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REVIEW

Adverse Cardiovascular Effects of Psychotropic Medications

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Abstract

Cardiovascular disease is the leading cause of death in people with serious mental health illnesses, including schizophrenia, major depression and bipolar disorder. The adverse cardiac risk profile of this population is related to the complex interplay between biological, patient-specific and healthcare system factors. A variety of psychotropic medications used to treat these conditions can in themselves produce cardiovascular side effects. This includes autonomic dysfunction, malignant ventricular arrhythmias, heart muscle disorders and vascular thromboembolic events, some of which have been linked with sudden cardiac death. As a result, there is a pressing need for physicians to be aware of the cardiotoxicity associated with psychotropic medication use. In this review, we summarise the main effects of psychotropic drugs on the cardiovascular system and the current recommendations for evaluation and continual monitoring of the many and rapidly increasing number of patients receiving psychotropic pharmacotherapy.

Key words: mental health illness; psychotropics; cardiovascular effects; arrhythmogenesis; sudden cardiac death; autonomic dysfunction; thromboembolism; myocardial contractility

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Introduction

Mental health disorders are a set of chronic conditions that affect mood, emotion and cognition, which can lead to substantial psychological distress and reduced social functioning. Severe mental illness consists of major depression, bipolar disorder and primary psychotic disorders, including schizophrenia. Mental health illness is among the top ten leading causes of disability worldwide, with common conditions affecting over 970 million people globally (GBD 2019 Mental Disorders Collaborators, 2022). It is estimated that the lifetime prevalence of any mental health disorder is approximately 29%, with a prevalence of 10% for mood disorders and 13% for anxiety disorders (Steel et al, 2014). To compound the public health problem, it is expected that the burden of mental disorders is likely to increase in the future due to the widening treatment gap, where >70% of patients in need of mental health services lack access to care (Wu et al, 2023). In the United Kingdom (UK), 9.88 million people are projected to experience mental health problems by

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2026, with the total socio-economic cost of mental health amounting to £118 billion per year or approximately 5% of UK gross domestic product (McDaid et al, 2022).

In addition to adverse effects on the quality of life, mental health disorders are a recognised risk factor for premature mortality (Carney and Freedland, 2017). The life expectancy of patients with severe mental health illness is 15–20 years lower than the general population (Hjorthøj et al, 2017). Cardiovascular disease (CVD) is the leading cause of death among these patients, with the rates of cardiovascular mortality being more than double compared to the rest of the population (Lambert et al, 2022). The reasons for this are complex but are likely explained by the combination of lifestyle, social and biological factors. Proposed pathophysiological mechanisms include excess accumulation of 'traditional' cardiovascular risk factors, the direct effects of the illness leading to reduced access to healthcare and lowered adherence to treatment. These lead to earlier development of atherosclerotic CVD, which necessitates a more aggressive approach to cardiovascular risk assessment in this cohort and proactive initiation of appropriate primary and secondary prevention strategies to improve long-term outcomes. Additionally, the psychiatric medications used to treat severe mental illness can have a direct and adverse impact on the cardiovascular system, which further exacerbates health disparities in these vulnerable patients.

Psychotropic medications (Table 1), including antipsychotics, antidepressants and mood stabilisers, are amongst the most widely used drugs for treating severe and persistent mental disorders, especially in countries where non-pharmacological interventions are difficult to access. Over the last decade, there has been a substantial global rise in the use of psychotropic medicines, which has been linked to increased awareness of mental health, greater willingness to seek treatment and longer duration of treatment (Brauer et al, 2021). Although these medications have advanced the treatment of psychiatric disorders, their beneficial effects must be closely counterbalanced against the increased risk of cardiovascular side effects and toxicity. The aim of this manuscript is to provide a contemporary overview of the main cardiovascular effects of psychotropic drugs in relation to autonomic dysfunction, sudden cardiac death (SCD), malignant ventricular arrhythmogenesis, heart muscle disorders and vascular thromboembolism. Furthermore, we will provide practical guidance on monitoring and evaluation of cardiovascular health in patients being considered for this treatment.

Cardiovascular Impact of Psychiatric Pharmacotherapy

Cardiac Autonomic Dysfunction

Myocardial autonomic regulation plays a key role in normal cardiovascular homeostasis (Hadaya and Ardell, 2020). Alterations in the autonomic nervous system (ANS) function are frequently observed with many common antipsychotics and antidepressants, which act on a number of central and peripheral target receptors. These include dopaminergic, histaminergic, serotonergic, muscarinic and alpha-adrenergic receptors. The non-specific nature of their pharmacologic action

Table 1. Classification of psychotropic medications.

Medication class	Medications
Antidepressants	SSRIs: citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, sertraline. SNRIs: venlafaxine. TCAs: amitriptyline, clomipramine, desipramine, dosulepin, imipramine, nortriptyline, trimipramine
Antipsychotics	First generation: haloperidol, pimozide, chlorpromazine, fluphenazine, promazine, thioproperazine, thioridazine, mesoridazine. Second generation: amisulpride, aripiprazole, clozapine, iloperidone, olanzapine, quetiapine, risperidone, trimipramine.
Anxiolytics	Benzodiazepines: alprazolam, chlordiazepoxide, clonazepam diazepam, etizolam, lorazepam, oxazepam.
Mood-stabilisers	Lithium, carbamazepine, valproic acid, lamotrigine.

TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors.

can frequently result in autonomic cardiovascular side effects related to orthostatic hypotension and reduced heart rate variability (HRV) (Piña et al, 2018). This can manifest clinically with symptoms such as dizziness, blurred vision, syncope, falls, seizures, cardiac ischaemia and stroke.

Orthostatic hypotension is the most frequent manifestation of autonomic dysregulation on psychotropic therapy, with the propensity to cause significant hypotension varying between different medications (Stogios et al, 2021). Of the older antipsychotics/neuroleptics, the potential for severe hypotension is highest with low-potency phenothiazines, such as chlorpromazine, thioridazine and mesoridazine. Among the newer/atypical antipsychotics, postural hypotension is most frequent with clozapine (9%), quetiapine (7%), risperidone (5%) and olanzapine (5%), and least frequent with ziprasidone and haloperidol (1%) (Gugger, 2011). In a recent meta-analysis, second-generation antipsychotics were associated with a 2-fold higher risk of postural hypotension (Bhanu et al, 2021). Moreover, the utilisation of combination therapy can often exacerbate symptoms. The risk is further increased in elderly patients on a low-salt diet or concurrent antihypertensive therapies including calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (Destere et al, 2024). However, it should be noted that the symptoms are usually more profound early after drug initiation or after rapid dose escalation, and frequently abate as patient tolerance develops. Of the antidepressant medications, tricyclic antidepressants (TCAs) including imipramine, amitriptyline and doxepin, are associated with the highest prevalence of orthostatic hypotension of up to 20% (Calvi et al, 2021). In contrast, newer selective serotonin reuptake inhibitor (SSRI) antidepressants including fluoxetine and citalopram, have little or no effect on resting heart rate or postural blood pressure.

A less studied cardiovascular side effect of psychotropic medications is the direct impact of these therapies on hypertension (Correll et al, 2015). Early an-

imal models showed a dose-dependent increase in blood pressure after initiation of olanzapine (Patil et al, 2006). These findings have been confirmed in clinical studies, which showed that some antipsychotics such as clozapine, ziprasidone and olanzapine are associated with hypertension, while risperidone and quetiapine have minimal effects on blood pressure (Abosi et al, 2018; Deepak et al, 2021). Blood pressure elevation has also been demonstrated with TCAs and duloxetine, as well as newer antidepressant agents such as venlafaxine, but not with SSRIs (Zhang et al, 2023). An increase in night-time systolic blood pressure has been reported in elderly patients on anxiolytic treatment with diazepam (Fogari et al, 2019), but this association has not been identified by other authors (Begum et al, 2023). The causal mechanisms for these effects are not well understood, but are thought to be mediated by increased sympathetic nerve activity and anticholinergic effects (Munoli et al, 2013).

Reduced HRV in some individuals on long-term psychotropic medications is another marker of ANS dysfunction, which is thought to be an important contributor to the increased risk of CVD, cardiac events and SCD (Hillebrand et al, 2013). This effect is mediated by a shift towards increased sympathetic and decreased vagal tone, with the most frequently implicated medications being antipsychotics and some antidepressants, including TCAs and non-selective monoamine oxidase inhibitors (MAOIs). Antipsychotic medications exert a dose-dependent effect on reducing the high and low-frequency components of HRV (Iwamoto et al, 2012). Newer/atypical antipsychotics have heterogenous effects on HRV suppression, with the most adverse impact caused by drugs with high alpha-1 adrenergic and muscarinic receptor affinity (clozapine and quetiapine, respectively), compared to drugs with lower affinity for these receptors (olanzapine, risperidone, ziprasidone and aripiprazole) (Huang et al, 2024). The method of drug administration can impact HRV, with longer-acting injectable aripiprazole, as an example, being associated with less autonomic dysfunction compared to daily oral preparation (Hattori et al, 2023). Reduced HRV can also manifest as sustained tachycardia in up to 25% of patients on clozapine and 7% of patients on other atypical antipsychotics or dose-dependent bradycardia in patients receiving amisulpride (Nilsson et al, 2017; Yuen et al, 2018). It remains to be established if interventions to improve HRV through exercise, beta blockade or scopolamine therapy result in prognostic benefits.

Sudden Cardiac Death

SCD is defined as an unexpected death from circulatory arrest in the absence of non-cardiac-related or extrinsic causes and is the most devastating consequence of psychotropic therapy. Although relatively uncommon, many typical and atypical antipsychotics as well as antidepressants have been associated with an increased risk of SCD. In a meta-analysis of 2557 patients on antipsychotic therapy, the risk of SCD was increased for quetiapine (odds ratio (OR): 1.72, 95% confidence interval (CI): 1.33–2.23), olanzapine (OR: 2.04, 95% CI: 1.52–2.74), risperidone (OR: 3.04, 95% CI: 2.39–3.86), haloperidol (OR: 2.97, 95% CI: 1.59–5.54), clozapine (OR: 3.67, 95% CI: 1.94–6.94) and thioridazine (OR: 4.58, 95% CI: 2.09–10.05) (Salvo et al, 2016). The increased risk associated with phenothiazines, specifically thiori-

dazine, compared to other antipsychotics has been consistently reported (Zhu et al, 2019). In relation to antidepressants, a meta-analysis of 355,158 patients has shown that SCD is least likely with TCAs (OR: 0.24, 95% CI: 0.028–1.2) followed by serotonin and norepinephrine reuptake inhibitors (SNRIs) (OR: 0.32, 95% CI: 0.038–1.6) and SSRIs (OR: 0.36, 95% CI 0.043–1.8) (Prasitlumkum et al, 2021). The mechanisms by which these medications increase the risk of SCD remain poorly understood but are thought to be multifactorial and related to arrhythmogenesis and cardiac muscle abnormalities, including myocarditis and dilated cardiomyopathy.

Malignant Ventricular Arrhythmogenesis

The effect of psychotropics on cardiac rhythm disturbance has gained increasing attention over the last two decades. Following the introduction of these drugs in the 1950s, abnormalities on electrocardiography (ECG), such as QRS complex widening, corrected QT interval (QTc) prolongation, non-specific ST segment depression and abnormal T morphology were recognised as relatively common findings with a prevalence of up to 25% (Bulatova et al, 2022). In normal hearts, most of these changes are generally benign and unlikely to be of clinical significance unless in the context of overdose or significant polypharmacy. However, significant QTc interval prolongation (>500 ms) is associated with an increased risk of cardiovascular mortality and the development of malignant ventricular arrhythmias, especially polymorphic ventricular tachycardia or Torsades de Pointes (TdP) (Fig. 1) (Ray et al, 2009). Although generally self-limiting, TdP can progress to ventricular fibrillation and SCD (Witchel et al, 2003). The mechanism of QTc prolongation in patients on psychotropic therapy is directly related to the suppression of the delayed rectifier potassium channels (IKR) responsible for ventricular repolarisation (Sicouri and Antzelevitch, 2018). The prevalence of QTc interval prolongation on psychotropic therapy ranges from 14.7% in men to 18.6% in women with a QTc threshold of 450 ms, reducing to 1.26% and 1.01% respectively with a QTc threshold of 500 ms (Nosè et al, 2016). A number of antipsychotic and antidepressant medications have consistently been demonstrated to prolong the QTc interval (Table 2).

Despite the large number of psychiatric drugs associated with the risk of QTc interval prolongation, clinically significant QTc interval prolongation is relatively rare in patients taking these drugs. Increased individual vulnerability to significant QTc interval prolongation may be related to a number of patient-specific factors, including female gender, age >65 years, bradycardia, irregular rhythm, alcohol misuse, hypomagnesaemia, hypokalaemia, co-existing CVDs such as hypertension, diabetes or stroke, concomitant QTc prolonging medication use and genetic predisposition (Vandael et al, 2017). Pro-arrhythmogenic substrate may also occur as a result of inhibition of sodium channels (INa), which are responsible for myocardial depolarisation (Yap et al, 2009). This has been observed with TCAs and occasionally SSRIs, which can unmask an underlying Brugada syndrome in patients with a genetic predisposition, promoting the development of ventricular arrhythmias through heterogeneous myocardial conduction (Lubna et al, 2018). At the other end of the spectrum, the delayed conduction caused by the inhibition of INa chan-

Table 2. Approximate QTc prolongation with psychotropic medications.

Antipsychotics	
QTc prolongation effect	Medications
Low (only in overdose or <10 ms at standard clinical doses)	Risperidone, olanzapine, aripiprazole, prochlorperazine, amisulpride, asenapine, clozapine, perphenazine, flupentixol, fluphenazine, sulpiride, loxapine, paliperidone.
Medium (>10 ms at standard clinical doses)	Haloperidol, quetiapine, amisulpride, levomepromazine, iloperidone, chlorpromazine, melperone, ziprasidone.
High (>20 ms at standard clinical doses)	Pimozide, sertindole, mesoridazine, thioridazine.
	Drugs used in combination or in doses higher than the recommended maximum.
Antidepressants	
QTc prolongation effect	Medications
Low	SSRIs: fluoxetine, paroxetine, sertraline. SNRIs: duloxetine, desvenlafaxine. Novel agents: bupropion, mirtazapine.
Medium	SSRIs: citalopram, escitalopram. SNRIs: venlafaxine. TCAs: clomipramine.
High	TCAs: amitriptyline, maprotiline.
	Drugs used in combination or in doses higher than the recommended maximum.

Table adapted from (Sicouri and Antzelevitch, 2018) and (Lambiase et al, 2019), available under Creative Commons License. SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitor; TCAs, tricyclic antidepressants; QTc, corrected QT interval.

nels by TCAs and mood stabilisers such as lithium and carbamazepine can increase the risk of symptomatic complete heart block in patients with baseline conduction defects, those receiving class 1 antiarrhythmic agents or in cases of overdose (Ye et al, 2018; Yekehtaz et al, 2013).

Many typical and atypical antipsychotics have a dose-dependent effect on prolonging the QTc interval (Ruiz Diaz et al, 2020). The addition of a second antipsychotic agent can increase the propensity to prolong the QTc (Abdelmawla and Mitchell, 2006). Among the individual antipsychotic drugs, first-generation agents such as droperidol, phenothiazines, haloperidol and chlorpromazine are strong predictors of QTc prolongation, whereas the risk associated with second-generation antipsychotics, including quetiapine, clozapine and risperidone is much lower (Bordet et al, 2023; Howell et al, 2019). Importantly, while newer atypical antipsychotics can prolong the QTc interval at therapeutic doses, this is generally insufficient to cause TdP (Glassman, 2005). A meta-analysis of randomized controlled trials has shown that olanzapine, aripiprazole and brexpiprazole do not significantly increase the QTc interval, whereas risperidone and quetiapine are associated with QTc interval prolongation and TdP, especially in drug overdose (Aronow and Shamliyan,

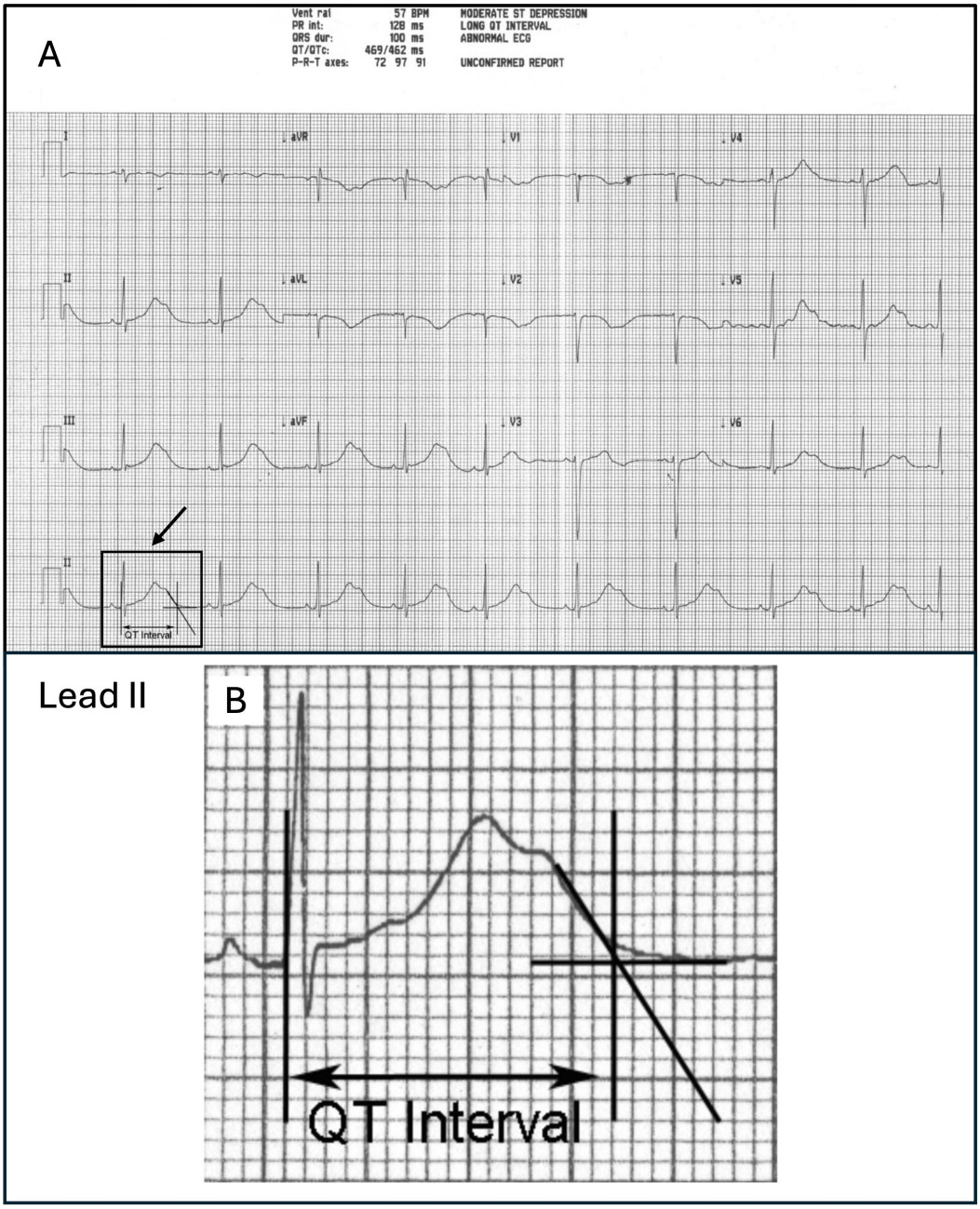

Fig. 1. The tangent method for QT interval assessment. (A) shows a 12-lead ECG with a prolonged QT interval. To reduce inconsistencies, Lead II (arrowed) or Lead V5 should be used for QT interval assessment. (B) illustrates the recommended technique for measuring the QT interval from the QRST complex using Lead II as an example. A tangent is drawn from the maximum downslope of the T wave to the isoelectric baseline on an ECG. QT interval is measured between the Q wave and the intersection of the tangent with the isoelectric baseline. An average of 3–5 beats should be evaluated and corrected for heart rate (QTc), commonly using the Fredericia formula (QTc = QT interval/(RR interval)$^{1/3}$).

2018). Lithium at toxic levels can also cause significant QTc interval prolongation, leading to malignant myocardial arrhythmias and SCD (Mehta and Vannozzi, 2017). These findings form the basis of guideline recommendations to avoid concurrent use of two or more antipsychotics and the need to perform ECG monitoring for QTc

prolongation in patients on antipsychotic therapy (Fanoe et al, 2014). Furthermore, it is recommended to exercise caution when prescribing antipsychotics and mood stabilisers in patients with a history of ischaemic heart disease (IHD), significant conduction disturbance or family history of SCD.

In patients on antidepressants, the propensity to cause QTc interval prolongation is greatest for TCAs, particularly amitriptyline and maprotiline, with an average increase in QTc interval of 10–20 ms even at therapeutic doses (Jasiak and Bostwick, 2014). As a result of the increased pro-arrhythmogenic potential, TCAs are not recommended in patients with IHD. In comparison, the effects of SSRIs and SNRIs on QTc interval lengthening are generally minor, but can increase at supra-therapeutic dosages. In a study of 38,397 patients, a dose-response association for QTc interval prolongation was identified for citalopram, amitriptyline and escitalopram but not for the other antidepressants including fluoxetine, paroxetine and venlafaxine (Castro et al, 2013). SNRIs like venlafaxine, duloxetine and desvenlafaxine do not prolong QTc interval in most patients, unless prescribed at supra-therapeutic doses (Behlke et al, 2020). The cardiovascular safety profile of SSRIs is an important area of research since these agents are considered first-line treatments of geriatric depression. A meta-analysis by the US Food and Drug Administration identified that citalopram produces the most effect on QTc prolongation of any SSRI, with a significantly higher risk of TdP and SCD when used in doses >40 mg/day (Vieweg et al, 2012). In a large study of adverse drug reactions in 61,788 patients, citalopram was identified as the third most likely drug to cause TdP (9/88, 10%) (Aström-Lilja et al, 2008). On this basis, it is recommended that citalopram doses of >20 mg/day should be avoided in older adults >65 years old and that dosages >40 mg/day should be avoided in all patients (Sicouri and Antzelevitch, 2018). Furthermore, it is strongly recommended that an ECG should be performed at baseline and periodically after citalopram initiation (Davies et al, 2023).

Cardiac Muscle Disorders

Heart muscle disorders on psychotropic therapy are rare and devastating but potentially reversible. Conditions affecting the heart muscle are characterised by structural myocardial alterations and abnormal repolarisation, which predispose to ventricular arrhythmias and SCD (Kumar et al, 2021). Therapeutic doses of antidepressant drugs do not have a significant impact on myocardial function. However, both typical and atypical antipsychotics such as clozapine, risperidone, chlorpromazine and haloperidol can directly cause cardiac toxicity and congestive heart failure (Zhu et al, 2019). Of these medications, clozapine-related myocardial toxicity has been reported most frequently, with the incidence of myocarditis being as high as 3% and cardiomyopathy in the region of 0.1% (Knoph et al, 2018). The development of clozapine-induced myocarditis is dose-independent and generally occurs within days to weeks after therapy initiation. The clinical presentation can be variable with symptoms and signs of flu-like illness, chest pain, syncope, arrhythmias, hypotension and elevated levels of troponin-I, B-type natriuretic peptide (BNP) and eosinophils (Alawami et al, 2014). Dilated cardiomyopathy related to

clozapine is also dose-independent but the onset is delayed, occurring one or more years after drug initiation. It is a particularly severe adverse effect of clozapine and confers an increased risk of mortality of up to 50% (Citrome et al, 2016).

At present, there is no consensus on the optimal strategy to assess or monitor patients on clozapine to reduce the incidence of cardiotoxicity. The benefits of routine investigations including ECG, chest X-ray, echocardiography or BNP are not supported by clinical evidence. As such, current recommendations include vigilant monitoring for heart failure signs and symptoms after clozapine initiation, which should prompt further investigations if drug cardiotoxicity is suspected. Where cardiotoxicity is confirmed, the drug should be discontinued since both dilated cardiomyopathy and myocarditis are largely reversible after clozapine cessation (Halawa et al, 2023).

Effects on the Vascular System

There is a direct association between psychopharmacological treatment and adverse vascular alterations, which increase the risk of thromboembolic events. According to a meta-analysis, antipsychotics are associated with an increased risk of deep vein thrombosis (DVT) (OR: 1.53, 95% CI: 1.33–1.77) and pulmonary embolism (PE) (OR: 3.69, 95% CI: 1.23–11.07), with the risk being 3 times higher in younger people (<60 years old) compared to the older patients (≥60 years old) (Di et al, 2021). In another meta-analysis, the higher risk of DVT was predominantly associated with clozapine, olanzapine and low-potency first-generation atypical antipsychotics (Jönsson et al, 2012). Furthermore, first- and second-generation antipsychotics have been associated with a significantly higher incidence of ischaemic stroke in a meta-analysis of 16,993 patients (OR: 1.49, 95% CI: 1.24–1.77) and a case-crossover study of 31,976 patients, respectively (Chen et al, 2017; Hsu et al, 2017). The risk of stroke was highest for antipsychotic medications with a high affinity for histamine H1 (quetiapine, olanzapine, clozapine, chlorpromazine, haloperidol, perphenazine), muscarinic M1 (chlorpromazine, thioridazine, quetiapine, olanzapine, clozapine) and adrenergic alpha2 (haloperidol, chlorpromazine, thioridazine, perphenazine, risperidone, quetiapine, olanzapine, clozapine) receptors (Wu et al, 2013). Increased risk of stroke has also been identified in bipolar patients on mood stabilisation therapy with carbamazepine (OR: 2.29; 95% CI: 1.49–3.51) and valproic acid (OR: 1.52; 95% CI: 1.24–1.88) but not lithium and lamotrigine (Wu et al, 2018). Amongst patients on antidepressants, the use of TCAs is associated with a significantly higher risk of myocardial infarction (MI) (Relative Risk (RR): 2.2; 95% CI: 1.3–3.7) (Cohen et al, 2000). In contrast, epidemiological studies suggest that SSRIs are associated with a decreased risk of MI, potentially due to the improvement of depression and the traditional risk factor profile, as well as attenuation of platelet and endothelial activation (Karlsen et al, 2023). As a result of their preferable safety profile, SSRIs are often recommended for the treatment of depression in the elderly.

Although the biological mechanisms that predispose to thromboembolic events on psychotropic therapy are not well understood, there are several possible hypotheses. Long-term psychopharmacotherapy has been linked to adverse cardiometabolic

changes characterised by weight gain, hyperlipidaemia and insulin resistance, which act as risk factors for vascular thromboembolic events by promoting oxidative stress on the vasculature (Sepúlveda-Lizcano et al, 2023). Psychotropic therapies also upregulate pro-inflammatory pathways by increasing the circulating levels of immunoreactive cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1), which are known to potentiate endothelial cell dysfunction and further metabolic abnormalities (Prestwood et al, 2021). Prothrombotic side effects may also be related to a pro-coagulable state in patients on psychiatric medications, which is driven at least in part by higher expression glycoprotein IIb/IIIa on the surface of platelets leading to increased platelet aggregation, hyperhomocysteinaemia and higher concentrations of anti-phospholipid antibodies (Moussaoui et al, 2024). However, further studies are essential to develop a better understanding of the interplay between psychotropic-induced immune upregulation, metabolic alterations and prothrombotic phenotype.

Clinical Perspectives: The Cardiovascular Risk Assessment in Psychiatric Patients

Despite the multiple benefits of psychotropic therapy in treating mental health disorders and the relative cardiovascular safety of most medications at therapeutic doses, it should be remembered that serious cardiovascular complications can arise in a sub-population of vulnerable patients. With the growing global burden of mental health illness and the steady rise in the use of psychiatric medications, it is important to increase awareness about the adverse cardiovascular effects associated with psychotropic therapy. Understanding the most common and concerning cardiovascular side effects related to autonomic dysfunction, SCD, pro-arrhythmic potential, cardiomyopathies and vascular thromboembolic events is important for helping clinicians to select appropriate treatment and recognise complications if they arise. Psychotropic medication prescribing must be informed, allowing effective treatment and prevention of psychiatric conditions within the acceptable parameters of cardiovascular risk. This is essential given the tendency of physicians to underappreciate the cardiovascular impact of psychotropic drugs (De Hert et al, 2011).

Multidisciplinary care models involving mental health specialists, cardiologists and primary care physicians are essential for mitigating cardiovascular risk and improving long-term outcomes in patients with severe mental illness (Polcwiartek et al, 2024). Lifestyle interventions to promote physical activity, smoking cessation, healthy eating and drug abuse treatment are essential. Primary prevention strategies with regular screening for hypertension, diabetes and hyperlipidaemia are important to identify modifiable cardiovascular risk factors early. Furthermore, standard secondary prevention medications should be offered in patients with a diagnosis of CVD. Additionally, careful consideration should be given to the potential adverse cardiovascular effects of psychotropic medications and agents with a more favourable cardiometabolic profile should be considered in higher-risk pa-

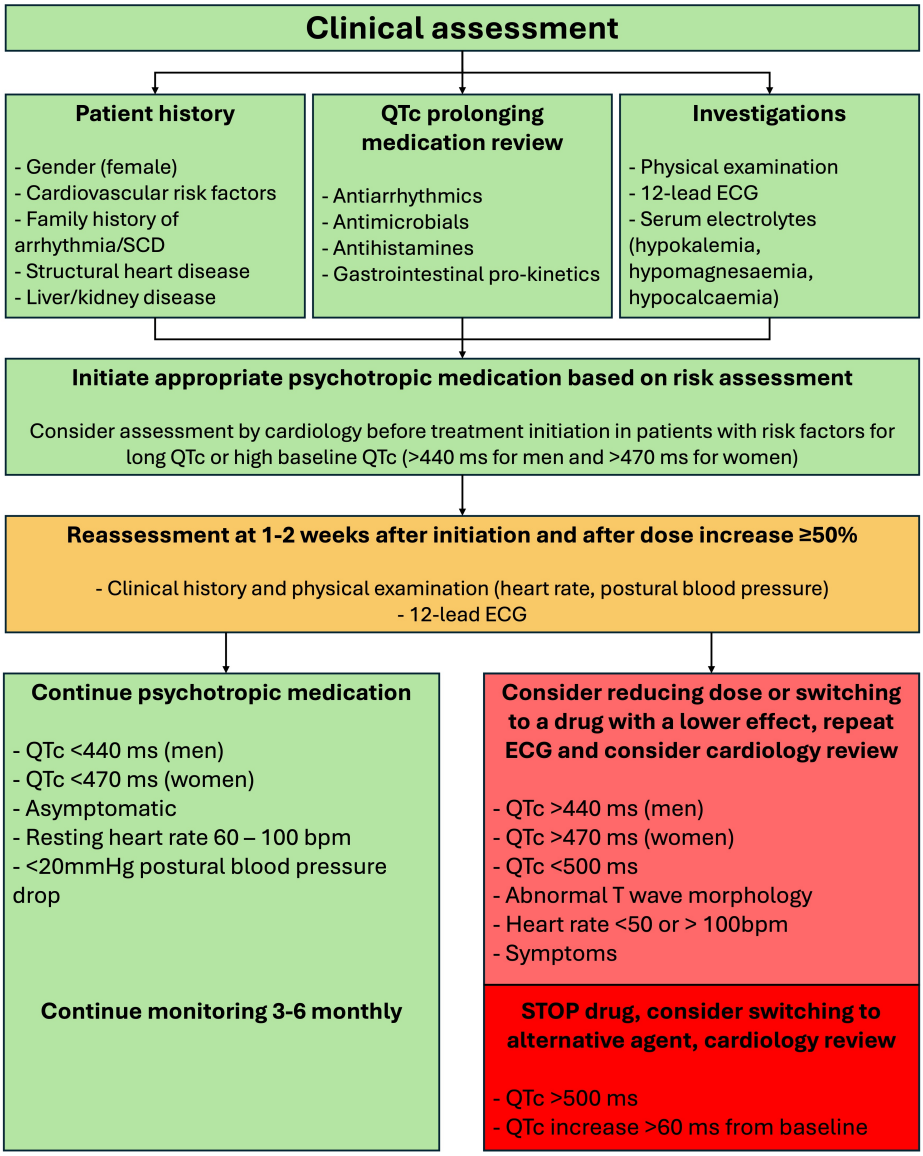

Fig. 2. An algorithm for assessing patients on psychotropic medications to reduce the risk of malignant ventricular arrhythmia. The figures were produced using Microsoft PowerPoint 365 (Microsoft Corporation, Redmond, WA, USA). Patients initiated on psychotropic medications should undergo a comprehensive clinical assessment at baseline, which involves a clinical history, physical examination, review of concurrent medications and investigations using blood tests and an ECG. Re-assessment of the clinical symptoms and a repeat ECG is recommended within 1–2 weeks after treatment initiation. Asymptomatic patients with no significant changes in QTc (<440 ms for men or <470 ms for women) can continue therapy with routine surveillance (every 3–6 months). In patients with some QTc prolongation (>440 ms for men or >470 ms for women, but <500 ms), consider reducing the medication dose or switch to an alternative drug with a lower effect on QTc interval prolongation, re-assess with a repeat ECG and consider cardiology review. In patients with significant QTc interval prolongation (>500 ms), stop the suspected causative drug, arrange cardiology review and consider switching to a drug with a lower effect on the QTc. Adapted from Lambiase et al (2019), Arrhythmia & Electrophysiology Review, available under Creative Commons License. ECG, electrocardiogram; QTc, corrected QT interval; SCD, sudden cardiac death.

tients. In patients with IHD requiring treatment for depression, SSRIs are generally considered to be the treatment of choice owing to their better tolerance, reduced cardiovascular effects and a safer profile in overdose. The prediction and management of cardiovascular risk in people with severe mental illnesses (PRIMROSE) model, which includes the psychiatric diagnosis, psychotropic medications, social deprivation score and alcohol use has been specifically developed and validated to assist clinicians with predicting the 10-year risk of CVD in patients with severe mental illness (Osborn et al, 2015).

A 12-lead ECG remains a fundamental tool to screen for underlying cardiac pathology, which should prompt a referral to cardiology for secondary evaluation and treatment when abnormalities are identified. Moreover, a baseline ECG is pivotal prior to the initiation of psychotropic medications and for continual monitoring whilst on treatment to assess for QTc interval prolongation. The lowest possible dose of psychotropics should be prescribed on initiation and an ECG should be performed on every admission, before discharge, at follow-up and within a week of reaching the therapeutic dose of moderate- and high-risk psychotropics. Drug-induced QTc interval lengthening should be used as a proxy for an increased risk of TdP and SCD, with QTc duration $>$500 ms or an increase $\geq$60 ms from baseline recommended as the thresholds for concern (Fanoe et al, 2014; Lambiase et al, 2019). In this scenario, the causative psychotropics should be discontinued and an alternative medication with a lower effect on QTc interval prolongation utilised. Cardiology review is also recommended to evaluate for predisposing factors leading to QTc prolongation, including electrolyte imbalance, cardiovascular risk factors and structural heart disease (Fig. 2).

Conclusion

Patients with severe mental illness should be considered as a high-risk group for increased cardiovascular morbidity and premature mortality. The contribution of psychotropic medications to the elevated risk is often under-appreciated by primary care physicians, psychiatrists and cardiologists. It is of fundamental importance that all physicians must have a good understanding of the potential cardiovascular toxicity related to these therapies owing to their increasingly widespread use. The decision to initiate psychotropic medications should be taken after careful evaluation of a patient's individual risk profile and by physicians with an awareness of the specific cardiovascular effects of individual treatments. In addition, thorough clinical evaluation, regular ECG monitoring and proactive clinical decision-making that minimises the number and the therapeutic doses of psychotropic drugs can reduce the risk of more serious adverse cardiovascular complications. Furthermore, monitoring cardiovascular risk factors and modifying these through adequate primary and secondary preventive measures along with social support and patient education play a crucial role in improving long-term clinical outcomes of psychiatric patients.

Key Points

- Patients with severe mental illness have a shortened life expectancy and die on average 15–20 years earlier compared to the rest of the population.
- The increased mortality is predominantly attributable to the development of cardiovascular disease.
- Psychotropic medications independently increase the cardiovascular risk through adverse drug reactions, which can predispose to (1) autonomic dysfunction, (2) sudden cardiac death, (3) malignant ventricular arrhythmias, (4) cardiomyopathies and (5) vascular thromboembolic events.
- In view of these risks, patients being considered for psychiatric therapy should undergo a comprehensive cardiovascular risk assessment to screen for pre-existing cardiac disease in order to better inform treatment selection.
- Based on the patient, biological and healthcare-related factors that increase the cardiovascular risk in severe mental illness, aggressive primary and secondary prevention strategies are crucial to improve long-term outcomes in this vulnerable cohort.

Availability of Data and Materials

Not applicable.

Author Contributions

VA, NM and RR made substantial contributions to conception of the manuscript. VA produced the manuscript. NM and RR contributed equally to the important editorial changes in the final manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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