

Graylands Hospital

Drug Bulletin

Cardiac Adverse Effects of Psychotropic Medication in Schizophrenia

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Introduction

Patients with psychiatric illness have an increased risk of dying from cardiovascular disease.¹

Epidemiological and clinical research has indicated a sharp increase in cardiovascular deaths among schizophrenia patients since the mid 1980s.² This unfortunate development has been attributed, in part, to treatment with second-generation antipsychotics (SGAs), which may produce metabolic syndrome, diabetes and dyslipidaemia that lead to coronary heart disease (CHD).² The importance is amplified because many such patients have poor medical health, are overweight, smoke and do not receive regular medical care.³

The antipsychotic drug clozapine has been reported to cause myocarditis or cardiomyopathy.⁴ Adverse reactions occur most frequently during the initiation of clozapine treatment and during the acute treatment and dose titration phase.⁵

Time and continued research have revealed that both first and second generation antipsychotics (as well as antidepressants) can cause a prolonged QTc interval on ECG, denoting a conduction change that increases the risk for serious arrhythmias.⁶

Orthostatic hypotension is the most common adverse autonomic side effect of antipsychotic drugs.⁷ 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 (e.g. chlorpromazine).^{6, 7} A benign, sustained tachycardia, characterised by an average increase in the 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.⁷

Cardiovascular Adverse Effects

Coronary heart disease and stroke are the principal components of cardiovascular disease.⁷

Risk factors for cardiovascular disease are listed in Table 1.

Psychotropic drugs may contribute to increased

cardiovascular morbidity and mortality.¹ This may occur through adverse effects such as hypotension or metabolic effects or through a direct effect on the heart such as cardiotoxicity of TCAs (which have a proarrhythmic effect) and clozapine.¹

Benzodiazepines, TCAs and SSRIs have the potential to cause palpitations or hypotension. MAOIs may increase blood pressure and the hypertensive crises associated with phenelzine and tranylcypromine can be fatal. SNRIs (e.g. venlafaxine) can also increase blood pressure.¹

Psychotropic drugs may have adverse effects on the management of cardiovascular disease e.g. drugs metabolised by Cytochrome P450 (CYP) 1A2 (e.g. fluvoxamine) or CYP 3A4 (e.g. carbamazepine) may alter the anticoagulant effects of warfarin.¹

Similarly, cardiovascular drugs may interact adversely with psychotropic drugs e.g. diuretics, angiotensin II receptor blockers and angiotensin converting enzyme inhibitors affect the clearance of lithium.¹

Table 1: Risk factors for cardiovascular Disease⁷

Modifiable	Non Modifiable
<ul style="list-style-type: none">➤ Smoking➤ Hypertension➤ Hyperglycaemia➤ Obesity➤ Dyslipidaemia➤ Physical Activity➤ Diet➤ Alcohol intake➤ Psychosocial factors	<ul style="list-style-type: none">➤ Genetic background➤ Biological sex➤ Age➤ Previously accumulated risks

Abbreviations:

TdP: Torsades de Pointes

TCAs: tricyclic antidepressants

ECG: electrocardiogram

SSRIs: selective serotonin reuptake inhibitors

MAOIs: monoamine oxidase inhibitors

SNRIs: Serotonin noradrenalin reuptake inhibitors

Myocarditis, Cardiomyopathy & Pericarditis

Myocarditis and cardiomyopathy, although relatively rare, are potentially reversible complications of psychotropic drug therapy.⁷ The clinical features of myocarditis are essentially non-specific.⁷ Symptoms include tachycardia, fever, flu-like symptoms, fatigue, dyspnoea and chest pain⁸ or there may be no symptoms.⁹ Eosinophilia, elevated cardiac enzyme levels and ECG changes may be present.¹⁰ Patient factors, such as psychiatric illness, which typically is poorly controlled at the time of clozapine initiation, make it difficult for patients to communicate symptoms they feel.⁹

Rises in C-Reactive Protein level and development of fever may be early indicators of myocarditis.⁹ Drugs such as clozapine, olanzapine and quetiapine have been linked with myocarditis.¹¹

The US Food and Drug Administration requires clozapine to carry five black box warnings including myocarditis and “other adverse cardiovascular and respiratory effects”.

In heart muscle disease, the number of potassium channels is reduced, the final net electrophysiological effect being the same as in long QT syndromes.⁷ The electrophysiological abnormalities combined with structural changes within the myocardium makes for a potent substrate for ventricular arrhythmias and sudden death.⁷

In the absence of a gold standard for the diagnosis of clozapine-induced myocarditis, a case definition (K.J.Ronaldson et al) is a simple algorithm that can assist clinicians to identify clozapine related myocarditis while excluding those with benign rises in eosinophil counts and heart rate.⁹

Possible mechanisms that may result in clozapine-induced myocarditis include type 1 IgE-mediated hypersensitivity reaction, clozapine-induced cytokine release or elevated catecholamines.⁷

There have been case reports of eosinophilia indicating sub-clinical clozapine-induced pericarditis¹², clozapine associated pericarditis and elevated Troponin I¹³, clozapine induced polyserositis (pericardial effusion, pleural effusion and pericarditis)^{14,15} and myocarditis during clozapine treatment.¹⁰

QTc Prolongation

The QT interval on the ECG is defined as that period from the onset of the Q wave (ventricular depolarisation) to the cessation of the T wave (ventricular repolarisation).⁷

As QT intervals normally shorten with increasing heart rate and lengthen with decreasing heart rate, a rate corrected QT (QTc) interval is often calculated.⁷

Changes in heart rate may precede the changes in QT interval by several beats.¹⁶

The normal range for QTc interval (expressed in milliseconds) differs with gender and age. For men <55years old, the range is 350-430ms. Women <55 years of age average slightly longer intervals, from 350-450ms.⁶ Older adults may have an interval of 450ms. A level of concern arises when the interval range is prolonged to 450-500ms. An interval greater than 500ms is considered clinically significant, that is, increases the risk for serious cardiac complications and even sudden death.⁶

Studies have shown that patients with prolonged QT intervals are at greater risk of cardiac arrhythmias, particularly the polymorphic ventricular arrhythmia (tachycardia) torsades de pointes.^{6,7}

The QT interval is only an indirect, surrogate marker of potential pro-arrhythmic toxicity.⁷

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.⁷

The risk of developing serious, potentially fatal arrhythmias are increased with comorbid conditions including coronary artery disease, diabetes mellitus, congestive heart failure, peripheral vascular disease and a history of myocardium infarct.⁶ Other risk factors that increase QT prolongation include female gender, increased age, electrolyte imbalances (particularly hypokalaemia, hypocalcaemia and hypomagnesaemia), decreased ejection fractions and co-prescription of medications known to significantly prolong the QTc interval by affecting the hepatic metabolic pathways, specifically the CYP450 system (i.e. slow metabolisers).^{6,7,16,17} Poor metabolisers not only are missing the hepatic component of CYP2D6-mediated metabolism but also lack right ventricular CYP2D6 expression.¹⁷ Risks of drug-induced QTc prolongation would be concomitantly prescribed CYP450 metabolic inhibitors of 2D6, 1A2 and 3A4.⁶

Some drugs that have the potential to prolong the QT interval and/or induce TdP are listed in Table 3.

Table 2: Physiologic risk factors for QTc prolongation and arrhythmia⁷

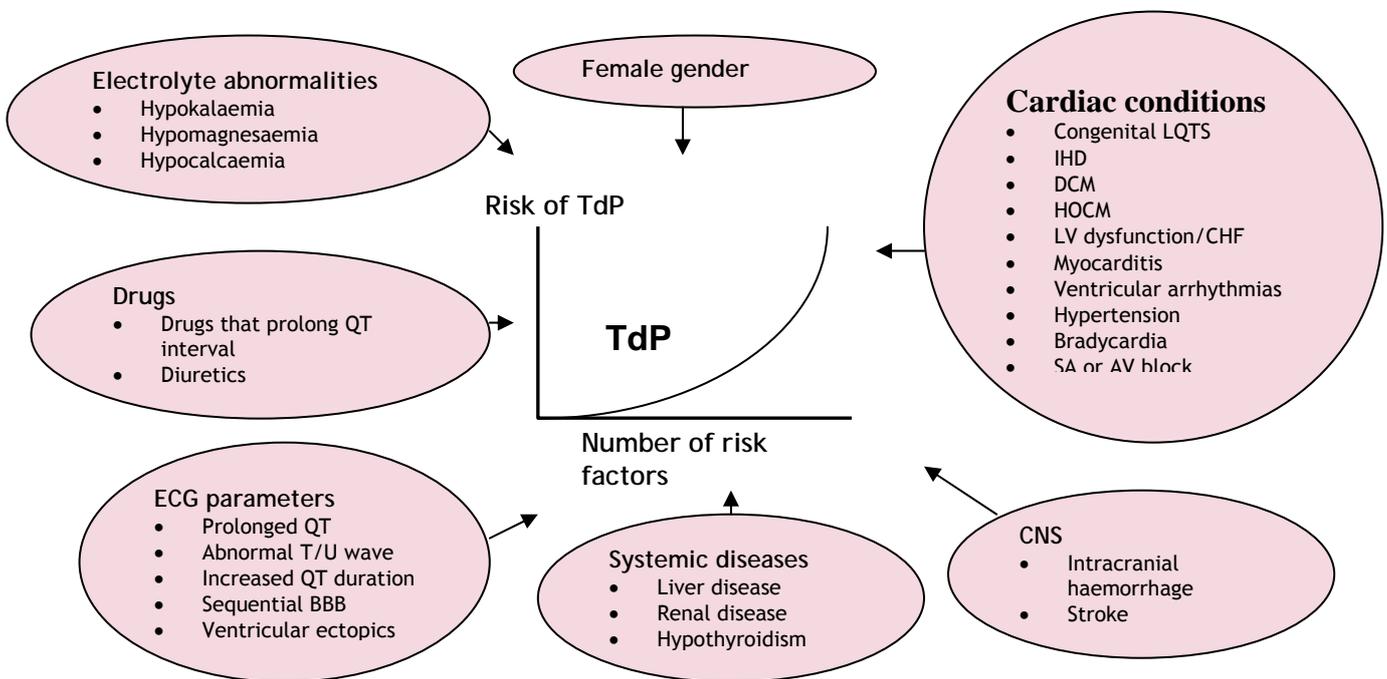
Cardiac	Metabolic	Others
Long QT syndrome Bradycardia IHD Myocarditis Myocardial infarction Left ventricular hypertrophy	Hypokalaemia Hypomagnesaemia Hypocalcaemia	Extreme physical exertion Stress or shock Anorexia nervosa Extremes of age Female gender

Antidepressants	Antipsychotics	Other	Other
Amitriptyline	Chlorpromazine	Amantadine	Fluconazole
Citalopram	Clozapine	Amiodarone	Indapamide
Clomipramine	Droperidol	Amphetamine	Lithium
Doxepin	Haloperidol	Atomoxetine	Methadone
Fluoxetine	Paliperidone	Azithromycin	Methylphenidate
Imipramine	Pimozide*	Chloral Hydrate	Phenylephrine
Nortriptyline	Quetiapine	Clarithromycin	Pseudoephedrine
Paroxetine	Risperidone	Cocaine	Terbutaline
Sertraline	Thioridazine*	Domperidone	Roxithromycin
Venlafaxine	Ziprasidone	Ephedrine	Salmeterol
		Loratadine	Trimethoprim/ sulphamethoxazole

Table 3: SOME drugs that may prolong the QT interval and/or induce Torsades de Pointes^{18, 19}

*Available via the Special Access Scheme

Table 4: Clinical features associated with increased risk of TdP⁶



KEY	LQTS-Long QT syndrome IHD-ischaeamic heart disease	DCM-dilated cardiomyopathy HOCM-hypertrophic obstructive cardiomyopathy CHF-congestive heart failure
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Table 5: Relative Risk of Psychotropics that may have an Effect on QTc⁷

No Effect	Low Effect	Moderate Effect	High Effect	Unknown Effect
Aripiprazole Paliperidone SSRIs(except citalopram) Reboxetine Mirtazapine MAOIs Carbamazepine Gabapentin Lamotrigine Valproate Benzodiazepines	Amisulpride Clozapine Flupenthixol Fluphenazine Olanzapine Risperidone Citalopram Moclobemide Venlafaxine Lithium Bupropion Prochlorperazine	Chlorpromazine Quetiapine Ziprasidone TCAs	Haloperidol Methadone Pimozide IV antipsychotics Drugs or combinations used in doses exceeding recommended maximum	Pipothiiazine Trifluoperazine Zuclopenthixol Anticholinergic Drugs (e.g. Benzhexol)

Torsades de Pointes

Torsades may be either congenital or acquired. Acquired refers to exposure to drugs that prolong the ventricular action potential.⁶

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.⁷ TdP is more likely to occur when the heart rate is slow and in the presence of extra systoles, so conditions associated with bradycardia such as heart block increase the risk of TdP.⁷

The most common mechanism underlying QT prolongation appears to be blockade of the delayed rectifier potassium channel in the myocardium which prevents the outward movement of potassium that is responsible for ventricular depolarisation.⁷

Table 4 illustrates the clinical features associated with increased risk factors for TdP.

Orthostatic Hypotension

It is defined as a decrease in systolic pressure of ≥ 20 mmHg, or a decrease of systolic blood pressure to <90 mmHg during an upright posture.⁷ For the majority this is transient and may occur more often in patients prescribed a combination of antipsychotics.⁷ Rarely, orthostatic hypotension may result in neurocardiogenic syncope defined as syncope occurring when the autonomic nervous system is incapacitated resulting in a failure of vasoconstrictor mechanisms and thereby in orthostatic hypotension.⁷ Complications of orthostatic hypotension include dizziness and visual disturbances, cognitive impairment and syncope resulting from cerebral hypoperfusion.⁷ 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.⁷

Recommendations

The causes of excess cardiovascular morbidity and mortality in severe mental illness 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.⁷

In addition other illness-specific factors may increase the risk of developing cardiovascular disease such as genetic predisposition, and patient-, physician- and healthcare system-related barriers to care.⁷

Recommended monitoring for cardiometabolic status of patients receiving antipsychotics include:⁷

- Personal/family history
- Body Mass Index
- Blood Pressure
- Fasting Plasma Glucose
- Fasting Lipid Profile

The effects of antipsychotic medications on cardiac conduction are complex and still not fully understood.⁶

- Ask about any history of cardiac rhythm problems in the patient or family. Ask even apparently healthy patients if they had syncope, if they have relatives with QT syndrome, or if they have relatives who died suddenly at a young age.⁶
- Before commencing antipsychotic treatment, where possible, an ECG should be recorded and examined for evidence of left ventricular hypertrophy and repolarisation abnormalities.⁷
- Start at the lowest possible therapeutic dose.⁶
- When prescribing for people with cardiovascular disease and mental illness, consider the risk of the drugs and also the risk profile of the patient.¹
- Drug interactions are a major cause of arrhythmias, and extra caution including ECG monitoring, is needed when a potential interaction is identified.⁷
- Be aware of medications that are metabolic inhibitors that could interfere with antipsychotic metabolism, as the prolongation effects can be dose-dependent.⁶
- Periodic ECG monitoring is recommended, especially if higher doses are used, in those receiving parenteral therapy and in individuals undergoing rapid dose escalation.⁷
- Interval monitoring of electrolytes is especially important.⁶

Cardiomyopathy should be suspected in any patient showing signs of heart failure. Presentation of cardiomyopathy varies somewhat so any reported symptoms of palpitations, sweating and breathing difficulties should be closely investigated. Signs include ECG changes (ST depression), enlarged heart on radiography/echo and eosinophilia.⁸

This Drug Bulletin was prepared by Promothini Pather and reviewed by the Graylands Pharmacy Department and Dr Mathew Samuel

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• References are available on request