

# Psychotropic Drugs, Cardiac Arrhythmia, and Sudden Death

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**Abstract:** A variety of drugs targeted towards the central nervous system are associated with cardiac side effects, some of which are linked with reports of arrhythmia and sudden death. Some psychotropic drugs, particularly tricyclic antidepressants (TCAs) and antipsychotic agents, are correlated with iatrogenic prolongation of the QT interval of the electrocardiogram (ECG). In turn, this is associated with the arrhythmia *torsades de pointes* (TdP). This review discusses the association between psychotropic agents, arrhythmia and sudden death and, focusing on TCAs and antipsychotics, considers their range of cellular actions on the heart; potentially pro-arrhythmic interactions between psychotropic and other medications are also considered. At the cellular level TCAs, such as imipramine and amitriptyline, and antipsychotics, such as thioridazine, are associated with inhibition of potassium channels encoded by *HERG*. In many cases this cellular action correlates with ECG changes and a risk of TdP. However, not all psychotropic agents that inhibit *HERG* at the cellular level are associated equally with QT prolongation in patients, and the potential for QT prolongation is not always equally correlated with TdP. Differences in risk between classes of psychotropic drugs, and between individual drugs within a class, may result from additional cellular effects of particular agents, which may influence the consequent effects of inhibition of repolarizing potassium current.

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It has long been recognized that some psychotropic drugs, including neuroleptics, antipsychotics, antidepressants, stimulants and antianxiety agents, can be associated with risks of cardiac arrhythmia<sup>1,2,3</sup> and sudden death. In addition, antiepileptics and drugs used for movement disorders may also result in cardiac effects in some patients (e.g. pimozide<sup>4</sup>). Sudden cardiac death is generally defined as death from unexplained circulatory arrest, usually due to

a cardiac arrhythmia occurring within an hour of onset of symptoms.<sup>5</sup> In many cases psychotropic drugs, particularly tricyclic antidepressants (TCAs) and antipsychotic agents, are correlated with iatrogenic prolongation of the QT interval of the ECG,<sup>6</sup> which is associated with the dangerous polymorphic ventricular tachyarrhythmia, TdP.<sup>7</sup> Furthermore, of all the drugs that are taken in lethal overdose, prescribed antidepressants are among the most common; when considering cardiotoxicity, psychotropic drugs must be considered in a completely different light from other drugs such as antiarrhythmics or non-sedating antihistamines because of the suicide risk.

Although it is thought that the savings in lives from the use of these psychotropic agents (due to their therapeutic actions) outweighs the risks of their being abused for self-poisoning and overdose (e.g.<sup>8</sup>), when considered within an epidemiological context, there are marked differences in overdose toxicity between drug classes and, in some cases, between individual drugs within a class.<sup>9</sup> This review is concerned with the connection between psychotropic drugs (particularly TCAs and antipsychotic agents), arrhythmia and sudden cardiac death, at normal therapeutic concentrations, during overdose, and in patients with established cardiovascular disease. The different classes of psychotropic drugs, and even different drugs within the same class, are associated with differential risks, and this will be described in detail. In order to provide an overview of the issues and evidence for this connection at the clinical and cellular level, the proposed mechanisms will be described at the level of cardiac electrophysiology and propositions for future research will be presented.

## CLINICAL ISSUES AND EVIDENCE

### Prolongation of the QT interval

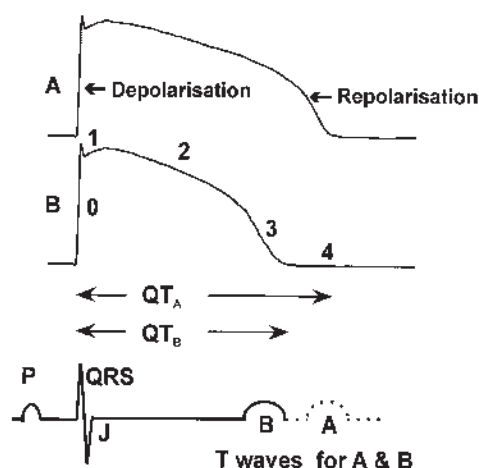
Given the link between the risk of cardiotoxicity and the prolongation of the QT interval by psychotropic drugs, it is beneficial to consider first the issue of QT prolongation. In addition to ventricular conduction time, the QT interval of the ECG reflects the duration of the ventricular action potential (AP) at the cellular level (Fig. 1). Thus, the prolongation of the QT interval may reflect effects on ion channels involved in ventricular AP generation. However, the QT interval also depends on the heart rate, and therefore the

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## ECG and Prolongation of Ventricular Action Potential



**FIG. 1.** QT interval correlates with ventricular action potential duration. The absolute QT interval is the QRS time course (representing propagation time of AP depolarization through ventricular tissue) plus the JT interval (representing the overall time course for the plateau phase plus ventricular repolarization to occur). Schematic diagrams of ventricular action potentials are shown, A being prolonged with respect to B. B is labeled with the phases of the AP: phase 0, rapid upstroke; 1, early repolarization; 2, plateau phase; 3, late repolarization; and 4, post-repolarization (slow depolarization in pacemaker tissues). Below are the respective QT intervals and a schematicized ECG showing their relative timing. The depolarization (or rapid upstroke) representing inward flux of  $\text{Na}^+$  ions, and the repolarization, representing primarily outward flux of  $\text{K}^+$  ions, are indicated in the upper ventricular action potential.

determination of QT prolongation in patients is usually measured using the heart rate corrected QT interval ( $\text{QT}_c$ ).  $\text{QT}_c$  can be calculated in several ways, including the Fridricia formula,  $\text{QT}_c = \text{QT} / \sqrt{\text{RR}}$ , or the more prevalent correction formula of Bazett,  $\text{QT}_c = \text{QT} / \sqrt{\text{RR}}$ , the latter being relatively inaccurate because it under- or over-estimates the true duration of repolarization at low and high rates, respectively.<sup>10</sup> Prolongation of the  $\text{QT}_c$  interval (in excess of 440–450 milliseconds (ms) in men and 460–470 ms in adult women<sup>11</sup>) is associated with an increased cardiovascular risk,<sup>12</sup> and  $\text{QT}_c$  prolongation is considered a marker of risk for TdP or sudden death by drug regulating authorities.<sup>11</sup> TdP is characterized by an ECG pattern of continuously changing morphology of the QRS complexes that seem to twist around an imaginary baseline.<sup>13</sup> In acquired long QT syndrome (LQTS) the  $\text{QT}_c$  interval is prolonged, and the surface ECG often shows accentuated T- and U-wave abnormalities.

### Vulnerability to iatrogenic QT prolongation

A wide range of non-cardiovascular therapeutic agents have been shown to prolong the QT interval, and the large

scope of this problem has made it an issue for drug developers and health authorities,<sup>10</sup> as well as being of critical importance for attending physicians. The non-cardiac agents associated with QT prolongation belong to many different pharmacological classes including psychotropic drugs, prokinetic medicines, antimalarial medicines, antibiotics belonging to several different chemical classes, antifungal agents and non-sedating antihistamines.<sup>14,15</sup> Among the psychotropic drugs associated with QT prolongation and the risk of sudden cardiac death under some circumstances (Table 1) are TCAs (e.g. imipramine and amitriptyline among others), tetracyclic antidepressants (e.g. maprotiline), phenothiazine derivative antipsychotics (e.g. thioridazine), potentially some new atypical antipsychotics (e.g. sertindole), and under limited circumstances drugs indicated for movement disorders including neuroleptics, antiepileptics and antiparkinsonian agents. Of these agents, the most well described risks are associated with TCAs.

**TABLE 1.** Selected drugs associated with arrhythmia risk factors

CNS drug	Clinical reference	HERG reference
Amitriptyline	16	17,18,19
Amoxapine	20,9	
Carbamazepine	With other factors, 21,22	
Chloral hydrate	Rare, 23	
Chlorpromazine	24	19
Citalopram	In overdose, 25	26
Clomipramine	27	
Clozapine	with other drugs, 28	
Desipramine	27	
Doxepin	29	
Droperidol	30	31
Fluoxetine	with other drugs, 32	26
Haloperidol	33	34
Imipramine	35	17
Lithium	with other drugs, 36	
Maprotiline	37	
Nortriptyline	38	
Olanzapine	Not significant, 39	40
Pergolide	+CAD or levodopa, 41	
Pimozide	4	42
Prochlorperazine	In overdose, 43	
Quetiapine	In overdose, 44,45	
Risperidone	Rare, 46	40
Sertindole	47	48
Sultopride	49	
Trazodone	In overdose, 50	
Thioridazine	6,51	52
Venlafaxine	In overdose, 53	
Zimeldine	With hypokalaemia, 54	
Ziprasidone	55	40

The putative arrhythmogenic effects of psychotropic and other selected CNS drugs. Clinical references refer to either evidence of TdP,  $\text{QT}_c$  prolongation, or sudden cardiac death. In some examples the citations refer to cases of overdose and poisoning.

Given this potentially large number of drugs associated with risk, it is important to note that among patients taking these drugs, significant  $QT_c$  prolongation ( $QT_c > 500$  ms) is a relatively uncommon occurrence, and that TdP is much more rare. For a given medication, arrhythmogenic risk must be understood to be partially dependent mechanistically on vulnerability that is intrinsic to the individual patient with regard to the particular drug. Acquired LQTS is typically seen during bradycardia, irregular rhythm, hypomagnesemia and/or hypokalemia,<sup>11</sup> and it appears to be more prevalent in women than in men. Vulnerability to medication-induced prolongation of the QT interval may also reside in the patient with respect to the underlying psychiatric diagnosis, any underlying medical illness (especially cardiovascular disease), genetic predisposition to drug-induced QT prolongation, and the patient's age, as described below.

There are cardiovascular risks associated with the patients' underlying psychiatric diagnosis, which has been well demonstrated in the case of depression. For example, the propensity for TCA-induced orthostatic hypotension is increased in the depressed state,<sup>56</sup> and the risk for cardiovascular mortality in post-MI patients is increased in the presence of depressive symptoms. Similarly, in schizophrenic patients there may be issues concerning self-care or overall medical compliance that may create risk. In many cases these risk factors can increase the vulnerability of the patient to other risk factors and possibly act in concert with the undesired pharmacological actions of some therapeutic agents to increase the risk of QT prolongation, TdP and sudden death. With psychiatric patients having known or putative risks, inspection of each patient's ECG may be important in assessing risk associated with drugs that can have arrhythmogenic properties.

## Cardiac effects of TCAs versus Selective Serotonin Reuptake Inhibitors (SSRIs)

### Cardiac effects of TCAs

TCAs are used for treatment of depression and other conditions including nocturnal enuresis, panic disorder, obsessive compulsive disorder and bulimia.<sup>57,58,59</sup> TCAs have cardiovascular side effects including orthostatic hypotension, atrioventricular conduction delay, reduced heart rate variability, tachycardia, syncope, and lengthening of the QT interval, particularly in cases with high dosages and in patients with concurrent cardiovascular disease.<sup>60</sup> TCAs are associated with a significant clinical risk of arrhythmia in patients with pre-existing heart disease or conduction abnormalities<sup>60,61</sup> and in overdose.<sup>9</sup> In the case of TCA overdose, delayed conduction may lead to a complete heart block or ventricular reentry arrhythmias. At therapeutic plasma concentrations of TCAs, depressed patients

with pre-existing conduction disease, particularly bundle branch block, are at a higher risk to develop symptomatic AV block than depressed patients that are free of conduction anomalies;<sup>62</sup> the severity of the patient's pre-existing condition is a greater determinant of vulnerability to such complications than the choice of which agent within a particular drug family is used.<sup>63</sup>

The cardiac actions of TCAs have been suggested to result from "quinidine-like" activity.<sup>64</sup> Quinidine, a class I antiarrhythmic, is known to cause slowing of phase 0 depolarization of the AP (Fig. 1) resulting in slowing of conduction through the His-Purkinje system and myocardium. It is well established that, in addition to its antiarrhythmic effects, quinidine can have pro-arrhythmic activity.<sup>65</sup> Previously, TCAs were known to have class I antiarrhythmic activity and were recommended for patients with ventricular arrhythmias.<sup>66</sup> Due to more recent evidence showing that after myocardial infarction (MI) some class I antiarrhythmics are associated with significantly increased mortality due to arrhythmia,<sup>67</sup> the cardiac actions of TCAs have led to the recommendation that alternatives to TCAs be considered under those circumstances.<sup>68</sup>

These cardiac effects of antidepressant drugs after MI are important because depression and MI are often comorbid, with the prevalence of symptoms of major depression in patients with MI being up to 18%,<sup>69</sup> as opposed to 5% in some cross-sectional studies of the adult population.<sup>70</sup> For some time, depression has been examined as an additional independent risk factor for mortality in cardiac patients, particularly with respect to sudden arrhythmic deaths.<sup>71-75</sup> Given the significant levels of depression associated with MI, antidepressants are considered to be underprescribed in this population, leading to morbidity and decreased quality of life.<sup>76,8,71</sup> Considering the overall data currently available regarding the relative merits of TCAs and SSRIs, it is now thought to be safer to treat depressed cardiac patients who also have established ischemic heart disease (IHD) with SSRIs than with TCAs, although treatment decisions must be individualized for each patient.<sup>77</sup>

### TCAs in psychiatric patients without established coronary artery disease

In psychiatric patients without established coronary artery disease (CAD), there have been several studies associating the therapeutic use of psychotropic drugs with incident MI, raising the possibility that psychotropic-induced sudden death could be mediated by CAD; however, the majority of sudden cardiac death patients have no evidence of recent MI, although many have active lesions.<sup>78,79</sup> In one case-control study of cardiovascular mortality in women aged 16-39 not designed to test any hypothesis about psychotropic drugs, one incidental finding was an unexpected 17-fold increase in the risk of fatal MI associated with the

current use of psychotropic medications.<sup>80</sup> Another cohort study of risk found associations between fatal MI and both benzodiazepine and antidepressant use.<sup>81</sup> Neither of these studies controlled for depression or other mental illnesses, but the Baltimore 'Epidemiologic Catchment Area' (ECA) survey follow-up did. After adjustment for major depressive episode and dysphoria, the Baltimore ECA follow-up found that the two most commonly prescribed classes of agents for depression at the time of their baseline interview, TCAs and benzodiazepines, were each associated with non-significant increased relative risks (RR) of ~1.3 for self-reported incident MI;<sup>82</sup> nevertheless, it is controversial as to whether sudden cardiac death may be secondary to acute ischemia in patients who have not developed enzymatic or ECG evidence of acute MI.<sup>5</sup>

Large epidemiological studies of the association between TCA use and total mortality are difficult to cite as proof of a causal connection. In a case-control study Weeke *et al.* compared the mortality rate for first hospitalized manic-depressive patients in the era before TCAs became available in Scandinavia to that after the introduction of TCAs, and they found that the rate in the post-TCA era was lower.<sup>83</sup> Similarly, Avery and Winokur found that mortality from cardiac causes over a three year follow-up was more prevalent among depressed patients who had received "inadequate" treatment for depression rather than those who had received adequate treatment;<sup>84</sup> unfortunately, this data is not prospective and is open to criticisms of poor health care overall in the "inadequate" population,<sup>73</sup> and a similar argument can be made for comparison of the pre- and post-TCA era mortality rate. Overall, the epidemiological data, especially data for non-suicide mortality, must be interpreted carefully because the causal links often lack pathological evidence, and the pathology of sudden death is often not definitive except in rare cases where the patient is hospitalized or being Holter monitored.<sup>85</sup>

### ***Mechanistic issues in the association of antidepressants and sudden death***

The statistical connection between psychotropic drugs and cardiac death can be further confounded by observations that the psychiatric disorders that indicate the use of these drugs are also associated with high rates of cardiovascular mortality. In 1937 Malzberg compared the mortality rate for patients hospitalized with involutional melancholia to that of the general population, and he reported that the non-suicide death rate was six times greater in the melancholia patients; this was consistent across the age span of 40 to 75 years.<sup>86</sup> In that study cardiac disease accounted for nearly 40% of all mortality among the melancholia patients, and the rate of cardiac death among the melancholia patients was eight times greater than in the general population. Other early evidence has supported Malzberg's conclu-

sion.<sup>87</sup> The importance of these studies is that they may represent the natural course of affective disorder, as there were no somatic treatments for depression available at the time.

Given the complexity of separating the putative cardiotoxic effects of therapeutic TCA use from those of the underlying psychiatric indications, more recent work has focused mechanistically on whether therapeutic TCA use is a significant risk factor for QT<sub>c</sub> interval lengthening. In a study by Reilly *et al.* of 495 psychiatric patients in various inpatient and community settings who were compared to normal controls, therapeutic use of TCAs was associated with QT<sub>c</sub> prolongation;<sup>6</sup> in that study stepwise regression analysis showed that the only other significant independent risk factors besides the use of specific psychotropic drugs were 'age > 65' and female gender. Furthermore, studies of "healthy" pediatric psychiatric patients do not support a differential risk between age groups, and they suggest that aggregate pediatric ECG findings are consistent with those found in adults, although desipramine, which can bind to noradrenaline reuptake sites in cardiac sympathetic neurons in man *in vivo*,<sup>88</sup> has been singled out as the cause of four pediatric nonsuicide deaths.<sup>89-91</sup> TCA-induced QT<sub>c</sub> prolongation may result from direct effects of TCAs on ion channels within the myocardium, and as shall be explained below, there is evidence that TCAs can inhibit repolarizing ionic current in cardiac ventricular myocytes, an observation that would account for drug-induced lengthening of the QT<sub>c</sub> interval of the ECG.

An advantage of SSRIs over TCAs is that they are rarely associated with QT<sub>c</sub> prolongation,<sup>92</sup> and they have fewer cardiotoxic side effects<sup>93</sup> and a higher margin of safety than TCAs.<sup>94</sup> In chronic use, some SSRIs cause a mild bradycardia of a few beats per minute.<sup>38</sup> There have been occasional reports of syncope and arrhythmia associated with fluoxetine in some patients.<sup>95,96</sup> However, clinical doses of the SSRIs fluoxetine, sertraline and paroxetine generally have been found thus far to be safe in patients with those forms of pre-existing heart disease that have been tested (e.g.<sup>97,98,38</sup>), although all of these studies were small, and the SSRIs are known to have effects on the cytochrome P450 system, raising the possibility of drug-drug interactions in patients with multiple medications. Data from national registries of suicides support a view that SSRIs, particularly fluoxetine, are in general dramatically safer (10-100 fold) than TCAs,<sup>9</sup> particularly with regard to cardiovascular effects and mortality.

### **Neuroleptic Agents**

It has long been known that some antipsychotic agents, particularly phenothiazines, are associated with ECG changes representing repolarization anomalies including QT prolongation,<sup>99,100</sup> and the first report of sudden arrhythmic death due to thioridazine was published in



1963.<sup>2</sup> The difference in toxicity of the different neuroleptics and antipsychotics was demonstrated by an Australian study of 299 consecutive patients admitted with neuroleptic poisoning; thioridazine was significantly more likely to cause tachycardia, prolonged  $QT_c > 450$  ms, a widened QRS ( $> 100$  ms) and arrhythmias ( $p = 0.004$ ) than chlorpromazine, trifluoperazine, pericyazine, haloperidol, prochlorperazine, fluphenazine, or other neuroleptics.<sup>43</sup> Likewise, a Finnish study of sudden unexplained deaths associated with psychotropic drugs found phenothiazines to be over-represented in the sample, and thioridazine was involved in a disproportionate number of cases.<sup>51</sup> TdP has been observed after thioridazine<sup>101,102</sup> and haloperidol overdose.<sup>103</sup>

Even at dosages used for therapy, Reilly *et al.* found that antipsychotic drugs, particularly thioridazine and droperidol, were associated with  $QT_c$  lengthening in a dose dependent manner;<sup>6</sup> this study was the first evidence mentioned in the announcement by the Committee on Safety of Medicines (UK) that indications for thioridazine were to be restricted and that droperidol was to be voluntarily discontinued by the manufacturer.<sup>104</sup> In the USA, therapeutic levels of traditional antipsychotic agents have also been associated with risk in a recently published epidemiological retrospective study; in that cohort of 481,744 persons aged 15–84 years, those patients currently (during the study period of 1988 to 1993) prescribed moderate doses of antipsychotics were found to be at a significantly increased risk of sudden cardiac death (multivariate risk ratio 2.39) compared to patients currently prescribed low doses of antipsychotics, formerly prescribed antipsychotics, or non-use, and the risks were higher when comparing patients with severe cardiovascular disease.<sup>105</sup>

### New Atypical Antipsychotic Agents

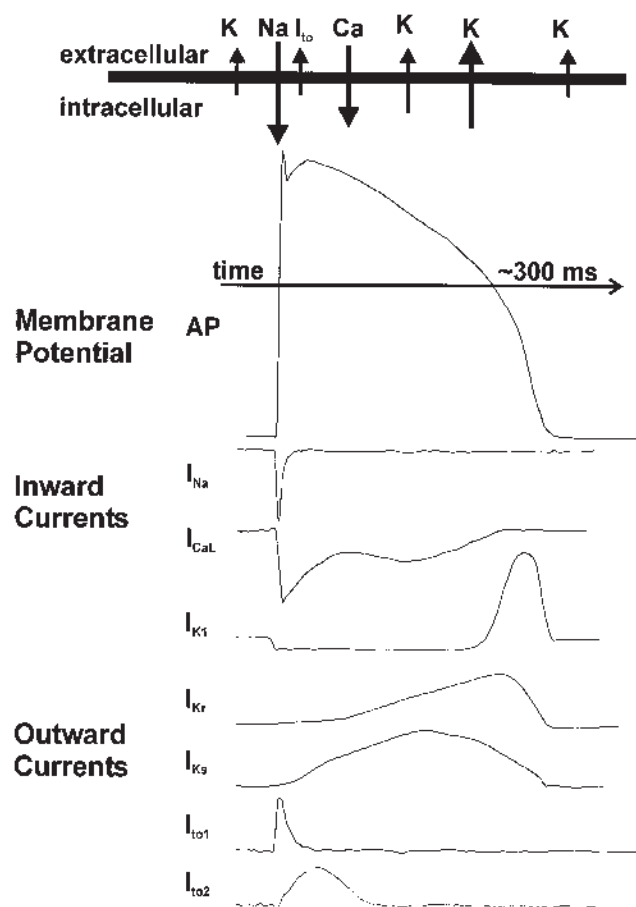
The new atypical antipsychotics, promising both greater efficacy and reduced side effects, have not yet been studied in as much detail as traditional antipsychotics, but, with the exceptions of sertindole and ziprasidone, they have not been consistently statistically proven to be associated with either QT prolongation or sudden cardiac death at therapeutic concentrations.<sup>106,107</sup> Sertindole is associated with an increase in the  $QT_c$  interval at therapeutic dosages,<sup>108,39</sup> and after release in the UK, accumulating evidence of unexplained deaths and serious but not fatal arrhythmias led the manufacturer to voluntarily withdraw the drug pending further study.<sup>106</sup> Overall, there is a difficulty in ascribing sudden deaths to particular antipsychotics at therapeutic doses because of the known association between schizophrenia and increased mortality due to cardiovascular causes,<sup>109,110</sup> and even in the case of sertindole in the UK, a statistically significant differential in sudden death compared to other new atypical antipsychotics was not shown.<sup>111</sup>

In the absence of long-term epidemiological data on standardized mortality ratios, data on QT prolongation, heart rate variability or self-poisoning suggests that the new atypical antipsychotic drugs have somewhat different profiles. Clozapine, which carries a risk of agranulocytosis and may show evidence of being associated with myocarditis and cardiomyopathy,<sup>112–115</sup> also significantly reduces measures of heart rate variability associated with parasympathetic control, and it significantly increases the LF/HF ratio, which is a measure of sympathovagal balance.<sup>39,116</sup> In a study of overdoses monitored by the National Poisons Information Service in London, clozapine overdose was associated with sinus tachycardia (as well as a number of non-cardiac symptoms) in over 66% of the single-agent overdoses reported;<sup>117</sup> in the same study over 66% of the patients reported with an overdose of risperidone were asymptomatic. Given the issues associated with the agranulocytosis risk and the arrhythmogenesis risk, it is not surprising that one survey of ordinary clinical practice in South London concluded that the new atypical antipsychotics appear to be replacing older neuroleptics as the first-line treatment of schizophrenia, while clozapine is mostly reserved for poor responders.<sup>118</sup>

In a recent clinical trial comparing mean  $QT_c$  (Bazett's) at maximal therapeutic dosages of ziprasidone, risperidone, olanzapine, quetiapine, thioridazine and haloperidol, as expected thioridazine increased  $QT_c$  the most (35.6 ms), followed by ziprasidone (20.3 ms), quetiapine (14.5 ms), risperidone (9.1 ms), olanzapine (6.8 ms) and haloperidol (4.7 ms).<sup>55</sup> Mechanistically, these figures cannot be assumed to correlate directly with arrhythmogenic risk, given the wide range of possible correction formulae for  $QT_c$ . An alternative investigation of risk is to characterize drugs for those cellular mechanisms associated with TdP. Indeed, in recent pre-clinical studies these drugs, as well as some drugs indicated for movement disorders that have been associated with arrhythmogenic risk (e.g. pimozide),<sup>4</sup> have also been shown to share the cellular mechanism believed to be responsible for acquired LQTS attributed to many traditional antipsychotics and to TCAs.<sup>42,55</sup>

### CELLULAR EFFECTS

The cellular mechanism of psychotropic-mediated effects on the AP can be examined using a broad range of *in vitro* models including heterologous expression systems (involving transference of the relevant genes into mammalian cell lines or into *Xenopus* oocytes), disaggregated cells (studied acutely or in culture), isolated tissues, and the isolated perfused heart.<sup>119</sup> Control of the duration of the AP in the ventricular myocyte is mediated by the equilibrium between inward and outward currents across the cell membrane<sup>120</sup> (Fig. 2). The longer action potential duration (APD) implicit in QT prolongation (Fig. 1) results from a



**FIG. 2.** Ionic activity during the cardiac ventricular action potential. Above is a schematic of the dominant ionic currents moving across the myocyte membrane over time (abbreviations: K = potassium, Na = sodium, Ca = calcium;  $I_{to}$  = transient outward current, which is a compound current). Below that is shown the resultant membrane voltage profile over time during an idealized action potential. Downward is polarized (negative voltages) and upward is depolarized (positive voltages). The arrow indicating the time occurs at 0 mV. The lower 7 traces show the main ionic currents contributing to the action potential over time; downward represents inward (depolarizing) currents, upward represents outward (repolarizing) currents. For the sake of simplicity, some currents have been omitted (e.g. Na/Ca exchange), and the current records only demonstrate relative polarities and time courses—relative amplitudes are not to scale.

disturbance of the normal balance between inward (depolarizing) and outward (repolarizing) currents during the AP plateau phase. Prolongation of the AP could theoretically arise from an increase in depolarizing current, or alternatively, from a decrease in repolarizing current carried by potassium ( $K^+$ ) ions. Both of these conditions have been found to exist in different forms of inherited LQTS.<sup>121</sup>

In assessing the effects of psychotropic (or other) drugs on APD in experimental systems, it is worth noting that the AP profile (and therefore underlying balance of

ionic currents) differs between species and according to regional origin of the preparation (e.g. atrium versus ventricle). Conclusions concerning APD from dissociated cell preparations should also be considered in the context that intrinsic variation in APD in those systems can occur.<sup>119</sup> Given these *caveats*, it is perhaps not surprising that the reported effects of psychotropic drugs on APD vary across the different experimental preparations studied. For example, imipramine causes shortening of the APD in isolated bovine<sup>122</sup> and guinea pig<sup>123</sup> ventricular myocytes, whereas in rabbit atrial myocytes<sup>124</sup> and rat atrial fibers,<sup>125</sup> it lengthens the APD. The differential effects of the psychotropics on AP repolarization will depend upon the balance between the inhibition of the various inward currents versus the inhibition of outward currents.

Several distinct  $K^+$  channels play prominent roles in the initiation and completion of AP repolarization. The rate of net  $K^+$  efflux, and by extension the rate of repolarization, is determined by the density and gating properties of different  $K^+$  channels. Of particular relevance to regulating the duration of the AP plateau is the delayed rectifier current ( $I_K$ ) comprised of rapid ( $I_{Kr}$ ) and slow ( $I_{Ks}$ ) components mediated by distinct channel subtypes with distinct kinetic properties<sup>126,127</sup> (Fig. 2). Composite  $I_K$  develops progressively during the plateau phase, opposing the inward currents underlying plateau depolarization. As the net balance of outward current exceeds inward current, repolarization occurs. At a cellular level, pharmacologically-induced slowing of AP repolarization can lead to spontaneous depolarizations generated on the falling phase of the AP plateau. Unlike the AP itself, these events (termed 'Early After Depolarizations' or 'EADs') are not synchronized with an excitatory stimulus (*in vivo* an incoming wave of excitation, experimentally an applied injection of current), and so can give rise to asynchronous tissue excitation and, thereby, arrhythmogenesis.

### Cloned channels responsible for delayed repolarization and LQTS

Molecular genetic studies have played important roles not only in establishing links between particular channelopathies and LQTS, but also in producing important insights into the function of individual ion channel types. Therefore, before considering the pharmacological modulation of ion channel currents involved in pharmacologically induced LQTS, it is first useful to consider the basis for 'inherited' or 'congenital' LQTS.

Thus far five genes have been identified as sites of mutation for the congenital disorder (Table 2). Genetic approaches have shown that all five of these genes are responsible for ion channel proteins that are present in the myocardium, providing insight into the electrophysiological causes of LQTS. A major breakthrough occurred when

**TABLE 2.** Channels associated with LQTS

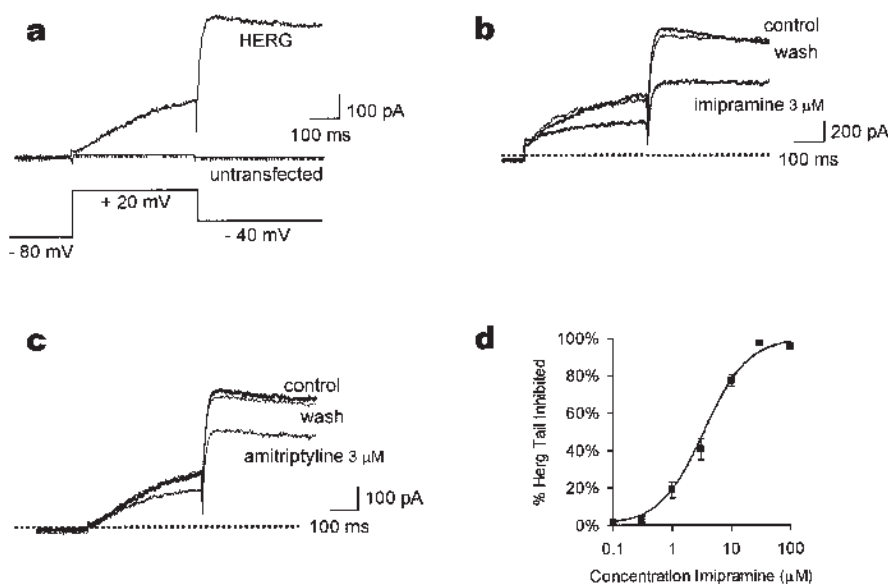
Original name	Channel type (subunit type)	Chromosomal location	Alternative nomenclature
HERG	K <sup>+</sup> (α)-I <sub>Kr</sub>	7q35-36	KCNH2
KvLQT1	K <sup>+</sup> (α)-I <sub>Ks</sub>	11p15.5	KCNQ1
SCN5A	Na <sup>+</sup> (α)	3p21-p24	hH1
minK	K <sup>+</sup> (β)-I <sub>Ks</sub>	21q21-p23	KCNE1
hMiRP1	K <sup>+</sup> (β)-I <sub>Kr</sub>	21q21-p23	KCNE2

*HERG* (*Human Ether-a-go-go Related Gene*; 7q35-q36) was identified as responsible for one form of LQTS;<sup>128,129</sup> this gene encodes the alpha (α) subunit (the main body of the ion channel) of a K<sup>+</sup> channel which mediates I<sub>Kr</sub>.<sup>130</sup> The discovery that *HERG*, a gene that codes for a cardiac ion channel subunit, was responsible for congenital LQTS, has supported the notion that pharmacological inhibition of cardiac K<sup>+</sup> channels was a possible mechanism for acquired LQTS.<sup>130</sup> Another K<sup>+</sup> channel protein associated with LQTS named KvLQT1<sup>131</sup> (locus 11p15.5) is the α-subunit responsible for I<sub>Ks</sub>.<sup>132</sup> The gene *KCNE1* (21q22.1-p22) encodes a K<sup>+</sup> channel β-subunit (an accessory subunit) called minK that associates with KvLQT1 to form functional channels mediating I<sub>Ks</sub>.<sup>132,133</sup> Another gene, *KCNE2* (21q11.1), encoding a K<sup>+</sup> channel β-subunit called MiRP1, which is part of the channel complex with *HERG* mediating I<sub>Kr</sub>, has recently been shown to be associated

with clarithromycin-induced arrhythmias, and mutations in this gene are thought to be clinically silent until combined with additional stressors.<sup>134</sup> Finally, mutations in a sodium (Na<sup>+</sup>) channel gene *SCN5A*<sup>135</sup> (locus 3p21-p23) can also cause congenital LQTS; rather than blocking an outward current of myocyte repolarization (as with K<sup>+</sup> mutations), this mutation interferes with channel inactivation, causing the channel to conduct a sustained inward current during the plateau phase of the AP, thereby delaying repolarization.<sup>121</sup>

### Psychotropic Effects on Potassium Channels

Whilst inhibition of either I<sub>Kr</sub> or I<sub>Ks</sub> might result in acquired LQTS, it is now well established that a diverse range of psychotropic drugs associated with LQTS also inhibit *HERG*/I<sub>Kr</sub><sup>14,136</sup> (Table 1), making *HERG* a likely primary mediator of acquired LQTS. Indeed, the TCAs imipramine<sup>137,17</sup> and amitriptyline<sup>17-19</sup> have been reported to inhibit *HERG*/I<sub>Kr</sub> at clinical dosages (Fig. 3), and to produce a profound channel block at higher dosages, although they can result in paradoxical AP shortening because of calcium (Ca<sup>2+</sup>) channel blockade.<sup>123</sup> The amitriptyline block of *HERG* is use-dependent and voltage-dependent.<sup>18</sup> The imipramine block shows weak voltage dependence, and some dependence on the extent of channel activation, as demonstrated by an 'envelope of tails' protocol.<sup>17</sup> Imipramine also delays the activation of the



**FIG. 3.** TCAs inhibit current mediated by heterologous *HERG*. (A) Shows the currents elicited from a CHO cell transfected with *HERG* and from an untransfected cell. Membrane potential was held at -80 mV, depolarized to +20 mV for 400 ms, before the tail current was observed at -40 mV. The *HERG* current of a typical cell in extracellular solution is shown in (B) in the absence of drug (control), in the presence of 3 μM imipramine, and after washout. The holding potential and voltage steps are identical to those in Figure 3a. Interpulse interval was 15 seconds. (C) Shows a typical cell superfused with 3 μM amitriptyline under the same conditions as in (B). The dotted line in (B) and (C) indicates zero current level. In (D), the concentration response curve shows mean (± SEM) inhibition of tail currents measured with the same protocol as above. Reproduced with permission, from reference<sup>17</sup>.

slowly activating  $K^+$  current ( $I_{Ks}$ ) in guinea pig ventricular myocytes,<sup>137</sup> which might also affect repolarization, but the block of  $I_{Kr}$  is more potent than that of  $I_{Ks}$ . Such data are in accord with the proposition that, of these two potassium channels, the pathological effects of imipramine are more likely to be mediated by blockade of  $I_{Kr}$ .

The associations between  $QT_c$  prolongation, the associated risk of mortality and some antipsychotics (e.g. thioridazine and droperidol) are stronger than those for TCAs;<sup>6</sup> likewise the potency of thioridazine for blocking HERG is higher than that of TCAs.<sup>19</sup> Whilst TCAs have effects on APD that vary between experimental preparations (see section on "Cellular Effects"), antipsychotics are generally seen to lengthen APD. The antipsychotic drug thioridazine prolongs the APD in guinea pig ventricular myocytes by inhibiting  $I_{Kr}$ ,<sup>52</sup> and the effects of thioridazine on  $I_{Kr}$  are over ten times more potent than its effects on  $I_{Ks}$ . Sertindole, which has been shown to produce QT prolongation in humans at therapeutic doses,<sup>108</sup> has also been shown to block HERG.<sup>48</sup> Data showing that the newer atypical antipsychotics ziprasidone, olanzapine and risperidone block HERG and  $I_{Kr}$  in a similar concentration range to haloperidol has been presented in abstract form.<sup>40</sup> Even amoxapine (which is classified as a TCA, but also possesses neuroleptic properties<sup>138</sup>) prolongs the APD in guinea pig isolated papillary muscles.<sup>139</sup> This correlates with British toxicology data from the early 1990s, which showed amoxapine to be associated with far more overdose-attributed deaths per million prescriptions (the fatal toxicity index – FTI) than any other antidepressant;<sup>9</sup> nevertheless, FTI figures would not be enough to label amoxapine as more dangerous than other TCAs, because the FTI figures do not control for the effects of the underlying indications.

TCAs have additional effects on other  $K^+$  channels. Another  $K^+$  current,  $I_{to1}$ , a transient outward current ( $I_{to}$ ) component ( $I_{to}$  can also include a chloride mediated current component,  $I_{to2}$ ) is important in repolarization occurring before the plateau phase. Antidepressant drugs with different chemical structures (including imipramine, amitriptyline, mianserin, maprotiline, and trazodone) have also been shown to block the transient outward potassium current,<sup>140</sup> and the consequences of  $I_{to1}$  blockade are a subject of intense research. Recordings obtained from canine cardiac tissue from different locations within the wall of the ventricular myocardium have shown a correlation between the density of  $I_{to1}$  and the brief repolarization that occurs before the plateau phase of the AP (the phase 1 "notch" – see figure 2),<sup>141,142</sup> suggesting that it is the reason that APs in some species in limited parts of the myocardium have a "spike and dome" morphology. In the mouse, the use of genetic methods to knock out  $K^+$  channel subunits mediating  $I_{to1}$  results in profound changes in-

cluding prolongation of the myocyte AP, EADs, and QT prolongation on the ECG.<sup>143</sup> In preparations in which  $I_{Kr}$  is small and  $I_{to1}$  dominates repolarization, the block by imipramine of  $I_{to1}$  is likely to explain the prolongation of APD in those cell types, such as rat,<sup>125</sup> rabbit,<sup>124</sup> and human<sup>144</sup> atrial and rat ventricular myocytes.<sup>145</sup> However, the human ventricular AP has a strong  $I_{Kr}$  component,<sup>146</sup> so the contribution of drug effects on  $I_{to1}$  to the net drug effects on the AP are likely to be complex. Overall, the existing data suggest that inhibition of  $I_{to1}$  (e.g. by TCAs) may change the electrical heterogeneity of the myocardium,<sup>147</sup> while TCA inhibition of HERG/ $I_{Kr}$  is likely to underlie or contribute very substantially directly to AP prolongation and to the pro-arrhythmia reported for this class of drugs.

Finally, an inwardly rectifying  $K^+$  current ( $I_{K1}$ ) regulates ventricular AP repolarization over the final rapid repolarization phase, and is also important in maintaining the normal resting potential.<sup>120</sup> In bovine ventricular myocytes, imipramine has been reported to enhance  $I_{K1}$  transiently, before then reducing it (by only 19% at 3.6  $\mu$ M).<sup>122</sup>

To summarise: many neuroleptics and TCAs can block HERG/ $I_{Kr}$ , and this potentially mediates the repolarization anomalies associated with the risk of TdP. This mechanism is more easily illustrated for neuroleptics; the connection between TCAs and  $QT_c$  prolongation is more complex.

### Psychotropic blockade of $Na^+$ or $Ca^{2+}$ inward currents

In addition to effects on outward  $K^+$  currents, various psychotropic drugs have been shown to inhibit inward ionic currents (especially those mediated by  $Na^+$  and  $Ca^{2+}$ ). In myocytes where  $I_{Kr}$  dominates the transition from plateau phase to repolarization, those psychotropic drugs that inhibit  $I_{Kr}$  will tend to lengthen the AP, but if there is also a concomitant inhibition of the inward  $Ca^{2+}$  currents during the plateau phase, the APD may be shortened. This may in part explain why some psychotropics that block HERG/ $I_{Kr}$  do not prolong the ventricular APD in some cellular models; for example, imipramine, which blocks HERG/ $I_{Kr}$ , shortens the APD in guinea-pig myocytes, which can be ascribed to imipramine's block of the L-type (dihydropyridine-sensitive) calcium current ( $I_{CaL}$ ) and of the late sodium current flowing during the plateau phase.<sup>123</sup> Pimozide, which is associated with inhibition of HERG and risk of TdP,<sup>42</sup> also blocks  $I_{CaL}$ , and in rat papillary muscles and ventricular myocytes it reduces both stimulation-induced twitch tension and intracellular  $Ca^{2+}$  transients, respectively.<sup>148</sup> Several psychotropic drugs including chlorpromazine, haloperidol and imipramine are associated with block of  $I_{Na}$  in cardiac myocytes,<sup>149</sup> showing use-dependence caused by a higher affinity of the drugs for the inactivated than for the resting state of sodium channels, and by a very



slow repriming of the drug-bound sodium channels from inactivation. Such effects could be antiarrhythmic or cardiotoxic, dependent on the health (e.g. CAD, or post MI) of the myocardium.

The net effect on APD of psychotropics that affect overlapping inward and outward currents will therefore depend on the overall balance between such currents during the AP plateau (Table 3), and their relative sensitivity to the particular agent in question; for many psychotropic drugs the overall effects of the altered balance of currents has not yet been determined.

### Psychotropics, QT prolongation, and arrhythmogenesis: future directions

The use of cellular electrophysiology has been a critical adjunct to measurements of the ECG from healthy animals for the assessment of mechanistic risk during drug design. Furthermore, cellular electrophysiology has revealed the mechanism for an important intervention in acquired LQTS. HERG is highly sensitive to extracellular  $K^+$  concentrations,<sup>130</sup> and repolarization abnormalities, caused by both HERG-linked inherited LQTS<sup>150,151</sup> and quinidine-induced acquired LQTS have been corrected by raising serum  $K^+$ . If the potency of particular psychotropic drugs as HERG blockers can be reduced by raising external  $K^+$  (as observed *in vitro* with amitriptyline<sup>18</sup>), then modulating serum  $K^+$  concentrations may also offer a

means of mitigating  $QT_c$  prolongation associated with TCAs or antipsychotic drugs.<sup>152</sup>

While current screening at the cellular level for risk of repolarization anomalies is focused on HERG or  $I_{Kr}$ , much work needs to be done to characterise this system for *in vitro in vivo* scaling, and further understanding of the complex relationship between cellular electrophysiology and QT prolongation is likely to involve an entire battery of electrophysiological measurements, rather than of just HERG. The potency of drug-induced block of  $I_{Kr}$  does not show a clear correlation with the risk of sudden death in patients with acquired LQTS.<sup>19</sup> In isolated feline hearts haloperidol lengthens the QT interval significantly more than sertindole,<sup>153</sup> yet (albeit in different heterologous systems) sertindole is 100–300 times more potent as a blocker of HERG<sup>48</sup> than haloperidol.<sup>34</sup> In addition, thioridazine and chlorpromazine have similar potencies for blockade of HERG,<sup>19</sup> yet in stepwise regression analysis of 495 psychiatric patients, thioridazine and TCAs were independently associated with  $QT_c$  prolongation, but chlorpromazine was not.<sup>6</sup> Assuming that these differences are not attributable to systematic errors,<sup>19</sup> these data would suggest that there exists one or more drug-induced mechanisms that makes the heart vulnerable to (or protected from)  $QT_c$  prolongation by blockade of the HERG potassium channel. If this is the case, the most dangerous modulating factors for  $QT_c$  prolongation would appear not to

**TABLE 3.** Selected sites of drug actions and associated  $IC_{50}$ 's

Drug	Class	Action	$IC_{50}$ ( $\mu M$ )	Model system
Imipramine	TCA	HERG blockade - $\downarrow I_{out}$	3.4	CHO cells*
Imipramine	TCA	$I_{CaL}$ blockade - $\downarrow I_{in}$	4	Isolated rat ventricular myocytes
Imipramine	TCA	5-HT uptake blockade	0.6	Crude rat brain synaptosomes
Imipramine	TCA	Metabolised (aromatic 2-hydroxylation)	$K_m = 25$	Human liver microsomes
Imipramine	TCA	$I_{Na}$ blockade - $\downarrow I_{in}$	3	Isolated guinea pig ventricular myocytes
Fluoxetine	SSRI	HERG blockade - $\downarrow I_{out}$	1.5	HEK cells*
Fluoxetine	SSRI	$I_{CaL}$ blockade - $\downarrow I_{in}$	2.8	Isolated rat ventricular myocytes
Fluoxetine	SSRI	5-HT uptake blockade	0.075	Rat spinal cord synaptosomes
Fluoxetine	SSRI	Metabolised to norfluoxetine	$K_m = 33$	Human liver microsomes
Fluoxetine	SSRI	Inhibits CYP 2D6	$K_i = 3$	Human liver microsomes†
Thioridazine	Pheno.	Inhibits HERG - $\downarrow I_{out}$	1	tsA201 cells
Thioridazine	Pheno.	Inhibits CYP 2D6	$K_i = 1.4$	Human liver microsomes‡
Thioridazine	Pheno.	Dopamine D2 receptor	$K_i = 0.01^{\dagger\dagger}$	Pig anterior pituitary
Haloperidol	Butyro.	Inhibits HERG - $\downarrow I_{out}$	1	Xenopus oocytes*
Haloperidol	Butyro.	$I_{CaL}$ blockade - $\downarrow I_{in}$	$EC_{50} = 20$	PC12 cells
Haloperidol	Butyro.	$I_{Na}$ blockade - $\downarrow I_{in}$	5	Isolated guinea pig ventricular myocytes
Haloperidol	Butyro.	Dopamine D2 receptor	$K_i = 0.0004$	Cloned human receptor
Haloperidol	Butyro.	Inhibits CYP 2D6	$K_i = 7.2$	Human liver microsomes‡

Comparison of  $IC_{50}$ 's for actions of selected drugs. Note that the *in vitro* model systems tested in the literature are diverse and may not be directly comparable due to access of drug site of action, intracellular solutions, etc.  $\downarrow I_{out}$  = decreases outward repolarising current.  $\downarrow I_{in}$  = decreases inward depolarising current. Pheno. = phenothiazine antipsychotic. Butyro. = butyrophenone antipsychotic.

\*Heterologous system in which channel was added using molecular techniques.

†Using desipramine as a substrate.

‡Using O-demethylation of dextromethorphan as a substrate.

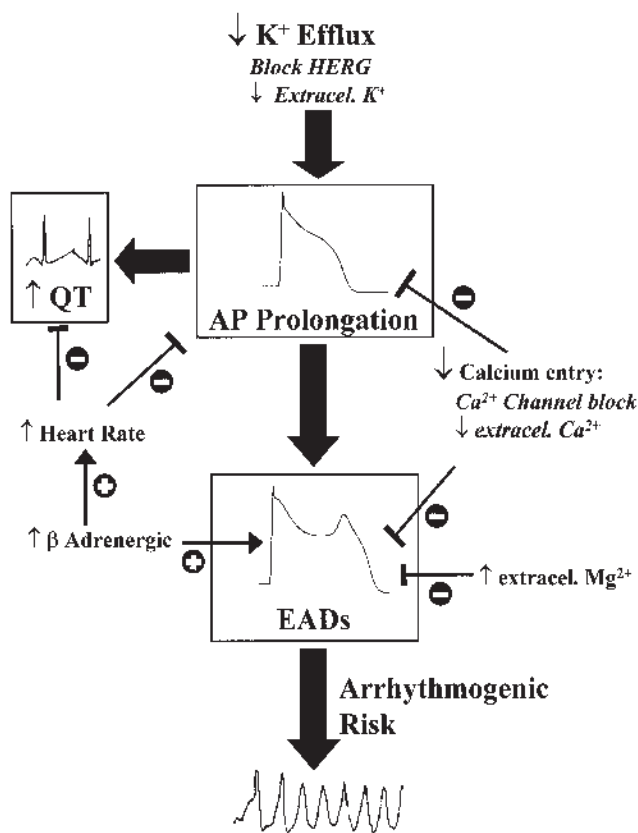
§Using  $^3H$ -spiperone as a ligand.

be associated with chlorpromazine but to be positively associated with TCAs and thioridazine.

QT interval prolongation is not an invariable precursor to TdP,<sup>7</sup> and there is no direct evidence that the extent of drug-induced QT<sub>c</sub> lengthening is associated directly with an increased risk of TdP or sudden death.<sup>154–157</sup> In an analysis of over 1000 family members in LQTS families enrolled in the International Registry who had a normal (<440 ms) QT interval, 6% of them experienced syncope or cardiac arrest.<sup>158</sup> In contrast, the HERG mutation A561V, a mutational hot spot for congenital LQTS originally associated with high penetrance, has been found to be associated in some families with a penetrance as low as 25%,<sup>159</sup> such that some family members have the genetic mutation but lack a prolonged QT<sub>c</sub> or any of the other clinical signs. This suggests that the variation in clinical phenotype is not simply a result of variation in known ion channel mutations, but may also depend on other putative genetic factors, which can vary from family to family. It is feasible that environmental triggers might also play a role. It seems likely that some asymptomatic gene carriers (most of whom are over 40 years of age) may be predisposed to the possible occurrence of drug-induced TdP.<sup>159</sup> Conversely, acquired LQTS may be a *forme fruste* of LQTS or a similar genetic repolarization abnormality,<sup>121</sup> appearing as an atypical form of the genetic disorder in which the full symptoms (i.e. QT<sub>c</sub> prolongation) do not appear until a QT-prolonging drug is administered.<sup>134,160</sup>

#### Sympathetic modulation of AP prolongation by K<sup>+</sup> channel inhibition

One further potential mechanism that may affect vulnerability to I<sub>Kr</sub>-inhibition-induced arrhythmias may be a local imbalance in cardiac autonomic activity.<sup>161,162</sup> In patients with CAD, increased sympathetic tone can be a causal factor in the generation of ventricular arrhythmias<sup>163</sup> (Fig. 4). Both depression<sup>164</sup> and schizophrenia<sup>165,166</sup> are known to increase plasma norepinephrine (NE) levels, and it is possible that psychotropic-induced arrhythmogenic risk may be augmented by psychotropic-induced blockade of NE reuptake.<sup>167</sup> For example, desipramine (a TCA associated primarily with NE reuptake blockade, and that does not lower NE when administered chronically<sup>164</sup>) had almost twice the incidence of QT<sub>c</sub> prolongation compared to other TCAs in one meta-analysis; in that meta-analysis the *average* QT<sub>c</sub> interval for desipramine was similar to the other TCAs,<sup>89</sup> suggesting that there may exist a subgroup of particularly susceptible patients. In anesthetized dogs, desipramine has been shown to potentiate the pressor, chronotropic, inotropic and coronary sinus blood flow responses to NE infusions,<sup>168</sup> suggesting that psychotropics that inhibit the reuptake of NE may increase the influence of spontaneous physiological increases in sympathetic activity. By contrast, increasing sero-



**FIG. 4.** Factors influencing arrhythmogenic risk. This diagram illustrates the influence of heart rate, HERG blockade, beta adrenergic activity, and calcium channel blockade within the myocardium upon the pathway from AP prolongation to arrhythmogenic risk. Small upward arrows (↑) indicate an increase in levels, whereas small downward arrows (↓) indicate a decrease. Larger arrows suggest the pathway indicated by the arrow is increased, whilst blunt (T shaped) arrows indicate that the pathway is attenuated (e.g. an increased heart rate *shortens* the cardiac ventricular action potential).

tonin, which has been associated with a reduction in sympathetic activity,<sup>169</sup> leads to a protective increase in the threshold for both extrasystoles and ventricular fibrillation in whole animal models.<sup>170–173</sup> This finding may help to explain the much higher fatal toxicity index of desipramine compared with clomipramine (a TCA associated primarily with serotonin reuptake blockade),<sup>9</sup> and may also explain the qualitatively higher incidence of QT<sub>c</sub> prolongation in pediatric patients associated with desipramine compared to other TCAs.<sup>89</sup>

However, adrenergic stimulation is mechanistically associated with opposing effects on arrhythmogenic risk (Fig. 4), in that the resulting increased heart rate will tend to shorten the APD and lower arrhythmogenic risk, while the increased Ca<sup>2+</sup> mobilization will tend to potentiate EADs and increase arrhythmogenic risk. The resultant effect on arrhythmogenic risk of these two opposing mecha-

nisms of adrenergic stimulation will depend on both the state of the myocardium and on the changes in heart rate. For example, in the clinical case of acquired LQTS, isoprenaline may be used to resolve acute cases of TdP because of its rate-increasing effects on the sinus rhythm. One possibility at the cellular level is that during situations of bradycardia, putative local increases in  $\beta$ -adrenergic stimulation to the Purkinje cells and M-cells would tend to increase the activity of the sarcoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase,  $I_{\text{CaL}}$ <sup>174</sup> and the sodium  $\text{Ca}^{2+}$  exchanger<sup>175</sup>, all three of which would act in concert to load the intracellular stores with  $\text{Ca}^{2+}$  and create conditions favoring after depolarizations.<sup>176,177</sup>

### **Blockade of $I_{\text{CaL}}$ concurrent with $I_{\text{Kr}}$ blockade**

In contrast to increased  $\text{Ca}^{2+}$  mobilization under sympathetic stimulation, simultaneous partial inhibition of  $I_{\text{CaL}}$  may decrease the arrhythmogenic risk associated with HERG blockade or QT prolongation. At a clinical level, hypothyroidism, chronic amiodarone administration, and severe hypocalcemia – all conditions in which there is considerable QT prolongation – are rarely associated with TdP unless there are unusual disturbances in other electrolytes; in all three of those conditions  $I_{\text{CaL}}$  is markedly attenuated. Additionally, the use of magnesium therapy, which may attenuate  $\text{Ca}^{2+}$  influx,<sup>178</sup> is efficient at abolishing arrhythmia in clinical TdP and in animal models, although it does not fully normalize the QT interval.<sup>179</sup> The mechanisms for these cardioprotective actions are uncertain but may involve elimination of reverse use-dependent effects<sup>180</sup> or changes in  $\text{Ca}^{2+}$  handling.<sup>181,182</sup> We have recently observed in a heterologous model system that the SSRIs fluoxetine and citalopram block HERG in a concentration range similar to that of TCAs, and that citalopram can also block  $I_{\text{CaL}}$ .<sup>26</sup> This may be an example of the above mechanism, in which the  $I_{\text{CaL}}$  blockade may attenuate the risks associated with HERG blockade, possibly explaining the low FTIs associated with SSRIs.

### **Vagal effects on arrhythmogenesis and the APD**

Vagal actions on the heart may be directly relevant to patient vulnerability to acquired LQTS, as elderly patients have decreased cardiac parasympathetic activity. Vagal effects in the heart tend to oppose sympathetic effects and are associated with reduced arrhythmogenesis under some circumstances, as well as with a decrease in the heart rate. In patients prescribed phenothiazines, antimuscarinic self-poisoning can lead to dysrhythmias and death,<sup>183,184</sup> although therapeutic doses of orphenadrine may antagonize the risks of phenothiazines by lowering their body concentrations.<sup>185</sup> In a whole animal ischemic model of arrhythmogenesis in the conscious dog, individual animals were categorized into arrhythmia-susceptible or -resistant groups during exercise combined with transient coronary

artery occlusion. Those animals that were susceptible were shown to be protected by vagal stimulation from exercise-ischemia-induced ventricular fibrillation,<sup>186</sup> even when the heart rate was kept constant by atrial pacing; atropine administration caused resistant animals to have novel or worsened arrhythmias in response to exercise and coronary artery occlusion.<sup>187</sup> However, the effects of vagal stimulation may be difficult to observe without an autonomic imbalance. Compared to conditions of low sympathetic stimulation, when the vagal effects on heart rate are relatively small, the vagal effects on heart rate in dogs have been shown to be significantly increased in the presence of sympathetic activity (*accentuated antagonism*)<sup>188</sup> and exercise,<sup>189</sup> and acetylcholine (ACh) has been observed to have only a very weak shortening effect on ventricular APD in the cat except after bilateral vagotomy.<sup>190</sup>

At the cell and tissue level, ACh in ferret papillary muscle is associated with a shortening of the APD and a negative inotropic effect, which are associated with an increase in background  $\text{K}^+$  current carried by muscarinic receptors and decreases in both inward  $\text{Ca}^{2+}$  current and the intracellular  $\text{Ca}^{2+}$  transient during the AP.<sup>191</sup> The hyperpolarization induced by ACh has a well described influence in decreasing the heart rate, and in isolated spontaneously beating AV nodal cells of the rabbit, ACh can abolish spontaneous beating and the associated  $\text{Ca}^{2+}$  transients.<sup>192</sup> In some systems the main ventricular effects of vagal stimulation or ACh may be mediated in the ventricle by the changes in heart rate<sup>193</sup> or conduction. Experimentally, the possibility of drug interactions is clearly illustrated in the atria; when the atria are driven at a constant rate, the prolongation of the APD in isolated guinea pig atria by  $I_{\text{Kr}}$  blockers (e.g. *d*-sotalol) is blunted by ACh.<sup>194</sup> This modulation of  $I_{\text{Kr}}$ -induced changes in the APD by agents with cholinergic or anticholinergic actions may be relevant to vulnerability to psychotropic drugs with the ability to block HERG/ $I_{\text{Kr}}$  that are also known to have antimuscarinic effects (e.g. imipramine), particularly in high risk populations, cases of self-poisoning, or the elderly.

### **High risk individuals**

There are also high risk individuals, which include those suffering from ischemic heart disease and heart failure, history of arrhythmias, and a history of MI. Hypokalemia and hypomagnesia will increase the ion channel effects of these drugs, the former affecting HERG as stated above; these effects may be important in patients with eating disorders. Genetic susceptibilities to adverse effects are an active area of research, including ion channel defects that may or may not appear on the ECG in the absence of pharmaceutical agents, as in the case for clarithromycin.<sup>134</sup> By contrast, the neuropharmacological adaptation of cardiovascular reflexes to long term administration of some

TCAs<sup>195</sup> may represent a potential physiological advantage not present in cases of self-poisoning occurring immediately after initial presentation.

### POTENTIALLY PRO-ARRHYTHMIC DRUG INTERACTIONS

The interactions between different psychotropic drugs used in combination, or used with other medications that have known effects on the cardiovascular system, may lead to QT prolongation and risk of arrhythmia. In some cases the degree of synergy between agents is known, whilst in other cases the degree of synergy, if any, has not been determined. While the psychotropics have a variety of interactions, many of which affect the CNS,<sup>196,197</sup> the non-cardiac interactions are outside the scope of this review and are covered in depth elsewhere.<sup>198–200</sup> The following discussion is limited to those effects that are potentially cardiotoxic, and is focused on illustrating the essential concepts surrounding this issue.

#### Pharmacodynamic and physiological interactions leading to QT prolongation

As the previous discussion demonstrates, a wide variety of psychotropic drugs have effects on QT prolongation, and psychotropics that have these effects (e.g. phenothiazines and TCAs) can interact with other drugs associated with AP prolongation (for a table of such drugs see<sup>14</sup>). In particular, the class III antiarrhythmics (e.g. sotalol, ibutilide or dofetilide) prolong APD, typically by cellular effects including blockade of HERG/ $I_{Kr}$ , and the potential for QT prolongation in the presence of both classes of drugs means that their concomitant use is not recommended. In accord with this, there has been a report of sudden cardiorespiratory arrest and death during intravenous infusion of the antiarrhythmic agent eproxidine into a volunteer who was later found to have received a depot injection of flupenthixol the previous day<sup>201</sup>. Pimozide and clarithromycin can interact to cause QT prolongation and sudden death<sup>202</sup>, presumably due to pharmacokinetic effects, but new mechanistic information on genetic susceptibilities to QT prolongation by clarithromycin<sup>134</sup> may suggest an additional physiological contribution to this interaction.

Previously TCAs were described as having class I antiarrhythmic effects<sup>203</sup>, and the combination of TCAs with class I antiarrhythmics could have an additive effect on slowing conduction via sodium channel blockade. These effects may be complicated by factors that modulate repolarization, including: hypokalemia, bradycardia, gender, cardiac hypertrophy and heart failure, metabolic factors, reduced repolarization reserve, and putative *formes frustes* of congenital LQTS<sup>119</sup>, and any of these may exacerbate the actions of psychotropics on the AP.

When the pharmacological action of a psychotropic agent interferes with that of a cardiac drug, there can be cardiotoxic effects, and these can be exacerbated by conduction defects. Pre-existing conduction defects, particularly AV node block and bundle branch block, are associated with risk in TCAs<sup>62</sup>, probably due to the TCAs' inhibition of  $Ca^{2+}$  channels. This would interfere with the nodal AP, which is depolarized primarily by  $Ca^{2+}$  rather than sodium, and thereby alter conduction through the node. There are both antipsychotics and antidepressants that can have anticholinergic (atropine-like) effects (e.g. tachycardia), and these can be exacerbated in the presence of other drugs with anticholinergic effects (e.g. disopyramide and quinidine). The combination of an antimuscarinic (e.g. orphenadrine) with a psychotropic that has known QT prolongation effects (e.g. thioridazine) would tend to increase the mechanistic risk of arrhythmogenesis.

#### Pharmacokinetic interactions

Enzyme inhibition, alterations in protein binding and, less commonly, absorption may be important influences in drug-drug interactions, and it has been proposed that compromised metabolism may play a role in the cardiotoxicity observed in patients taking psychotropic drugs<sup>204</sup> (Table 4). Inhibition of the cytochrome P450 system-mediated oxidative metabolism of drugs, particularly by some SSRIs, is of particular clinical relevance with regard to psychotropic drug-drug interactions; in tandem with the advance of *in vitro* measures of physiological activities, these pharmacokinetic activities are increasingly researched at the *in vitro* level, as model systems (e.g. liver microsomes, liver slices, hepatocyte culture, cell lines and expressed enzyme) are further characterized<sup>205,206</sup>. Many TCAs, SSRIs and neuroleptics are metabolized by cytochrome P450IID6 (CYP2D6) and compete for metabolism via this oxidative system<sup>207,208,209</sup>; for example fluoxetine can lead to increased levels of TCAs and to concomitantly increased risk of increasing cardiotoxic effects when used in combination (e.g.<sup>32</sup>). There can be differences between SSRIs in their *in vitro* and clinical potency for this effect<sup>210,211,212</sup>, with fluoxetine and paroxetine being the most potent inhibitors, and sertraline, citalopram and fluvoxamine showing substantially less effect. In contrast, the newer atypical antipsychotics have not been identified as significant inhibitors or inducers to any co-administered medication<sup>213</sup>.

Psychotropic drugs can also interfere with medications relevant to the cardiovascular system, and such pharmacokinetic effects may add to risk associated with some antiarrhythmic medications<sup>67</sup>. In addition to fluoxetine leading to raised levels of TCAs<sup>214</sup>, fluoxetine can also lead to increased levels of some antiarrhythmics (e.g. flecainide) because some class IC antiarrhythmics and some  $\beta$ -blockers, such as propranolol and metoprolol, are metabolized by



**TABLE 4.** Examples of pharmacokinetic interactions of psychotropics relating to LQTS

Metabolic Pathway	Inhibitors	Prevents Metabolism of	CV Reaction
CYP2D6	Fluoxetine Paroxetine	TCAs Phenothiazines Pindolol Metoprolol Flecainide Desipramine	Orthostatic Hypot. ↑ QT Bradycardia Bradycardia
CYP2D6	Quinidine Propafenone		Orthostatic Hypot.
CYP2A2	Fluvoxamine	Propranolol Theophylline Imipramine Ca <sup>2+</sup> channel blockers	Bradycardia Tachycardia Orthostatic Hypot. Flushing
CYP3A4	Ketoconazole Itraconazole Mibefradil	Terfenadine Astemizole Imipramine Amitriptyline Amiodarone Dofetilide Quinidine Propafenone Disopyramide Tamoxifen Erythromycin	↑ QT ↑ QT Orthostatic Hypot. Orthostatic Hypot. ↑ QT ↑ QT ↑ QT ↑ QT ↑ QT ↑ QT ↑ QT
	<i>Less strongly:</i> Fluoxetine Fluvoxamine		↑ QT ↑ QT

CV reaction - cardiovascular effects of interaction

Orthostatic Hypot. - orthostatic hypotension

↑ QT - may prolong the QT interval, with associated risk of arrhythmia

CYP2D6<sup>215,216</sup>. Conversely, quinidine (a class 1a antiarrhythmic) potentially inhibits CYP2D6<sup>217</sup>, as does the type I antiarrhythmic propafenone<sup>218</sup>, which can lead to raised levels of desipramine<sup>219</sup>. It is worth noting that the CYP2D6 system is subject to genotypic variation, such that about 10% of Northern Europeans will have low levels and be at risk of developing high plasma levels of drugs that are substrates for this system<sup>216,220</sup>; this predisposes them to cardiac toxicity from TCAs, or drug combinations, on what would otherwise be therapeutic doses. In addition to a modest effect on cytochrome CYP2D6, fluvoxamine is a potent inhibitor of CYP2A2<sup>221</sup>; the metabolism of propranolol, theophylline and imipramine involves CYP2A2, and these drug levels may be increased by fluvoxamine<sup>222,223,212</sup>.

Studies on human liver microsomes indicate that CYP3A4 isoforms on average constitute the largest component (approximately 30%) of identified cytochromes, and there is large inter-individual variability in the ability to biotransform CYP3A4 substrates<sup>224</sup>. The SSRIs fluoxetine and fluvoxamine can interact with CYP3A4<sup>225,226</sup>; in the case fluoxetine, it is a less potent inhibitor of CYP3A4 than its metabolite norfluoxetine<sup>227</sup>, the latter often remaining in the blood stream for weeks after discontinuation of fluoxetine. The SSRI-mediated inhibition of CYP3A4 isoforms can affect the metabolism of non-psychotropic drugs that can lead

to cardiac effects at high concentrations. For example, Ca<sup>2+</sup> channel blockers are metabolized by CYP3A4 and the emergence of flushing on these drugs has been noted with the addition of fluoxetine<sup>228</sup>. Some H1-specific non-sedating antihistamines, in particular the piperidines terfenadine or astemizole, which can be associated with QT prolongation, are also metabolized by this pathway; these antihistamines may interact with psychotropic drugs (e.g. fluvoxamine, nefazodone, sertraline and potentially fluoxetine<sup>229,230</sup>) and are not recommended in combination. The azole antifungal agents ketoconazole and itraconazole block some CYP3A4 isoforms more strongly than SSRIs do<sup>230</sup>, and there is a potential risk when used in combination with CYP3A4-metabolized psychotropics that may be associated with HERG block (e.g. imipramine and amitriptyline).

The level of binding of antidepressants to plasma proteins may be important where this will lead to competition with cardiovascular treatments. For example warfarin and digoxin are both highly protein bound and have a narrow therapeutic window. A number of antidepressants are highly protein bound, and although in general their plasma concentrations are low, they can vary widely between individuals<sup>231</sup>. In interaction studies, fluvoxamine elevated warfarin levels and prothrombin time<sup>222</sup> and paroxetine interacted with digoxin<sup>232</sup>. However, although such interactions with other SSRIs may not be viewed as

clinically important<sup>233,234</sup>, these studies were generally small and case reports suggest that it is prudent to monitor such patients more closely during the co-administration of SSRIs<sup>235</sup>.

## CONCLUSION

Advances in drug discovery have led to an increasing choice in the number of psychotropic drugs, and these new drugs may benefit from advances in specificity, efficacy and, most importantly, safety. More novel compounds are less well studied than older compounds, but the mounting data concerning either drug-induced QT<sub>c</sub> prolongation or sudden cardiac death are likely to play a major role in the drug discovery and approval process. It is postulated that some agents will only cause complications in a sub-population of vulnerable patients<sup>134</sup>, and recent examples (e.g. sertindole<sup>48</sup>) suggest that it remains difficult to detect absolutely all psychotropic agents with potential problems before they reach the market. As has been shown with non-sedating antihistamines<sup>236</sup>, it is possible to distinguish electrophysiologically agents that do and do not affect the ionic currents responsible for repolarization and to correlate that data with clinical experience of arrhythmogenesis. However, as discussed in this review, inhibition of HERG/I<sub>Kr</sub> at the cellular level may not, by itself, always be a predictor of arrhythmogenic potential *in vivo*.

Haverkamp *et al.* and von Moltke *et al.* have recently considered in detail the merits of various testing strategies<sup>119,206</sup>, which involve tests at *in vitro* as well as *in vivo* levels before beginning phase I/II clinical trials. Given the pressures on drug development, the employment of combinatorial chemistry and the use of high throughput screening, it seems likely that the use of whole animal tests on a large number of candidate drugs would be both time-consuming and expensive. However, the diversity of the compounds that have been found to block I<sub>Kr</sub>/HERG may lead to the conclusion that routine screening is one of the only viable options at the present time—suggesting that measurements in single cells be used to buttress data from *in vivo* ECG and Langendorff perfused hearts<sup>10</sup>. Current strategies for new psychotropic agents can include experiments using expressed HERG as a rapid screen early in the testing process<sup>10</sup>.

However, other cellular tests in addition to HERG blockade will likely be found to be useful additions to the battery of screening tests for arrhythmogenic potential. While the pathophysiology of psychotropic-induced LQTS is generally agreed to involve repolarization anomalies, the precise nature of all these mechanisms has yet to be established, and as such, even QT<sub>c</sub> prolongation can only be considered a diagnostic tool rather than a mechanistic explanation. Mechanistic questions still remain, therefore,

and these might most usefully be addressed in a 'research' rather than 'screening' context. As we have noted, TCAs have a wide spectrum of actions including inhibition of nor-adrenaline and 5-hydroxytryptamine reuptake at nerve endings, as well as anti-histaminergic activities, anticholinergic activities, and blockade of sodium, Ca<sup>2+</sup> and K<sup>+</sup> channels<sup>237,60,123,17</sup>. The precise combination of some of these effects may influence the risks of QT<sub>c</sub> prolongation and sudden death. Future experimental design may benefit from an integrated approach examining more than a single variable at a time, thus correlating psychotropic drug effects on repolarizing currents, the ECG, and other known activities for each agent.

It is to be hoped that, as more becomes known about the cellular and molecular basis for the cardiac effects of particular psychotropic drugs and classes, this will facilitate improved high throughput drug development. One potentially attractive strategy will be to use compounds that are currently associated with psychotropic-induced arrhythmias as the basis of new chemical structures that preserve the clinical effects of the parent compound but are modified to avoid undesired molecular interactions with the relevant cardiac channel or channels.

## NOTE ADDED IN PROOF

A description of HERG blockade by a selection of atypical antipsychotics has now been reported in Kongsamut *et al.*, 2002, *Eur J Pharmacol* 450:37–41; they report that the IC<sub>50</sub> for olanzapine's blockade of heterologous HERG in a mammalian cell is at least 50-fold higher than those for ziprasidone, risperidone, thioridazine or sertindole. In addition, mutations of the gene encoding the cardiac ryanodine receptor (RyR2; 1q42–p43) have been linked to familial polymorphic ventricular tachycardia (Priori *et al.*, 2001, *Circulation* 103:196–200).

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