine > 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 D_2 or 5-HT_{2A} receptors relative to their HERG channel affinities, and olanzapine had the greatest selectivity for dopamine D_2 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 D_2 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 IC_{50} and their QTc prolongation effect [147]. Based upon this *in vitro* results drug's selectivity (between their target receptor affinity and their HERG channel IC_{50} value) seems to be a predictive factor for appearance of QT prolongation in clinic. It would be expected that olanzepine 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_{Kr} and induce TdP. IC_{50} values for inhibiting I_{Kr} 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/proarrhytmic 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_{Kr} 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_{Kr} 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 [5] 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.

NIH-PA Author Manuscript

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.

NIH-PA Author Manuscript

Acknowledgements

This work was supported by the grant ETT 053/2003 of Hungarian Ministry of Health. The authors are indebted to Szilvia Bercsenyi, Mrs K. Barna, and Mr J. Balogh for their assistance during the preparation of the manuscript.

ABBREVIATIONS

TCA(s)
: Tricyclic antidepressant(s)

SSRI(s)
: Selective serotonin reuptake inhibitor antidepressant(s)

ECG
: Electrocardiogram

5-HT
: 5-hydroxytryptamine

APD
: Action potential duration

APD_{50}
: 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

References

References 173–175 are related articles recently published in Current Pharmaceutical Design.

1. Glassman AH. Cardiovascular effects of tricyclic antidepressants. Annu Rev Med 1984;35:503–11. [PubMed: 6372670]
2. Goldberg RJ, Capone RJ, Hunt JD. Cardiac complications following tricyclic antidepressant overdose. Issues for monitoring policy. JAMA 1985;254:1772–5. [PubMed: 4032678]
3. Pacher P, Ungvari Z, Nanasi PP, Furst S, Kecskemeti V. Speculations on difference between tricyclic and selective serotonin reuptake inhibitor antidepressants on their cardiac effects. Is there any? Curr Med Chem 1999;6:469–80. [PubMed: 10213794]
4. De Ponti F, Poluzzi E, Montanaro N. QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience. Eur J Clin Pharmacol 2000;56:1–18. [PubMed: 10853872]
5. De Ponti F, Poluzzi E, Cavalli A, Recanatini M, Montanaro N. Safety of non-antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: an overview. Drug Saf 2002;25:263–86. [PubMed: 11994029]
6. Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. Drugs 2002;62:1649–71. [PubMed: 12109926]
7. Witchel HJ, Hancox JC, Nutt DJ. Psychotropic drugs, cardiac arrhythmia, and sudden death. J Clin Psychopharmacol 2003;23:58–77. [PubMed: 12544377]
8. Pacher P, Ungvari Z, Kecskemeti V, Furst S. Review of cardiovascular effects of fluoxetine, a selective serotonin reuptake inhibitor, compared to tricyclic antidepressants. Curr Med Chem 1998;5:381–90. [PubMed: 9756980]
9. Pacher P, Ungvari Z. Selective serotonin-reuptake inhibitor antidepressants increase the risk of falls and hip fractures in elderly people by inhibiting cardiovascular ion channels. Med Hypotheses 2001;57:469–71. [PubMed: 11601871]
10. Burckhardt D, Raeder E, Muller V, Imhof P, Neubauer H. Cardiovascular effects of tricyclic and tetracyclic antidepressants. JAMA 1978;239:213–6. [PubMed: 579392]
11. Glassman AH, Bigger JT Jr. Cardiovascular effects of therapeutic doses of tricyclic antidepressants. A review. Arch Gen Psychiatry 1981;38:815–20. [PubMed: 7247643]
12. Kantor SJ, Bigger JT Jr, Glassman AH, Macken DL, Perel JM. Imipramine-induced heart block. A longitudinal case study. JAMA 1975;231:1364–6. [PubMed: 1173081]
13. Vohra J, Burrows G, Hunt D, Sloman G. The effect of toxic and therapeutic doses of tricyclic antidepressant drugs on intracardiac conduction. Eur J Cardiol 1975;3:219–27. [PubMed: 1183474]
14. Giardina EG, Bigger JT Jr, Glassman AH, Perel JM, Kantor SJ. The electrocardiographic and antiarrhythmic effects of imipramine hydrochloride at therapeutic plasma concentrations. Circulation 1979;60:1045–52. [PubMed: 487538]
15. Glassman AH, Bigger JT Jr, Giardina EV, Kantor SJ, Perel JM, Davies M. Clinical characteristics of imipramine-induced orthostatic hypotension. Lancet 1979;1:468–72. [PubMed: 85056]
16. Roose SP, Glassman AH, Giardina EG, Walsh BT, Woodring S, Bigger JT. Tricyclic antidepressants in depressed patients with cardiac conduction disease. Arch Gen Psychiatry 1987;44:273–5. [PubMed: 3827520]
17. Glassman AH, Roose SP, Bigger JT Jr. The safety of tricyclic antidepressants in cardiac patients. Risk-benefit reconsidered. JAMA 1993;269:2673–5. [PubMed: 8487453]

18. Crome P, Newman B. Fatal tricyclic antidepressant poisoning. J R Soc Med 1979;72:649–53. [PubMed: 552568]
19. Callaham M, Kassel D. Epidemiology of fatal tricyclic antidepressant ingestion: implications for management. Ann Emerg Med 1985;14:1–9. [PubMed: 3964996]
20. Hulten BA. TCA poisoning treated in the intensive care unit. Pharmacopsychiatry 1990;23(Suppl 1): 14–6. [PubMed: 2408086]
21. Bigger JT, Giardina EG, Perel JM, Kantor SJ, Glassman AH. Cardiac antiarrhythmic effect of imipramine hydrochloride. N Engl J Med 1977;296:206–8. [PubMed: 318730]
22. Giardina EG, Bigger JT Jr. Antiarrhythmic effect of imipramine hydrochloride in patients with ventricular premature complexes without psychological depression. Am J Cardiol 1982;50:172–9. [PubMed: 6178282]
23. Giardina EG, Barnard T, Johnson L, Saroff AL, Bigger JT Jr, Louie M. The antiarrhythmic effect of nortriptyline in cardiac patients with ventricular premature depolarizations. J Am Coll Cardiol 1986;7:1363–9. [PubMed: 3711494]
24. Biederman J. Sudden death in children treated with a tricyclic antidepressant. J Am Acad Child Adolesc Psychiatry 1991;30:495–8. [PubMed: 2055889]
25. Boeck V, Jorgensen A, Fredricson Overo K. Comparative animal studies on cardiovascular toxicity of tri- and tetracyclic antidepressants and citalopram; relation to drug plasma levels. Psychopharmacology (Berl) 1984;82:275–81. [PubMed: 6427813]
26. Overo, KF. Citalopram: A New Antidepressant from Lundbeck Research. Montgomery, SA., editor. Amsterdam, The Netherlands: Excerta Medica; 1989. p. 22-30.
27. Wong DT, Bymaster FP, Engleman EA. Prozac (fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: twenty years since its first publication. Life Sci 1995;57:411–41. [PubMed: 7623609]
28. Zarzar MN, Kingsley RS. Use of fluoxetine in a person with cardiac arrhythmias. Psychosomatics 1990;31:235–6. [PubMed: 1691856]
29. Roose SP, Glassman AH, Attia E, Woodring S, Giardina EG, Bigger JT Jr. Cardiovascular effects of fluoxetine in depressed patients with heart disease. Am J Psychiatry 1998;155:660–5. [PubMed: 9585718]
30. Roose SP. Treatment of depression in patients with heart disease. Biol Psychiatry 2003;54:262–8. [PubMed: 12893102]
31. Pacher P, Ungvari Z. Use of selective serotonin reuptake inhibitors and myocardial infarction. Circulation 2002;105:e84. [PubMed: 11940561]
32. Enemark B. The importance of ECG monitoring in antidepressant treatment. Nord J Psychiatry 1993;47(suppl 30):57–65.
33. Buff DD, Brenner R, Kirtane SS, Gilboa R. Dysrhythmia associated with fluoxetine treatment in elderly patients with cardiac disease. J Am Psychiatry 1991;52:174–176.
34. Friedman EH. Fluoxetine-induced bradycardia. J Clin Psychiatry 1991;52:174–176. [PubMed: 2016253]
35. Friedman EH. The role of the right hemisphere in fluoxetine-induced bradycardia and syncope [letter]. J Clin Psychiatry 1991;52:138–139. [PubMed: 2005081]
36. Gardner SF, Rutherford WF, Munger MA, Panacek EA. Drug-induced supraventricular tachycardia:a case repore of fluoxetine. Ann Emerg Med 1991;20:194–7. [PubMed: 1996805]
37. Spier SA, Frontera MA. Unexpected deaths in depressed medical patients treated with fluoxetine. J Clin Psychiatr 1991;52:377–382.
38. Masquelier I, Saint JO, Bourdiol MC, Boiffin A, Bouchon JP. Bradycardia and hypothermia in an elderly patient receiving fluoxetine. Presse Med 1993;22:553–58. [PubMed: 8511088]
39. Drake WM, Gordon GD. Heart block in a patient on propranolol and fluoxetine. Lancet 1994;343:425–426. [PubMed: 7905586]
40. Hussein S, Kaufman BM. Bradycardia associated with fluoxetine in an elderly patient with sick sinus syndrome. Postgrad Med J 1994;70:56–60. [PubMed: 8140029]
41. Roberge RJ, Martin TG. Mixed fluoxetine loxapine overdose and atrial flutter. Ann Emerg Med 1994;23:586–590. [PubMed: 8135440]

42. Appleby M, Mbewu A, Clarke B. Fluoxetine and ventricular torsade-is there a link? Int J Cardiol 1995;49:178–180. [PubMed: 7628890]

43. Graudins A, Vossler C, Wang R. Fluoxetine-induced cardiotoxicity with response to bicarbonate therapy. Am J Emerg Med 1997;15:501–503. [PubMed: 9270390]

44. Anderson J, Compton SA. Fluoxetine induced bradycardia in presenile dementia. Ulster Med J 1997;66:144–145. [PubMed: 9414948]

45. Marchiando RJ, Cook MD. Probable terfenadine-fluoxetine-associated cardiac toxicity. Ann Pharmacotherapy 1995;29:937–38.

46. Ravina T, Suarez ML, Mendez-Castrillon J. Fluoxetine-induced QTU interval prolongation, T wave alternans and syncope. Int J Cardiol 1998;65:311–3. [PubMed: 9740491]

47. Neely JL. Tonic clonic seizures and tachycardia induced by fluoxetine (Prozac) overdose. WV Med J 1998;94:283–5.

48. Ellison JM, Milofsky JE, Ely E. Fluoxetine- induced bradycardia and syncope in two patients. J Clin Psychiatry 1990;51:385–386. [PubMed: 2211552]

49. Cherin P, Colvez A, Deville de Periere G, Sereni D. Risk of syncope in the elderly and consumption of drugs: a case-control study. J Clin Epidemiol 1997;50:313–320. [PubMed: 9120531]

50. McAnally LE, Threlkeld KR, Dreyling CA. Case report of a syncopal episode associated with fluoxetine. Ann Pharmacother 1992;26:1091–1091.

51. Sternbach H. Fluoxetine-associated potentiation of calcium-channel blockers. J Clin Psychopharmacol 1991;11:390–91. [PubMed: 1770159]

52. Livshits ATL, Danenberg HD. Tachycardia, orthostatic hypotension and profound weakness due to concomitant use of fluoxetine and nifedipine. Pharmacopsychiatry 1997;30:274–275. [PubMed: 9442553]

53. Rich JM, Njo L, Roberts KW, Smith KP. Unusual hypotension and bradycardia in a patient receiving fenfluramine, phentermine and fluoxetine. Anesthesiology 1998;88:529–531. [PubMed: 9477076]

54. Langlois RP, Paquette D. Sustained bradycardia during fluvoxamine and buspirone intoxication. Can J Psychiatry 1994;39:126–7. [PubMed: 8149317]

55. Konig F, Hafele M, Hauger B, Loble M, Wossner S, Wolfersdorf M. Bradycardia after beginnig therapy with metaprolol and paroxetine. Psychiart Prax 1996;23:244–5.

56. Erfurth A, Loew M, Dobmeier P, Wendler G. ECG changes after paroxetine. 3 case reports. Nervenarzt 1998;69:629–31. [PubMed: 9715482]

57. Personne M, Persson H, Sjoberg G. Picture of poisoning in citalopram overdose. Convulsions and ECG Symptoms can occur. Lakartidningen 1997;94:1603–4. [PubMed: 9182160]

58. Rodriguez de la Torre B, Dreher J, Malevany I, Bagli M, Kolbinger M, Omran H, et al. Serum levels and cardiovascular effects of tricyclic antidepressants and selective serotonin reuptake inhibitors in depressed patients. Ther Drug Monit 2001;23:435–40. [PubMed: 11477329]

59. Cherin P, Colvez A, Deville de Periere G, Sereni D. Risk of syncope in the elderly and consumption of drugs: a case-control study. Clin Epidemiol 1997;50:313–20.

60. Fuller RW, Holland DR, Yen TT, Bemis KG, Stamm NB. Antihypertensive effects of fluoxetine and L-5-hydroxytryptophan in rats. Life Sci 1979;25:1237–42. [PubMed: 316092]

61. Pacher P, Ungvari Z, Kecskemeti V, Koller A. Serotonin reuptake inhibitor, fluoxetine, dilates isolated skeletal muscle arterioles. Possible role of altered Ca2+ sensitivity. Br J Pharmacol 1999;127:740–6. [PubMed: 10401565]

62. Ungvari Z, Pacher P, Koller A. Serotonin reuptake inhibitor fluoxetine decreases arteriolar myogenic tone by reducing smooth muscle [Ca2+]i. J Cardiovasc Pharmacol 2000;35:849–54. [PubMed: 10836717]

63. Pacher P, Ungvari Z, Kecskemeti V, Friedmann T, Furst S. Serotonin reuptake inhibitors fluoxetine and citalopram relax intestinal smooth muscle. Can J Physiol Pharmacol 2001;79:580–4. [PubMed: 11478591]

64. Ungvari Z, Pacher P, Kecskemeti V, Koller A. Fluoxetine dilates isolated small cerebral arteries of rats and attenuates constrictions to serotonin, norepinephrine, and a voltage-dependent Ca(2+) channel opener. Stroke 1999;30:949–54. [PubMed: 10229726]

65. Rawling D, Fozzard H. Effects of imipramine on cellular electrophisiological properties of cardiac Purkinje fibers. J Pharmacol Exp Ther 1979;209:371–375. [PubMed: 439013]

66. Tamargo J, Rodriguez S. Electrophysiological actions of chlorimipramine on guinea-pig ventricular fibres. Experimentia 1979;35:366–7.

67. Rodriguez S, Tamargo J. Elektrophysiological effects of imipramine on bovine ventricular muscle and Purkinje fibres. Br J Pharmacol 1980;70:15–20. [PubMed: 7426828]

68. Wang CM, Parker CH Jr, Maxwell RA. Electrophysiological Effects of Antidepressants on Mammalian Hearts and Crayfish Giant Axon. J Cardiovasc Pharmacol 1981;3:101–112. [PubMed: 6160339]

69. Muir WW, Strauch SM, Schaal SF. Effects of tricyclic antidepressant drugs on the electrophysiological properties of dog Purkinje fibers. J Cardiovasc Pharmacol 1982;4:82–90. [PubMed: 6176805]

70. Delpon E, Tamargo J, Sanchez-Chapula J. Further characterization of the effects of imipramine on plateau currents in guinea-pig ventricular myocytes. N-S Arch Pharmacol 1991;344:645–652.

71. Valenzuela C, Chapula SJ, Delpon E, Elizalde A, Perez O, Tamargo J. Imipramine Blocks Rapidly Activating and Delays Slowly Activating K^+ Current Activation in Guinea Pig Ventricular Myocytes. Circ Res 1994;74:687–699. [PubMed: 8137505]

72. Delpon E, Tamargo J, Sanchez-Chapula J. Effects of imipramine on the transient outward current in rabbit atrial single cells. Br J Pharmacol 1992;106:464–469. [PubMed: 1382783]

73. Casis O, Sanchez-Chapula JA. Mechanism of block of cardiac transient outward K^+ current (I(to)) by antidepressant drugs. J Cardiovasc Pharmacol 1998;32:527–34. [PubMed: 9781920]

74. Giles WR, Imaizumi Y. Comparison of potassium currents in rabbit atrial and ventricular cells. J Physiol 1988;405:123–145. [PubMed: 2855639]

75. Isenberg G, Tamargo J. Effect of imipramine on calcium and potassium currents in isolated bovine ventricular myocytes. Eur J Pharmacol 1985;108:121–131. [PubMed: 2579831]

76. Rouet RH, Tisne-Versalles J, Adamantidis MM, Vincent A, Dupuis BA. Fundam Comparative *in vivo* and *in vitro* study of the cardiac effects of midalcipran and imipramine. Clin Pharmacol 1989;3:237–44.

77. Delpón E, Valenzua C, Tamargo J. Tonic and frequency dependent V_{max} block induced by imipramine in guinea-pig ventricular muscle fibres. J Cardiovasc Pharmacol 1990;15:414–420. [PubMed: 1691365]

78. Manzanares J, Tamargo J. Electrophysiological effects of imipramine in nontreated and in imipramine pretreated rat atrial fibres. Br J Pharmacol 1983;79:167–175. [PubMed: 6871541]

79. Matsuo S. Comparative effects of imipramine and propranolol on the transmembrane potentials of the isolated rabbit atria. Jpn J Pharmacol 1967;17:279–286. [PubMed: 4384072]

80. Shibata E, Drury T, Refsum H, Aldrete V, Giles W. Contribution of a transient outward current to repolarization in human atrium. Am J Physiol 1989;257:H1773–1781. [PubMed: 2557769]

81. Ogata N, Narahashi T. Block of sodium channels by psychotropic drugs in single guinea-pig cardiac myocytes. Br J Pharmacol 1989;97:905–913. [PubMed: 2547491]

82. Escande D, Coulombe A, Faivre J, Deroubaix E, Coraboeuf E. Two types of transient outward currents in adult human atrial cells. Am J Physiol 1987;252:H142–H148. [PubMed: 3028160]

83. Casis O, Sanchez-Chapula JA. Mechanism of block of cardiac transient outward K^+ current (I(to)) by antidepressant drugs. J Cardiovasc Pharmacol 1998;32:527–34. [PubMed: 9781920]

84. Pacher P, Magyar J, Szigligeti P, Banyasz T, Pankucsi C, Korom Z, et al. Electrophysiological effects of fluoxetine in mammalian cardiac tissues. Naunyn Schmiedebergs Arch Pharmacol 2000;361:67–73. [PubMed: 10651149]

85. Magyar J, Rusznak Z, Harasztosi C, Kortvely A, Pacher P, Banyasz T, et al. Differential effects of fluoxetine enantiomers in mammalian neural and cardiac tissues. Int J Mol Med 2003;11:535–42. [PubMed: 12632110]

86. Pacher P, Bagi Z, Lako-Futo Z, Ungvari Z, Nanasi PP, Kecskemeti V. Cardiac electrophysiological effects of citalopram in guinea pig papillary muscle comparison with clomipramine. Gen Pharmacol 2000;34:17–23. [PubMed: 10793264]

87. Mitchell MR, Powell T, Terrar DA, Twist VW. The effects of ryanodin, EGTA and low-sodium on action potentials in rat and guinea-pig ventricular myocytes:evidence for two inward currents during the plateau. Br J Pharmacol 1990;81:543–550. [PubMed: 6320942]

88. Khalifa M, Daleau P, Drolet B, Turscon. Block of sodium channels underlies unheraldded cardiac toxicity observed with the antidepressant agent venlafaxine. J Mol Cell Cardiol 1998;30:A136.

89. Tytgat J, Maertens C, Daenens P. Effect of fluoxetine on a neuronal, voltage-dependent potassium channel (Kv1.1). Br J Pharmacol 1997;122:1417–1424. [PubMed: 9421290]

90. Pancrazio JJ, Kamatchi GL, Roscoe AK, Lynch C. Inhibition of neuronal Na+ channels by antidepressant drugs. J Pharmacol Exp Ther 1998;284:208–214. [PubMed: 9435180]

91. Farrugia G. Modulation of ionic currents in isolated canine and human jejunal circular smooth muscle cells by fluoxetine. Gastroenterology 1996;110:1438–45. [PubMed: 8613049]

92. Reeve HL, Nelson DP, Archer SL, Weir EK. Effects of fluoxetine, phentermine and venlafaxine on pulmonary arterial pressure and electrophysiology. AJP 1999;276:L213–219.

93. Choi JS, Hahn SJ, Rhie DJ, Yoon SH, Jo VH, Kim MS. Mechanism of fluoxetine block of cloned voltage-activated potassium channel Kv1.3. J Pharmacol Exp Ther 1999;291:1–6. [PubMed: 10490879]

94. Thomas D, Gut B, Wndt-Nordahl G, Kiehn J. The antidepressant drug fluoxetine is an inhibitor of human ether-a-go-go-related gene (HERG) potassium channels. J Pharmacol Exp Ther 2002;300:543–8. [PubMed: 11805215]

95. Park KS, Kong IK, Park KC, Lee JW. Fluoxetine inhibits L-type Ca2+ and transient outward K+ currents in rat ventricular myocytes. Yonsei Med J 1999;40:144–151. [PubMed: 10333718]

96. Stauderman KA, Gandhi VC, Jones DJ. Fluoxetine-induced inhibition of synaptosomal (^{3}H)5-HT release: possible Ca^{2+}-channel inhibition. Life Sci 1992;50:2125–2138. [PubMed: 1608295]

97. Deák F, Lasztóczi B, Pacher P, Petheö GL, Kecskeméti V, Spät A. Inhibition of voltage-gated calcium channels by fluoxetine in rat hippocampal pyramidal cells. Neuropharmacol 2000;39:1029–1036.

98. Choi BH, Choi JS, Ahn HS, Kim MJ, Rhie DJ, Yoon SH, et al. Fluoxetine blocks cloned neuronal A-type K+ channels Kv1.4. Neuroreport 2003;14:2451–5. [PubMed: 14663209]

99. Choi JS, Choi BH, Ahn HS, Kim MJ, Rhie DJ, Yoon SH, et al. Mechanism of block by fluoxetine of 5-hydroxytryptamine3 (5-HT3)-mediated currents in NCB-20 neuroblastoma cells. Biochem Pharmacol 2003;66:2125–32. [PubMed: 14609737]

100. Terstappen GC, Pellacani A, Aldegheri L, Graziani F, Carignani C, Pula G, et al. The antidepressant fluoxetine blocks the human small conductance calcium-activated potassium channels SK1, SK2 and SK3. Neurosci Lett 2003;346:85–8. [PubMed: 12850554]

101. Wang SJ, Su CF, Kuo YH. Fluoxetine depresses glutamate exocytosis in the rat cerebrocortical nerve terminals (synaptosomes) via inhibition of P/Q-type Ca2+ channels. Synapse 2003;48:170–7. [PubMed: 12687635]

102. Kobayashi T, Washiyama K, Ikeda K. Inhibition of G protein-activated inwardly rectifying K+ channels by fluoxetine (Prozac). Br J Pharmacol 2003;138:1119–28. [PubMed: 12684268]

103. Hajdu P, Ulens C, Panyi G, Tytgat J. Drug- and mutagenesis-induced changes in the selectivity filter of a cardiac two-pore background K+ channel. Cardiovasc Res 2003;58:46–54. [PubMed: 12667945]

104. Bian JT, Yeh JZ, Aistrup GL, Narahashi T, Moore EJ. Inhibition of K+ currents of outer hair cells in guinea pig cochlea by fluoxetine. Eur J Pharmacol 2002;453:159–66. [PubMed: 12398899]

105. Witchel HJ, Pabbathi VK, Hofmann G, Paul AA, Hancox JC. Inhibitory actions of the selective serotonin re-uptake inhibitor citalopram on HERG and ventricular L-type calcium currents. FEBS Lett 2002;512:59–66. [PubMed: 11852052]

106. Maertens C, Droogmans G, Verbesselt R, Nilius B. Block of volume-regulated anion channels by selective serotonin reuptake inhibitors. Naunyn Schmiedebergs Arch Pharmacol 2002;366:158–65. [PubMed: 12122503]

107. Pato MT, Murphy DL, Devane CL. Sustained plasma concentrations of fluoxetine/or norfluoxetine four or eight weeks after fluoxetine discontinuation. J Clin Psychopharmacol 1991;11:224–225. [PubMed: 1741813]

108. Potter, WZ.; Hollister, L. Basic and Clinical Pharmacology Antipsychotic agents and lithium. Katzung, B., editor. New York: McGraw-Hill Company; 2001. p. 478-97.

109. Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, et al. Aripiprazole, a novel antipsychotic is a high-affinity partial agonist at human D2 receptors. J Pharmacol Exp Ther 2002;302:381–89. [PubMed: 12065741]
110. Jordan S, Koprivica V, Chen R, Tottori K, Kikuchi T, Altar CA. The antipsychotic aripiprazole as a potent partial agonist at the human 5-HT1A receptor. Eur J Pharmacol 2002;441:137–40. [PubMed: 12063084]
111. Taylor DM. Aripiprazole: a review of its pharmacology and clinical use. Int J Clin Pract 2003;63:49–54. [PubMed: 12587943]
112. Henderson RA, Lane S, Henry JA. Life-threatening ventricular arrhythmia (torsades de pointes) after haloperidol overdose. Hum Exp Toxicol 1991;10:59–62. [PubMed: 1673626]
113. Metzger E, Friedman R. Prolongation of the corrected QT and torsades de pointes cardiac arrhythmia associated with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993;13:128–32. [PubMed: 8463445]
114. Committee on Safety of Medicines. QT interval prolongation with antipsychotics. Curr Problems in Pharmacovigilance 2001;27:4.
115. Krahenbuhl S, Sauter B, Kupferschmiedt H, Krause M, Wyss PA, Meier PJ. Case report: reversible QT prolongation with torsades de pointes in a patient with pimozide interaction. Am J Med Sci 1995;309:315–6. [PubMed: 7771501]
116. Barnett AA. Safety concerens over antipsychotic drug, sertindole. Lancet 1996;348:256–57.
117. Pezawas I, Quinner S, Moertl D, Tauscher J, Barnes C, Kufferle B, et al. Efficacy, cardiac safety and tolerability of sertindole: a drug surveillance. In Clin Psychopharmacol 2000;15:207–14.
118. Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsades de pointes, suddend death. Am J Psychiatry 2001;158:1774–82. [PubMed: 11691681]
119. Warner JP, Barnes TR, Henry JA. Electrocardiographic changes in patients receiving neuroleptic medication. Acta Psychiatr Scand 1996;93:311–3. [PubMed: 8712033]
120. Bucley NA, Whyte JM, Dawson AH. Cardiotoxicity more common in thioridazine overdose than with other neuroleptics. J Toxicol Clin Toxicol 1995;33:199–204. [PubMed: 7760442]
121. Lande G, Drouin E, Gauthier C, Chevallier JC, Godin JF, Chiffoleau A, et al. Arrhythmogenic effects of sultopride chlorhydrate clinical and cerllular electrophysiological correlation. Ann Fr Anaesth Reanim 1992;11:629–35.
122. Gajwani P, Pozuelo L, Tesar GE. QT interval prolongation associated with quietapine (Seroquel) overdose. Psychosomatica 2000;31:63–5.
123. Beelen AP, Yeo KT, Lewis LD. Asymptomatic QTc prolongation associated with quetiapine fumarate overdose in a patient being treated with risperidone. Hum Exp Toxicol 2001;20:215–219. [PubMed: 11393275]
124. Angelink MW, Majewski T, Wurthmann C, Lukas K, Ullrich H, Linka T, et al. Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisupride, olanzapine, sertindole and clozapine. J Clin Psychopharmacol 200;21:8–13.
125. Ravin DS, Levenson JW. Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997;31:867–70. [PubMed: 9220048]
126. Zarate CA, Baldessarini RJ, Siegel AJ, Nakamura A, McDonald J, Muir-Hutchinson LA, et al. Risperidone in elderly: a pharmacoepidemiologic study. J Clin Psychiatry 1997;58:311–7. [PubMed: 9269252]
127. Psychopharmacological Drugs Advisory Committee: Briefing document for Zeldox capsules (Ziprasidone HCl) The Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services; Rockville, MD; 18 July 2000; NDA-825: 1–173.
128. Mehtonen OP, Aranko K, Malkonen L, Vapaatalo H. A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. Acta Pschaitr Scand 1991;84:58–64.
129. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000;355:1048–52. [PubMed: 10744090]
130. Flockhart DA, Drici MD, Kerbusch T, Soukhova N, Richard E, Pearle PL, et al. Studies on the mechanism of fatal clarithromycinpimozide interaction in a patient with Tourette syndrome. J Clin Psychopharmacol 2000;20:317–24. [PubMed: 10831018]

131. Hunt N, Stern TA. The association between intravenous haloperidol and torsade de pointes three cases and a literature review. Psychosomatics 1995;36:541–49. [PubMed: 7501784]
132. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. Arch Gen Psychiatry 2001;58:1161–1167. [PubMed: 11735845]
133. Czekalla J, Beasley CM Jr, Delva MA, Berg PH, Grundy S. Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis. J Clin Psychiatry 2001;62:191–98. [PubMed: 11305706]
134. Suspension of Avaialbility of Serdolect (Sertindole). London, UK Department of Health. Committee on Safety of Medicine, Dec2, 1998
135. Ruschena D, Mullen PE, Burgess P, Cordner SM, Barry-Walsh J, Drummer OH, et al. Sudden death in psychiatric patients. Br J Psychiatry 1998;172:331–336. [PubMed: 9715336]
136. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry 2000;177:212–21. [PubMed: 11040880]
137. Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999;354:1841–1845. [PubMed: 10584719]
138. Hagg S, Spigset O, Bate A, Sonderstorm DG. Myocarditis releted to clozapine treatment. J Clin Psychopharmacol 2001;21:382–388. [PubMed: 11476122]
139. Capel MM, Colbridge MG, Henry JA. Overdose profiles of new antipsychotic agents. Int J Neuropsychopharmacol 2000;3:51–4. [PubMed: 11343578]
140. Sheridan DJ. Drug-onduced proarrhythmic effects: assessment of changes in QT interval. Br J Clin Pharmacol 2000;50:297–302. [PubMed: 11012551]
141. Witchel HJ, Hancox JC. Familial and acqired long QT syndrome and the cardiac rapid delayed rectifier potassium current. Clin Exp Pharmacol Physiol 2000;27:753–66. [PubMed: 11022966]
142. DeCicco M, et al. Pharmacokinetic and pharmcodynamic effects of high doses continous intravenous verapamil infusion. Crtl Care Med 1999;27:332–339.
143. Winters SL, Schetzer P, Kupersmith J, Gomes JA. Verpamil-induced polyporphous ventricular tachycardia. J Am Coll Cardiol 1985;6:257–259. [PubMed: 4008783]
144. Roden DM. Acquired long QT syndromes and the risk of proarrhythmia. J Cardiovasc Electrophysiol 2000;11:938–940. [PubMed: 10969760]
145. Drolet B, Zhang S, Deschenes D, Rail J, Nadeau S, Zhou Z, et al. Droperidol lengthens cardiac repolarization due to block of the rapid component of the delayed rectifier potassium current. J Cardiovasc Electrophysiol 1999a;10:1597–1604. [PubMed: 10636190]
146. Suessbrich H, Schönherr R, Heinemann SH, Attali B, Lang F, Busch AE. The inhibitory effect of the antipsychotic drug haloperidol on HERG potassium channels expressed in Xenopus oocytes. Br J Pharmacol 1997;120:968–74. [PubMed: 9138706]
147. Kongsamut S, Kang J, Chen XL, Roehr J, Rampe D. A comparison of the receptor binding and HERG channel affinities for a series of antipsychotic drugs. Europ J Pharmacol 2002;450:37–41.
148. Crumb, WJ.; Beasley, CM., Jr; Thornton, A.; Breier, A. Cardiac ion channel blocking profile of olanzapine and other antipsychotics. 38th Annual Meeting American College of Neuropsychopharmacology; Acapulco, Mexico. 1999.
149. Drolet B, Vincent F, Rail J, Chahine M, Deschenes D, Nadeau S, et al. Thioridazine lengthens repolarization of cardiac ventricular myocytes by blocking the delayed rectifier potassium current. J Pharmacol Exp Ther 1999b;288:1261–68. [PubMed: 10027867]
150. Shuba YM, Degtiar VE, Osipenko VN, Naidenov VG, Woosley RL. Testosterone-mediated modulation of HERG blockade by proarrhythmic agents. Biochem Pharmacol 2001;62:41–9. [PubMed: 11377395]
151. Magyar J, Bányász T, Bagi Zs, Pacher P, Szentandrassy N, et al. Electrophyssiological effects of risperidone inmammalian cardiac cells. Naunyn Schmiedebergs Arch Pharmacol 2002;366:350–6. [PubMed: 12237749]
152. Gluais P, Bastide M, Caron J, Adamantidis M. Risperidone prolongs cardiac action potential through reduction of K+ currents in rabbit myocytes. Eur J Pharmacol 2002;444:123–32. [PubMed: 12063072]

153. Rampe D, Murawsky MK, Grau J, Lewis EW. The antipsychotic agent sertindole is a high affinity antagonist of the human cardiac potassium channel HERG. J Pharmacol Exp Ther 1998;286:788–93. [PubMed: 9694935]
154. Kang UG, Kwon JS, Ahn YM, Chung SJ, Ha JH, Koo ZJ, et al. Electrocardiographic abnormabilities in patients treated with clozapine. J Clin Psychiatry 2000;61:441–46. [PubMed: 10901343]
155. Drolet B, Yang T, Daleau P, Roden DM, Turgeon J. Risperidone prolong cardiac repolariyation by blocking the rapid component of the delayed rectifier potassium current. J Cardiovasc Pharmacol 2003;41:934–37. [PubMed: 12775973]
156. Enyeart JJ, Dirksen RT, Sharma VK, Williford DJ, Sheu SS. Antipsychotic pimozide is a potent Ca2+ channel blocker in heart. Mol Pharmacol 1990;37:752–757. [PubMed: 2160063]
157. Kang J, Chen XL, Rampe D. The antipsychotic drugs sertindole and pimozide block erg3, a human brain K+ channel. Biochem Biophys Res Commun 2001;286:499–504. [PubMed: 11511086]
158. Tie H, Walker BD, Valenzuela SM, Breit SN, Campbell TJ. The heart of psychotropic drug therapy. Lancet 2000;355:1825. [PubMed: 10832858]
159. Drici MD, Wang WX, Liu XK, Woosley RL, Flockhart DA. Prolongation of QT interval in isolated feline hearts by antipsychotic drugs. J Clin Psychopharmacol 1998;18:477–81. [PubMed: 9864081]
160. Abbott GW, Sesti F, Splawski I, Buck M, Lehmann MH, Timothy KW, et al. MiRpP1 forms IKr potassium with HERG and is associated with cardiac arrhythmia. Cell 1999;97:175–87. [PubMed: 10219239]
161. vonMoltke LL, Greenblatt DJ, Schmide J, Wright CE, Harmatz JS, Shader RJ. *In vitro* approaches to predicting drug interactions *in vivo*. Biochem 1998;55:113–22.
162. Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Anzelevitch C, et al. The potential for QT prolongation and pro-arrhythmia by non- antiarrhythmic drugs: Clinical and regulatory implications. Report on a Policy Conference of the European Society of Cardiology. Cardiovasc Res 2000;47:219–33. [PubMed: 10947683]
163. Fermini B, Fossa AA. The impact of drug-induced QT interval prolongation on drug discovery and development. Nature Review 2003;2:439–47.
164. Ito K, Nakayawa K, Koiyumi S, Liu M, Takeuchi K, Hashimoto T, et al. Inhibition of antipszchotic drugs of L/type Ca2+ channel current in PC12 cells. Eur J Pharmacol 1996;314:143–50. [PubMed: 8957230]
165. Gessner G, Heinemann SH. Inhibition of hEAG1 and HERG1 potassium channels by clofilium and its tertiary analogue LY97241. Br J Pharmacol 2003;138:161–71. [PubMed: 12522086]
166. Habuchi Y, Furukawa T, Tanaka H, Tsujimura Y, Yoshimura M. Block of Na+ channels by imipramine in guinea-pig cardiac ventricular cells. J Pharmacol Exp Ther 1991;256:1072–1081. [PubMed: 1848626]
167. Bou-Abboud E, Nattel S. Molecular mechanisms of the reversal of imipramine-induced sodium channel blockade by alkalinization in human cardiac myocytes. Cardiovasc Res 1998;38:395–404. [PubMed: 9709400]
168. Teschemacher AG, Seward EP, Hancox JC, Witchel HJ. Inhibition of the current of the heterologously expressed HERG potassium channels by imipramine and amitriptyline. Brit J Pharmacol 1999;128:479–485. [PubMed: 10510461]
169. Jo SH, Youm JB, Lee CO, Earm YE, Ho WK. Blockade of the HERG human cardiac K + channel by the antidepressant drug amitriptyline. Brit J Pharmacol 2000;129:1474–1480. [PubMed: 10742304]
170. Barber M, Starmer CF, Grant AO. Blockade of cardiac sodium channels by amitriptyline and diphenylhidantoin. Evidence for two use-dependent binding sites. Circ Res 1991;69:677–696. [PubMed: 1651817]
171. Hahn SJ, Cho JS, Rhie DJ, Oh CS, Jo YH, Kim MS. Inhibition by fluoxetine of voltage-activated ion channels in rat PC12 cells. Eur J Pharmacol 1999;367:113–118. [PubMed: 10082273]
172. Hamplova-Peichlova J, Krusek J, Pacit I, Slavicek L, Lisa V, Vyskocil F. Citalopram inhibits L-type calcium channel current in rat cardiomyocytes in culture. Physiol Res 2002;51:317–321. [PubMed: 12234126]
173. de Paulis T. The discovery of epidepride and its analogs as high-affinity radioligands for imaging extrastriatal dopamine D(2) receptors in human brain. Curr Pharm Design 2003;9(8):673–96.

174. Ito C. Analysis of overall gene expression induced by amphetamine and phencyclidine: novel targets for the treatment of drug psychosis and schizophrenia. Curr Pharm Design 2002;8(2):147–53.
175. Takano H, Ohtsuka M, Akazawa H, Toko H, Harada M, Hasegawa H, Nagai T, Komuro I. Pleiotropic effects of cytokines on acute myocardial infarction: G-CSF as a novel therapy for acute myocardial infarction. Curr Pharm Design 2003;9(14):1121–7.

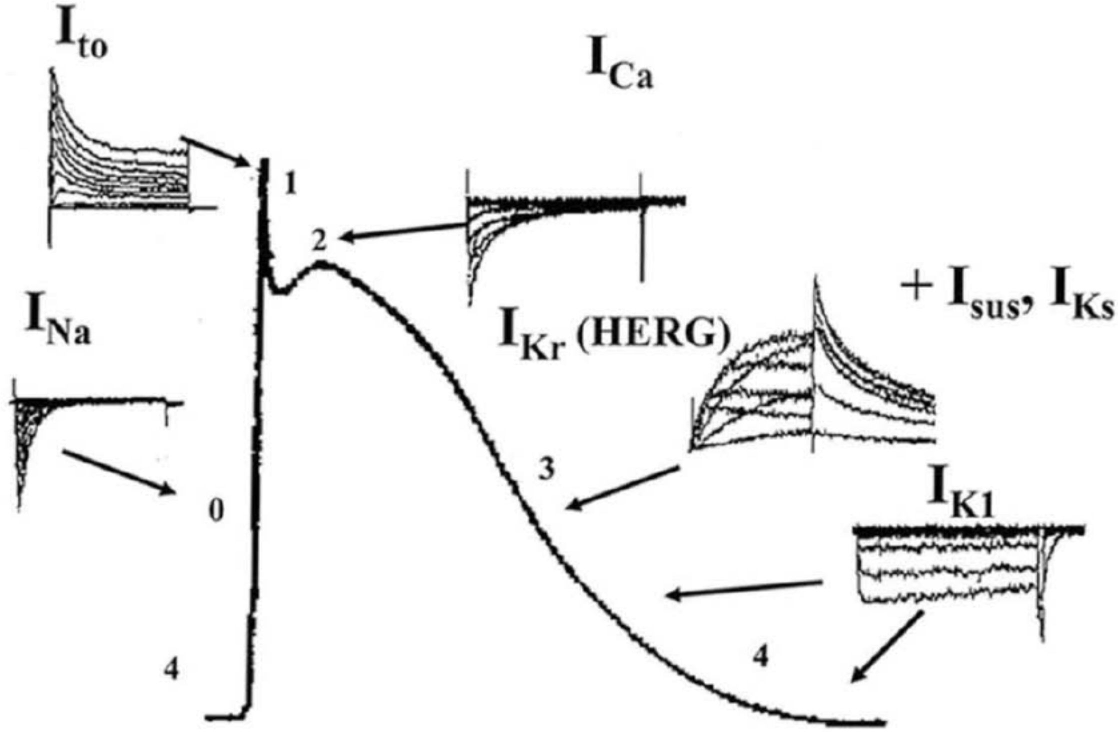

Fig. 1.

Ionic currents during cardiac action potential. Downward reperesents 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.

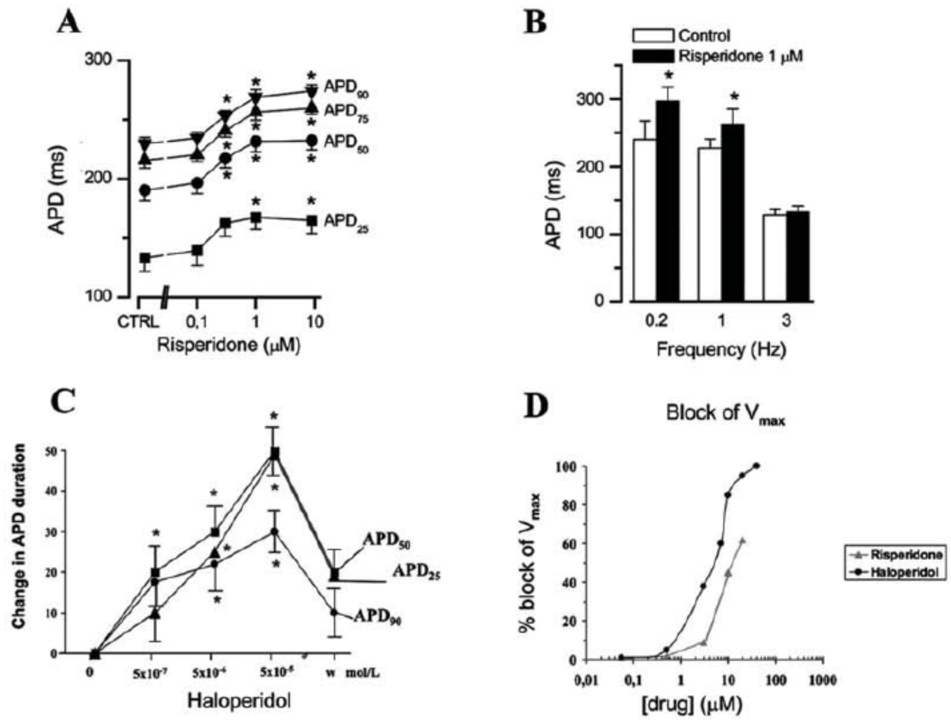

Fig. 2.

Cummulative 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 lenghetening effect of 1 μM risperidone on APD_{90} studied in night guinea-pig ventricular preparations. D: Comparison of the effect of haloperidole (●) and risperidone (▲) on the maximal velocity of depolarization of AP (V_{max}). The effect was demonstrated as the percent change of decrease of V_{max}.

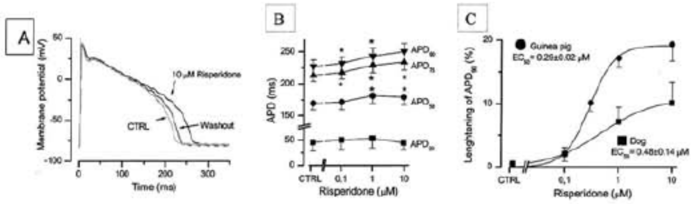

Fig. 3.

Effects of risperidone (10 μM) 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 APD_{90} was normalized to control APD_{90} and expressed as its percent. Solid lines were obtained by fitting the data to the two-state Boltzmann model in order to determine EC_{50} values.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

IC_{50} Values of Antidepressants for Ionic Currents/Channels

Compound	Model system	Potassium channels/currents			Calcium channels/ current	Sodium channels/ currents	References
		KV/delayed rectifier (rapid) I_{Kr}	Transient outward I_{to}	HERG	Ca_L		
				TRICYCLIC DRUGS			
Imipramine	Guinea-pig ventricular myocytes				≥ 1 μM	≥ 1 μM	77
	Rabbit atrial myocytes		≥ 1 μM			≥ 1 μM	72
	Guinea-pig ventricular myocytes	≥ 1 μM					70
	Guinea-pig ventricular myocytes					3μM	166
	Human cardiomyocyes					≥ 1 μM	167
	Rat ventricular myocytes				4 μM	5 μM	95
	CHO			3.4 μM			168
Amitriptyline	CHO			~4 μM 4.7 μM			169 168
	Rabbit atrial and ventricular myocytes					≥ 1 μM	170
	Rat ventricular myocytes				3.75 μM		95
			SELECTIVE SEROTONIN REUPTAKE INHIBITORS				
Fluoxetine	Rat pheochromocytoma (PC12) cell	16 μM			13.4 μM	25.6 μM	171
	HEK - 293			1.5 μM 3.1 μM			105 94
	Rat ventricular myocytes		40 μM		2.8 μM		95
	Canine ventricular myocytes				5.4 μM		84
Citalopram	HEK -293			3.97 μM			105
	Rat ventricular myocytes				≥ 10 μM		172
Sertaline	Rat ventricular myocytes		38 μM		2.3 μM		95
Venlafaxine	Guinea –pig ventricular myocytes					~ 8μM	88

Table 2

IC_{50} Values of Antipsychotics for Ionic Currents/Channels

Compound	Model system	Potassium channels/currents				Calcium channels/ current	Sodium channels/ currents I_{Na}	References
		KV/delayed rectifier I_{Kr}	Transient outward I_{to}	Inward rectifier I_{K1}	HERG	I_{CaL}		
Chlorpromazine	CHO				1.47 µM			157
Clozapine	HEK-293		>50 µM		320 nM		29 µM	148
Droperidol	Ventricular myocytes HEK-293	28 nM			32.2 µM			145
Fluspirilene	Xenopus oocytes				2.34 µM			150
Haloperidol	PC12 cells					20 µM		164
	Ventricular myocytes						5 µM	81
	HEK-293		>10 µM	>100 µM	26.8 nM		14.4 µM	148
					20 nM			165
	Xenopus oocytes				1.36 µM			150
	Xenopus oocytes				1.0 µM			146
Olanzapine	HEK-293		>100 µM	>100 µM	731 nM		>100 µM	148
	CHO				6013 nM			147
Pimozide	HEK-293		>100 µM	>100 µM	54.6 nM		21.9 µM	148
	Xenopus oocytes				1.74 µM			150
	CHO				18 nM			154
Quetiapine	CHO				5765 nM			147
Risperidone	canine ventricular myocytes				0.92 µM			151
	HEK-293		>100 µM	>100 µM	148 nM		>50 µM	148
	CHO				167 nM			147
	CHO				261 nM			155
Sertindole	HEK-293		>10 µM	>10 µM	14 nM		>10 µM	148
	HEK-293			21 µM	14.7 nM			153
	CHO				3 nM			147
Thioridazine	Ventricular myocytes	1.25 µM						149
	tsA201							
	CHO				1.25 µM			
	CHO				1.07 µM			158
	HEK-293				91 nM			147
			27 µM		33.2 nM		7 µM	148
Ziprasidone	HEK-293		>10 µM	> 10 µM	125 nM		>10 µM	148
	CHO				169 nM			147

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