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***Abstract*:** Some antidepressant agents can cause electrophysiological changes of cardiac function leading to ventricular arrhythmias and sudden death. However, antidepressants have also protective effects on the heart through their capacity to modulate cardiac autonomic-mediated physiological responses. Heart rate variability and QTc length are two strictly linked parameters that allow us to appreciate the effects of different drugs on cardiac physiology. Heart rate variability reflects functioning of the autonomic nervous system and possibly also regulation by the limbic system. Autonomic regulation of cardiac activity influences also cardiac repolarization and QT length, both directly and via its effects on heart rate. In this review we present the methodologies adopted to study the effect of antidepressant drugs on QT length and heart rate variability and we summarize data on electrophysiological changes related to antidepressant treatment. Clinical implications for the choice of different antidepressants in different clinical populations are discussed.

***Keywords*:** heart rate, long-QT syndrome, tachyarrhythmias

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Introduction

Psychiatric patients had been identified as a population at risk for cardiovascular problems [Glassman, 2002; Ruschena *et al*. 1998]. Mortality rates are higher in psychiatric patients than in the general population [Politi *et al*. 2002] and the pharmacological treatment itself might produce side-effects that affect mortality through cardiovascular effects [Hannerz and Borga, 2000].

Moreover, major depressive disorder (MDD) predicts incidence of coronary heart disease (CHD) in otherwise healthy individuals [Bloor, 2000; Carney *et al*. 1988] and increases the risk of mortality in people affected by acute coronary syndrome (ACS) [Jiang and Davidson, 2005; Carney and Freedland, 2003; Carney *et al*. 1988].

Electrophysiological changes of cardiac function have been studied in animal models of depression showing that rodents, when exposed to a novel environmental stressor, showed elevated sympathetic cardiac tone and a decreased threshold for ventricular dysrhythmias, with increased heart rate (HR), reduced heart rate variability (HRV) and exaggerated pressor and HR responses [Grippo *et al*. 2004; Carney and Freedland, 2003; Carney *et al*. 1988]. HRV refers to the beat-to-beat alterations in heart rate. Reduced HRV has been used as a marker of reduced vagal activity [Grossman, 1992].

In humans, depression is frequently associated with an upregulation of the inflammatory response system with hyperproduction of proinflammatory cytokines and with dysfunction of the hypothalamic–pituitary–adrenal (HPA) system. These changes may cause increased artery rigidity, remodelling of peripheral arteries and arterial hypertension, finally contributing to development of ischaemic heart disease [Steptoe *et al*. 2003]. Moreover changes in sympathetic tone, cardiac rhythm disturbances, elevated resting heart rate, reduced heart rate variability and a disruption in ventricular electrophysiology may mediate cardiovascular events associated with depressive disorder [Davidson *et al*. 2000]. In particular, at least

three prospective epidemiological studies [Kawachi *et al.* 1994a, 1994b; Haines *et al.* 1987], and one case-crossover study [Mittleman *et al.* 1995] have suggested a relationship between high levels of anxiety and risk of CHD.

Given the susceptibility of depressed patients to develop cardiac dysfunction, it would be very important for clinicians to know electrophysiological properties of antidepressant treatments and the methodologies adopted to study their effect on cardiac electrophysiology. In this review we first introduce the QTc interval and the HRV as markers of arrhytmhogenic risk and the methods adopted to measure these parameters. We then report the data on antidepressants effects on cardiac rhythm. In particular we identified all original research papers and reviews published in English over a 20-year period (1977–2007) that dealt with antidepressant action on QT prolongation, HR, HRV and sympathetic tone, through a comprehensive Medline search (the search terms used were: antidepressant, QT, HRV, sudden death). A manual search of bibliographic cross-referencing complemented this search.

Electrophysiological mechanisms for QT interval prolongation and long-QT-related arrhythmias

During the last few decades, the QT interval has been extensively studied as marker of proarrhythmia. The QT interval is the duration from the beginning of the QRS complex to the end of the T wave of the electrocardiogram and provides an estimate of the time from the earliest ventricular depolarization to the latest ventricular repolarization thus reflecting the duration of the cardiac action potential.

The duration of the cardiac action potential is controlled by a balance between inward (depolarizing) and outward (repolarizing) currents including the fast inward sodium current (INa), the inward slow Ca^{2+} current (ICa) and four potassium currents (IK): the transient outward potassium current (Ito), the rapid component of outward delayed rectifier potassium channel (IKr), the slow component of outward delayed rectifier potassium channel (IKs) and the inward rectifying potassium current (IK1). Drugs that show blocking properties on different ion channels may affect both depolarization and repolarization phases of the action potential, while drugs that selectively block outward currents may lengthen repolarization [Sala *et al.* 2006].

In vitro studies, particularly patch clamp studies, allow the measurement of the degree of ion current block by testing different drugs, the determination of the IC50 (i.e. the concentration required to produce a 50% block of each studied current) and determination of the APD50 and APD90 (the time to achieve 50% or 90% repolarization), two parameters commonly used to quantitatively assess the prolongation of repolarization by pharmacological agents. Patch clamp studies involve the transfer of relevant genes for the various channels into mammalian cell lines, such as human embryo kidney (HEK) cells, mouse fibroblast cells and Chinese hamster ovary cells (CHO), or into *Xenopus* oocytes.

Drugs that are relatively selective for the Ikr channel compared with other cardiac ion channels (e.g. cisapride or sertindole) have virtually superimposable concentration-dependent curves for the inhibition of IKr, and for APD90 and QT-interval prolongation. Those drugs (i.e. sertindole and cisapride) can be associated with torsades de pointes (TdP), a specific, potentially fatal, polymorphic ventricular tachicardia arrhythmia, when plasma drug concentrations enter the range for inhibition of IKr. Conversely, for drugs with mixed ion channel activity, as with the majority of antidepressants, concentrations required for prolongation of APD90 and QT interval are dissociated from those blocking IKr. For these drugs, it is conceivable that the plasma concentration required for arrhythmogenesis could be quite specific; at certain concentrations the combined ion channel effects may interact to produce the right conditions for arrhythmogenesis, with risk of TdP. On the contrary, the arrhythmogenic risk is reduced if the concentrations are above or under the critical point. In fact, interaction with multiple cardiac ion channels can either mitigate or exacerbate the prolongation of APD and QT that would ensue from block of IKr currents alone, and delay of repolarization per se is not necessarily torsadogenic [Sala *et al.* 2006; Redfern *et al.* 2003].

Importantly, in the heart there is an intrinsic heterogeneity of action potential duration, giving rise to dispersion of repolarization [Shimizu and Antzelevitch, 1999]. A drug that delays myocardial repolarization may amplify this intrinsic spatial dispersion of repolarization thus creating a potential substrate for the development of re-entry (return of the same impulse to an already activated zone of the heart muscle)

[Antzelevitch and Shimizu, 2002]. In addition, the longer the cardiac action potential, the higher the likelihood of 'early after' depolarizations (EADs) which are spontaneous depolarizations generated the repolarization action potential and that may act as trigger for TdP.

Some authors have suggested a 30-fold margin between the effective therapeutic plasma concentration and the IC50 value for IKr block as margin of safety relative to the risk of TdP [Redfern *et al.* 2003]. However it is important to notice that it is difficult to relate *in vivo* plasma concentrations to the concentrations of drug perfused in isolated cell preparations, as some factors such as tissue accumulation and presence of active metabolites affect the action of the drug on human myocytes [Delpon *et al.* 1991]. Moreover, the contribution of the different ion currents to the shape and duration of the AP is species dependent. Thus, using different experimental preparations, changes in APD50 and APD90 produced by the same antidepressant, can vary greatly [Witchel *et al.* 2003] particularly for drugs with multiple actions on different ion channels, such as antidepressants. Therefore, information regarding the prolongation of QT by different pharmacological agents that has been obtained in *in vitro* studies is only partially useful when attempting to clarify the effects of those drugs in humans. Also, for each drug, the potential for QT prolongation is not always strictly correlated with the risk of TdP and sudden death.

The discrepancies between the electrophysiological properties of antidepressants and their effects on QT interval may be due, at least partially, to individual susceptibility. In particular, the IKr channel is encoded by the human ether-a-go-go-related gene (HERG), and is the most studied cardiac channel. Mutations in HERG have been shown to cause chromosome-7-linked inherited long QT syndrome (LQT2) [Curran *et al.* 1995] and several drugs that block IKr cause acquired long QT syndrome and TdP [Roy *et al.* 1996].

Many common polymorphisms in the HERG gene are functionally silent, and have been traditionally regarded as benign and without physiological consequences. Subtle modification of IKr by HERG polymorphisms, whether through altered current density or channel kinetics, could indirectly contribute to the proarrhythmic effects of HERG blockers by reducing the repolarization reserve [Saenen *et al.* 2007; Crotti *et al.* 2005; Fitzgerald and Ackerman, 2005]. Finally, QT length is particularly sensitive to changes in heart rate and the duration of previous cardiac lengths.

Recently, Fossa *et al.* [2006, 2005] adopted a methodology commonly used in scientific fields dealing with highly variable relationships, known as bootstrapping, to assess normal changes in the QT interval with autonomic changes in HR. The increased risk of developing arrhythmia and TdP was defined as combinations of QT and RR intervals, as presented as the upper bound of the dynamic beat-to-beat confluence of data, or 'cloud'. The bootstrap sampling method was adopted to represent the non-uniformity of the clouds, and it computes the mathematical centre of the uncorrected beat-to-beat QT value. The authors suggested that QT-RR combinations outside the 95% 'normal' range of such combinations may be associated with an increased arrhythmogenic risk. A joint distribution of QT and RR that represents the normal range of these values for a normal individual was proposed.

Chan *et al.* [2007] have recently converted the QT-RR cloud diagram developed from human preclinical studies into a QT nomogram (QT *vs* HR) which have been shown to accurately predict the arrhythmogenic risk for drug-induced QT prolongation. Particularly, they analysed 130 cases of drug-induced TdP and compared the sensitivity and specificity of the QT nomogram versus the at-risk lines defined by Bazett's formula for cases of drug-induced TdP.

Although Bazett's formulas had a better sensitivity and a similar specificity at QTc = 440 ms versus QT nomogram, sensitivity and specificity of Bazett's formula at QTc = 500 ms performed worse compared with QT nomogram. Moreover authors demonstrated that the QT nomogram performs better than Bazett's formulas when used on an intention-to-treat basis, including patients with tachycardia or bradycardia. Thus, this nomogram attempts to overcome the limitation inherent in the use of population mean correction factors, such as that proposed by Bazzet's formula and represent a useful tool applicable in clinical practice, allowing us to assess many patients as not at risk and therefore not requiring cardiac monitoring.

Heart rate variability

Since the QT interval of the ECG is particularly sensitive to changes in HR and the duration of previous cardiac cycle lengths, during the last few decades, researchers have also focused their attention on changes on HR and HRV following antidepressant treatment. Under resting conditions, the ECG of healthy individuals exhibits periodic variation in R–R intervals. This rhythmic phenomenon, known as respiratory sinus arrhythmia (RSA), fluctuates with the phase of respiration (cardio-acceleration during inspiration, and cardio-deceleration during expiration). RSA is predominantly mediated by respiratory gating of parasympathetic efferent activity to the heart: vagal efferent traffic to the sinus node occurs primarily in phase with expiration and is absent or attenuated during inspiration.

The major reason for the interest in measuring HRV stems from its ability to predict survival after heart attack, independent of other prognostic indicators such as ejection fraction [Turner and Malik, 1995]. Moreover, a small number of studies have begun to suggest that reduced HRV may predict risk of survival even among individuals free of CHD [Sloan *et al*. 1994]. Originally, HRV was assessed manually from calculation of the mean R–R interval and its standard deviation measured on short-term (e.g. 5 min) electrocardiograms (time-domain measurement). Recent developments in microprocessor technology has enabled the calculation of *frequency* measures based on mathematical manipulations performed on the same ECG-derived data [Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996]. Frequency measures involve the spectral analysis of HRV. Briefly, R–R interval data are represented on a tachogram, in which the *y*-axis plots the R–R intervals, and the *x*-axis the total number of beats. Spectral analysis of the tachogram transforms the signal from time to frequency on the *x*-axis, by representing the signal as a combination of sine and cosine waves, with different amplitudes and frequencies. The approach uses Fourier transforms.

The HRV spectrum contains two major components: the high-frequency (0.18–0.4 Hz) component, which is synchronous with respiration and is identical to respiratory sinus arrhythmia (RSA). The second is a low-frequency (0.04 to 0.15 Hz) component that appears to be mediated by both the vagus and cardiac sympathetic nerves. The power of spectral components is the area below the relevant frequencies presented in absolute units (square milliseconds). The total power of a signal, integrated over all frequencies, is equal to the variance of the entire signal. Some investigators have used the ratio of the low-to-high frequency spectra as an index of parasympathetic–sympathetic balance [Ishii *et al*. 1996].

Spectral analysis of long-term HR or heart period (HP) time series can be used to obtain powers in frequency bands such as ultra-low-frequency power (ULF: 0–0.0033 Hz), very-low-frequency power (VLF: 0.0033–0.04 Hz), low-frequency power (LF: 0.04–0.15 Hz), and high-frequency power (HF: 0.15–0.5 Hz). High-frequency power is related to RSA, thus reflecting cardiac vagal function, whereas LF power is mediated dually by vagal and sympathetic systems [Liljeqvist and Edvardsson, 1989; Pomerantz *et al*. 1985; Akselrod *et al*. 1981]. Although controversial, some investigators have used the LF/HF ratios as indicative of sympathovagal interaction [Cacioppo *et al*. 1994; Pagani *et al*. 1986].

Over the past decade, distinguishing deterministic chaos from noise has become an important problem in many diverse fields; for example, physiology [Iasemidis *et al*. 1990], economics [Sugihara *et al*. 1990]. This is due, in part, to the availability of numerical algorithms for quantifying chaos using experimental time series as for determination of HRV. Actually, several investigators have demonstrated the nonlinear nature of the HR or HP time series and have also shown the additional utility of nonlinear measures to the traditionally used time and frequency domain measures [Curione *et al*. 1998; Goldberger and West, 1992; Glenny *et al*. 1991]. In particular, methods exist for calculating correlation dimension (D_2) [Mrowka *et al*. 1996], Kolmogorov entropy [Finn *et al*. 2003], and Lyapunov characteristic exponents [Chen, 2007]. Dimension gives an estimate of the system complexity; entropy and characteristic exponents give an estimate of the level of chaos in the dynamic system.

Lyapunov exponents, which could be used to characterize the dynamic system, quantifies sensitivity of the system to initial conditions. An *m*-dimensional dynamic system has *m* Lyapunov exponents. The presence of positive Lyapunov exponents indicates chaos. It also quantifies the amount of instability or predictability of the system.

Experimental and clinical studies on antidepressant and QTc prolongation

Experimental results obtained using patch clamp studies suggest that at least five antidepressants (imipramine, amitriptyline, citalopram, fluoxetine, maprotiline) may have blocking properties at both ICa [Zahradnik *et al.* 2008; Traboulsie *et al.* 2006] and Ikr [Fossa *et al.* 2007; Jo *et al.* 2000; Teschemacher *et al.* 1999], with imipramine, amitriptyline, citalopram and fluoxetine also blocking INa [Dick *et al.* 2007]. Other antidepressants like fluvoxamine selectively block Ikr [Milnes *et al.* 2003].

Data regarding the *in vitro* and *in vivo* effects of antidepressants on cardiac ion currents and QT interval remain insufficient to correctly understand the profile of risk associated with the use of each drug at a certain dose. Thus, collection of clinical data remain an important source of information on cardiological effects of psychotropic drugs.

Cases of TdP have been reported in patients during mirtazapine treatment [Goodnick *et al.* 2002] or after fluoxetine or citalopram poisoning [Tarabar *et al.* 2008; Kanjanauthai *et al.* 2007; Sala *et al.* 2006]. Moreover Vieweg and Wood reported 13 cases of sudden death in patients treated with tricyclic antidepressants. The agents most commonly associated with TdP were amitriptyline and maprotiline [Vieweg and Wood, 2004]. Moreover desipramine, imipramine and nortriptyline have been reported to cause sudden death in children and old patients [Amitai and Frischer, 2006; Goodnick *et al.* 2002; Wilens *et al.* 1996]. Cardiotoxicity with intraventricular conduction delay and QTc prolongation has been observed after bupropion and venlafaxine overdose [Letsas *et al.* 2006; Curry *et al.* 2005].

Only a very few pharmacological pharmacokinetic–pharmacodynamic studies have examined the time course of QT prolongation after a certain drug ingestion. Variation of QT length over time, after ingestion of doses higher than normally used in clinical practice, gives important information for clinical management of cases of intoxication.

Citalopram is the only antidepressant studied until now through pharmacokinetic–pharmacodynamic (PKPD) studies that included individual-specific HR correction factors. In those studies, authors show a delayed QT prolongation associated with citalopram intoxication that was controlled by rapid administration of charcoal [Friberg *et al.* 2006; Isbister *et al.* 2006]. On the contrary one study reported no significant effects of citalopram on PQ, QRS, or QTc in a prospective study on healthy volunteers ($n = 23$) and in a retrospective study on 1,789 citalopram-treated patients [Rasmussen *et al.* 1999].

Importantly, cases of QT prolongation and also of TdP have also been reported during normal antidepressant treatment, particularly during fluoxetine treatment [Wilting *et al.* 2006; Varriale, 2001; Ravina *et al.* 1998; Appleby *et al.* 1995]. Also, Dubnov [2005] reported the case of a newborn of a mother treated with fluoxetine throughout pregnancy with a prolonged corrected QT interval (QTc) on the initial routine ECG.

There is a clinical entity that can be linked to antidepressant treatment that is associated with high risk of sudden death: Brugada syndrome (BS). This syndrome [Brugada and Brugada, 1992] is characterized by an ECG pattern of downsloping ST-segment elevation in leads V1 to V3 in association with right bundle branch block, with normal QTc interval coupled with sudden death due to primary tachyarrhythmias, including TdP. Ventricular fibrillation is the most commonly terminal arrhythmia.

According to the available data, BS results from amplification of heterogeneities intrinsic to the early phases of the action potential among the different transmural cell types due to a rebalancing of currents active during phase 1, including a decrease in I_{Na} or I_{Ca} or augmentation of any of a number of outward currents [Antzelevitch, 2004].

ST segment elevation occurs as a consequence of the accentuation of the action potential notch eventually leading to loss of the action potential dome in the right ventricular epicardium. Loss of the dome gives rise to a transmural as well as an epicardial dispersion of repolarization. Transmural dispersion is responsible of ST segment elevation and of the creation of a vulnerable window across the ventricular wall whereas the epicardial dispersion gives rise to phase II re-entry which provides the extra systole that captures the vulnerable window, thus precipitating final arrhythmias [Antzelevitch, 2005].

Electrocardiographic findings consistent with the Brugada syndrome have been reported after tricyclic antidepressant overdose [Goldgran-Toledano *et al.* 2002], fluoxetine overdose

[Rouleau *et al*. 2001], desipramine overdose [Akhtar and Goldschlager, 2006; Babaliaros and Hurst, 2002], amitriptyline overdose [Bolognesi *et al*. 1997] mirtazapine overdose [Bolognesi *et al*. 1997], nortriptyline overdose [Tada *et al*. 2001], lithium overdose [Laske *et al*. 2007; Strohmer and Schernthaner, 2007] and during combined treatments with trifluoperazine and loxapine [Rouleau *et al*. 2001], or amitriptyline and a phenotiazine [Rouleau *et al*. 2001].

Antidepressant action in precipitating BS may be related to genetic variant of the sodium channel gene SCN5A. In particular, the SCN5A promoter haplotype (so-called HapB) has been showed to be associated with longer PR and QRS intervals as well as a more exaggerated response to sodium channels blockers [Bezzina *et al*. 2006; Priori and Cerrone, 2005; Napolitano *et al*. 2003]. Antidepressant action on cardiac ion channels and reported cases of QTc prolongation, TdP, Brugada syndrome and sudden death are summarized in Table 1.

Clinical studies on antidepressant and their effect on HRV

Several studies have now suggested a link between negative emotions (such as anxiety, hostility, depression) and reduced HRV. Kawachi *et al*. [1995] reported a cross-sectional association between anxiety and reduced HRV (as assessed by two time-domain measures) in 581 men.

Moreover, different authors [Sullivan *et al*. 2004; Yeragani *et al*. 1993, 1990] have published a series

Table 1. Antidepressant action on cardiac ion channels and reported cases of QTc prolongation, torsades de pointes (TdP), Brugada syndromes and sudden death

	Inhibition of cardiac ionic currents						
	I_{Kr}	I_{Ca}	I_{Na}	QTc prolongation or TdP at therapeutic dosage	Reported cases TdP after poisoning	Reported cases of sudden death	Drug induced Brugada syndrome
Imipramine	Teschemacher *et al*. 1999	Zahradnik *et al*. 2008	Dick *et al*. 2007		Tzivoni *et al*. 1984	Witchel *et al*. 2006	Goldgrand Toledano *et al*. 2002
Amitriptyline	Teschemacher *et al*. 1999	Zahradnik *et al*. 2008	Dick *et al*. 2007			Vieweg *et al*. 2004	Bolognesi *et al*. 1997
Nortriptyline			Dick *et al*. 2007				Tada *et al*. 2001
Clomipramine		Zahradnik *et al*. 2008					
Desipramine		Zahradnik *et al*. 2008	Dick *et al*. 2007			Amitai *et al*. 2006	Babaliaros *et al*. 2002; Akhtar *et al*. 2006
Maprotiline	Jo *et al*. 2007	Zahradnik *et al*. 2008	Dick *et al*. 2007			Vieweg *et al*. 2004	
Venlafaxine	Fossa *et al*. 2007		Khalifa *et al*. 1999				
Citalopram	Fossa *et al*. 2007	Zahradnik *et al*. 2008		Rasmussen *et al*. 1999	Tarabar *et al*. 2008; Kanjanauthai *et al*. 2008		
Fluoxetine	Fossa *et al*. 2007	Traboulsie *et al*. 2006	Dick *et al*. 2007	Appleby *et al*. 1995; Ravina *et al*. 1998; Varialle *et al*. 2001; Wilting *et al*. 2006	Sala *et al*. 2006		Rouleau *et al*. 2001
Fluvoxamine	Milnes *et al*. 2003						
Mirtazapine						Goodnick *et al*. 2002	Bolognesi *et al*. 1997

of reports indicating reduced HRV (using both time domain and spectral measures) among DSM-III diagnosed panic disorder patients compared to normal control subjects. Also, other studies reported lower resting HRV in patients with post-traumatic stress disorder (PTSD) compared to controls, suggesting increased sympathetic and decreased parasympathetic tone [Cohen *et al*. 2000].

Yeragani and Rao [2003a] used the largest Lyapunov exponent (LLE) of instantaneous heart rate (HR) and QT interval series to study 28 normal control subjects, 36 patients with panic disorder and 18 patients with major depression in supine and standing postures. They showed an increase in relative cardiac sympathetic activity and a decrease in certain aspects of cardiac vagal function in patients with anxiety as well as depression. Interestingly, at least two studies showed that HRV measures may be useful in assessing response to antidepressant therapy [Fraguas *et al*. 2007; Khaykin *et al*. 1998].

Different studies on clinical populations and also on healthy subjects evaluated the effects of different antidepressants agents on HRV (see Table 2). Yeragani and Rao [2003b] studied the effects of two antidepressants, nortriptyline ($n = 13$), and paroxetine ($n = 16$), on HRV in patients with panic disorder. Using the LLE in pre- and post-treatment HR time series, authors showed that nortriptyline is associated with a decrease in LLE of high frequency (HF: 0.15–0.5 Hz) filtered series, which is most likely due to its anticholinergic effect, while paroxetine had no such effect. Paroxetine significantly decreased sympathovagal ratios as measured by a decrease in LLE of LF/HF.

One study reported effects on HRV using spectral analysis in 22 depressed subjects after venlafaxine treatment, showing that venlafaxine reduced HRV. The observed decrease could be due to the norepinephrine-uptake-inhibiting properties of venlafaxine [Davidson *et al*. 2005]. Rechlin [1994] and Rechlin *et al*. [1994] studied the effects of the treatment of depressed patients with paroxetine, amitriptyine, doxepine and fluvoxamine on HRV and found that amitriptyine and doxepine reduced HRV while paroxetine and fluvoxamine showed a safer profile. Two other studies compared treatment with antidepressant agents in depressed subject and healthy control. Tulen *et al*. [1996] reported reduction of HRV during treatment with mirtazapine and imipramine and Straneva-Meuse *et al*. [2004] reported reduction of HRV during treatment with buproprion but not with paroxetine. Importantly, one study [Lederbogen *et al*. 2001] compared the effect of treatment with 150 mg of amitriptyline versus 40 mg of paroxetine in a sample of 28 depressed subjects showing that a dose of 40 mg of paroxetine influenced heart rate variability in a manner similar to that of tricyclic antidepressants. Some authors also studied the effects of antidepressants on healthy volunteers. Pentilla *et al*. [2001] designed a randomized placebo-controlled study on eight healthy volunteers to study the effects of amitriptyline, reboxetine and citalopram on the autonomic nervous system. They showed that reboxetine, despite its low antimuscarinic activity *in vitro*, had distinct effects on the HF power of R–R interval variability.

Another study on healthy volunteers [Pohl *et al*. 2003] compared the effect of 20 mg daily of fluoxetine ($n = 7$), 56.25 mg of pemoline ($n = 7$) or placebo ($n = 9$). Pemoline, but not fluoxetine, decreases heart period variability (HPV) in the HF power, suggesting a vagolytic effect on cardiac autonomic function. Finally Siepmann *et al*. [2003] studied six male volunteers treated with sertraline (50 mg/die) and six male volunteers treated with placebo. Sertraline caused a significant reduction of heart rate whereas HRV was not changed.

Interestingly, the effect of different antidepressants on HR or HRV has also been studied in populations of patients with ischaemic heart disease. An open-label fluoxetine study was conducted in 27 depressed patients with cardiac disease (heart failure and/or conduction disease and/or ventricular arrhythmias) [Roose *et al*. 1998a]. Patients received up to 60 mg/d fluoxetine for seven weeks. Fluoxetine induced a significant decrease in heart rate of 5 beat/min but had no clinically significant effect on blood pressure, cardiac conduction, or ventricular ectopic activity.

Yeragani *et al*. [2002] studied the effect of antidepressant treatment with nortriptyline or with paroxetine on LLE in 44 depressed patients with ischaemic heart disease. In this study, authors compared 20 h awake and sleep heart period nonlinear measures using quantification of nonlinearity and chaos in two groups of patients with major depression and ischaemic heart disease (mean age 59–60 years) before

Table 2. Studies on antidepressant effect on heart rate (HR) and heart rate variability (HRV), cardiac sympathetic activity and cardiac vagal function

Studies in patients with PD	Studies in patients with depression	Studies in healthy subjects	Studies in patients with Heart Disease
Yeragani and Rao, 2003b	Davidson *et al*. 2005	Pentilla *et al*. 2001 8 male volunteers randomly assigned to treatment with AMI (75 mg), CIT (20 mg), REB (4 mg) and placebo. Reboxetine increased heart rate and blood pressure and reduced the HF power of RRI	Roose *et al*. 1998a 27 depressed pts with heart disease treated with FLU (60 mg/die) and 60 depressed pts with heart disease treated with NOR (60 mg/die)
16 pts treated with PAR (20 mg/die)	22 pts treated with PAR (40 mg/die)		FLU induced a statistically significant 6% decrease in HR, a 2% increase in supine systolic pressure, and a 7% increase in ejection fraction.
13 pts treated with NOR (100 mg/die) NOR-treatment was associated with decrease in LLE of high frequency PAR-treatment decreased sympatho-vagal ratios as measured by a decrease in LLE of LF/HF	22 pts treated with VEN (225 mg/die) VEN-treatment was associated with decrease in R–R interval variation and in RSA		
	Rechlin, 1994 8 pts treated with AMI (150 mg/die)	Pohl *et al*. 2003 7 healthy volunteers treated with FLU (20 mg/die)	Yeragani *et al*. 2002 24 depressed pts with heart disease treated with PAR (20–30 mg/die) and 20 depressed pts with heart disease treated with NOR (190–570 nmol/l) Significant decrease in the LLE after treatment with NOR but not PAR
	8 pts treated with DOX (150 mg/die) 8 pts treated with FLV (150 mg/die) 8 pts treated with PAR (20 mg/die)	7 healthy volunteers treated with PEM (56.25 mg/die) 9 healthy volunteers treated with placebo (20 mg/die) Pemoline was associated with a significant decrease in the high frequency (HF) power (0.15–0.5 Hz, $p = 0.02$) and fractal dimension of RR time series ($p = 0.03$).	
	32 unmedicated HC Reduced HRV after treatment with AMI and DOX but not with FLV and PAR		

Rechlin *et al.* 1994 12 pts treated with AMI (150 mg/die) 12 pts treated with PAR (20 mg/die) 24 unmedicated HC Reduced HRV after treatment with AMI but not with PAR	Siepmann *et al.* 2003 6 healthy male volunteers treated with placebo and 6 healthy male volunteers treated with SER (50 mg/die) No changes in HRV after SER	Roose *et al.* 1998b 81 depressed pts with ischemic heart disease were randomized to receive either NOR (50-150 ng/mL) or PAR at 20 to 30 mg/die NOR but not PAR was associated with significantly increased HR and reduced HRV compared with baseline values
Straneva-Meuse *et al.* 2004 17 pts treated with BUP (200-450 mg/day) 17 pts treated with PAR (10-50 mg/day) 15 unmedicated HC Reduced HRV after treatment with BUP but not with PAR		Glassmann, 2002 26 depressed pts after acute myocardial infarct treated with SER (50–200 mg/die) for 16 weeks. No clinically significant effect on heart rate, blood pressure, cardiac conduction, or left ventricular ejection fraction
Tulen *et al.* 1996 10 pts treated with IMI (150 mg/day) 10 pts treated with MIR (30 mg/day) 20 unmedicated HC Reduced HRV after treatment with IMI and with MIR		Glassmann, 2007 258 depressed pts after acute coronary syndrome treated for 16 weeks with SER or placebo. Both SER treatment and symptomatic recovery from depression were associated with increased HRV compared with placebo-treated and nonrecovered post-acute coronary syndrome control groups.
Lederbogen *et al.* 2001 14 depressed pts treated with AMI (150 mg/day) 14 depressed pts treated with PAR (40 mg/day) Reduction of SDNN and SDANN both after AMI and PAR treatment.		

Legend: RRI: R–R interval; RSA: respiratory sinus arrhythmia; LLE: largest Lyapunov exponent; LF/HF: low frequency/high frequency ratio; SDNN: standard deviation of all normal R–R interval; SDANN: standard deviation of the averages of N–N intervals; SSRI: selective serotonin reuptake inhibitors; TCA: Tricyclic antidepressants; pts: patients; PD: panic disorder; PAR: paroxetine; NOR: nortriptyline; VEN: venlafaxine; AMI: amitriptyline; IMI: imipramine; MIR: mirtazapine; CIT: citalopram; REB: reboxetine; SER: sertraline; PEM: pemoline; DOX: doxepine; FLV: fluvoxamine; BUP: Bupropion.

and after six weeks of treatment with paroxetine or nortriptyline. Twenty-four patients received paroxetine 20–30 mg/day, and 20 patients received nortriptyline targeted to 190–570 nmol/l for six weeks. There was a significant decrease in the largest Lyapunov exponent (LLE) after treatment with nortriptyline but not paroxetine, probably because nortriptyline has stronger vagolytic effects on cardiac autonomic function compared with paroxetine.

In another comparative study [Roose *et al*. 1998b] 81 depressed patients with ischaemic heart disease were randomized to receive either nortriptyline at a therapeutic plasma level (50–150 ng/ml) or paroxetine at 20–30 mg/d for six weeks. In this study, nortriptyline but not paroxetine was associated with significantly increased heart rate and reduced HRV compared with baseline values. Paroxetine exhibited a considerably safer cardiac profile compared with nortriptyline in patients with ischaemic heart disease, with no clinically significant effect on heart rate, blood pressure, cardiac conduction or cardiac rhythm.

An open-label pilot study of sertraline included 26 patients with DSM-IV major depression and an ejection fraction of N35% at 5–30 days after acute MI. After 16 weeks of treatment at a dose of 50–200 mg/d, sertraline had no clinically significant effect on heart rate, blood pressure, cardiac conduction or left ventricular ejection fraction, and no patient discontinued treatment because of adverse cardiac events [Glassman *et al*. 2002]. Recently, Glassman *et al*. [2007] studied 290 depressed patients after acute coronary syndrome and assessed HRV from 24-hour Holter electrocardiogram recordings at baseline in and, for 258 of these patients, 16 weeks after randomization to sertraline or placebo. They found that both sertraline treatment and symptomatic recovery from depression were associated with increased HRV compared with placebo-treated and non-recovered post-acute coronary syndrome control groups.

Discussion

Antidepressants agents affect cardiovascular function through different mechanisms. First, they can affect the duration of the action potential through their channel blocking properties, leading to QT prolongation and increasing the risk of ventricular arrhythmias, TdP and sudden cardiac death. Second, they affect HRV. Particularly, HRV could change in medically healthy depressed patients as a pharmacological effect of the antidepressant drug, a consequence of improvement in depressive illness, or a combination of both [Fraguas *et al*. 2007; Glassman *et al*. 2007].

Regarding the arrythmogenic risk, most antidepressants are classified in the fourth risk category in the QT drug list by risk groups (www.qtdrugs.org). This means that antidepressants belong to the category of drugs weakly associated with TdP, except for venlafaxine which belong to category 3 (drugs to be avoided for use in patients with diagnosed or suspected congenital long-QT syndrome). Thus most cases of antidepressant-induced TdP occurs after antidepressant overdose or in combination with other QT-prolonging agents or condition. In fact, antidepressants are more likely to predispose to BS phenotype rather than TdP, because they exert a predominant effect to inhibit inward currents such as I_{Na} and I_{Ca} instead of inhibiting outward currents such as I_{K}.

Although various experimental studies may lead to an understanding of the mechanisms involved in the modulation of cardiac electrical activity, there are significant discrepancies between *in vitro* data describing the action of antidepressants on the AP, data from clinical trials on QT prolongation by antidepressants and risk of TdP and thus it is difficult to recommend instituting safety measures. In fact, the QT prolongation potential of many antidepressants, particularly newer antidepressants like serotonin reuptake inhibitors and serotonin–norephinephrine reuptake inhibitors, is based on case reports or FDA-approved drug labelling (www.torsades.org) but these drugs may not cause clinically important QT prolongation. The effects of concurrent use of multiple QT prolonging drugs is also uncertain. For most of these combinations, available data consist of case reports of TdP or deaths that are presumed to have resulted from a drug combination, and there is no systematic process to verify or refute this risks [Lasser *et al*. 2002]. It is not known whether the risk increase when multiple QT prolonging drugs are taken for chronic conditions or in patients who are more susceptible of arrhythmias (elderly patients, patients with impaired renal function and women) [Vieweg, 2002]. A proactive mechanism for detecting potentially dangerous prescribing patterns is crucial and only national pharmaceutical claims databases will be useful for real time analyses of physicians'

prescribing behaviours [Mantel-Teeuwisse *et al.* 2001; Mann, 1998].

Regarding antidepressant action on HRV, the International Consensus Group on Depression and Anxiety recently advised that according to risk–benefit analysis there is no reason not to treat depressed cardiac patients with a safe drug; they would benefit from relief of their depression and a potential improvement in their cardiovascular risk profile [Ballenger *et al.* 2001].

The reduction in autonomic nervous system control to the heart may be one link between psychopathology and heart disease. After myocardial infarction, reduction in beat-to-beat heart rate variability, a measure of cardiac autonomic innervation by the brain, is a strong predictor of death [Gorman and Sloan, 2000]. Clinical data to date support the use of selective serotonin reuptake inhibitors (SSRIs) to treat comorbid depression in the patient with ischaemic heart disease. SSRIs have a benign cardiovascular profile compared with both tricyclic antidepressants (TCAs) and placebo and are well tolerated in patients with cardiac disease. Several studies suggested that in patients with panic disorder, depression and also comorbid ischaemic heart disease, treatment with the selective serotonin reuptake inhibitors normalizes heart rate variability. Hence there is potential for the treatment of psychiatric disorders to affect positively the development and course of cardiovascular disease.

Further research is needed to provide a threshold of risk for each drug, through adequately scaled and properly conducted PKPD studies, allowing the definition of the window between therapeutic dose and doses associated with QT–RR or QT–HR combination risk. Also, to our knowledge, there are no published studies that investigated the role of QT-prolonging drugs in subjects with genetic variant of cardiac channels that are associated to a reduced repolarization reserve. To date, four HERG polymorphisms have been identified and studied through heterologous expression systems [Anson *et al.* 2004]. For one of these polymorphisms, K897T, IKr current density was lower than the currents measured through the other polymorphic channels. Subtle modification of IKr by HERG polymorphisms, whether through altered current density or channel kinetics, could indirectly contribute to the proarrhythmic effects of HERG blockers by reducing the repolarization reserve. Prospective studies patients with ischaemic heart disease will assess the safety of longer-term use of SSRIs and establish whether treatment of depression can reduce cardiac morbidity and mortality.

Conflict of interest statement

None declared.

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