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REVIEW ARTICLE

Cardiac side effects of psychiatric drugs†

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This review describes the common effects of psychotropic drugs on the cardiovascular system and offers guidance for practical management. Selected reports from the literature describing common side effects associated with psychotropic drugs are reviewed, and suggestions for further reading are given throughout the text. Orthostatic hypotension is the most common adverse autonomic side effect of antipsychotic drugs. Among the atypical antipsychotics the risk of orthostatic hypotension is highest with clozapine and among the conventional drugs the risk is highest with low potency agents. Rarely, orthostatic hypotension may result in neurocardiogenic syncope. QTc prolongation can occur with all antipsychotics but an increased risk is seen with pimozide, thioridazine, sertindole and zotepine. QTc prolongation is a marker of arrhythmic risk. Torsade de pointe, a specific arrhythmia, may lead to syncope, dizziness or ventricular fibrillation and sudden death. Heart muscle disease presents most commonly in the elderly as chronic heart failure, but myocarditis and cardiomyopathy, although relatively rare, are devastating, but potentially reversible complications of psychotropic drug therapy have been particularly linked to clozapine treatment. Patients with severe mental illness (SMI) are a 'high risk' population with regard to cardiovascular morbidity and mortality. It is probable that many patients accumulate an excess of 'traditional' risk factors for the development of cardiovascular disease, but other mechanisms including psychotropic drugs may also be influential in increasing risk in this vulnerable group. These risks need to be seen in the context of the undoubted therapeutic efficacy of the psychotropic armamentarium and the relief that these drugs bring to those suffering from mental disorder.

KEY WORDS — psychotropic drugs; cardiovascular system; severe mental illness; orthostatic hypotension; heart muscle disease

INTRODUCTION

This paper reviews the effects of psychotropic drugs on the cardiovascular system. This includes a discussion of orthostatic hypotension, the direct effects of psychotropic drugs on cardiac repolarisation and heart muscle disease related to psychiatric drugs. For each the key clinical features and management are discussed. In addition the contribution of psychotropic drugs to cadiovascular risk is considered. Patients with severe mental illness (SMI) should, in general terms, be considered as a 'high risk' population with regard to cardiovascular morbidity and mortality. It is probable that many patients accumulate an excess of 'traditional' risk factors for the development of cardiovascular disease, but other mechanisms including psychotropic drugs may also be influential in increasing risk in this vulnerable group. This risks need to be seen in the context of the undoubted therapeutic efficacy of the psychotropic armamentarium and the relief that these drugs bring to those suffering from mental disorder.

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ANTIPSYCHOTIC-RELATED ORTHOSTATIC HYPOTENSION AND SYNCOPE

Many of the commonly prescribed antipsychotic drugs interact with numerous receptors both centrally and peripherally. These include dopaminergic, serotonergic, histaminergic, α-adrenergic and muscarinic receptors. The antagonistic and agonistic properties of these drugs may be important in determining their mode of efficacy, but the non-specific nature of their pharmacologic action may result in adverse cardiovascular side effects such as orthostatic hypotension and syncope.

Orthostatic hypotension

Orthostatic hypotension is the most common adverse autonomic side effect of antipsychotic drugs, and is defined as a decrease in systolic blood pressure of $\geq$20 mm Hg, or a decrease of systolic blood pressure to $<$90 mm Hg during an upright posture. Hypotension has been reported in up to 75% of patients treated with antipsychotic drugs, although for the majority this is transient (Stanniland and Taylor, 2000). Hypotension may occur more often in those patients prescribed a combination of antipsychotics. Studies have reported a disparity in the rates of reported dizziness and clinically detectable hypotension. For example 19% of 342 clozapine-treated patients reported dizziness, but a drop in systolic blood pressure following a change in posture was detected in only 9% (FDA, 2001a). Similarly, dose-effectiveness trials of quetiapine in 2300 patients reported a prevalence of dizziness in 10% but hypotension in only 7% (FDA, 2001c). These observations may reflect both the central (dizziness) and peripheral (hypotension) action of the drugs.

Different classes of antipsychotic drugs have differing propensities to cause autonomic nervous system dysfunction. Low potency drugs (such as chlorpromazine and thioridazine) are more likely to cause significant hypotension than mid- to high-potency drugs. Atypical antipsychotics are also associated with bradycardia and hypotension. Clozapine, olanzapine, quetiapine and risperidone have all been associated with changes in blood pressure related to posture (FDA, 1999, 2001a, 2001b, 2001c). The potent antagonist properties of clozapine on cholinergic and α_1-adrenergic receptors may underlie the association between clozapine and hypotension. A benign, sustained tachycardia, characterised by an average increase in heart rate of between 10 and 15 beats per minute occurs in up to 25% of clozapine-treated patients. The causal mechanism is not well understood, but the tachycardia may resolve following switching to another drug without significant adrenergic or muscarinic antagonist properties (Cohen *et al*., 2001).

Syncope

Rarely, orthostatic hypotension may result in neurocardiogenic syncope, which has been defined as: 'syncope occurring when the autonomic nervous system is incapacitated resulting in a failure of vasoconstrictor mechanisms and thereby in orthostatic hypotension (Brignole *et al*., 2001).

The incidence of syncope varies from around 0.2% in olanzapine and risperidone-treated patients (FDA, 1999, 2001b), 1% in patients treated with quetiapine (FDA, 2001c) to 6% following exposure to clozapine (FDA, 2001a). Studies of clozapine (25 mg) in healthy volunteer subjects report that almost two-thirds developed orthostatic hypotension and 47% developed bradycardia below 40 beats per minute. Pooled pre-marketing studies of intramuscular or oral olanzapine reported that 7.5% developed clinically relevant bradycardia, with three cases of sinus arrest that remitted spontaneously. Forty of the 64 cases of bradycardia were associated with a drop in resting blood pressure, or a postural drop consistent with neurally mediated bradycardia and syncope (FDA, 2001b).

Identifying those at risk of hypotension and syncope

The complications of orthostatic hypotension include dizziness and visual disturbances, cognitive impairment and syncope resulting from cerebral hypoperfusion. The risk of falls may increase with resulting bone fractures, particularly in the elderly. Individuals with compromised myocardial or renal function may also develop ischaemia and acute deterioration of end-organ function. The elderly and those with pre-existing cardiovascular disease or autonomic nervous system dysfunction may be particularly susceptible to antipsychotic-induced orthostatic hypotension and syncope, and these individuals require careful monitoring, especially upon initiation of therapy. Those with impaired hepatic function may also develop orthostatic hypotension, as all antipsychotic drugs are metabolised by the hepatic cytochrome enzyme system. Individual variation in phenotypes resulting from genetic polymorphisms within the cytochrome P450 enzyme system may also render some individ-

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uals 'poor metabolisers' and thus reduce clearance of drug from the circulation. Further studies are needed to elucidate the relationship between genetic polymorphisms of the cytochrome P450 system and pathophysiological outcomes.

Managing the risk of hypotension and syncope

For the majority of individuals, tolerance to the hypotensive effects of antipsychotic drugs occurs. More persistent problems with blood pressure regulation may arise following intramuscular administration or rapid dose titration. For this reason, limiting the initial dose and titrating upwards over several days may minimise the risk, particularly in the elderly or in those with pre-existing autonomic or hepatic disease. Should hypotension arise, temporarily reducing the dose before returning to the titration schedule may be sufficient, although a permanent reduction in dose may be indicated for those in whom hypotension is persistent. Antipsychotic drugs that are known to produce clinically significant hypotension should be used with caution in individuals with conditions which predispose to hypotension such as dehydration, hypovolaemia and concurrent antihypertensive therapy.

Advising against abrupt postural changes, standing still for extended periods of time, straining during micturition and defecation, severe exertion and alcohol use may reduce the risk of developing hypotension. Some individuals may benefit from support stockings or volume expansion by increased fluid intake. It is rarely necessary to refer to a physician for pharmacological intervention. Salt-retaining steroids such as fludrocortisone or α-adrenergic agents may have some benefit in such circumstances.

ABNORMALITIES OF CARDIAC REPOLARISATION AND ARRHYTHMIAS

It has been recognised for many years that a variety of conditions, congenital and acquired, can cause prolonged or abnormal cardiac repolarisation (QT interval prolongation and/or abnormal T or T/U wave morphology on the electrocardiogram [ECG]). The QT interval on the ECG (Figure 1) is defined as that period from the onset of the Q wave (ventricular depolarisation) to the cessation of the T wave (ventricular repolarisation). As QT intervals normally shorten with increasing heart rate, and lengthen with decreasing heart rate, a rate corrected QT (QT_c) interval is often calculated.

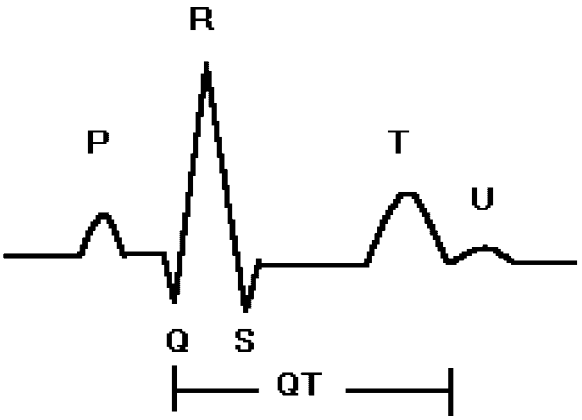

Figure 1. The QT interval is measured from the beginning of ventricular depolarisation (Q wave) to the end of ventricular repolarisation (end of the T wave)

The QT interval and risk of arrhythmia and death

Studies have shown that patients with prolonged QT intervals are at greater risk of cardiac arrhythmias, particularly the polymorphic ventricular arrhythmia torsades de pointes (TdP), where QRS complexes 'twist' around an isoelectric line in a sinusoidal fashion (see Figure 2). Symptoms of TdP include palpitations, syncope and seizure-like activity. The arrhythmia is usually self-limiting but may degenerate into ventricular fibrillation and cause sudden cardiac death.

The QT interval is only an indirect, surrogate marker of potential pro-arrhythmic toxicity. There is no clear relationship between the degree of QT prolongation and the likelihood of the development of TdP, which can occur without significant prolongation of the QT interval. However, the risk appears to increase with more extreme QT interval prolongation. TdP appears to be rare if the QT interval is less than 500 ms, and in one study the mean QT interval prior to the onset of TdP was 580 ms (Stratmann and Kennedy, 1987). It is also noteworthy that in individuals susceptible to ventricular arrhythmias, QT prolongation may be a useful antiarrhythmic mechanism; drugs which prolong the QT interval such as amiodarone, are effective anti-arrhythmic drugs for this reason.

The evidence linking QT prolongation with mortality is conflicting. A relative risk of all cause mortality over 15 years has been reported with QT_c prolongation of 440 ms (Schouten *et al*., 1991), and de Bruyne *et al*. (1999) also reported increased cardiac and all cause mortality in the elderly. Conversely, Goldberg *et al*. (1991) showed no statistically significant increase in overall risk of death, or sudden

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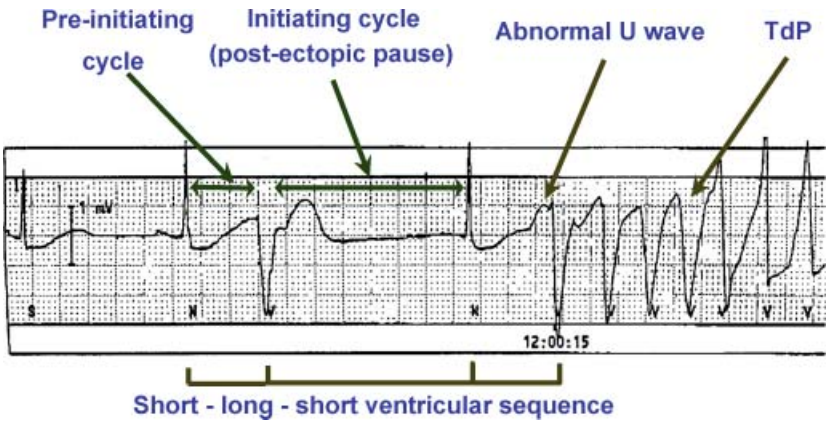

Figure 2. An ectopic beat is followed by a long post-ectopic pause, a normal QRS complex and then an abnormal U wave prior to the onset of TdP

death, in patients with QT_c interval >440 ms in data derived from the Framingham Heart Study. There is clearer evidence linking QT prolongation with increased risk of arrhythmia and death in patients with known cardiovascular disease, and a link has also been demonstrated with liver disease (Day *et al.*, 1993).

Drug-induced QT prolongation

The number of drugs associated with QT prolongation is ever increasing. A list of psychotropic drugs, together with other classes of drugs which have been reported to be associated with QT prolongation, is given in Table 1. The most common mechanism underlying QT prolongation appears to be blockade of the delayed rectifier potassium channel (I_{KR}) in the myocardium which prevents the outward movement of potassium that is responsible for ventricular depolarisation. This mechanism is exploited as a primary pharmacological action of some antiarrhythmic drugs, but in the case of psychotropic drugs there is no therapeutic advantage of I_{KR} blockade.

Some drugs are more potent than others with regard to causing QT prolongation; QT prolongation is caused by some drugs that appear not to have a true potential to cause cardiac toxicity. For this reason, this surrogate marker of pro-arrhythmicity requires careful and precise ECG analysis to allow for meaningful evaluation of the effects of particular drugs on cardiac electrophysiology.

The effects of individual drugs on QT prolongation have been reviewed elsewhere (Clements-Jewery and

Table 1. Drugs reported to be associated with prolonged QT interval and TdP

Psychotropic drugs	Chlorpromazine droperidol
	Haloperidol
	Pimozide
	Sertindole
	Ziprasidone
	Amitriptyline
	Clomipramine
	Desipramine
	Nortriptyline
	Citalopram
	Lithium
	Chloral hydrate
Antiarrhythmic drugs	Type 1A (e.g. quinidine, procainamide)
	Type 1C (e.g. flecainide)
	Type 3 (e.g. amiodarone, sotalol)
Antihistamines	Hydroxyzine
	Loratadine
	Mizolastine
Antimicrobial and antimalarial drugs	Clarithromycin
	Clindamycin
	Erythromycin
	Ketoconazole
	Pentamidine
	Quinine
	Chloroquine
	Amantadine
Immunosuppressant	Tacrolimus
Antidiuretic hormone	Vasopressin
Others	Adenosine
	Papaverine
	Cocaine
	Methadone

Adapted from (Yap and Camm, 2003). NB: this list is not comprehensive.

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Curtis, 2003; Malik, 2003; Taylor, 2003; Thomas and Ferrier, 2003). A study of 495 psychiatric patients, the majority of whom were taking typical agents, reported that droperidol and thioridazine caused QT_c prolongation in a dose-related manner (Reilly *et al*., 2000). A further study identified an excess of sudden deaths in patients taking thioridazine (Reilly *et al*., 2002). Subsequent to these observations, droperidol was withdrawn from the market and changes were made to the licensed indications for thioridazine. Other reports have described QT interval prolongation following treatment with chlorpromazine and haloperidol taken at doses exceeding 20 mg per day (Kriwisky *et al*., 1990). Data regarding the other typical agents are inconclusive, although several other studies have reported QT interval prolongation in patients receiving a variety of typical agents, even at conventional doses (Kitayama *et al*., 1999; Warner *et al*., 1996). A study of 65 patients taking antipsychotic drugs from the North East of England reported that only 2 (3%) of patients had a prolonged QT_c interval (Mackin and Young, 2005).

The advent of increasing regulatory control and post-marketing drug surveillance has resulted in better-quality studies assessing the effect of antipsychotic drugs, particularly the newer atypical agents, on cardiac function. Sertindole has a clear association with QT prolongation (Agelink *et al*., 2001), and there appears to be a dose-related effect of risperidone (Tran *et al*., 1997) and clozapine (Kang *et al*., 2000). Olanzapine (Czekalla *et al*., 2001) and quetiapine (Small *et al*., 1997) appear not to have significant effects on cardiac electrophysiology in clinical studies, and data for amisulpiride are too few to draw any meaningful conclusions. In animals, however, there is evidence that haloperidol, clozapine, olanzapine, risperidone and sertindole cause QT prolongation that is concentration related (Drici *et al*., 1998).

Tricyclic antidepressants (Reilly *et al*., 2000) and methadone (Krantz *et al*., 2002), particularly at high doses have also been shown to cause QT prolongation, and it is recommended at patients requiring more than 100 mg of methadone per day should be closely monitored.

Patient related factors

The QT interval is known to increase with age (Mackin and Young, 2005), and a number of clinical conditions may give rise to increased risk of developing TdP (see Figure 3). Patients with pre-existing cardiac disease or arrhythmias may be at heightened risk of developing arrhythmias following treatment with drugs that further prolong ventricular repolarisation. Abnormalities of the T wave, large U waves or QT prolongation are indicators of abnormal repolarisation. Left ventricular dysfunction and left ventricular hypertrophy are also risk factors. TdP is more likely to occur when the heart rate is slow and in the presence of extrasystoles, so conditions associated with bradycardia such as heart block increase the risk of TdP. Electrolyte abnormalities (hypokalaemia, hypocalcae-

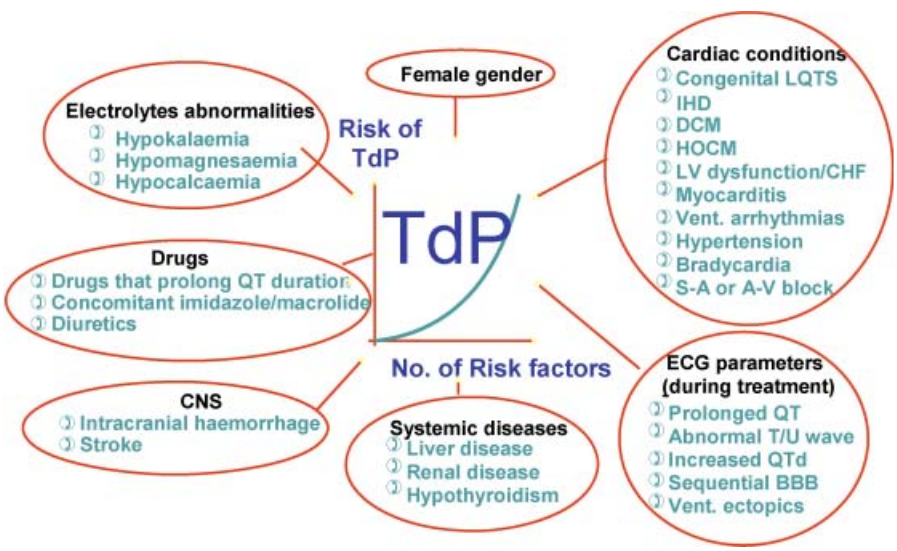

Figure 3. Clinical features associated with increased risk of TdP

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mia and hypomagnesaemia) are associated with TdP, as is treatment with diuretic medication (possibly related to resulting electrolyte disturbance). The risk of the arrhythmia may be increased in patients with chronic alcohol misuse as this may be associated with liver disease which increases the risk of sudden death (Day *et al*., 1993). Women have a longer QT on average than men (Rautaharju *et al*., 1992), and a disproportionate number of drug-induced TdP occur in women (Makkar *et al*., 1993). Patients with anorexia nervosa are at particular risk as they are usually female, often have electrolyte abnormalities and relatively high doses of drug may be used relative to body weight.

Measurement of the QT interval

ECGs used to assess QT interval changes need to be recorded under strict resting conditions. When the heart rate accelerates or decelerates the QT interval shortens or prolongs, respectively. This adaptation, however, is not instantaneous, and studies have shown that about 2 min are required to achieve 90% of the adaptation of the QT interval following an abrupt change in heart rate (Lau *et al*., 1988). Failure to allow for this adaptation will result in a false QT interval influenced by the previous heart rate. QT interval may also vary due to diurnal effects, electrolyte imbalance, autonomic fluctuations, ECG acquisition technique, as well as intra- and inter-observer variability (Gupta *et al*., 2007).

In 1920, Bazett proposed a formula dividing the longest QT interval by the square root of the RR interval. Although there is no universal heart rate correction formula, Bazett's formula remains the gold standard even though this correction may overestimate drug-induced QT prolongation, particularly when the heart rate is outside a narrow physiologic window (Malik, 2003). Automatic measurements of QT intervals performed by most modern ECG machines are accurate only in normal noise-free recordings where the pattern of the T wave is well-defined without any morphological abnormalities. Ideally, manual measurements taken by experienced electrographically trained cardiologists should be performed.

There is no universally accepted upper normal limit for the QT_c interval. QT_c intervals <440 ms are clearly normal. Intervals of 440–460 ms in men and 440–470 ms in women are considered borderline (Gupta *et al*., 2007). Decisions about switching or stopping potentially cardiotoxic psychotropic drugs on the basis of QT interval measurements clearly need to be informed by a careful risk benefit analysis, and in cases of doubt the opinion of a cardiologist should be sought.

Managing the risk of drug-induced QT prolongation

It should be remembered that in patients with SMI the risk of QT prolongation and subsequent ventricular arrhythmia is relatively insignificant compared with the considerable risk from coronary artery disease (Thomas and Ferrier, 2003). However, all reasonable steps should be taken to minimise the risk of drug-induced arrhythmias. Attention should be paid to the general physical health of patients with SMI, and in particular cardiovascular risk factors should be identified and appropriately managed. Selecting an antipsychotic drug with a low propensity to cause abnormalities of cardiac repolarisation may be especially important in those with other risk factors for developing cardiac arrhythmias, and high dose antipsychotic medication should only be used if there is a clear therapeutic advantage in doing so. Although it has been suggested that combination antipsychotic medication should be avoided because of an increased risk of QT prolongation (Taylor, 2003), there is little evidence to support this assertion; indeed one study reported a statistical trend toward a lower QT interval in patients receiving antipsychotic polypharmacy (Mackin and Young, 2005).

Before commencing antipsychotic treatment, where possible, an ECG should be recorded and examined for evidence of left ventricular hypertrophy and repolarisation abnormalities. This is particularly important in those with established cardiovascular disease or when a high risk drug or parenteral therapy is being considered. It may also be prudent to check blood electrolyte levels paying particular attention to serum potassium levels before commencing such therapy, especially in those at high risk of biochemical perturbations. There is little evidence to guide the clinician in decisions about the frequency of ECG monitoring in those treated with psychotropic agents. The summary of product characteristics of several antipsychotic drugs recommends periodic ECG monitoring, especially if higher doses are used, and it would be prudent to monitor cardiac electrophysiology in those receiving parenteral therapy and in individuals undergoing rapid dose escalation. Drug interactions are a major cause of arrhythmias, and extra caution, including ECG monitoring, is needed when a potential interaction is identified. Although wide scale monitoring may prevent some cases of TdP, it is likely that this number would be very small in

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comparison to the huge number of ECGs and blood tests that would be required, and further research is needed to evaluate the cost effectiveness of this approach.

HEART MUSCLE DISEASE

Heart muscle disease presents most commonly in the elderly as chronic heart failure, but myocarditis and cardiomyopathy, although relatively rare, are devastating, but potentially reversible complications of psychotropic drug therapy. In heart muscle disease, the number of potassium channels is reduced, the final net electrophysiological effect being the same as in the long QT syndromes, that is delayed repolarisation. The electrophysiological abnormalities combined with structural changes within the myocardium makes for a potent substrate for ventricular arrhythmias and sudden death.

Clozapine

Myocarditis and cardiomyopathy have most consistently been linked with clozapine treatment (Fitzsimons *et al*., 2005). A pharmacovigilance data mining study using the World Health Organisation's database concluded that myocarditis and cardiomyopathy are significantly more often associated with clozapine than other antipsychotic medications (231 clozapine reports compared with 89 reported for all other antipsychotics) (Coulter *et al*., 2001). Estimates of the incidence of clozapine-related myocarditis have ranged from 1 in 500 patients (Killian *et al*., 1999) to 1 in 10 000 (Warner *et al*., 2000). A 2002 report from the drug's manufacturer found a total of 213 cases of myocarditis, internationally, including 50 deaths, and that 85% of all cases presented within the first 2 months of treatment (Novartis, 2002). A more recent retrospective review of all adverse drug reactions reported voluntarily to the Australian Adverse Drug Reactions Unit mentioning suspected myocarditis identified 116 cases from January 1993 through December 2003 (incidence between 0.7% and 1.2% of treated patients) (Haas *et al*., 2007). Median patient age was 30 years, and the condition developed within a median of 16 days of commencing clozapine. Sixty (51.8%) of patients recovered from their episode, whereas 17 (14.7%) had not recovered, 27 (23.3%) had an unknown outcome and the remaining 12 (10.3%) died.

The risk of developing cardiomyopathy has been estimated to be up to five times greater in patients treated with clozapine than that seen in the general population (Killian *et al*., 1999). The onset of cardiomyopathy is generally longer than for myocarditis, the mean onset having been reported in one study to be 12 months (range 2–36 months) after commencing clozapine treatment. Similar time frames have also been reported by the FDA (La Grenade *et al*., 2001). It is possible that non-fulminant, even subclinical, clozapine-induced myocarditis may progress to dilated cardiomyopathy (Merrill *et al*., 2005), a condition characterised by cardiac dysfunction and often symptoms of congestive cardiac failure. Cardiomyopathy is itself associated with a significant morbidity and mortality, with one-half of the patients dying within 5 years of diagnosis (Merrill *et al*., 2005).

Other drugs

There is limited evidence that other psychotropic drugs can also cause myocarditis. Quetiapine, for example has been associated with myocarditis (Roesch-Ely *et al*., 2002), and an enhanced risk has been suggested with lithium, chlorpromazine, fluphenazine, haloperidol and risperidone (Coulter *et al*., 2001). These associations require further detailed investigation.

Pathophysiology of clozapine-induced myocarditis

It has been argued that clozapine-induced myocarditis results from a type 1 IgE-mediated hypersensitivity reaction (Killian *et al*., 1999). The time of onset and the peripheral eosinophilia and eosinophilic infiltrates commonly seen in the disorder all support this hypothesis. Other possible mechanisms include clozapine-induced cytokine release or elevated catecholamines.

Clinical features

The clinical features of myocarditis are essentially non-specific. Although fever, tachycardia, chest pain, dyspnoea, flu-like symptoms, eosinophilia, elevated cardiac enzyme levels and ECG changes may all be present, no single finding is pathognomonic (Merrill *et al*., 2006). Even myocardial biopsy, the diagnostic gold standard, has limited sensitivity and specificity.

Clozapine-induced myocarditis may be also present in a non-fulminant form which temporally and symptomatically may resemble normal clozapine dose titration. Many characteristics of myocarditis

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(e.g. fever, tachycardia and fatigue) are common during clozapine treatment. Fever has been reported in 20% of patients commencing treatment with clozapine (Tham and Dickson, 2002), and it is often regarded as a benign, self-limiting phenomenon. However, pyrexia may herald the onset of clozapine-induced myocarditis and patients developing a fever, particularly within the first 2–3 weeks of commencing clozapine treatment, warrant further investigation and careful monitoring.

Management of clozapine-induced heart muscle disease

Progression to fulminant clozapine-induced myocarditis may be rapid, and its attendant mortality rate dictates that prompt diagnosis, discontinuation of clozapine and referral to a cardiologist are imperative. Beta-blocking agents, angiotensin-converting enzyme inhibitors and diuretics may be helpful in the management of myocarditis, and may have immunomodulatory as well as haemodynamic therapeutic benefits (Burian *et al*., 2005). The use of adjunctive corticosteroids remains controversial (Merrill *et al*., 2005). Rechallenge with clozapine would normally be contraindicated because the majority of patients, although not all, experience recurrence of myocarditis when the drug is recommenced (Merrill *et al*., 2005).

Patients who develop cardiomyopathy while receiving clozapine treatment should again be referred to a cardiologist for an expert opinion about further management. Although discontinuing clozapine may be indicated, given the likely treatment resistant nature of the mental disorder the individual is probably suffering from, and the known efficacy of clozapine in treatment resistant schizophrenia, a careful risk–benefit analysis of discontinuing treatment should be undertaken, and ideally involve the patient, cardiologist and members of the treating mental health team.

PSYCHOTROPIC DRUGS AND CARDIOVASCULAR DISEASE

Cardiovascular disease

Coronary heart disease (CHD) and stroke are the principal components of CVD, and worldwide CVD is estimated to be the leading cause of death and loss of disability-adjusted life years (Murray and Lopez, 1996). There are well-established risk factors for the development of CVD (see Table 2), and many of these are modifiable. In a large case-control study performed in 52 countries, representing every inhabited continent, the effect of risk factors on the development of acute myocardial infarction was investigated. Abnormal lipids, smoking, hypertension, diabetes, abdominal adiposity, psychosocial factors, consumption of fruits, vegetables and alcohol and physical activity accounted for more than 90% of the risk of an acute myocardial infarction (Yusuf *et al*., 2004). These modifiable risk factors are important targets for the prevention of CVD.

Table 2. Risk factors for cardiovascular disease

Modifiable	Non-modifiable
Smoking	Genetic background
Hypertension	Biological sex
Hyperglycaemia	Age
Obesity	Previously accumulated risks
Dyslipidaemia	
Physical activity	
Diet	
Alcohol intake	
Psychosocial factors	

CVD mortality in mental illness

Cardiovascular mortality in schizophrenia exceeds that in the general population. A meta-analysis of causes of death in schizophrenia reported a standardised mortality ratio (SMR) of 110 (95% confidence interval (CI), 105–115) for deaths related to cardiovascular disease (Brown, 1997), and a 13-year follow-up study of 370 patients with schizophrenia in the South of England reported a SMR of 187 (95% CI, 102–298) for cardiovascular deaths (Brown *et al*., 2000). A further study reported a reduction in life-span of approximately 10 years in schizophrenia which was attributable, in part, to CVD (Hannerz *et al*., 2001). More recently 46 136 people with SMI were compared with 300 426 people without SMI from the United Kingdom's General Practice Research Database (Osborn *et al*., 2007). Hazard ratios for CHD mortality in people with SMI compared with controls were 3.22 (95% CI, 1.99–5.21) for people 18 through 49 years old, 1.86 (95% CI, 1.63–2.12) for those 50 through 75 years old and 1.05 (95% CI, 0.92–1.19) for those older than 75 years. Furthermore, increased hazard ratios for CHD mortality occurred irrespective of sex, SMI diagnosis or prescription of antipsychotic medication. However, a higher prescribed dose of

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antipsychotic medication predicted a greater risk of CHD mortality.

CVD morbidity in mental illness

Various psychiatric disorders are associated with an increased prevalence of cardiovascular disease. This is particularly well recognised with depression which appears to have both an aetiological role (i.e. depression preceding the development of CHD) as well as a prognostic role (i.e. depression altering the course of established CHD). A recent systematic review of the published literature between December 2003 and December 2005 identified 8 studies examining the aetiological role of depression in the development of CVD, 16 studies which reported the prognostic significance of depression with regard to CVD progression, 2 publications with both types of data and 23 review papers. The authors conclude that recent literature continues to support an aetiological as well as a prognostic role of depression in CHD (Frasure-Smith and Lesperance, 2006). The pathophysiological mechanisms underpinning the association between CVD and depression are not well understood. Pro-thrombotic and inflammatory markers and autonomic nervous system dysfunction have been studied in depressed patients, and may have aetiological significance.

A recent study from the Northeast of England reported 10-year risk estimates for a number of cardiovascular outcomes in community psychiatric patients treated with antipsychotic drugs compared with a control group without mental illness. The sample of 90 subjects included individuals from across the diagnostic spectrum (bipolar disorder = 35.6%; schizophrenia = 30%; schizo-affective disorder = 10%; other = 24.4%). SMI patients had statistically greater mean 10-year risk estimates than controls for all outcomes (cardiovascular disease, myocardial infarction and CVD death) with the exception of stroke (but there was a statistical trend toward a greater 10-year risk for stroke in SMI patients). The increased risk was consistent across all diagnostic groups and was not explained by an excess of smoking in the patient group (Mackin *et al*., 2007).

Several studies have reported increased cardiovascular co-morbidity in patients with schizophrenia (e.g. Enger *et al*., 2004; Goff *et al*., 2005).These include a study of the 10-year risk estimated of developing CHD in 689 subjects who participated in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study in schizophrenia. Subjects were compared with 687 age, race and gender-matched controls from the National Health and Nutrition Examination Survey (NHANES) III. The average 10-year risk of developing CHD was 9.4% in males with schizophrenia compared with 7.0% in male control subjects; in female patients with schizophrenia the risk was 6.3% compared with 4.2% in female controls (Goff *et al*., 2005).

Causes of excess cardiovascular morbidity and mortality in SMI

The causes of excess cardiovascular morbidity and mortality in SMI are not fully understood, and are likely to include an accumulation of 'traditional' risk factors including metabolic disease, overweight and obesity, smoking, lack of exercise and dietary factors. In addition there are other illness-specific factors which may increase the risk of developing CVD such as genetic predisposition, and patient-, physician- and healthcare system-related barriers to care. Illness-specific factors include psychotropic medication.

The role of psychotropic drugs

Pharmacological treatment is a cornerstone in the management of mental disorders. No psychotropic agent is free from potentially hazardous side effects, and many have been shown to be associated with the development of cardiovascular disease risk factors. The advent of the second generation, or 'atypical', antipsychotics heralded a new era in the management of SMI, and although many of these agents have a superior neurological side-effect profile, concerns have been raised in recent years about their propensity to cause weight gain, disorders of glucose homeostasis and dyslipidaemias. There is a burgeoning literature examining this often controversial association, and the reader is directed to a number of excellent reviews and consensus statements that consider the recent evidence in this field of research, as well as providing recommendations for monitoring cardiometabolic risk (Barnett *et al*., 2007; Consensus Development Conference, 2004; Haupt, 2006; Newcomer, 2005). A summary of the recommendations for monitoring cardiometabolic risk in patients treated with antipsychotic drugs from a recent UK consensus statement is given in Table 3.

It should be pointed out that other classes of psychotropic drugs including antidepressants, 'mood stabilisers' and anticonvulsants are also associated with metabolic dysregulation which may result in weight gain and impaired glucose tolerance. Patients with SMI are often treated with a number of different

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Table 3. Recommended monitoring of cardiometabolic status in patients receiving antipsychotic drugs

	Initial visit[a]	4 weeks	8 weeks	12 weeks	6 monthly	Annually
Personal/family history	×					×
Height/weight (BMI)[b]	×	×	×	×	×	
Blood pressure	×			×	×	
Fasting plasma glucose (FPG)[c]	×	(×)	(×)	×	×	
Fasting lipid profile[d]	×			×	×	

BMI, body mass index.
[a]Based on clinical presentation, some assessments may not be possible at initial evaluation. Clinical judgment should be used to establish which evaluations can be carried out at a later date.
[b]Measurement of height/weight to calculate BMI should be performed, unless trained staff are able to calculate waist circumference, however, the same method must be used for all visits for an individual. Measurement of height will only be required at initial visit.
[c]FPG levels are considered the gold standard, although random glucose levels are acceptable in patients where fasting levels are impractical. Simple finger prick tests can also be carried out at 4 and 8 weeks to capture early cases (×), formal laboratory screening tests can then be carried out where necessary.
[d]Fasting lipid levels are considered ideal, although random total cholesterol/HDL cholesterol levels are acceptable in patients where fasting levels are impractical.

psychotropic drugs, from different classes, and although there is little data reporting the effects of combination treatment on metabolic and cardiovascular risk, monitoring in these patients should be particularly vigilant.

Overcoming barriers to care

Use of medical care often decreases after the onset of a psychiatric disorder (Jeste *et al*., 1996), and even when patients are engaged in healthcare services, rates of undiagnosed physical illnesses are often high (Mackin *et al*., 2005). Other patient characteristics may also contribute to poor detection and diagnosis of physical illness such as impaired ability to verbalise concerns (Lieberman and Coburn, 1986; Massad *et al*., 1990), poor insight into illness (Massad *et al*., 1990), denial of illness (Goldman, 1999) or an unwillingness to consult a doctor other than their psychiatrist. When patients are cared for by psychiatrists, primary care physicians and physicians from other disciplines, there may be a shared assumption that a colleague is taking responsibility for managing a particular medical problem, when in fact the problem is not being attended to at all.

There are few studies specifically examining the impact of differing models of care on physical wellbeing and co-morbidity in SMI. One randomised trial from the USA valuated an integrated model of primary medical care for a cohort of patients with serious mental disorders, and the authors concluded that on-site, integrated primary care was associated with improved quality and outcomes of medical care (Druss *et al*., 2001). There is a growing acknowledgment, backed up by a burgeoning literature on physical co-morbidity in SMI, that health professionals involved in the care of these people must be mindful of the possibility of co-existing physical illness. There is a need for greater communication and collaboration at the primary/secondary care interface, and for the establishment of clear guidelines outlining responsibilities and protocols for screening and managing physical health and disease in patients with SMI.

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