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Psychotropic Medications and Heart

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ABSTRACT

Knowledge of cardiac actions and adverse effects of psychotropic medications is essential for safe prescribing of medications and take informed decisions in a clinically defensible manner. The main groups of psychotropic medications (antipsychotics, antidepressants, and mood stabilizers) have actions on cardiac conduction, rhythm, blood pressure; and are associated with potentially serious cardiovascular side-effects. They are occasionally associated with serious adverse events such as myocarditis and cardiomyopathy. Second-generation antipsychotics and antidepressants are routinely prescribed as first-line treatments for psychiatric conditions, but they are also associated with cardiovascular side-effects and, in case of some of second-generation antipsychotics, higher burden of cardiometabolic side-effects. Once started on treatment, careful monitoring and vigilance is required. This article summarizes the cardiovascular side-effects associated with the three major classes of psychotropic medications and makes recommendations about cardiovascular monitoring during treatment.

INTRODUCTION

There is increasing evidence that severe mental illnesses (SMI) such as Schizophrenia, Bipolar Disorder, Major Depression, are associated with higher risk of developing coronary heart disease (CHD), and shortened life expectancy [1].

Several psychotropic medications have significant cardiovascular side-effects. Many patients are on combination of medications, for psychiatric and physical health disorders. It is therefore essential that the psychiatrists possess skills in obtaining detailed medical (including cardiac) history, family history of cardiac disease, reading and interpreting ECG, being aware of potential drug interactions, and monitoring for side-effects, so that timely and clinically defensible decisions are taken to address emerging issues.

Psychotropic Medications and Cardiac Side-Effects

Conduction defects, rhythm abnormalities and sudden cardiac death: Arrhythmias can occur with Tricyclic antidepressants (TCA), antipsychotics, anticholinergics, rarely Lithium; or in states of toxicity. TCA's have type Ia (quinidine-like) properties, and they slow cardiac conduction (increased duration of QRS on the ECG) [2]. While this is unlikely to cause clinically significant issues in healthy individuals with normal hearts, in persons with pre-existing conduction problems (e.g., second degree heart block, bundle branch block, bradycardia and sick sinus syndrome) or who are on anti-arrhythmic agents, TCA's should be avoided. TCA's also cause sinus tachycardia because of vagolytic and anticholinergic action [3]. In healthy individuals without underlying cardiac disease, these do not cause significant issues.

TCA's are associated with reduced heart rate variability (HRV), which is a risk factor for arrhythmias [3]. This is relevant because evidence is emerging that SMI's are associated with reduced HRV [4].

All TCA's with exception of Clomipramine can prolong ventricular repolarization, manifested in the ECG as prolonged QTc interval, which increases the risk of the patients developing torsades de points [5-7]. The impact and risks are negligible in healthy individuals with no cardiac history, in therapeutic doses [8]. Older age, female sex, electrolyte imbalance (hypokalaemia and hypomagnesemia), thyroid abnormalities are other risk factors [9].

Selective Serotonin Reuptake Inhibitors (SSRI's), at therapeutic doses, are unlikely cause serious cardiac adverse events. Sertraline is often recommended as a first line antidepressant for patients

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with coronary artery disease and heart failure [10]. All SSRI's may reduce the risk of ischemic cardiac events by interfering with platelet aggregation [11] and have minimal effect on HRV [12].

Citalopram, at dose higher than 40mg / day is associated with statistically increased risk of QTc prolongation, cardiac arrhythmias and sudden cardiac death [13]. Among Serotonin and Noradrenaline Reuptake Inhibitors (SNRI's), Venlafaxine, at toxic levels, can cause QTc prolongation [14], while Duloxetine has minimal impact on cardiac conduction [15]. Noradrenaline Reuptake Inhibitor (NARI), Reboxetine, has minimal impact on cardiac conduction even at high doses [16].

Mirtazapine and Trazodone have minimal effect on heart rate, HRV and QTc prolongation [6,7,12]. Monoamine Oxidase Inhibitors (MAOI's) are rarely considered these days as first-line treatment for depression; however, they have a definite place in the treatment of refractory depression. In therapeutic doses MAO's are commonly associated with tachycardia [17] because of its sympathomimetic action.

First generation (FGA) and second generation (SGA) antipsychotics are commonly associated with sinus tachycardia, linked to anticholinergic activity and blockade of α1 receptors. Low potency FGA's share the type Ia antiarrhythmic action of TCA's. Antipsychotics carry dose-dependent increased risk of sudden cardiac death due to ventricular arrhythmias [18]; however, there is significant variability, and risk is higher with low potency FGAs (e.g., Thioridazine, Chlorpromazine) [19] and intravenous Haloperidol [20]. Amongst atypical antipsychotics, Clozapine is associated with higher risk of sinus tachycardia, QTc prolongation [21] and reduced HRV [22]. Olanzapine, Quetiapine and Risperidone are associated with moderate risks [23]. Aripiprazole, Lurasidone, Amisulpiride and Cariprazine are associated with the lowest risk [21,23-25].

Lithium, one of the most effective mood stabilisers, is uncommonly associated with serious cardiac side-effects. At therapeutic levels, ECG-repolarization-changes (T wave inversion) mimicking old infract and hypokalaemia, without clinical correlation, are the commonest dysfunctions reported [26]. Sinus node dysfunction resulting in sinus bradycardia and rarely sino-atrial block are also known to occur at therapeutic levels [26]. More vigilance is required, therefore, when Lithium is considered for patients with additional risk factors, e.g., ischemia (particularly inferior wall MI), cardiomyopathies, infiltrative diseases such as sarcoidosis and hemochromatosis, and when the patient is taking other drugs that affect S-A node firing.

Brugada syndrome (BrS) is a rare inherited cardiac disorder, first identified by the Brugada brothers in 1992, with characteristic ECG pattern (Coved ST segment elevation >2mm in >1 of V1-V3 followed by a negative T wave). It is associated with high risk of sudden cardiac death in the absence of structural heart disease. Some antipsychotics (Trifluoperazine, Loxapine), antidepressants (Amitriptyline, Clomipramine, Nortriptyline, and Desipramine) and Lithium can unmask or induce BrS (although the evidence is conflicting) and should be avoided in established diagnosis of BrS [27]. Other antidepressants (Doxepin, Imipramine, Fluoxetine) and antipsychotics (Thioridazine, Perphenazine) should preferably be avoided in established BrS patients.

Blood pressure changes: Orthostatic hypotension (>20mmgHg drop in systolic and >10mmHg drop in diastolic blood pressure) is one of the commonest side-effects of typical antipsychotics (more with low potency drugs (e.g. Chlorpromazine, Thioridazine) than medium-to-high potency drugs (e.g. Haloperidol and Trifluoperazine) [28]. All the SGA's are also associated with orthostatic hypotension and neurocardiogenic syncope, though the incidence is higher with Clozapine, early in treatment.

Orthostatic hypotension is a frequent side-effect of MAOI [17] and TCA's (more common with tertiary antidepressants such as Imipramine and Amitriptyline, than secondary antidepressants such as Nortriptyline). In healthy individuals, this has little impact, but the hypotension can be dramatic in those with impaired left ventricular function [29]. α-1 adrenergic and cholinergic receptor blockade is the postulated mechanism of orthostatic hypotension. Orthostatic hypotension is also reported with SSRI's [30], Mirtazapine [31] and Trazodone [32], though it is rarely problematic in clinical setting.

Venlafaxine is associated with sustained dose-dependent increase in diastolic BP (>300mg / day), the risk being higher with immediate release (IR) preparation (3-13%) than sustained release (XR) preparation (0.5-3%) or Desvenlafaxine (0.7-1.3%) [33]. A hypertensive crisis is a known complication of MAOI treatment when tyramine-containing food is ingested [34]. Hypertension is seen in up to 4% of patients treated with Clozapine and is common in the initial four weeks of titration [35].

Myocarditis and cardiomyopathy: Myocarditis is a known adverse effect (up to 3% incidence) of Clozapine, the majority of reported cases occurring in the first 4-8 weeks of treatment [36]. Clozapine-induced myocarditis (CIM) can present with mild symptoms, but, if missed, can progress rapidly to fulminant symptoms, heart failure and death [37]. Increasing age, concomitant administration of Sodium Valproate and increased rate of dose-titration are significant risk-factors for CIM [38]. Given the clinical difficulties in detecting mild CIM, it is suggested that all patients have baseline troponin and CRP, in addition to resting pulse and BP, and ECG [39]. If there is history or treatment of congestive cardiac failure, baseline brain natriuretic peptide (BNP) or N-Terminal pro-B-type natriuretic peptide (NTproBNP) should be measured. Weekly CRP and troponin should be done in the first month of titration and levels repeated once after stable dose of Clozapine is reached. The dose increase should not be rapid. An increase in troponin above upper limits or an increase in CRP should trigger consideration of CIM. Literature suggests that troponin levels greater than 2x the upper normal limit are indicative of acute myocarditis [40]. CRP is raised on average 3 days before any increase in troponin levels is detected [40].

Quetiapine, Risperidone and Olanzapine have also been rarely associated with myocarditis [41-43]. Toxic doses (overdose of very high dose) of the MAOI Phenelzine are associated with myocarditis [44]. Cardiomyopathy is significantly more associated with Clozapine treatment than other antipsychotic medication [45]. Unlike myocarditis, cardiomyopathy is usually a longer-term complication of Clozapine treatment (range: 2-36 months) [46].

Metabolic syndrome: Metabolic adverse effects comprising altered glucose metabolism, dyslipidaemia and weight gain are commonly associated with most SGA's, the risk being highest with Clozapine and Olanzapine [46]. The risk is considerably lower with Aripiprazole, Cariprazine [46] and Lurasidone [47]. Collectively, metabolic side-effects are associated with higher risk of developing type 2 diabetes mellitus and death from coronary heart disease (CHD) [47,48].

Work-up Before Starting Psychotropic Medications

Before starting the patient on psychotropic medications, the following steps should be taken:

- Detailed history of existing and past medical diagnoses and associated symptomatology should be obtained.
- Family history of cardiac problems (e.g., CHD, cardiac arrhythmias sudden death (e.g., before the age of 40), diagnosis of long QT syndrome) should be obtained.
- An accurate note of all the medications the patient is currently taking, and previous medications tried (including side-effects) should be made-from the patient, family and general practitioner (GP).
- All the baseline blood investigations, including HbA1c, cholesterol, liver function tests, renal function tests, thyroid function tests, full blood count (FBC), should be obtained, for all patients. Additional investigations (CRP and troponin) should be ordered for specific medications such as Clozapine.
- Baseline electrocardiogram (ECG). Where is doubt, obtain advice from a physician.

CONCLUSION

Pharmacological treatment is the mainstay of the treatment of SMI. Effective pharmacological treatments are available, which reduce the burden of morbidity associated with the SMI. Effective pharmacological treatments also reduce the risk of mortality. All the SMI's by definition are chronic conditions which follow a remitting, relapsing course, necessitating long term pharmacological treatments, which, in a large proportion of patients, are lifelong.

All the pharmacological treatments are associated with side-effects, which are potentially perilous, and can appear in unpredictable manner. These side-effects increase the risk of developing CVD. The cardio-vascular side-effects appear at different stages of pharmacological treatment. Some appear acutely and dramatically (e.g., myocarditis) while others are insidious in onset (components of metabolic syndrome, cardiomyopathy) and can be missed without due vigilance. It is important to keep in mind that some of the risk factors associated with the development of CVD are potentially modifiable.

In treatment of depression, while newer antidepressants with better side-effects profile than TCA's and MAOI's are available, TCA's and MAOI's undoubtedly have a place in the management of severe, depressions which respond inadequately to newer antidepressants. The SGA's have superior neurological side-effects-profile compared to FGA's, but they are more commonly associated with risk factors for CVD.

In order to make medically informed treatment decisions about pharmacological treatments, the psychiatrists must have, among other things, an understanding of cardiac physiology, awareness of factors which contribute to the risks and their interactions with one another, and skills in interpreting ECG. This would reduce the chances of psychiatrists either completely avoiding highly effective medications because of their generic concerns about potentially serious cardiac side- effects or taking an insouciant approach to treatment that would expose the patients to higher risks. High index of suspicion, regular monitoring, and ordering investigations in a timely manner would go a long way towards managing the risks effectively and improving the prognosis of these highly debilitating conditions.

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