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Cardiovascular Adverse Effects of Antipsychotic Drugs

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Contents

Abstract

Minor cardiovascular adverse effects from antipsychotic drugs are extremely common. They include effects such as postural hypotension and tachycardia due to anticholinergic or α_1-adrenoceptor blockade, and may occur in the majority of patients at therapeutic dosages. There are a number of pharmacological effects that are of uncertain clinical significance, such as blockade of calmodulin, sodium and calcium channels and α_2-adrenoceptors in the central nervous system. The most serious consequences of treatment, arrhythmias and sudden death, are probably uncommon and are most likely to be caused primarily by blockade of cardiac potassium channels such as HERG. Incomplete evidence suggests that arrhythmias and

sudden death are a particular problem with certain drugs (thioridazine and droperidol), high risk populations (elderly, pre-existing cardiovascular disease, inherited disorders of cardiac ion channels or of antipsychotic drug metabolism) or people taking interacting drugs (such as drugs that prolong the QT interval, e.g. tricyclic antidepressants, drugs that inhibit antipsychotic drug metabolism, or diuretics). Clozapine may be unique in also causing death from myocarditis and cardiomyopathy. Much further research is required to more clearly identify high risk drugs and the populations that are at risk of sudden death, as well as the mechanisms involved and the extent of the risk.

Antipsychotic drugs are a pharmacologically and structurally diverse group of drugs that achieve their antipsychotic effects through dopamine or serotonin receptor blockade. However, almost universally, they have effects on other receptors and physiological systems. Many of these affect cardiovascular function, both directly and indirectly. This may lead to a wide variety of adverse effects, including postural hypotension, tachycardia, palpitations, heart failure and arrhythmias. These have been noted in up to 75% of patients receiving these drugs in clinical trials and observational studies. However, the association with sudden death is perhaps the most notorious but least understood problem with antipsychotic drug use.

Sudden death associated with antipsychotic drug use was first reported in the 1960s and has continued to be reported with various drugs up to the present.[1-3] The discovery that phenothiazines had quinidine-like antiarrhythmic effects was initially taken as evidence that these drugs were safe for people with heart disease, and they were in fact recommended for people with arrhythmias. The association of antiarrhythmic drugs with syncope and sudden death had long been recognised, but it had been assumed that the overall risk-benefit analysis remained favourable. However, with the publication of the Cardiac Arrhythmia Suppression Trial (CAST) and a number of other studies examining the role of antiarrhythmic drugs, it became apparent that most pure class I and class III agents increase rather than decrease the risk of death, and the absolute increase in risk of death in high risk populations was as high as 10% per year.[4-6] This included one study which used moricizine, a phenothiazine derivative with class I antiarrhythmic properties.[7] This has lead to recommendations for antipsychotic drugs that parallel those for antiarrhythmic drugs in terms of the patients at risk, although this is largely based on speculation.

Concerns are further raised by data on the mortality in schizophrenia, which is increased over that in the general population and is not fully accounted for by suicide or accidental death. A 10-year cohort study[8] found a 1.33-fold relative risk of death in a schizophrenic population compared to the non-schizophrenic population. The leading cause of death was 'circulatory disease' and the independent risk factors for death included antipsychotic drug polypharmacy [relative risk 2.46; 95% confidence interval (CI) 1.1 to 5.47] and absence of anticholinergic drug therapy (relative risk 3.33; 95% CI 0.99 to 11.1), perhaps indicating use of low potency antipsychotic drugs in these patients.

In contrast with antiarrhythmic drugs, the actions of antipsychotic drugs on the cardiovascular system are not class effects. All cardiovascular effects vary significantly between drugs, particularly when they are used in therapeutic dosages. Thus, some drugs may be much safer than others in patients with cardiovascular disease, whereas others may be particularly dangerous. At this time, both the mechanisms and the pharmacology of these drugs are incompletely investigated. Determining which drugs are safer will depend on better knowledge of the pharmacology of these drugs and the mechanisms involved in sudden death and other serious adverse cardiovascular effects. The recent withdrawal of the new antipsychotic drug sertindole because of proarrhythmia[9] indicates that not only can new drugs not be assumed to be safer than old drugs, but that much further understanding of the pharmacology needs to be developed in order to avoid extensive preclinical

and clinical development of drugs that may ultimately have to be withdrawn on safety grounds.

1. Potential Mechanisms of Cardiac Adverse Effects

The range of mechanisms whereby antipsychotic drugs can influence cardiovascular function is very broad and includes direct effects such as blockade of muscarinic receptors in the heart, blockade of α_1-adrenoceptors, blockade of sodium, potassium and calcium channels and blockade of calmodulin. There are also indirect effects through blockade of α_2-adrenoceptors in the central nervous system. There are other adverse effects that are occasionally reported for which there is no pharmacological mechanism, such as polyserositis[10] and myocarditis.[11]

1.1 Anticholinergic Effects

Anticholinergic effects on the heart are mediated through type 2 muscarinic receptors (M_2).[12] These receptors in the heart are responsible for vagal inhibition, and mediate this effect through increased potassium conductance and inhibition of calcium channels. Blockade of these receptors leads to tachycardia. This may increase myocardial oxygen demand, but is generally believed to be a benign adverse effect of antipsychotic drugs. Tolerance to the anticholinergic effects occurs with continued use. The tachycardia is generally modest as the inhibition of parasympathetic tone in the absence of sympathetic stimulation leads to the heart beating at the intrinsic rate.

1.1.1 Heart Rate Variability

Heart rate and blood pressure are under autonomic control. It has been demonstrated that reduced heart rate variability is a risk factor for subsequent death.[13] The greatest interest in heart rate variability has been in patients with myocardial infarction and cardiac failure.[14] In this population of patients, heart rate variability has been shown to be one of the most predictive factors of increased risk of cardiac death.[15] Observational data suggests that reduced heart rate variability is not only a predictor of sudden arrhythmic death but also of non-arrhythmic cardiac events such as myocardial infarction, progression of coronary artery disease and death from heart failure.[13,16] It has evolved as a marker of poor prognosis.

Medications have been shown to alter heart rate variability. This has been documented for most of the modalities utilised as therapy in cardiac failure.[15] Data on the effects of antipsychotic drugs on heart rate variability are limited. Reduced heart rate variability has been demonstrated in a small clinical series comparing clozapine or fluphenazine with placebo in patients with chronic schizophrenia.[17] This effect has been confirmed in a larger series with clozapine[18] and has been negatively correlated with clozapine plasma concentrations.[19] It is postulated that the reduced heart rate variability is due to the anticholinergic effects, possibly in combination with an increase in noradrenaline (norepinephrine) outflow. Data on the effects of other antipsychotic drugs on heart rate variability and the long term consequences of reduced heart rate variability in patients utilising antipsychotic drugs are awaited.

1.2 α_1-Adrenergic Blockade

α_1-Adrenoceptors mediate vasoconstriction in certain vascular beds, and blockade of these receptors via antipsychotic drugs leads to vasodilation. The effect of this is most marked on blood pressure in the standing position, when sympathetic tone is important to maintain adequate blood pressure. The vasodilation also leads to a reflex tachycardia. α_1-Adrenoceptor blockade leads to tachyphylaxis, meaning the hypotensive effect decreases rapidly with continued use. The postural hypotension may lead to syncope with risk of injury; antipsychotic drug use is associated with an increased risk of hip fracture (relative risk 2.0; 95% CI 1.6 to 2.6).[20] These findings were confirmed in a cohort study, with psychotropic drug use directly accounting for about a third of all falls in nursing homes.[21] α_1-Blockers have also been associated with worsening of angina, presumably because of increased myocardial oxygen demand from the reflex tachycardia.

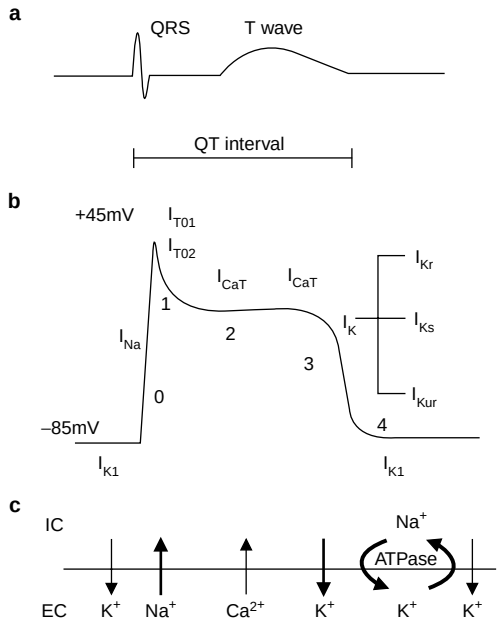

Fig. 1. The cardiac action potential. (**a**) Surface electrocardiogram. The QT interval is measured from the beginning of the QRS complex to the return of the T wave to the isoelectric baseline. (**b**) Action potential showing the 4 phases of cardiac depolarisation and repolarisation with the various sites of the ion channel effects. I_{CaL} = L-type calcium channel; I_{CaT} = T-type calcium channel; I_{Na} = depolarising sodium channel; I_{K1} = inwardly rectifying potassium current; I_{Kr} = rapidly activating delayed rectifier potassium current; I_{Ks} = slowly activating delayed rectifier potassium current; I_{Kur} = ultra rapidly activating delayed rectifier potassium current; I_{T01} and I_{T02} = transient outward potassium currents. (**c**) Ion current directions during activation of the various ion channels. **EC** = extracellular; **IC** = intracellular.

1.3 Ion Channel Blockade

1.3.1 Prolongation of the QT Interval and Torsade de Pointes

Antipsychotic drugs are known to have effects on various ion channels. Our understanding of these channels and the mechanisms leading to the resultant malignant arrhythmias have improved with the expanding knowledge of the genetic forms of the long QT syndromes (LQTS).

Prolongation of the cardiac repolarisation phase (QT interval) has been shown to result from both potassium and sodium channel defects in the inherited form of the LQTS (fig. 1).[22,23] Potassium channel genes known to be involved include KVLQT1-I_{Ks} (slowly activating delayed rectifier potassium current), HERG (human ether-a-go-go related gene)-I_{Kr} (rapidly activating delayed rectifier potassium current), and KCNE1 and KCNE2 (minK)-I_{Ks} (encoding an auxiliary potassium channel subunit). The sodium channel gene shown to affect the QT interval is the SCN5A gene encoding I_{Na}, a phase 0 sodium channel.

Drugs may prolong the QT interval by exerting effects on any of these known channels. However, the best studied of these is the HERG-I_{Kr} channel. The antipsychotic drugs haloperidol and sertindole have been shown to induce prolongation of the QT interval and potently block HERG channels.[24-26] It is tempting to speculate that the QT prolongation seen with antipsychotic drugs is solely related to the blockade of this channel. However, as outlined earlier in this section, a number of other potential pharmacological targets exist.

Prolongation of the QT interval is associated with the development of polymorphic ventricular tachycardia (PMVT). Torsade de pointes describes the ventricular arrhythmia which results in the progressive twisting of the QRS axis around an imaginary baseline associated with a prolonged QT interval in the last sinus beat preceding the onset of arrhythmia.[27] Although several mechanisms have been suggested for the development of torsade de pointes, early afterdepolarisations (EAD) have been acknowledged as one of the important underlying mechanisms.[28] EAD are depolarisations occurring during phase 2 and 3 of the transmembrane potential before repolarisation is complete (fig. 1). These may give rise to one or more premature action potentials, resulting in multifocal ventricular extrasystoles and PMVT/torsade de pointes. Torsade de pointes can result in pre-syncope, syncope and sudden death (ventricular fibrillation). This is often speculated as being the cause of antipsychotic-induced death.

It has been postulated that drug-induced prolongation of the QT might represent a genetically mediated 'forme fruste' of the LQTS. More recently, it has been recognised that persons with the LQTS

mutations may have normal QT intervals.[29] These mutations by themselves produce an alteration of the repolarisation currents that is insufficient to prolong the QT interval at rest, and carriers may be especially sensitive to any drug that affects potassium currents. Future development of genetic screens for these known defects may solve or clarify the extent of this problem.

Bazett[30] showed that the QT interval is related to ventricular systole and that its duration is influenced by the heart rate, and developed the first formulae to correct the QT for rate ($QTc = QT/RR^{1/2}$). However, there is increasing recognition of concealed forms of the LQTS. Hence, it is recommended that in screening patients for the LQTS, attention should be focused not only on the QTc length, but also on the morphology of the TU segment for the presence of 'biphasic T waves' or 'T wave humps'.[31]

1.3.2 Sodium Channel Blockade

Using guinea pig myocytes, Ogata and Narahashi[32] showed that haloperidol could block cardiac sodium channels and exert a quinidine-like effect caused by slowing of sodium flux into cells. Blockade of sodium channels by a class 1C antiarrhythmic drug (flecainide) has been shown to increase the risk of ventricular arrhythmias and sudden death when used to treat patients with asymptomatic ventricular extrasystoles after myocardial infarction,[6] despite the negligible effect on the QT interval.[33] It is unclear whether the risk of sudden death from flecainide is due to arrhythmias or myocardial infarction. *In vitro* studies have shown that haloperidol requires the cooperation of 2 drug molecules for 1 channel site, whereas the binding of antiarrhythmic agents is by 1 : 1 stoichiometry.[32] Theoretically, this suggests that the sodium channel blockade effects of antipsychotic drugs may be minimal below a threshold which would possibly be seen only in overdose or intoxicated states.

However, analogous to the LQTS, some individuals may be more susceptible to adverse effects of sodium channel blockade. Brugada and Brugada[34] described the characteristic electrocardiogram (ECG) changes of right bundle branch block and ST segment elevation in V1 to V3 (Brugada sign) associated with a propensity for sudden death from PMVT or ventricular fibrillation in patients with structurally normal hearts. With increasing recognition of the syndrome it has become apparent that the characteristic ECG change can normalise transiently.[35] Sodium channel blockers such as ajmaline, procainamide and flecainide can then unmask these ECG changes.[35,36] More recently, gene defects in the sodium channel gene SCN5A have been shown to account for some cases of the Brugada syndrome.[37] Reports of coexistence of the LQTS with the Brugada syndrome suggest that a single gene defect may result in both conditions.[38-40] It is estimated that between 0.05 and 3% of the healthy population have the Brugada sign, with substantial racial variation.[31,40-42] It is recognised that drugs may result in the Brugada sign and, while this has not been reported explicitly for antipsychotic drugs, it has been for tricyclic antidepressants,[43] and right bundle branch block is a well recognised consequence of overdose with some antipsychotic drugs.[44] Thus it is conceivable that, particularly in susceptible individuals, antipsychotic drugs with sodium channel blocking activity may precipitate the changes associated with the Brugada syndrome and lead to sudden death. This is speculative, as at present there is no evidence as to whether any antipsychotic drugs significantly block sodium channels at therapeutic dosages.

1.3.3 Calcium Channel Blockade

There are 2 types of calcium ion channels with distinct electrophysiological properties that have been identified within the cardiovascular system: L-type (high voltage) and T-type (low voltage).[45] The L-type channels are responsible for conduction through the atrioventricular node and for sinoatrial node automaticity. These are the main targets for the phenylalkylamine and benzothiazepine calcium antagonists (diltiazem and verapamil). Dihydropyridine calcium antagonists (e.g. nifedipine) act chiefly on peripheral vasculature to cause vasodilation. The T-type channels are mainly located in pacemaker cells which demonstrate spontaneous phase 4 activity.

Several concerns have been raised about the use of calcium antagonists in patients with coronary artery disease.[46,47] These case-control studies have raised the issue of increased myocardial infarction and mortality after myocardial infarction in patients taking dihydropyridine calcium antagonists, in particular short acting nifedipine. These concerns are probably related to the profound vasodilatory effects of these agents, which result in a reflex tachycardia. These effects are not seen with the non-dihydropyridine calcium antagonists. Furthermore, there have been small studies showing a possible beneficial role in decreasing mortality with the use of the non-dihydropyridine calcium antagonist after myocardial infarction.[48]

Many antipsychotic drugs can block calcium channels (L-type). The resultant effects would be expected to be similar to those caused by the nondihydropyridine calcium antagonists. Thus, they might be expected to cause bradycardia and heart block and exert a negative inotropic effect. However, although antipsychotic agents have had these effects demonstrated *in vitro*, the importance of these mechanisms *in vivo* is probably not substantial.

1.4 Blockade of Calmodulin

Calmodulin is an intracellular calcium binding protein. When bound to calcium it is capable of activating several different calmodulin dependent kinases, thus acting as a second messenger system in a variety of cells. One such process is the regulation of protein degradation. Elevated intracellular calcium suppresses protein degradation, and calmodulin antagonists have been shown to stimulate protein degradation.

Thioridazine, a phenothiazine, has been shown to be a potent inhibitor of calmodulin, whereas haloperidol, a butyrophenone, is known to be less cardiotoxic and has only weakly inhibitory effects on calmodulin.[49] It has been speculated that these effects of the phenothiazines on calmodulin may result in protein degradation causing structural damage and the toxic cardiomyopathy that may result from overdoses of some antipsychotic drugs.[49]

If calmodulin blockade is shown to be an important mechanism in the cardiotoxicity related to antipsychotic drugs it will have significant clinical implications, as these drugs have varying degrees of action on calmodulin.

1.5 Myocardial Infarction

The toxic cardiomyopathy related to antipsychotic drugs has frequently been attributed to myocardial infarction. A case control study[50] investigating the association between cardiac disease and oral contraceptives in women aged between 16 and 39 years reported an incidental finding of a 17-fold increase in risk of total myocardial infarction associated with the use of psychotropic drugs. Myocardial infarction in this study was identified by postmortem findings of coronary artery occlusion by thrombus, histological evidence of recent infarction of the myocardium, a positive electrocardiographic report or evidence of raised cardiac enzyme levels. This association was seen across all psychotropic drugs, not specifically antipsychotic drugs, but there was a significant increase in phenothiazine use in those with myocardial infarction (relative risk 6.2; 95% CI 2 to 19.1). A similar association was seen with thioxanthine use (relative risk 4.2; 95% CI 0.9 to 24).[50]

An accompanying editorial concluded that the association was confounded by the risk of cardiac disease being increased in psychiatric patients and that, given the broad range of drug classes involved, a mechanistic explanation was unlikely.[51] However, this study raises the possibility that psychotropic drugs themselves increase the risk of myocardial infarction. Possible mechanisms would include the induction of thrombosis or vasospasm. The antipsychotic drugs have thus far not been shown to have these properties. Interestingly, all 3 classes of psychotropic drugs included in this study are calmodulin antagonists,[52] suggesting that a cause and effect relationship cannot be entirely excluded. In contrast, animal studies have suggested a possible protective role in acute myocardial ischaemia with the use of calmodulin antagonists. This effect is yet to be observed in the clinical setting.[53] Further stud-

ies specifically addressing this association are required.

1.6 Myocarditis and Cardiomyopathy

Cardiomyopathy and myocarditis have been reported during the therapeutic use of antipsychotic drugs.[3,11,54] Clozapine is the only drug implicated where a causal relationship has been demonstrated, with an incidence of at least 0.29% in one series. Myocarditis occurred within 3 weeks of commencing therapy in all 15 patients in this series. Histopathology was performed in 5 patients and showed that an eosinophilic or lymphocytic infiltrate was responsible for the myocarditis, suggesting an immunological rather than a pharmacological aetiology.[11]

2. Relative Cardiovascular Effects of Antipsychotic Drugs

The effects of antipsychotic drugs through all the above mechanisms are not generally considered to be related to their antipsychotic drug action, although it has been speculated that related mechanisms may be involved. The closest correlation with effective dose has been found with dopamine D_2 receptor binding affinity for the older antipsychotic drugs. Antimuscarinic effects in the brain may be desirable to minimise extrapyramidal adverse effects, but this is mediated through M_1 receptors (not the M_2 receptors involved in the cardiac effects). Ideally, it should be possible to rank all of these drugs in terms of their effects on all of these cardiac parameters. However, this is not possible with many drugs as they have not been studied. The comparative data that are available include:

- *in vitro* data (e.g. receptor binding affinity)
- *in vivo* data (e.g. effects on blood pressure or ECG in animals)
- trial data (e.g. frequency of cardiovascular effects in humans in clinical trials, which have often excluded patients at risk of cardiovascular complications)
- effects in overdose
- case control studies (e.g. examining for adverse effects)
- data from post-mortem files on the frequency of which these drugs are linked to death and the concentrations at which death has occurred.

2.1 *In Vitro* Data

We have endeavoured to convert the *in vitro* data into tabular format (table I). The *in vitro* data compare the potency with which these drugs block various receptors, and thus it is important to correct this for the usual concentrations used in therapeutic use. We have elected to do this by comparing the ratio of the potency at each cardiovascular receptor with the potency at the dopamine receptor. There are problems with this approach, which fails to account for possible differences in concentrations between the heart and the brain due to drug distribution characteristics. However, no other mechanism of accounting for the relative antipsychotic potency is available.

2.2 *In Vivo* Data

There are very little *in vivo* published data on cardiovascular adverse effects that compare the different antipsychotic drugs. The simplest *in vivo* parameter, the dose causing 50% mortality (LD_{50}), does not distinguish between cardiac and noncardiac causes of death. There is a substantial difference between these drugs in the LD_{50} after correcting for the defined daily dose.

The study by Hull and Lockwood[49] on the effects on protein degradation in the myocardium found that structural disorganisation was found with thioridazine and trifluoperazine at 10^{-5} mol/L but no effect of haloperidol was seen at 8×10^{-6} mol/L. At this concentration, haloperidol completely suppressed contractile activity. These concentrations are well above those found with haloperidol in therapeutic use, but are only 10-fold higher than those found with thioridazine and trifluoperazine in therapeutic use. Trifluoperazine caused some effects at concentrations as low as 5×10^{-7} mol/L.

Table I. Potency ($10^{-7}/K_d$) of antipsychotic drugs at blocking dopamine D_2 receptors, muscarinic M_2 receptors and α_1-adrenoceptors, and their direct cardiac effects.[3,12,25,26,32,55-59] Drugs are listed in ascending order of D_2 potency. Values shown in bold indicate that a pharmacological effect is likely in some patients at therapeutic dosages.

Drug	D_2 potency	M_2 potency	M_2/D_2	α_1 potency	α_1/D_2	Direct cardiac effects
Quetiapine	0.13	0.071[a]	0.55	12	92.3	
Clozapine	0.47	0.714	1.52	15	31.9	
Promazine	0.625	0.238	0.381			
Molindone	0.83	0.0002	0.0003	0.04	0.048	
Thioridazine	3.8	1.96	0.52	20	5.26	EAD, QTc, TdP
Olanzapine	5.1	2.8[a]	0.55	2.3	0.451	
Mesoridazine	5.3	0.833	0.16	50	9.43	
Chlorpromazine	5.3	0.442	0.083	38	7.17	EAD, I_{Na}, QTc
Loxapine	6.1	0.132	0.022	3.6	0.59	
Chlorprothixene	12.5	0.769	0.062			
Prochlorperazine	14	0.0714	0.005	4.2	0.3	
Risperidone	27	0.0029[a]	0.0001	37	1.37	QTc
Sertindole	37	0.02[a]	0.0005	25	0.676	HERG, QTc, TdP
Trifluoperazine	38	0.0457	0.0012	4.2	0.111	QTc
Ziprasidone	39	0.041[a]	0.0011	38	0.974	
Haloperidol	39	0.0128	0.0003	5.9	0.151	HERG, I_{Na}, QTc, TdP
Perphenazine	71	0.0345	0.0005	10	0.141	QTc
Fluphenazine	125	0.0417	0.0003	11	0.088	
Pimozide	154	2.8[a]	0.018	1.2	0.0078	QTc, TdP
cis-Tiotixene	222	0.036	0.0002	9.1	0.041	

a Nonspecific antimuscarinic potency.

EAD = induces early after-depolarisations *in vivo*; **HERG** = blocks the inward rectifying potassium channel (I_{Kr}); **I_{Na}** = blocks the depolarising sodium channel; **K_d** = dissociation constant; **QTc** = causes significant QTc prolongation in clinical use; **TdP** = causes torsade de pointes (any dose).

2.3 Epidemiological Data

None of the epidemiological or clinical data allow meaningful comparisons between drugs, but they do give an indication of the extent of the problem and highlight some drugs that clearly have common cardiovascular adverse effects.

Postural hypotension was found in 77% of people receiving antipsychotic drugs *vs* 15% receiving placebo.[60] There was only a poor correlation with drug dosage. There was no apparent difference between the drugs in the frequency of postural hypotension, and it follows therefore that either other effects than α_1-adrenoceptor blockade are involved in the postural hypotension or that all the drugs studied had similar clinical effects despite differences in potency.

ECG changes in patients receiving antipsychotic drugs are also common.[61] QTc prolongation (>2 standard deviations above a reference healthy population) was seen in 8% of 495 psychiatric patients. Age over 65 years (odds ratio 3.0; 95% CI 1.1 to 8.3), use of tricyclic antidepressants (odds ratio 4.4; 95% CI 1.6 to 12.1), thioridazine (odds ratio 5.4; 95% CI 2.0 to 13.7) and droperidol (odds ratio 6.7; 95% CI 1.8 to 24.8) and antipsychotic dosage (high dosage odds ratio 5.3; 95% CI 1.2 to 24.4; very high dosage odds ratio 8.2; 95% CI 1.5 to 43.6) were disproportionately associated with QTc lengthening. An association with haloperidol use just failed to reach statistical significance (odds ratio 3.6; 95% CI 0.96 to 13.6). In this study 15 of 64 and 6 of 37 patients receiving thioridazine and droperidol, respectively, had QTc prolongation but, in contrast, many other antipsychotic drugs were not associated with any increase in QTc prolongation.[55]

In another study[61] of 111 patients receiving antipsychotic drugs compared with 42 control individ-

uals receiving no medication, the heart rate was higher (83 *vs* 72 beats/min, difference 11; 95% CI 6 to 16) and the QTc was longer (404 *vs* 388 msec, difference 16; 95% CI 8 to 25). No significant differences were seen in the PR or QRS interval or QTc dispersion. There was a weak correlation between QTc prolongation and dosage in chlorpromazine equivalents (r = 0.39) after adjustment for age. A major shortcoming of this study is that the drugs being taken were not specified. In another cohort study,[62] long term treatment with antipsychotic drugs (chlorpromazine, levomepromazine, thioridazine and haloperidol) at low dosages prolonged the QTc interval and increased QTc dispersion compared with control individuals not receiving these drugs. The QTc interval prolongation was not uniform between drugs, although the subgroups were too small to allow meaningful comparisons. Further studies comparing these effects are still necessary.

2.3.1 Sudden Death

The use of antipsychotic drugs in therapeutic doses has been associated with sudden death.[2] In one series of 49 deaths associated with therapeutic doses of antipsychotic drugs, over half the cases were associated with thioridazine. Thioridazine was associated with 75% of the deaths in the group taking a single antipsychotic. This was a disproportionate result compared to the market share of thioridazine (18.4%).[1]

Other antipsychotic drugs that have (less commonly) been associated with sudden death in young adults include risperidone, chlorpromazine and trifluoperazine.[56,63] Where details are given it is clear that many cases involve multiple drugs, high dosages and/or high serum concentrations.[63]

2.4 Clinical Studies

The vast majority of clinical trials with antipsychotic drugs have excluded people with heart disease, the elderly and those receiving multiple drugs. The common adverse effects, such as postural hypotension and tachycardia, have been commonly reported in most antipsychotic drug trials, although the incidence varies substantially. The rates of these adverse events varied widely in the placebo groups between trials, and both the patient populations and the method of collection of adverse events presumably also vary widely between trials. Trials that have compared 2 different antipsychotic drug treatments should give a more reliable measure of these effects. The vast majority have compared the new agents with established agents and thus the relative problems of the old agents with each other have generally not been compared. On the basis of their comparative clinical trials, the incidence of cardiovascular adverse events does not appear to be substantially lower with the newer atypical antipsychotic drugs. Trials have reported tachycardia, postural hypotension and ECG changes with sertindole, risperidone and quetiapine, and postural hypotension and tachycardia with all the other new antipsychotic drugs.[64] The data currently available do not suggest a major improvement in cardiovascular adverse effects with the newer antipsychotic drugs (whereas such an improvement was seen with the selective serotonin reuptake inhibitors versus the older antidepressants).

A few clinical studies have highlighted particular risks but have not made comparisons. An experimental study on healthy males[65] found that thioridazine in a single dose of 50mg significantly reduced standing systolic and diastolic blood pressures, increased the standing heart rate and prolonged the QTc interval (difference 22 $msec^{-½}$; 95% CI 11 to 33), but had no effect on QT dispersion. Torsade de pointes occurred in 8 of 223 patients receiving intravenous haloperidol in intensive care. None of these patients had any other risk factors for QT prolongation and the risk increased with the dose of haloperidol used.[66] Torsade de pointes is not the only arrhythmia reported with these drugs and other pro-arrhythmic mechanisms may be important. For example, atrial fibrillation has been reported with clozapine.[67]

2.5 Overdose

The diversity of these drugs in terms of their cardiac (and other) effects is readily apparent from the data on poisoning with these drugs. In a large series

Table II. Fatal toxicity indices (deaths per million prescriptions) for antipsychotic drugs in the UK, 1983-92 (from Buckley and McManus,[70] with permission)

Drug	Deaths	Thousand prescriptions	Deaths per million prescriptions	95% confidence interval
Loxapine	2	18	111.1	13.5-401
Remoxipride	1	12	86.2	2.2-480
Chlorpromazine	137	5595	24.5	20.6-28.9
Zuclopenthixol	2	132	15.2	1.8-54.9
Fluphenazine	2	180	11.1	1.3-40.2
Thioridazine	50	7623	6.6	4.9-8.6
Trifluoperazine	23	4874	4.7	3.0-7.1
Promazine	3	1021	2.9	0.6-8.6
Haloperidol	5	2011	2.5	0.8-5.8
Sulpiride	1	498	2	0.1-11.2
Perphenazine	1	561	1.8	0-9.9
Flupenthixol	3	3337	0.9	0.2-2.6
Trifluperidol	0	3	0	0-1419
Chlorprothixene	0	8	0	0-473
Thiopropazate	0	10	0	0-384
Levomepromazine	0	18	0	0-207
Benperidol	0	54	0	0-67.9
Droperidol	0	67	0	0-54.9
Periciazine	0	181	0	0-20.4
Pimozide	0	569	0	0-6.5
Total	231	26 962	8.6	7.5-9.8

of antipsychotic drug overdoses, compared to other drugs ingested thioridazine was more likely to cause tachycardia (odds ratio 1.7; 95% CI 1.1 to 2.9; p = 0.03), a prolonged QT interval (odds ratio 5.2; 95% CI 1.6 to 17.1; p = 0.006), prolonged QTc (>450 $msec^{-1/2}$) [odds ratio 4.7; 95% CI 2.7 to 7.9; p = 0.001], a widened QRS (>100 msec) [odds ratio 3.1; 95% CI 1.5 to 6.3; p = 0.001) and arrhythmias (odds ratio infinity; 95% CI 2.4 to infinity; p = 0.004).[68] There are insufficient data on overdose with most antipsychotic drugs to do further comparisons. Tachycardia, hypotension and ECG changes have been reported with most drugs, but ventricular arrhythmias in overdose (iatrogenic or self-poisoning) have only been reported with thioridazine, haloperidol, sulpiride, mesoridazine, pimozide, chlorpromazine, sertindole and remoxipride.[69]

The range of acute toxicity is also shown in the number of deaths from antipsychotic drug overdose per million prescriptions in the UK, which ranged from zero to over 100 (see table II).[70] Obviously, these deaths may involve noncardiac modes of death, but many would be assumed to be due to cardiac effects.

3. Clinical Implications

The clinical implications can be considered from 3 perspectives: the high risk individual, the high risk drug interactions and the high risk drugs. It follows that avoiding or minimising these risks is the basis of both prevention and management of cardiovascular adverse events.[3]

3.1 High Risk Individuals

The increased risk of cardiac adverse effects with these drugs in special populations has generally not been specifically studied. However, it is clear from data on cardiac drugs that share the same pharmacological effects that there are high risk individuals. The most important identifiable risk factors are known heart disease, including heart failure, history of arrhythmias and myocardial infarction. Electrolyte disturbances, particularly hypo-

kalaemia and hypomagnesaemia, will increase the ion channel effects of these drugs. Diuretic use was more common in psychiatric patients with QTc prolongation, although the results were not statistically significant (odds ratio 3.0; 95% CI 0.8 to 11.0).[55]

There are a range of other potential genetic characteristics that may increase risk, including 'poor metabolisers' who may have a 5- to 10-fold higher concentrations of the drug and/or cardiotoxic metabolites after a given dose,[71] and those with inherited defects of ion channels which may or may not be apparent on the surface ECG.[72] Other risk factors would include increasing age[55,73] and autonomic dysfunction. The need for use of high dosages of drugs also increases the risk, as all the cardiac effects appear to be dose related.[55,61,65,74,75]

3.2 Drug Interactions

Drug interactions may either increase the concentration of the antipsychotic drug or increase the cardiac effects directly. All of these drugs are hepatically metabolised and many have a large first pass effect. In addition, they may have active metabolites that are also generally hepatically metabolised.[76] The major enzymes involved are cytochrome P450 (CYP) 2D6, 1A2 and, to a lesser extent, 3A4, all of which are known to be inhibited or induced by a large number of drugs, many of them in common use in psychiatry.[77]

Other drug classes that share some of the same pharmacological effects include most antiarrhythmic and antihypertensive drugs, antihistamines (sedating and nonsedating), anticholinergic drugs, tricyclic antidepressants, amantidine, scopolamine and lithium.[55,77,78]

3.3 High Risk Drugs

The data from table I indicate that it is difficult to choose a drug in common use that has no adverse cardiac effects. Other considerations (e.g. treatment resistance, extrapyramidal effects) have led to increased use of 'atypical antipsychotic drugs' despite the fact that their non-neuropsychiatric adverse effect profile (e.g. bodyweight gain, cardiovascular and anticholinergic effects) is no better and often worse than that of conventional antipsychotic drugs.[9,61] In patients where there is a particular concern about cardiac effects, high potency antipsychotic drugs (e.g. haloperidol, flupenthixol and fluphenazine) have less anticholinergic and α-blocking effect and are likely to also have fewer other cardiac effects. Conversely, by most measures thioridazine is clearly associated with more marked cardiac effects.

4. Conclusions and Future Research Directions

Antipsychotic drugs have generally been regarded as safe.[3] However, cardiovascular adverse effects from antipsychotic drugs are common and a potentially serious consequence of treatment. Both the pharmacological and clinical data on the existing drugs and risk factors for serious adverse effects are not sufficient to clearly rank these drugs in terms of their cardiovascular adverse effects. Even the magnitude of the problem of sudden death in people receiving antipsychotic drugs is largely unknown. An incidence as high as 2 to 4% per year in at-risk populations (as observed in the CAST trial with antiarrhythmic drugs) has not been excluded with available data on any of these drugs. On the contrary, some of the patchy data that are available are far from reassuring.[1,50,61,62] Further epidemiological studies on psychiatric patients who die suddenly should be a priority for future research. At least 1 large study is currently under way in the UK.[79]

The ideal antipsychotic drug would be 'atypical' in its psychiatric and extrapyramidal effects. However, it would also be selective, meaning that peripheral adverse effects, including cardiovascular effects, would be uncommon at therapeutic dosages. However, such a drug has not been developed to date. Nor are the mechanisms of cardiovascular toxicity sufficiently well understood to allow confident preclinical screening of these drugs, although screening for HERG binding would seem prudent. However, as these effects may be related to active metabolites as well as the parent drug,[80] such screening would not in any case exclude cardiovascular effects and continuing postmarketing surveillance would be necessary.

Thus, the expansion of our understanding of the molecular biology underlying the various cardiac disease processes and channelopathies should lead to development of safer drugs, better understanding of risks leading to informed choices from existing drugs, and safer prescribing practices. Genetic screens combined with a better understanding of the features of concealed forms of the LQTS and Brugada syndrome may facilitate pre-prescription screening. Finally, there is the possibility that further research into the cardiovascular effects of antipsychotic drugs may even lead to new cardiovascular indications for these drugs (or related drugs), such as cardioprotection in myocardial ischaemia.

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